THE PREPARATION AND STUDY OF SOME QUINAZOLINO[3,2-b]CINNOLINES AND RELATED COMPOUNDS.

A thesis
Presented to the University of Cape Town
for the Degree of
Doctor of Philosophy

by

MAURICE JACOB KORT, B.Sc. (Hons).

Department of Chemistry,
University of Cape Town.
October, 1965.

To My Parents

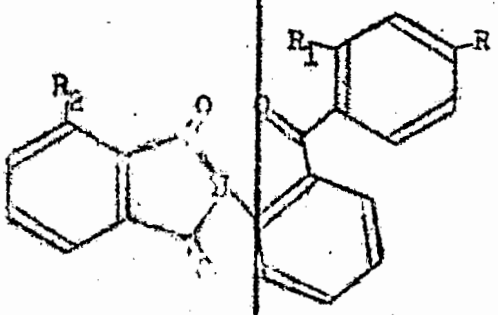
C O N T E N T S

C O N T E N T S

The numbered structures follow in numerical order. For convenience, a structure is sometimes repeated but its old number is retained.

INTRODUCTION

In the [illegible] synthesis [illegible] necessary to [illegible] to protect [illegible] at this function. The amino group is usually protected by forming the N-p-toluene-sulphonyl derivative. This group was used to protect the amino group in anthranilic acid [illegible] the synthesis of o-aminobenzophenones by the Friedel-Crafts reaction with substituted benzenes, its removal was found to be difficult by Thesis, Ingalls and Wilson[1]. They therefore used the phthalimido group to protect the amino function by using phthalanthranilic acid to prepare various o-aminobenzophenones. Phthalanthranilic acid was converted to the chloro-compound with phosphorus pentachloride or thionyl chloride [illegible] Gabriel[2], and the chloro-acid was used in typical Friedel-Crafts reactions with benzene, and a variety of substituted benzenes. The products obtained analysed correctly for, and were considered to be, 2-phthalimidobenzophenones (I) on chemical and spectral evidence.



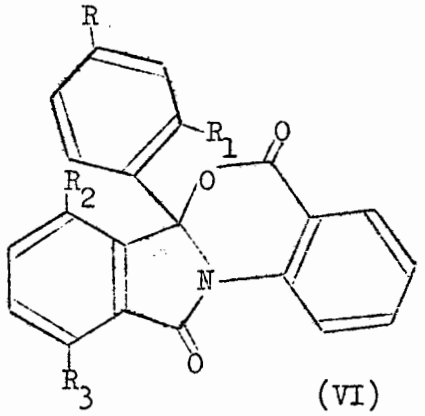
(I)

(Ia): R = OCH_3; R_1 = R_2 = H.
(Ib): R = R_1 = OCH_3; R_2 = H.
(Ic): R = SCH_3; R_1 = R_2 = H.
(Id): R = R_1 = OCH_3; R_2 = [illegible].
(Ie): R = Br; R_1 = R_2 = H.

In this manner they prepared what they thought to be 4-methoxy- (Ia)[2], 2,4-dimethoxy- (Ib)[1], 4-methylthio- (Ic)[3] 2'-phthalimidobenzophenones, and 2,4-dimethoxy-2'-(3-nitrophthalimido)benzophenone (Id)[3] by the Friedel-Crafts reaction with anisole, dimethylresorcinol, thioanisole and dimethylresorcinol,

acid and for its chloro-compound, respectively.

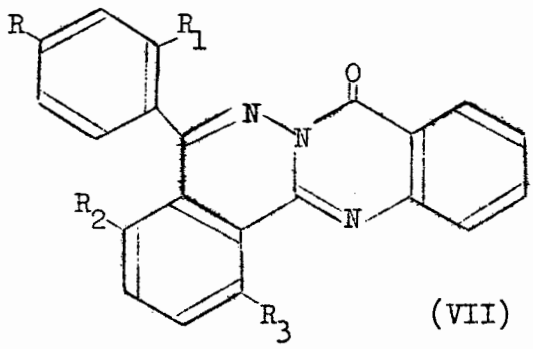
In the light of these corrected structures for phthalanthranilic acid, and for its chloro-compound, to the compounds formerly reported as the phthalimide derivatives (Ia), (Ib), (Ic), and (Id), they assigned the benzoxazine structures (VIa), (VIb), (VIc), and (VId), respectively.



(VI)

(VIa): R = OCH_3; $R_1 = R_2 = R_3 = H$.
(VIb): R = $R_1 = OCH_3$; $R_2 = R_3 = H$.
(VIc): R = SCH_3; $R_1 = R_2 = R_3 = H$.
(VId): R = $R_1 = OCH_3$; R_2 or $R_3 = NO_2$; R_3 or $R_2 = H$.
(VIe): R = Br; $R_1 = R_2 = R_3 = H$.

With the knowledge of the exact structures for these compounds, it became clear that the triazepine structures for compounds (II) could not be correct. The benzoxazine (VIe) was obtained mixed with the phthalimide (Ie) when bromobenzene was used in the Friedel-Crafts reaction, but could be prepared in purer form and better yield by fusion of o-(4-bromobenzoyl)benzoic acid with methyl anthranilate[7]. Treatment of this compound with hydrazine gave a compound which had chemical properties and an infrared spectrum similar to those of the compounds to which the triazepine structure (II) had been assigned. This compound was shown[8] by X-ray crystallographic analysis to have the structure (VIIa). Hence the compounds which had been assigned the



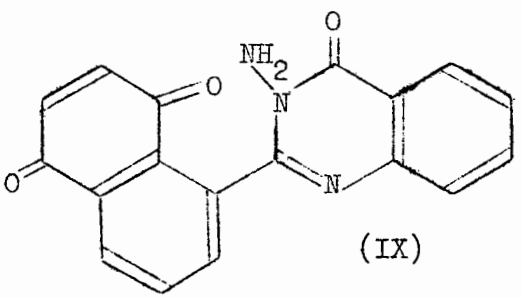
(VII)

(VIIa): R = Br; $R_1 = R_2 = R_3 = H$.
(VIIb): R = OCH_3; $R_1 = R_2 = R_3 = H$.
(VIIc): R = $R_1 = OCH_3$; $R_2 = R_3 = H$.
(VIId): R = SCH_3; $R_1 = R_2 = R_3 = H$.
(VIIe): R = $R_1 = OCH_3$; R_2 or $R_3 = NO_2$; R_3 or $R_2 = H$.

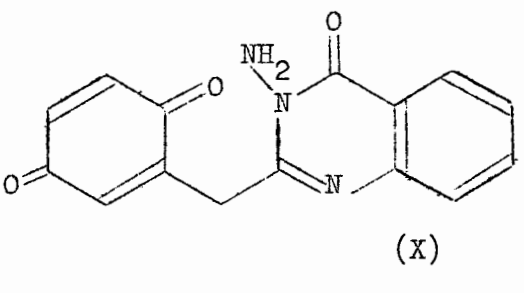
structures (IIa), (IIb), (IIc), and (IId) would have the structures (VIIb), (VIIc), (VIId), and (VIIe), respectively.

Lamchen[9] proposed the following mechanism for the reaction in which hydrazine converted the substituted benzoxazines, e.g. (VIe), to the substituted phthalazino[1,2-b]quinazolines, e.g. (VIIa), shown below,(page 5).

If this mechanism is correct, an intramolecular nucleophilic attack by the amino group of the quinazolino half of the molecule onto a benzophenone carbonyl group must have occurred. This is illustrated in the intermediate structure (VIII) in this reaction sequence. It would be of interest to determine whether a similar reaction would occur if a quinonyl carbonyl group was substituted for this benzophenone carbonyl group. If a similar nucleophilic attack occurred, the quinone compounds (IX) and (X) should ring close to

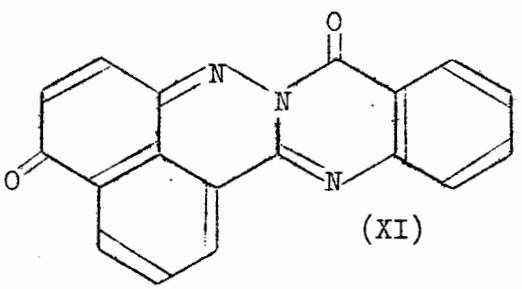


(IX)

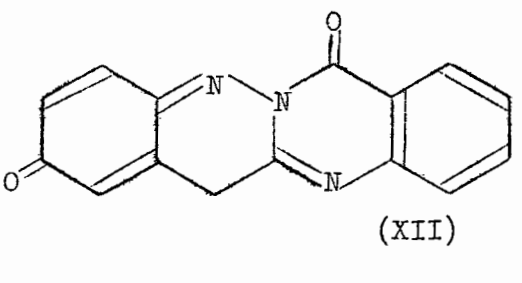


(X)

give the products (XI) and (XII) respectively.

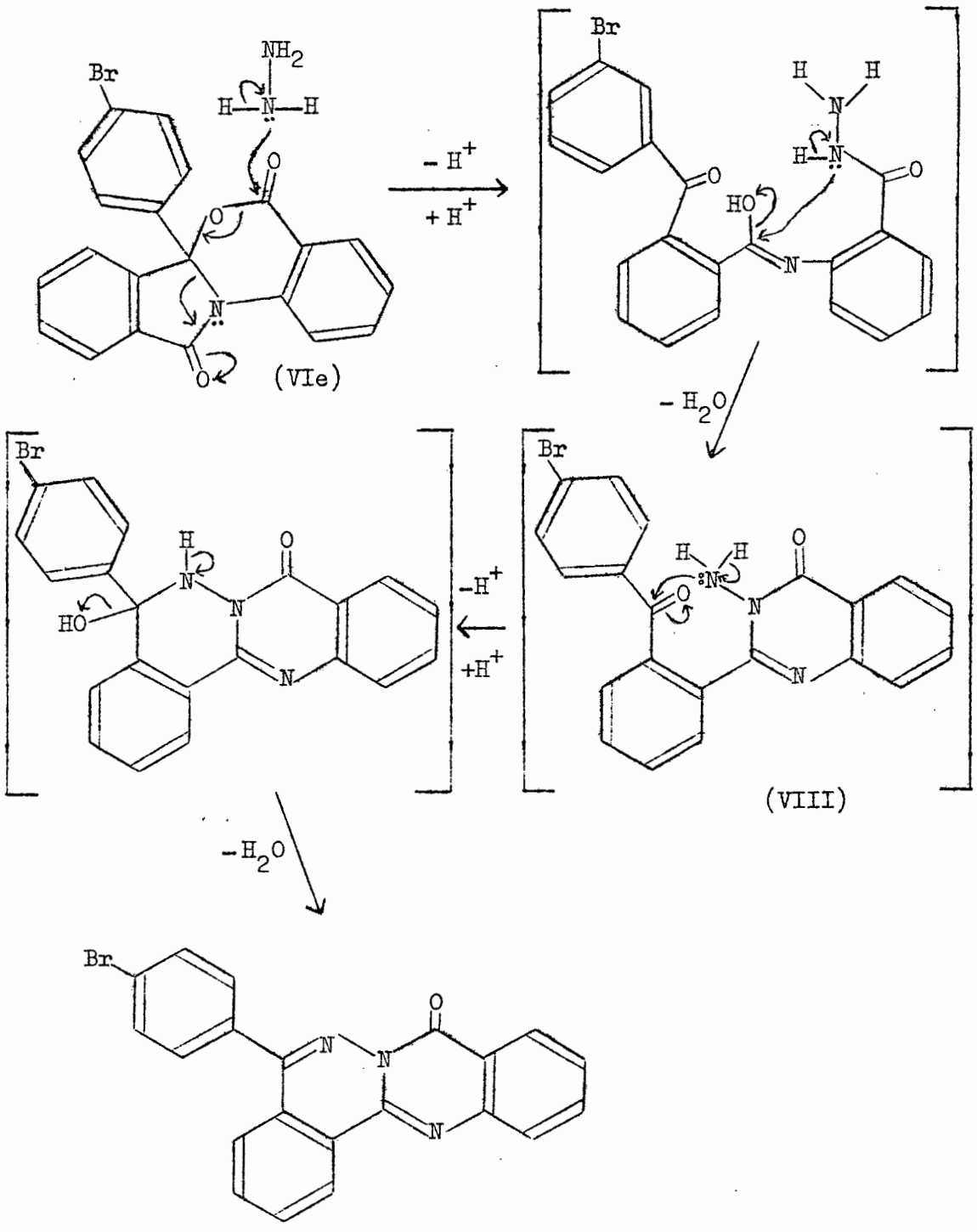


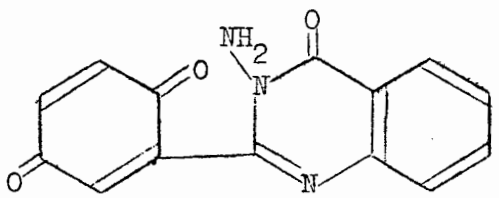
(XI)



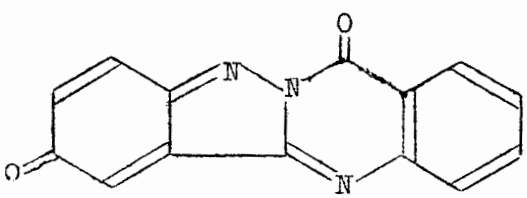
(XII)

Further, if it was found that such ring-closure did occur, it would be of interest to determine whether the quinone (XIII) would give an analogous ring-closure to form the compound (XIV) containing


Br
NH2
H
N
H
O
O
N
O
(VIe)
- H+
+ H+
Br
H
H
N
H
N
O
HO
N
O
- H2O
Br
H
N
N
O
HO
N
-H+
+H+
Br
H
H
N
O
N
N
(VIII)
- H2O
Br
N
N
O
N
(VIIa)



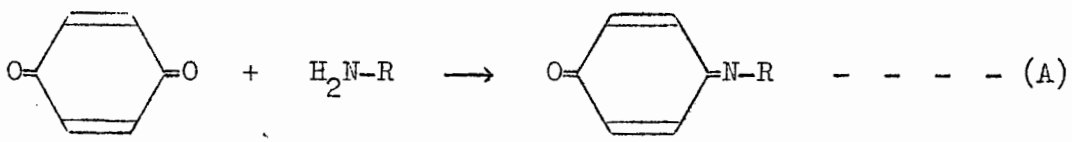
(XIII)



(XIV)

a fused five-membered ring structure.

In the ring-closure envisaged in the quinones (IX), (X), and (XIII), the reaction under consideration was between an amino group and a quinone function. It would thus be valuable at this point to consider known or possible reactions between such functions. The reaction could be of the type illustrated in (A). If R represented



(A)

an hydroxyl group (hydroxylamine), a quinone-oxime would result, and if R was replaced by the hydrogen atom (ammonia), a quinone-imine would be the product. Where R represented the C_6H_5-NH- group (phenylhydrazine), or this group with substituents in the aromatic nucleus (phenylhydrazines), quinonephenylhydrazones or substituted quinonephenylhydrazones would be the products of this reaction. Similarly, quinone-semicarbazones and quinone-aminoguanidones would result if R represented the H_2N-CO-NH- and H_2N-(C=NH)-NH- groups respectively. Each of these classes of compounds is discussed briefly.

Quinone-oximes[10].

From the methods of formation and their reactions, p-benzoquinonemonoximes could have either structures (XV) or the tautomeric p-nitrosophenol structures (XVI)[11]. Thus p-benzoquinone with hydroxylamine hydrochloride in aqueous solution[12] and, for

(XV) (XVI)

example, the reaction of nitrous acid and phenol[13] produced the same p-benzoquinonemonoxime, tautomeric with p-nitrosophenol.

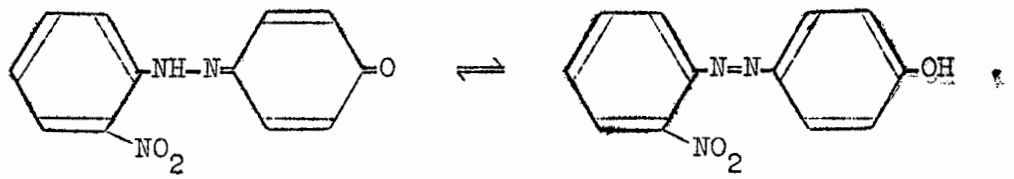
Similarly, p-benzoquinonedioximes could be prepared by the action of hydroxylamine hydrochloride on p-benzoquinones or on p-nitrosophenols[14]. The base, hydroxylamine, reduced p-benzoquinone to hydroquinone[15].

Quinone-imines.

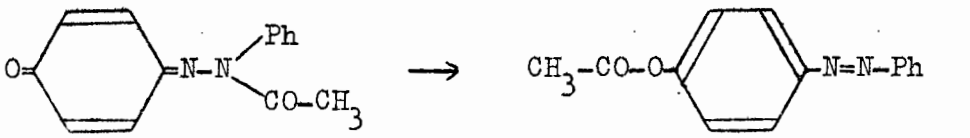
Condensation of the amino group with the carbonyl group of the quinone should produce the quinone-imine systems shown in the polycyclic compounds (XI), (XII), and (XIV). However, quinone-imines are not synthesised by the condensation of ammonia with quinones, but by the oxidation of o- and p-aminophenols and p-phenylenediamines with silver oxide or lead(IV) oxide in ether[16].

Quinonephenylhydrazones.

The reduction of quinones by hydrazine to the corresponding hydroquinone derivatives was only reported in 1962[17]. Phenylhydrazine and as-alkylphenylhydrazines also reduce[15] p-benzoquinone to hydroquinone. However, 2-nitro- and 2,4-dinitrophenylhydrazine give condensation products, identical with the products obtained by the coupling of 2-nitro- and 2,4-dinitrobenzenediazonium salts with phenol showing again the tautomeric nature of the products, e.g.



α-Acylphenylhydrazines condensed with quinones forming the α-acylphenylhydrazones, e.g. p-benzoquinone-N-acetyl-phenylhydrazone (XVII). Ready migration of the acyl group from the nitrogen to the oxygen atom, with the formation of the corresponding O-acetylhydroxy-azobenzene[18] (XVIII), occurred.

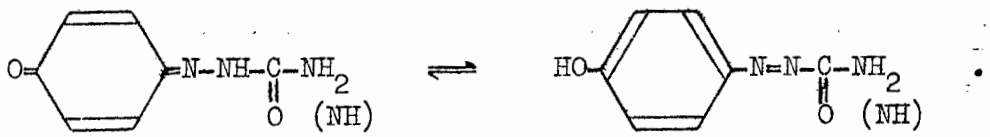


(XVII) (XVIII)

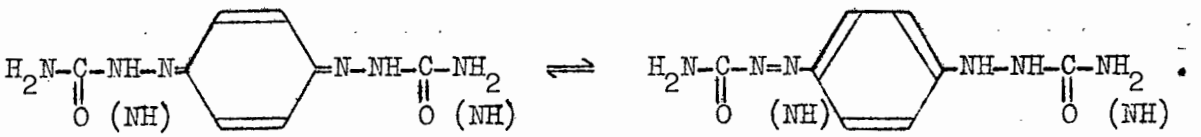
The N,N-disubstituted hydrazone system would be present in the polycyclic compounds (XI), (XII), and (XIV), the disubstituents forming a ring, although this system would be more analogous to an N-substituted semicarbazone system.

Quinone-semicarbazones and -aminoguanidones.

Like ketones, quinones condense with semicarbazide and aminoguanidine, to form the mono- and bis-semicarbazones and mono- and bis-aminoguanidones[19]. Here again, the quinone-monosemicarbazones and -monoaminoguanidones are tautomeric with the corresponding hydroxyazo compounds, viz.



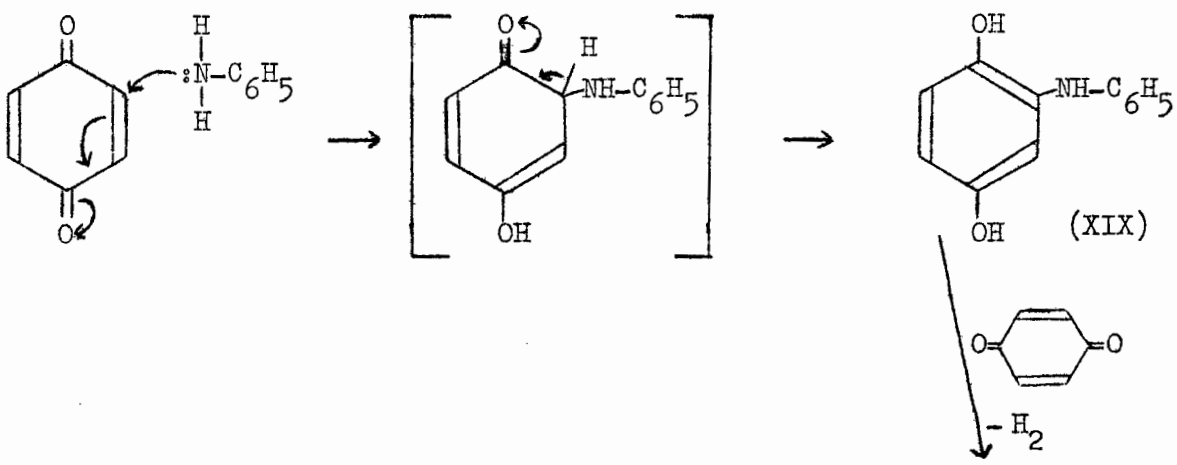
The bis-substituted functional derivatives are tautomeric with the corresponding substituted aminoazo compounds,

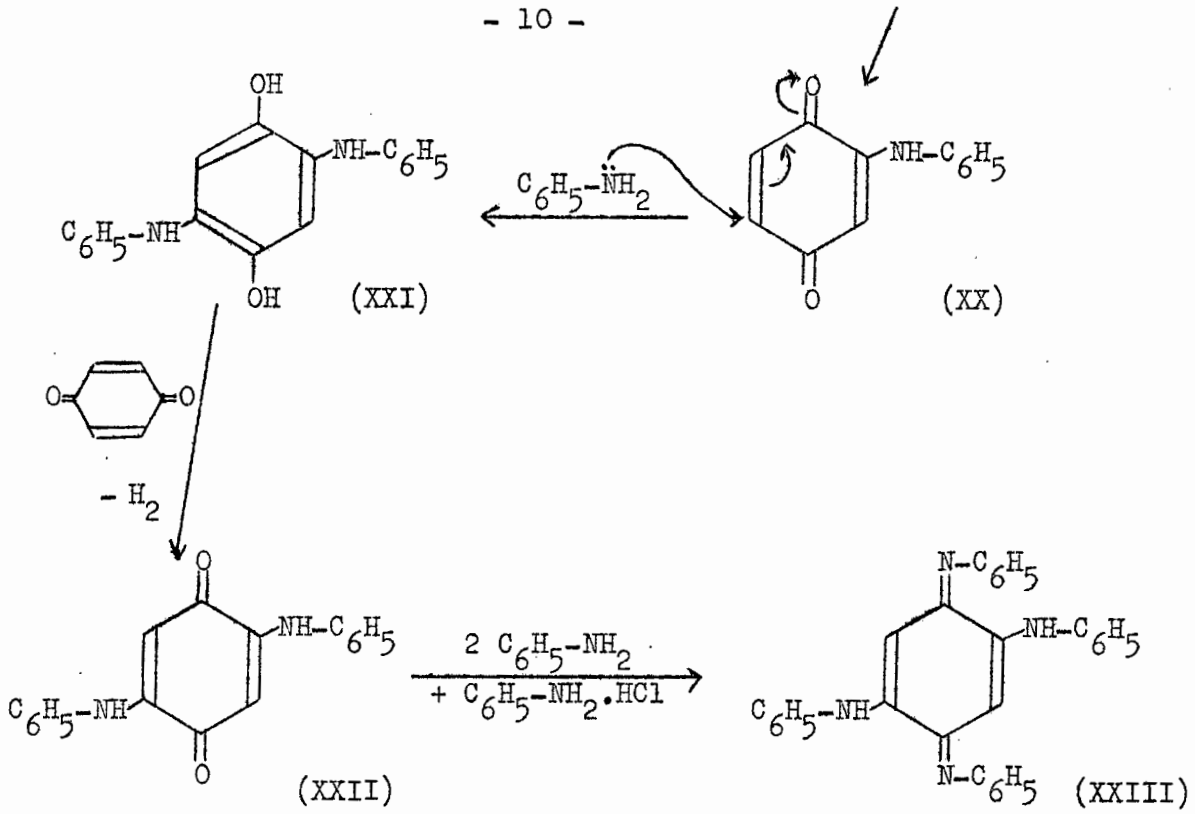


In all the above examples with the exception of the α-acylphenylhydrazone (XVII), the "condensation" compounds are mixtures of tautomers. In the quinones (IX), (X), and (XIII) above, if ring-closure occurred no such tautomerism would be possible in the polycyclic products (XI), (XII), and (XIV), there being no hydrogen atom on the bridged nitrogen atom (cf. α-acylphenylhydrazones).

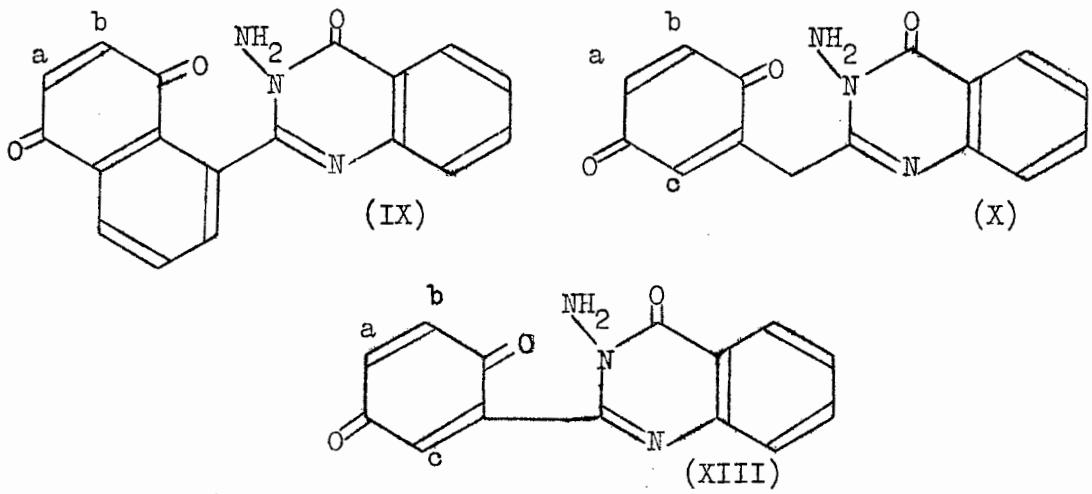
1,4-Addition to p-benzoquinones.

A property of quinones, very pertinent to this ring-closure, is the ease with which they undergo 1,4-addition reactions across the C=C-C=O system. With hydrogen chloride, hydrogen cyanide, aniline, etc., substituted dihydroxybenzenes are obtained, but may undergo oxidation to a substituted quinone by unreacted starting quinone. This is illustrated by the addition of aniline to p-benzoquinone[20] to form the intermediate 2-anilinohydroquinone (XIX) which will be oxidised to 2-anilinobenzoquinone (XX) by unreacted p-benzoquinone. A second molecule of aniline can add to the substituted quinone (XX) giving 2,5-dianilinohydroquinone (XXI) which will be oxidised to 2,5-dianilino-p-benzoquinone (XXII). In the presence of aniline hydrochloride[21], two molecules of aniline will condense with the substituted quinone (XXII) to give 2,5-dianilino-p-benzoquinonedianil (azophenine), (XXIII).



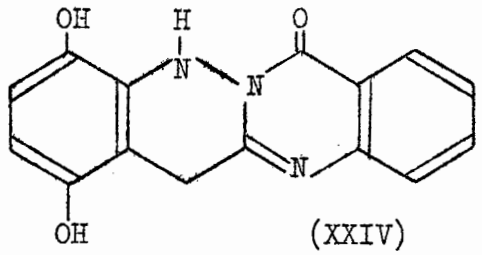


1,4-Addition to the quinones (IX), (X), and (XIII) would give substitution in positions a, b, or c of the quinone nucleus.

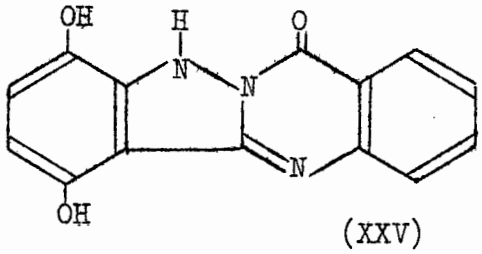


Internal 1,4-addition of the amino group to the quinone nucleus giving substitution in positions a, and b were eliminated for steric reasons,

substantiated by the use of "Dreiding" models. Internal 1,4-addition could occur at position c in the quinones (X), and (XIII) to give the polycyclic compounds (XXIV), and (XXV), respectively. This internal addition could not occur with the quinone (IX).



(XXIV)



(XXV)

The problem to be investigated in this thesis was therefore three-fold;

(1) to synthesise the three quinones (IX), (X), and (XIII);

(2) to investigate whether ring-closure occurred; and

(3) to confirm whether this ring-closure proceeded as in Lamchen's work, the amino group condensing with the quinonyl carbonyl group, or by 1,4-addition of the amino group to the quinone nucleus in the compounds (X) and (XIII).

It was found to be more convenient to treat the synthesis and attempted ring-closure of each of the quinones as a unit. Hence Section I is devoted to 3-amino-2-(1,4-benzoquinonylmethyl)quinazolin-4(3H)-one (X), Section II to 3-amino-2-(1,4-naphthaquinon-5-yl)-quinazolin-4(3H)-one (IX), and 3-amino-2-(1,4-benzoquinonyl)-quinazolin-4(3H)-one (XIII) is dealt with in Section III.

D I S C U S S I O N

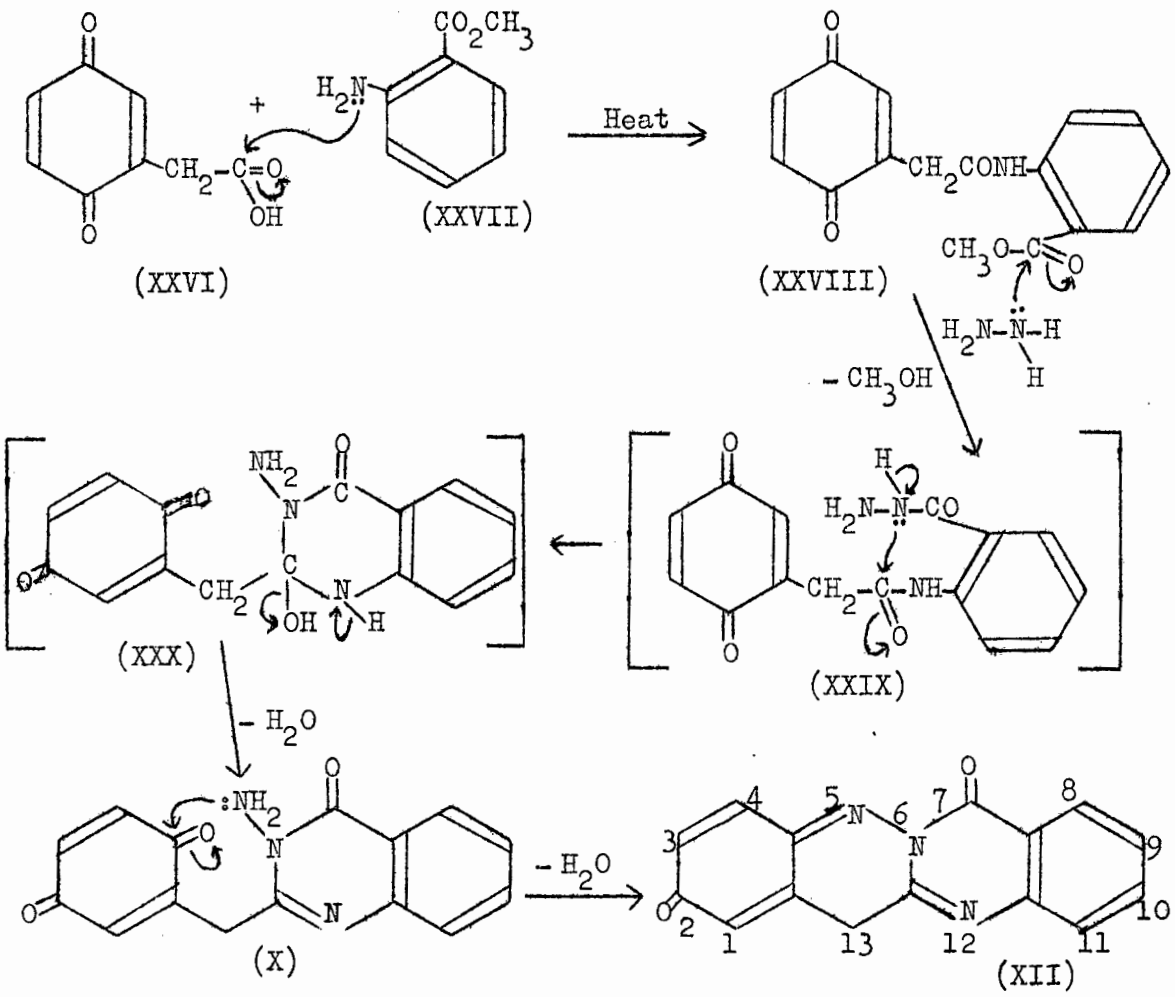
S E C T I O N I

S E C T I O N I

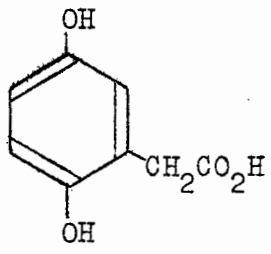
THE SYNTHESIS AND RING-CLOSURE OF 3-AMINO-2-(1,4-BENZOQUINONYLMETHYL)QUINAZOLIN-4(3H)-ONE.

§ 1. Proposed synthesis of 3-amino-2-(1,4-benzoquinonylmethyl)quinazolin-4(3H)-one, (X).

The simplest route to the first of the three quinones (X) under investigation, and its attempted ring-closure to the compound (XII) is illustrated in the following scheme, starting with p-benzoquinonylacetic acid (XXVI), and methyl anthranilate (XXVII). The product of these two reactants, methyl o-(α-1,4-benzoquinonylacetamido)benzoate (XXVIII), on treatment with hydrazine could form the required quinone (X) via the intermediates (XXIX) and (XXX), as follows:



p-Benzoquinonylacetic acid may be synthesised very readily from homogentisic acid (2,5-dihydroxyphenylacetic acid), (XXXI), by oxidation with either sodium dichromate and sulphuric acid[22] at 0°, or with ferric chloride[23].

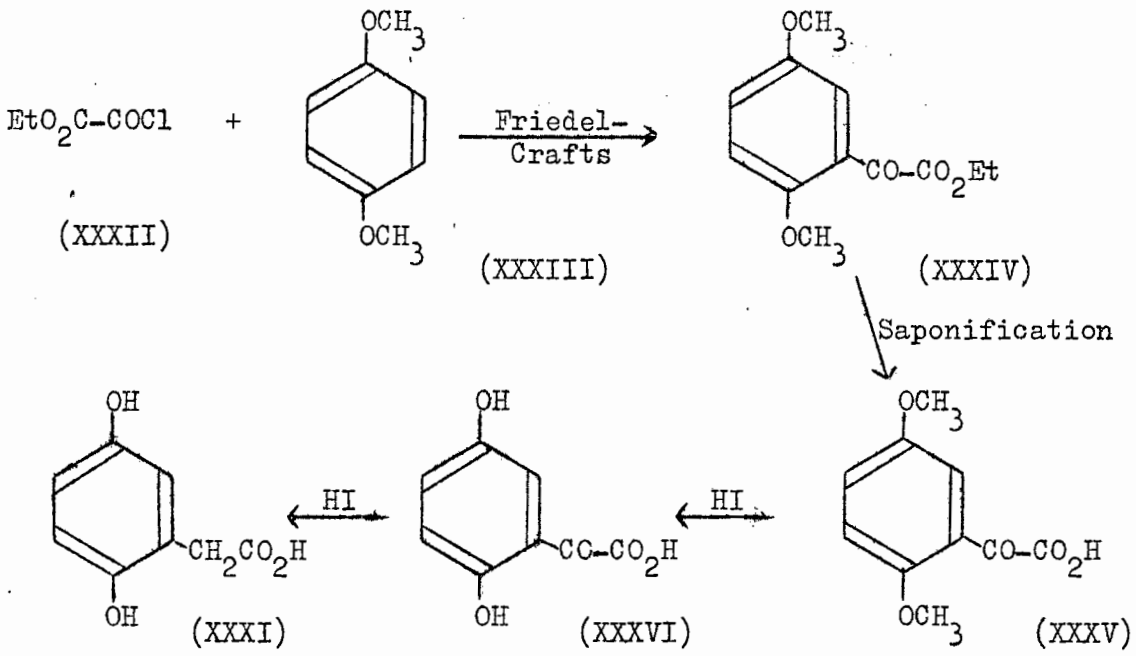


(XXXI)

§ 2. Synthesis of homogentisic acid.

Homogentisic acid has been synthesised by various routes in the past[24,25,26,27,28,29,30]. The six-step method of Hahn and Stenner[24] giving homogentisic acid in a yield of only 26% and Baumann and Fränkel's method[25] which gave poor yields were stated to be unsatisfactory by Abbott and Smith[26] and by Leaf and Neuberger[27]. Leaf and Neuberger[27] gave a preferred method for the preparation of homogentisic acid which also involved a six-step synthesis. Abbott and Smith[26] also dismissed the methods of Osborne[28], of Neubauer and Flatow[29], and of McElvain and Cohen[30], for the synthesis of this compound. In their own synthesis[26], although only three steps, for which they claimed good yields (69%, 64%, and 93%) the steps are long and very cumbersome. Because these syntheses for homogentisic acid were long, cumbersome or tedious, the following synthesis of homogentisic acid, based on the preparation of 5-(2',5'-dihydroxyphenyl)-pentanoic acid[31], was attempted.

Mono-ethyl oxalyl chloride[32] (XXXII), and p-dimethoxybenzene (XXXIII) have been condensed in a Friedel-Crafts reaction to obtain 2,5-dimethoxyphenylglyoxylic acid ethyl ester[33] (XXXIV). Saponification of this ester should yield the acid (XXXV) which could be expected to demethylate on treatment with fuming hydriodic

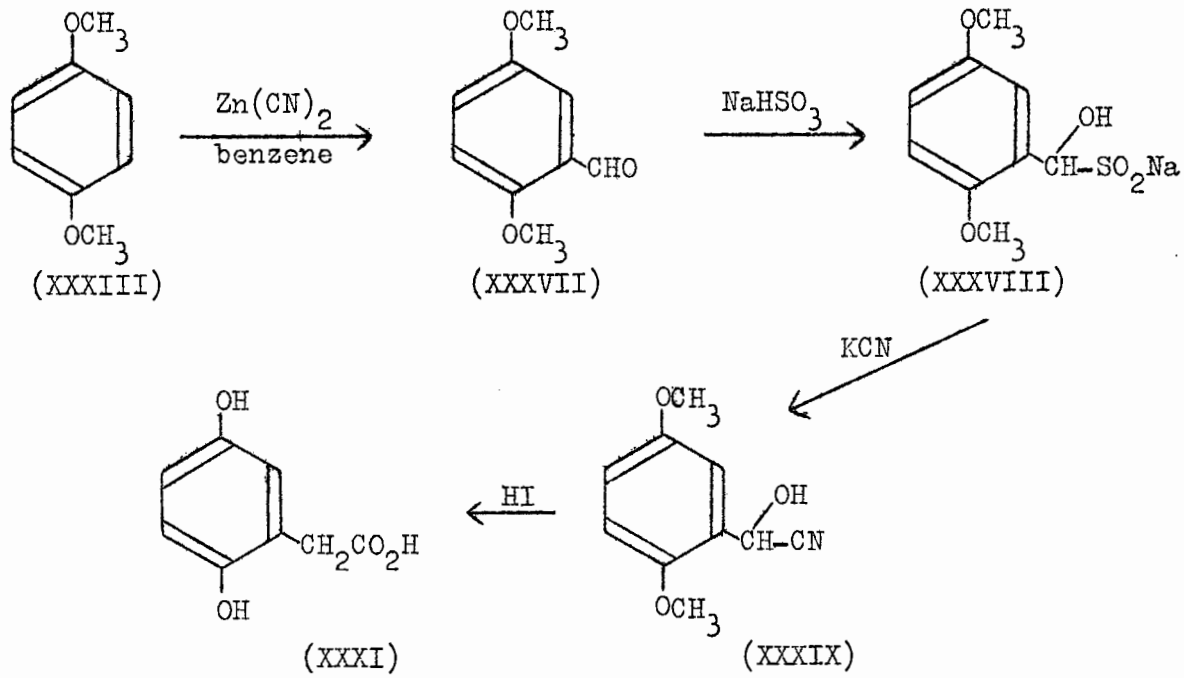


acid to 2,5-dihydroxyphenylglyoxylic acid (XXXVI). Neubauer and Flatow[34] in fact prepared homogentisic acid (XXXI) from this hydroxy acid by hydriodic acid treatment. It was considered that demethylation to the compound (XXXVI) and reduction to the acid (XXXI) could be effected in the same operation.

The Author therefore converted oxalic acid to mono-ethyl oxalyl chloride, in good yield, via the mono-ethyl oxalate[32]. The procedure of Kauffmann and Grombach[33] for the Friedel-Crafts reaction to form the ester (XXXIV) was adopted, except that tetrachloroethane was used as the solvent instead of carbon disulphide. Tetrachloroethane, being non-inflammable and easy to dry, is considered to be superior as a solvent[35] in Friedel-Crafts reactions, usually equalling or improving the yields where carbon disulphide was used. An extremely low yield of the ester (9%) was obtained. Kauffmann and Grombach[33] quoted no figures for the yields they obtained. Because of the low yield realised in this initial step, this approach was considered to be unprofitable, and was abandoned.

A second approach entailed the use of 2,5-dimethoxybenzaldehyde (XXXVII) which has been prepared[36] by a Gatterman

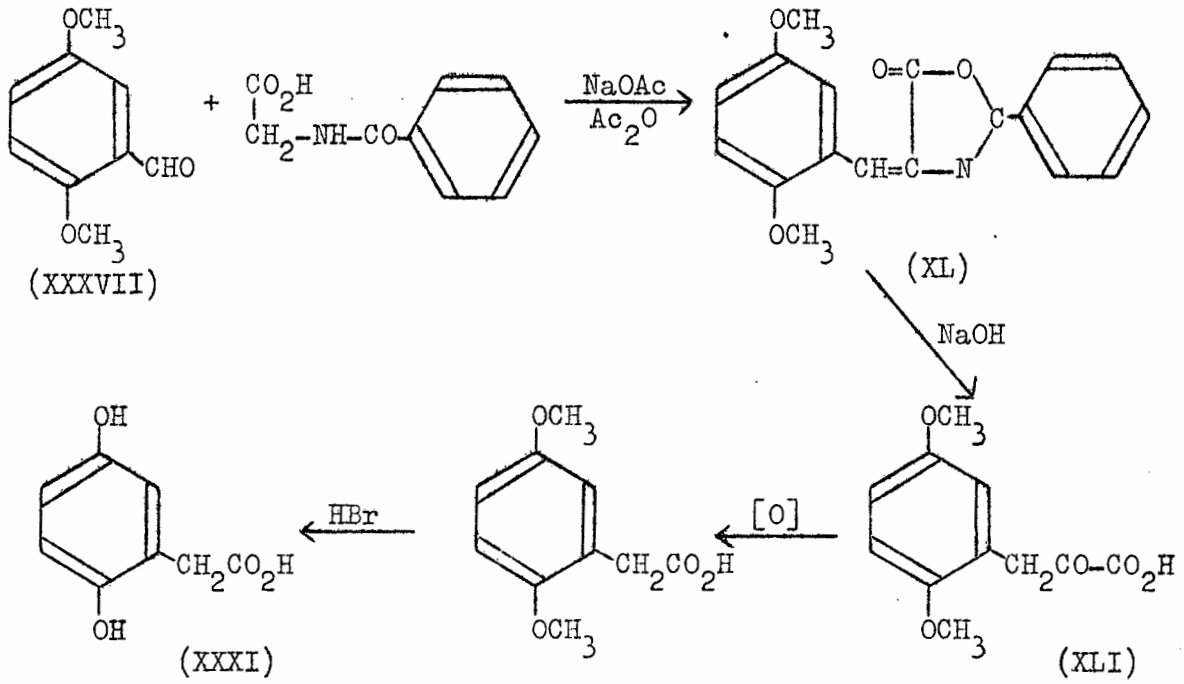
synthesis from p-dimethoxybenzene (XXXIII). Treatment of the aldehyde with sodium bisulphite yielded the sodium bisulphite addition compound (XXXVIII). It was hoped that addition of the sodium bisulphite addition compound to an aqueous solution of potassium cyanide would produce 2,5-dimethoxymandelonitrile (XXXIX), after the method of Czaplicki et al.[37] who prepared o-methoxymandelonitrile in this way. From this nitrile they obtained o-hydroxyphenylacetic acid by one hour's treatment with hydriodic acid. Simultaneous demethylation, reduction, and hydrolysis occurred. Hydriodic acid treatment of the cyanohydrin (XXXIX) could form homogentisic acid in an analogous reaction. Neubauer and Flatow[34] successfully used fuming hydriodic acid to reduce 2,5-dihydroxymandelic acid to homogentisic acid (XXXI).



Freshly prepared[38] zinc cyanide was used in the preparation[36] of 2,5-dimethoxybenzaldehyde (XXXVII) and this was converted[39] to the bisulphite addition compound (XXXVIII). The 2,5-dimethoxymandelonitrile was not isolated from the reaction, but the crude oil was treated with hydriodic acid. A gum was isolated from

which no homogentisic acid could be obtained.

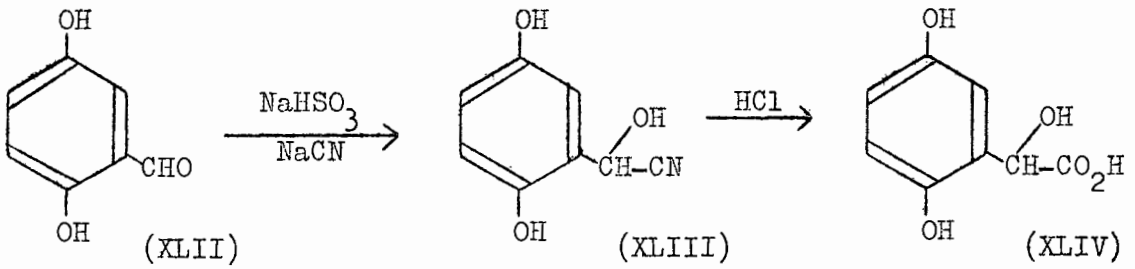
As another route, starting with the aldehyde (XXXVII) is known[27], and since Abbott and Smith[26] also found similar demethylation with hydriodic acid unsatisfactory, it was decided to follow this alternative route, represented below:



The azlactone (XL) formed readily, but the high yield quoted for the hydrolysis to the acid (XLI) could not be realised, a yield of only 10.6% being obtained. Since two more steps had to follow, such a low yield made this route unattractive.

A final attempt to find a new synthesis of homogentisic acid, applicable to a large scale preparation was made by the Author. Since the demethylation in the second attempted method proved unsatisfactory, it was decided to start with 2,5-dihydroxybenzaldehyde (XLII). This would be converted to the bisulphite addition compound with sodium bisulphite and then treated with sodium cyanide in an attempt to form 2,5-dihydroxymandelonitrile (XLIII). The conditions used by Ladenburg *et al.*[40] for the synthesis of *o*-hydroxymandelonitrile

from salicylaldehyde would be followed. Treatment of the cyanohydrin (XLIII) with fuming hydriodic acid would probably simultaneously reduce and hydrolyse the compound to homogentisic acid as had been the experience of Czaplicki *et al.*[37] with *o*-methoxymandelonitrile (where demethylation also occurred). Since a previous, unsuccessful attempt at the preparation of homogentisic acid from the cyanohydrin (XXXIX) involved demethylation, hydrolysis, and reduction in one operation, it was not certain which step was responsible for the failure. Therefore it was decided to perform the hydrolysis and reduction as separate steps. The conditions used in the hydrolysis of mandelonitrile to mandelic acid[41] would be used for hydrolysing the cyanohydrin (XLIII) to 2,5-dihydroxymandelic acid (XLIV). This acid could be submitted to reduction, for example with hydriodic acid[34], to obtain the desired homogentisic acid (XXXI).

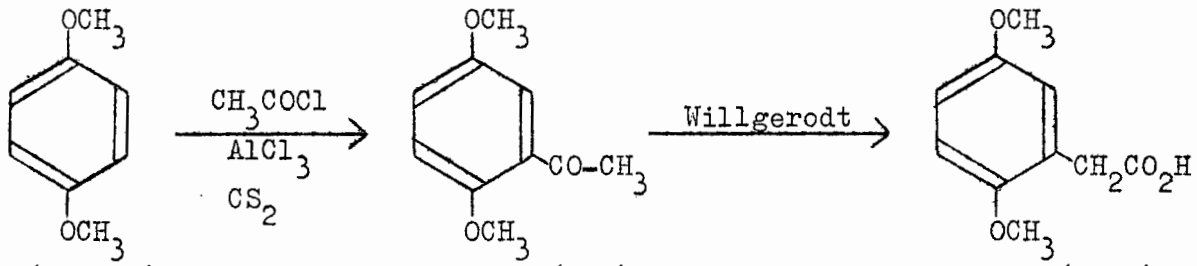


(XLII) (XLIII) (XLIV)

2,5-Dihydroxybenzaldehyde (XLII) was prepared[42] from salicylaldehyde and submitted to the same treatment which Ladenburg *et al.*[40] gave 2-hydroxymandelonitrile. A black gum was obtained. Without isolating the cyanohydrin[40], this gum was treated with concentrated hydrochloric acid in the same way that mandelonitrile was hydrolysed[41] to mandelic acid. Very little gum was obtained and all attempts at crystallisation failed.

Having failed to find a new, rapid synthesis of homogentisic acid, the method of Abbott and Smith[26] was successfully used. This involved the preparation of 2,5-dimethoxyacetophenone (XLV) by a Friedel-Crafts reaction on *p*-dimethoxybenzene (XXXIII) using carbon disulphide as solvent. A Willgerodt reaction on the

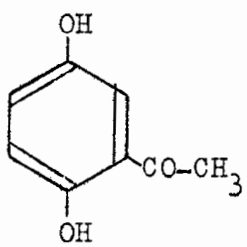
ketone (XLV) yielded 2,5-dimethoxyphenylacetic acid (XLVI) which was demethylated to homogentisic acid (XXXI) by treatment with hydrobromic acid.



(XXXIII) (XLV) (XLVI)

The full procedure of Abbott and Smith was used throughout the synthesis. Tetrachloroethane was used in place of the carbon disulphide as the solvent for the Friedel-Crafts reaction. By this modified procedure a better yield of the acetophenone (XLV) was obtained.

Although homogentisic acid was obtained, the synthesis used still involved a demethylation, and the method was long and tedious. A further plausible method, similar to the method of Abbott and Smith, but which eliminated the demethylation step was attempted. This would entail a Willgerodt reaction on 2,5-dihydroxy-acetophenone (XLVII) which should produce homogentisic acid directly.



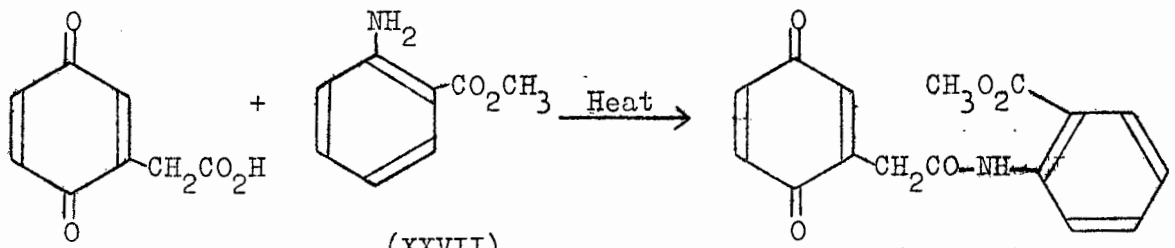
(XLVII)

This acetophenone has been obtained by a Friedel-Crafts reaction using acetyl chloride and hydroquinone diacetate[43], and by a Fries rearrangement[44,45] on hydroquinone diacetate.

Hydroquinone diacetate was obtained[46] quantitatively by acetylating hydroquinone, and the Friedel-Crafts reaction was performed on this yielding the acetophenone (XLVII). The Willgerodt reaction to obtain homogentisic acid yielded material which melted over 61° higher than the melting point reported for homogentisic acid. As this reaction had been performed with the specific purpose of synthesising homogentisic acid, the constitution of the product obtained was not investigated.

§ 3. Synthesis of methyl o-(α-1,4-benzoquinonylacetamido)benzoate, (XXVIII).

Oxidation[23] of homogentisic acid afforded p-benzoquinonylacetic acid (XXVI) in excellent yield. Mörner[47] repeatedly stressed the extreme instability of this compound to heat, immediate decomposition occurring, decomposition even occurring in an aqueous solution at room temperature. Its fusion with methyl anthranilate (XXVII) to form the quinone (XXVIII) was therefore impractical.



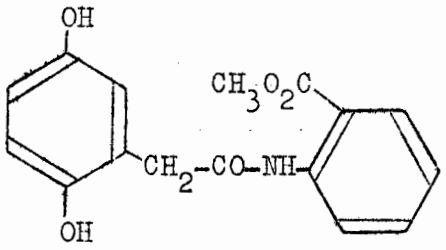
(XXVI) (XXVII) (XXVIII)

Indeed, in an attempted fusion only a small quantity of black material, which could not be recrystallised, was obtained.

In addition, this fusion was undesirable because of the possibility of 1,4-addition of the amine to the -C=C-C=O group of p-benzoquinonylacetic acid. This would not produce the quinone (XXVIII).

It was, however, possible to fuse homogentisic acid and

methyl anthranilate to form the amide (XLVIII) and to oxidise this with ferric chloride to the quinone (XXVIII).



(XLVIII)

A complex molecule such as the amide (XLVIII) would have a complicated infrared spectrum. It was, however, possible to obtain confirmation for the proposed structure from the spectrum. A nujol mull gave a band at 3270 $cm.^{-1}$ with a shoulder at 3220 $cm.^{-1}$ which were assigned[48,49] to the N-H stretching vibration of a bonded secondary amide and to the O-H stretching vibration, intermolecularly hydrogen bonded, respectively. The strong absorptions at 1694 and 1672 $cm.^{-1}$ could be assigned to the C=O stretching vibrations of the ester and amide I bands, respectively. Absorptions at 1604, 1585, 1512, and 1463 (shoulder) $cm.^{-1}$ were probably due to the aromatic C=C in-plane stretching vibrations while the absorption at 1528 $cm.^{-1}$ may have been due to the amide II band (combination bands of N-H deformation and C-N stretching vibrations).

Similarly, the infrared spectrum of the oxidation product of the dihydroxy compound (XLVIII) confirmed the expected structure (XXVIII) for the quinone. Here, absorptions at 3260, 1700, and 1684 $cm.^{-1}$ were assigned as in the compound (XLVIII), to the N-H and to the C=O stretching vibrations. The shoulder at 3220 $cm.^{-1}$ assigned to the O-H stretching vibration in the spectrum of the dihydroxy compound (XLVIII) was absent in the spectrum of the quinone. However, a new absorption maximum in the spectrum of this compound at 1653 $cm.^{-1}$ was in the range of the C=O stretching vibrations of quinones. An infrared spectrum of p-benzoquinonylacetic acid in nujol showed C=O stretching absorptions at 1690 $cm.^{-1}$ (carboxylic acid) and at 1647

cm.$^{-1}$ (quinone). Similarly, an infrared spectrum of p-benzoquinone in nujol had a band at 1657 cm.$^{-1}$ with a shoulder at 1652 cm.$^{-1}$ due to the C=O stretching vibrations of the quinone. Josien and Deschamps[50] gave two bands for p-benzoquinone, at 1669 and 1656 cm.$^{-1}$, the lower frequency band being appreciably weaker. Further absorption maxima in the spectrum of the quinone (XXVIII) at 1602, 1586, and 1448 cm.$^{-1}$, and at 1531 cm.$^{-1}$ were assigned to the aromatic C=C in-plane stretching vibrations, and to the amide II band, respectively, as in the spectrum of the dihydroxy compound (XLVIII). The interpretation of the infrared spectrum of the amide (XLVIII), and of the quinone (XXVIII) formed from it, is summarised in Table 1.

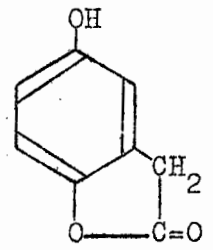
Table 1.

		Amide (XLVIII)	Quinone (XXVIII)
		cm.$^{-1}$	cm.$^{-1}$
N-H stretching vibration of a bonded secondary amide		3270	3260
O-H stretching vibration, intermolecularly hydrogen bonded		3220sh.	—
C=O stretching vibrations :	of the ester	1694	1700
	of the amide I band	1672	1684
	of the quinone	—	1653
Aromatic C=C in-plane stretching vibrations		1604, 1585, 1512,1463sh.	1602,1586, 1448
Amide II band		1528	1531
sh. = shoulder.			

Effect of heat on the amide (XLVIII).

The amide (XLVIII) could be recrystallised from acetone or from ethanol, but as it was only sparingly soluble even in the hot solvents, large quantities of the solvents were required for the

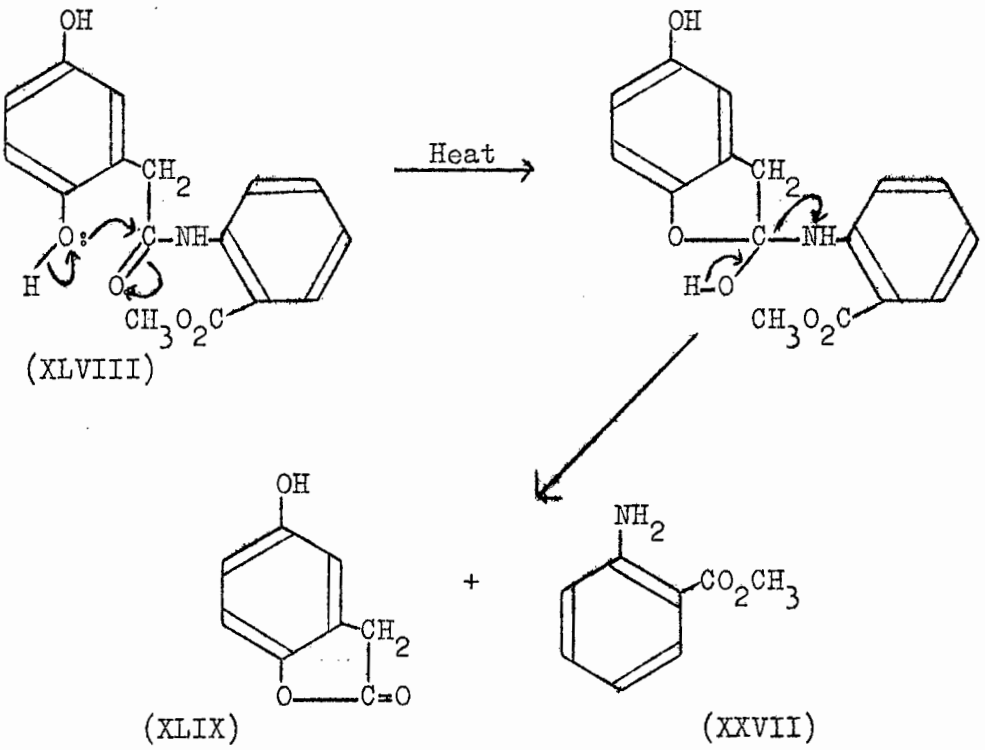
crystallisation. An attempt was made to find a better solvent for the recrystallisation. The amide was fairly soluble in a number of solvents and crystallised from amyl acetate or from ethyl acetate but large volumes of the solvents were also required. However, the compound was only sparingly soluble in cold tetrachloroethane and crystals were readily obtained from a small volume of the hot solvent. This recrystallisation lowered the melting point from 213 - 213.5° to 179 - 181°. Further crystallisation from tetrachloroethane raised the melting point to 188 - 189°. This low melting material contained no nitrogen and was shown to be the lactone of homogentisic acid, (XLIX),



(XLIX)

by melting point, mixed melting point, and comparison of its infrared spectrum with the authentic lactone, prepared by the method of Abbott and Smith[26]. Thin layer chromatography on silica gel of the hot tetrachloroethane solution of the amide (XLVIII) revealed the presence of the lactone, a small amount of undecomposed amide, and methyl anthranilate.

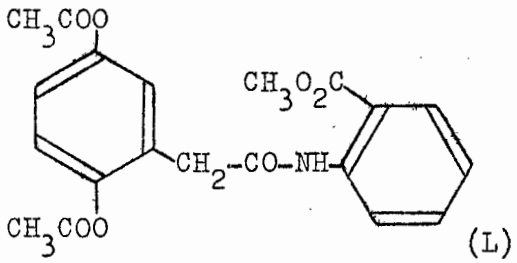
Although aromatic amides are very stable to hydrolysis, the amide in question is an aliphatic amide, and thus less stable. Phenols are not strong nucleophiles. The formation of the lactone (XLIX) from the amide (XLVIII) would be by an intramolecular nucleophilic attack on the amido carbonyl group by the lone pair of electrons of the oxygen atom of the phenolic hydroxyl group. The mechanism is illustrated in the following reaction sequence:



The two groups would be favourably placed for such a ring-closure with attendant decomposition.

§ 4. Formation of Methyl o-(α-1,4-diacetoxyphenylacetamido)benzoate, (L).

Reductive acetylation of the quinone (XXVIII), using the conditions used for p-benzoquinone[51] afforded the same diacetyl derivative (L) as acetylation of the dihydroxy compound (XLVIII)



(L)

using the conditions used for hydroquinone[46].

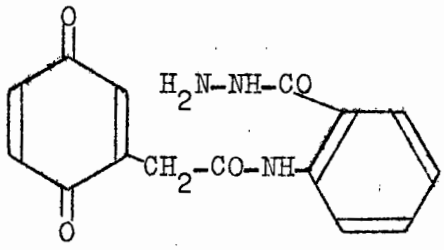
The infrared spectrum of the compound (L) in potassium chloride indicated that the N-H, amide, and ester groups present in the dihydroxy compound (XLVIII) and in the quinone (XXVIII) were still present. The bands were at 3180 (N-H), 1705 (C=O of ester), 1695 (C=O of amide), and 1539 cm.$^{-1}$ (amide II band). The aromatic C=C in-plane stretching vibrations were in the same ranges, being at 1608, 1595, and 1500 cm.$^{-1}$. However, the O-H stretching absorption band in the spectrum of the dihydroxy compound was absent in the spectrum of this compound. An additional strong absorption at 1764 cm.$^{-1}$ was assigned to the C=O stretching vibration of the phenolic ester. This supported the structure (L) indicated by the analysis of this compound. The interpretation of the infrared spectrum of the diacetate (L) is summarised in Table 2.

Table 2.

		Diacetate (L)
		cm.$^{-1}$
N-H stretching vibration of a bonded secondary amide		3180
C=O stretching vibrations :	of phenolic ester	1764
	of ester	1705
	of amide	1695
Aromatic C=C in-plane stretching vibrations		1608,1595,1500
Amide II band		1539

§ 5. Effect of hydrazine on p-benzoquinone.

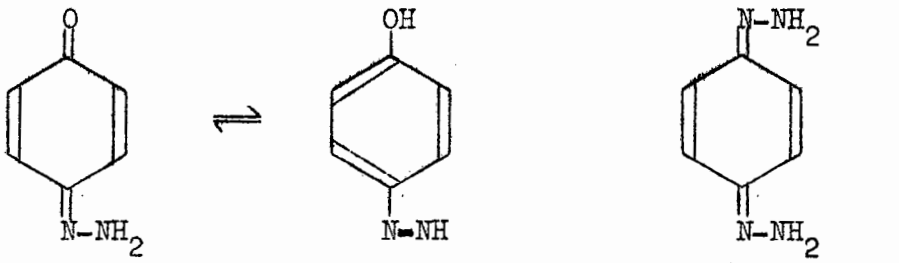
Before attempting the formation of the hydrazide (XXIX) from the quinone (XXVIII) with hydrazine, more information concerning the effect of hydrazine on the quinone system was required. It was therefore decided to treat p-benzoquinone with hydrazine to test the effect of hydrazine on the quinone group as the



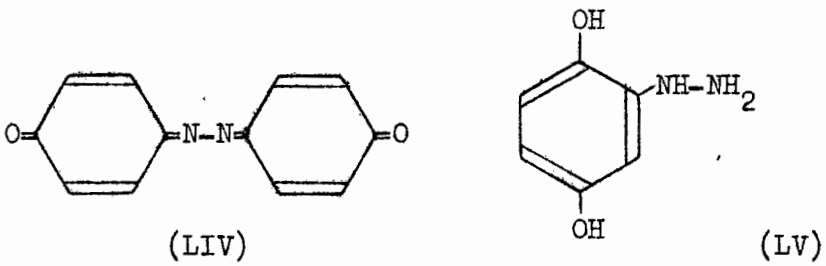
(XXIX)

only mention of this reaction in the literature[17] appeared after this investigation was undertaken.

There were three possibilities, (a) reduction of the quinone to hydroquinone, as occurs with hydroxylamine[15], phenylhydrazine[15], and as-alkylphenylhydrazines[15]; (b) formation of quinone-monohydrazone (LI), tautomeric with the structure (LII), or quinone-dihydrazone (LIII), or quinoneazine (LIV); and (c) 1,4-addition to form 2,5-dihydroxyphenylhydrazine (LV).



(LI) (LII) (LIII)



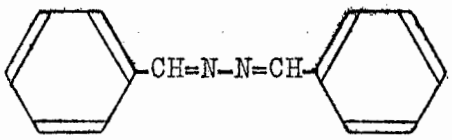
(LIV) (LV)

Chloranil was reduced by hydrazine to tetrachlorohydroquinone[52] with which hydrazine formed a 1:1 molecular complex[53], which melted at 183° with decomposition. Evaporation of an aqueous solution of the complex caused its decomposition with the formation of

tetrachlorohydroquinone.

The product of the reaction of p-benzoquinone and hydrazine also melted with decomposition. Analysis of the product indicated that a 1:1 molecular complex between hydroquinone and hydrazine had formed. Three experiments were performed to confirm whether the product of the reaction of hydrazine on benzoquinone was indeed the hydroquinone plus hydrazine salt.

(a) The product was dissolved in methanol plus sulphuric acid (the method of preparing Brady's reagent) and benzaldehyde was added to the solution. The yellow precipitate which formed was shown to be benzalazine (LVI) by mixed melting point with authentic material[54] and



(LVI)

by a comparison of their infrared spectra.

(b) Acetylation of the product of the reaction of hydrazine on p-benzoquinone yielded hydroquinone diacetate. This was again confirmed by mixed melting point and comparison of its infrared spectrum with authentic hydroquinone diacetate[46].

(c) Evaporation of an ethanolic solution of the product of the reaction of hydrazine on p-benzoquinone decomposed it with the formation of hydroquinone. This was confirmed by a similar comparison of its physical properties with those of authentic hydroquinone.

These three experiments indicated reduction of p-benzoquinone to hydroquinone followed by the formation of a hydroquinone plus hydrazine salt. Final confirmation was achieved by the formation of the same salt from hydrazine and hydroquinone.

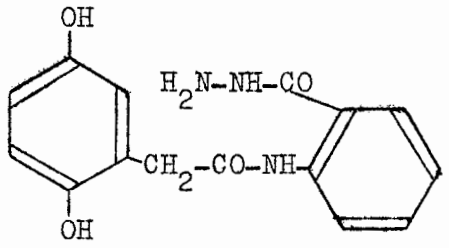
The infrared spectrum of the complex showed sharp bands

at 3320 and 3212 cm.$^{-1}$ due to the associated N-H stretching vibrations, and a broad band centred at 2585 cm.$^{-1}$ assigned to intramolecular hydrogen bonded O-H stretching vibrations. A band at 1627 cm.$^{-1}$ was assigned to aromatic C=C in-plane stretching vibrations.

§ 6. Synthesis of the quinazolinone (LVIII).

From the increased knowledge of the effect of hydrazine on p-benzoquinone, it was suspected that hydrazine would reduce the quinone (XXVIII) instead of forming the hydrazide (XXIX). This was indeed observed. An ethanolic solution of the quinone was heated under reflux with hydrazine and when the clear solution was cooled, needles of the dihydroxy compound (XLVIII) were deposited.

It should be possible to form the hydrazide (LVII) by

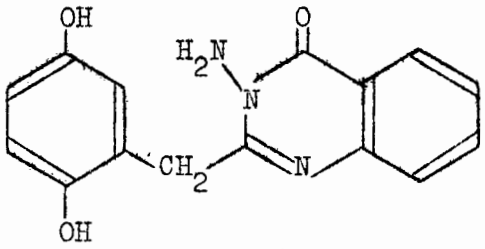


(LVII)

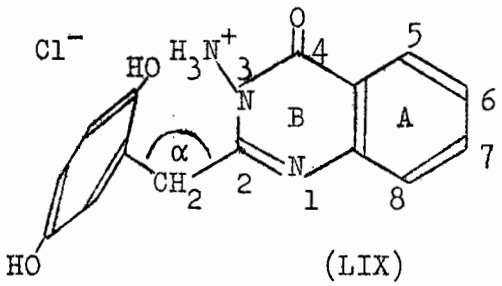
treating a suspension of the dihydroxy compound in ethanol with hydrazine. The reason that no hydrazide (LVII) had been obtained after the reduction of the quinone (XXVIII) to the dihydroxy compound (XLVIII) by the hydrazine was that the solution was too dilute. When ethyl benzoate was heated under reflux with hydrazine in ethanol, no hydrazide formed, but when ethyl benzoate was heated under reflux with hydrazine alone, a good yield of the hydrazide was obtained.

When a suspension of the dihydroxy compound (XLVIII) in ethanol was treated with an excess of hydrazine by boiling under reflux, the hydrazide (LVII) was produced, but, similar to the results obtained by Heller *et al.*[55], it spontaneously ring-closed to

produce the quinazolinone (LVIII). This quinazolinone structure was suggested by analysis and conclusively established by X-ray crystallographic studies[56] on the hydrochloride (LIX), which formed



(LVIII)

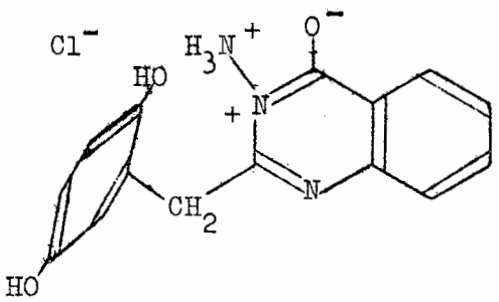


(LIX)

readily when the quinazolinone was dissolved in dilute hydrochloric acid.

X-Ray crystallographic results.

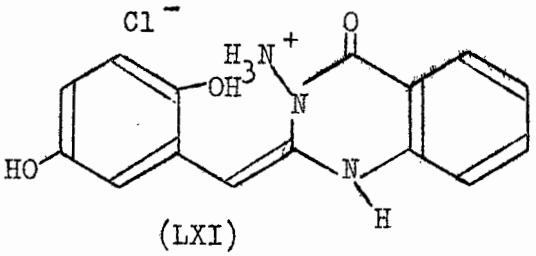
The X-ray crystallographic studies revealed that rings A and B and the amino group in position 3 of the quinazolinone system (LIX) were in the same plane. This indicated a large contribution from the canonical form (LX). The dihydroxyphenyl group was inclined at an angle of 80° to this plane due to the tetrahedral nature of the carbon atom in position 2 of the quinazolinone system. The angle α in the structure (LIX) was found[56] to be 111.6°. The C-C bond length



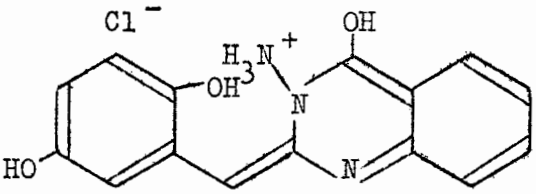
(LX)

between the methylene group at position 2 of the quinazolinone nucleus and the carbon atom in position 2 of the quinazolinone nucleus was found to be 1.48 Å. This angle is between the tetrahedral angle of 109° 28' and the ethylene angle of 120°. In addition, the

bond length is between the C-C bond length of 1.54 Å and the C=C bond length of 1.34 Å, indicating partial double bond character at this position. A double bond is present in this position in the tautomeric structures (LXI) and (LXII). The crystallographic studies



(LXI)



(LXII)

therefore indicated that this compound existed in the δ-lactam structure (LIX) but that there was contribution from a tautomeric form such as structure (LXI) or the "enol" form (LXII).

Infrared spectroscopic data of the quinazolinone (LVIII) and of its hydrochloride (LIX).

In the infrared spectrum of the quinazolinone, the only band in the carbonyl absorption frequency range was at 1687 cm.$^{-1}$. The position reported[57] for the C=O stretching vibration of the amide I band of cyclic amides larger than β- and γ-lactams is about 1680 cm.$^{-1}$. Ring fusion of γ- and β-lactams raised the frequency of the C=O absorption compared with the unfused systems[57]. However, the fusion of an additional ring to the larger-ring cyclic amides did not appear to alter the frequency appreciably[58]. The observed band at 1687 cm.$^{-1}$ must therefore be due to the C=O stretching vibration of the amide I band of the ring-fused δ-lactam. The formation of the hydrochloride (LIX) produced a markedly different infrared spectrum from the spectrum of the quinazolinone. There remained, however, only one band in the carbonyl absorption frequency range, at 1720 cm.$^{-1}$. This elevation of frequency is similar to the shift to

higher frequencies found in amino-acids when they are converted to the hydrochlorides[59].

Culbertson et al.[60] examined the infrared spectra of a number of quinazolines, quinazolinones, and quinazolinediones. These showed three bands termed quinazoline I, II, and III bands at 1628 - 1618, 1581 - 1566, and 1517 - 1478 cm.$^{-1}$, respectively. Owing to the complex nature of the quinazolinone (LVIII) and of its hydrochloride, their infrared spectra were so complicated that no specific absorptions could definitely be assigned to these quinazoline I, II, and III bands, although the two compounds possessed the quinazolinone structure, confirmed by the X-ray crystallographic studies. The band at 1614 cm.$^{-1}$ in the two spectra was in the range where the quinazoline I band is found, but could be due to aromatic C=C in-plane stretching vibrations. The N-H stretching vibrations of the primary amine at 3340 cm.$^{-1}$ in the spectrum of the quinazolinone

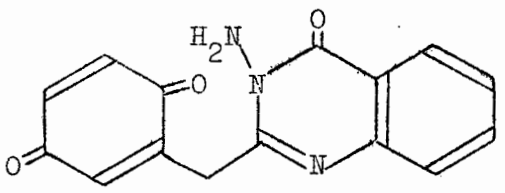
Table 3.

	Quinazolinone (LVIII)	Hydrochloride (LIX)
	cm.$^{-1}$	cm.$^{-1}$
N-H stretching vibration of primary amines	3340	—
NH_3^+ stretching and deformation vibrations	—	3359, 3290, 3130
O-H stretching vibrations, intramolecularly hydrogen bonded	2730	2600
C=O stretching vibration of amide I band of ring-fused δ-lactams	1687	1720
Quinazoline I band	1614(?)	1614
Quinazoline II band	1566	1577
Quinazoline III band	1518	1512
Aromatic C=C in-plane stretching vibrations	1614(?), 1596	1604, 1546
C=N stretching vibration	1658	1650

(LVIII) was replaced by the more complex NH_3^+ stretching and deformation vibrations at 3359, 3290, and 3130 cm.$^{-1}$ in the spectrum of the hydrochloride. The O-H stretching vibration in the infrared spectra of the two compounds at 2730 and 2600 cm.$^{-1}$, respectively, were in the region indicating intramolecular hydrogen bonding. The interpretation of the spectra of the quinazolinone and the hydrochloride is summarised in Table 3, above.

Solubility properties of the quinazolinone (LVIII) and of its hydrochloride.

Although very sparingly soluble in water, the quinazolinone was found to be fairly soluble in dilute hydrochloric acid giving an orange solution and readily soluble in dilute ammonia and dilute sodium hydroxide giving purple solutions. The alkaline solutions faded on standing, to green in ammonia, and to yellow in sodium hydroxide. This fading in the alkaline solution indicated a reaction, e.g. an oxidation by molecular oxygen dissolved in the sodium hydroxide solution. It is known that hydroquinones are readily oxidised in alkaline medium with the formation of the corresponding quinone and hydrogen peroxide[61,62,63]. It was therefore possible that in the sodium hydroxide solution, the hydroquinone group in the quinazolinone (LVIII) could be oxidised to a p-benzoquinone group, forming the quinone (X).



(X)

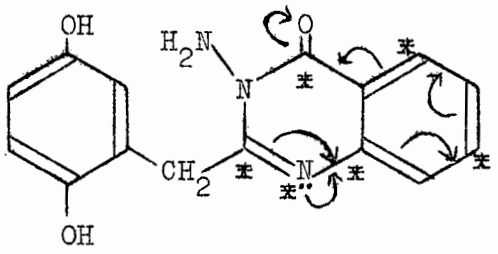
The oxidation of the quinazolinone (LVIII) in sodium hydroxide solution and the visible and ultraviolet absorption spectra of the quinazolinone are discussed later, on page 59. The colours of

the solutions of the quinazolinone in the alkaline solvents are also discussed in that sub-section.

In addition to its solubility in the aqueous alkaline and acid solutions, the quinazolinone was readily soluble in pyridine and dimethylformamide giving stable purple solutions, and in acetic acid giving a red solution. These solubility properties indicated the amphoteric nature of the quinazolinone.

The quinazolinone was found to be sparingly soluble in weakly polar organic solvents giving pink solutions. It was insoluble in non-polar organic solvents, as was expected.

The change in colour of the solutions of the quinazolinone from pink in the weakly polar solvents to red in acetic acid could be attributed to the lower solubility of the quinazolinone in the weakly polar solvents rather than to a bathochromic shift. The purple solutions of the quinazolinone in pyridine and dimethylformamide may also be due to the increased solubility of the quinazolinone in these solvents. The visible colour with a wavelength of about 480 mμ indicated a long conjugated system and/or a large amount of oscillation of charge in the quinazolinone. In structure (LXIII), the



(LXIII)

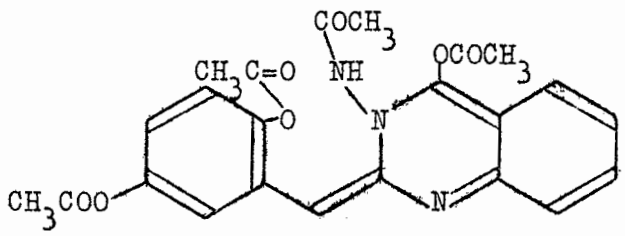
starred positions, which result from the flow of electrons indicated by the arrows, show the positions between which the positive charge may oscillate.

The quinazolinone hydrochloride was insoluble in neutral organic solvents and in water. The insolubility of the hydrochloride in water was probably due to the large size of the molecule, despite its being a salt, cf. the insolubility of resins in water. As both

the quinazolinone and its hydrochloride were sparingly soluble in water, the quinazolinone was readily liberated from its hydrochloride simply by washing it with water and filtering off the quinazolinone.

Acetyl derivative of the quinazolinone (LVIII).

Combustion analyses of the acetate, obtained by heating the quinazolinone (LVIII) with acetic anhydride and a catalytic amount of concentrated sulphuric acid, suggested the tetra-acetate structure (LXIV). Strong support for this structure was obtained from a study



(LXIV)

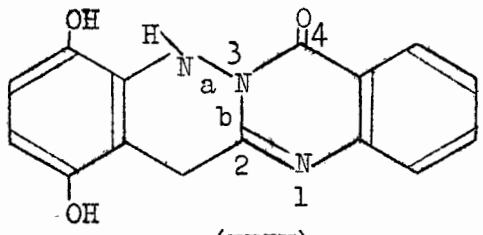
Table 4.

		Tetra-acetate (LXIV)
		cm.$^{-1}$
Free N-H stretching vibrations of the secondary amide		3425
C=O stretching vibrations:	of phenolic esters	1770 sh., 1758
	of vinyl acetate	1728
	of secondary amide	1697
Aromatic C=C in-plane stretching vibration		1604
Quinazoline II band		1574
Quinazoline III band		1498
C-H deformation vibrations		1477, 1370
Aromatic =C-H stretching vibration		3088
C-H stretching vibrations of the C-CH_3 groups		2955
C-H deformation vibration of the C-CH_3 groups		1440

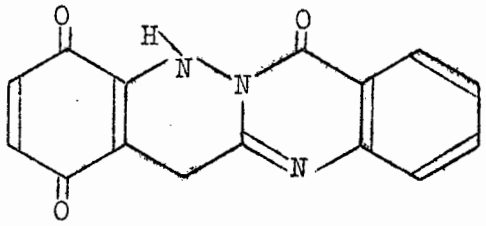
of the infrared spectrum of this compound in potassium chloride. No O-H stretching vibration bands were present. However, there were four bands in the C=O absorption region, at 1770 (shoulder), 1758, 1728, and 1697 cm.$^{-1}$. The C=O absorption of the δ-lactam of the quinazolinone (LVIII) at 1687 cm.$^{-1}$ was no longer present in the spectrum of the acetate. On the basis of a study of the range[48] of frequencies where the C=O absorption of phenolic and vinyl esters and secondary amides occur, the vibrations shown in Table 4 above were assigned to these four bands. The interpretation of the remaining bands in the infrared spectrum is included in Table 4.

§ 7. Oxidation of the quinazolinone (LVIII) to the quinone (X).

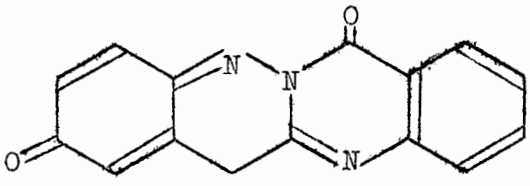
If the quinazolinone (LVIII) was oxidised to the quinone (X), two possible reactions could occur. (a) If a reaction similar to that of p-benzoquinone with aniline to give 2,5-dianilino-p-benzoquinone occurred, the quinazolino[3,2-b]cinnoline (XXIV) would be produced. An excess of oxidising agent could oxidise this to the quinone compound (LXV). (b) If, however, the amino group condensed with the carbonyl group of the quinone, a product such as the compound (XII) would result. To investigate whether the



(XXIV)



(LXV)



(XII)

quinazolinone would ring close and how it would ring close, it was treated with two different oxidising agents.

First method of oxidation.

In the first, the quinazolinone was dissolved in ethanolic hydrochloric acid and treated with aqueous ferric chloride solution. The solution immediately turned red and a red compound rapidly crystallised from the solution. This compound contained ionic chlorine and proved to be a hydrochloride of a base. The free base was obtained from the hydrochloride simply by washing it well with water, as had been achieved with the hydrochloride of the quinazolinone (LVIII).

No solvent could be found to recrystallise the free base or its hydrochloride which were, however, formed in pure form in their preparation. The purity of the compounds was shown by paper chromatography as single streaks were obtained in a number of solvent systems.

Attempted determination of the molecular weight of the base.

A non-aqueous titration of the base to determine the equivalent weight was unsuccessful. The colour of the methyl violet indicator was completely masked by the deep orange colour of the acetic acid solution of the base. Because of the markedly different colours of the solutions of the base in aqueous acid (orange) and alkali (purple) media, an attempt was made to perform the non-aqueous titration using the base as its own indicator. However, no definite colour change at the end point was observed.

Orange-red crystals of the perchlorate of the base were isolated from the non-aqueous titration medium.

Attempted formation of the picrate of the base.

The picrate of the base possibly formed, but it could not be recrystallised. The base itself was too insoluble, and picric acid too soluble, in all the solvents attempted.

The structure of the base.

The analyses of the base, and of its hydrochloride and perchlorate suggested the structure (XII) and definitely not the structure (LXV). The infrared spectra of this base and of its salts in nujol supported the structure (XII) which was therefore assigned to the base.

The infrared spectroscopic data of the base and of its salts.

The C=O stretching frequency of the ring-fused δ-lactam at 1687 $cm.^{-1}$ in the infrared spectrum of the quinazolinone (LVIII) was raised to 1718 $cm.^{-1}$ in the spectrum of the base (XII). Although Edwards and Singh[58] state that ring fusion of δ-lactams did not alter the frequency appreciably, the fusion of a second ring, as is present in the base (XII) appeared to raise the frequency considerably. Ring fusion of γ- and β-lactams raised the frequency of the carbonyl absorption[57]. A far higher frequency of the C=O absorption of the ring fused δ-lactam was found in the infrared spectra of the hydrochloride and of the perchlorate of the base, at 1752, and 1737 $cm.^{-1}$, respectively. This phenomenon had occurred in the C=O absorption of the δ-lactam band in the infrared spectra of the quinazolinone (LVIII) and of its hydrochloride. The bands at 2739, and 2740 $cm.^{-1}$ in the infrared spectra of the hydrochloride and of the perchlorate were assigned to the $=NH_2^+$ vibrations. No such band would be, or was, found in the infrared spectrum of the base (XII). The interpretation of the bands in the infrared spectra of the three compounds is summarised in Table 5, below.

Table 5.

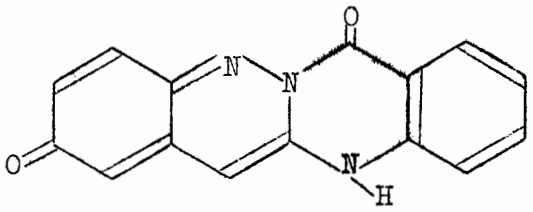
	Free base (XII)	Hydrochloride	Perchlorate
	$cm.^{-1}$	$cm.^{-1}$	$cm.^{-1}$
C=O absorption of the ring fused δ-lactam	1718	1752	1737
C=O absorption of the α,β-α',β'-unsaturated ketone	1629	1643	1655
Quinazoline I band	1616	1626	1620
Quinazoline II band	1568	1576	1579
Quinazoline III band	1487	1484	1486
Aromatic C=C in-plane stretching vibrations	1598, 1527, 1428	1616, 1596, 1527sh., 1424sh.	1594, 1518, 1415
N-H deformation frequency of secondary amines OR: Combination of C=C and C=N stretching vibrations in heterocyclic aromatic compounds	1547	1540	1547
C-N stretching vibration of secondary aromatic amines	1317	1300	1308
Amide III band	1279	1288	1289
N-H deformation frequency of secondary amines	3412*	3412*	3477
Aromatic =C-H stretching vibrations	3080*	3061*	3090
$=NH_2^+$ vibrations	——	2739*	2740

The position of the proton in the hydrochloride and in the perchlorate of the base.

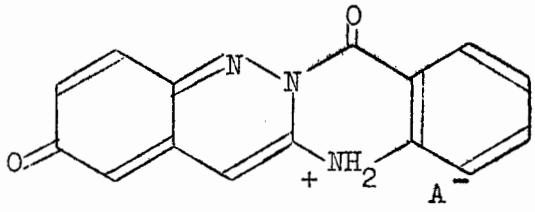
There are three nitrogen atoms in the base. An attempt has been made, using the infrared spectroscopic evidence, to assign

* In potassium chloride.

the proton in the hydrochloride and in the perchlorate of the base to one of these nitrogen atoms. A combination band of the C=C and C=N stretching vibrations in nitrogen heterocyclic aromatic compounds is usually found[64] in the frequency range 1580 - 1550 cm.$^{-1}$. The N-H deformation frequencies of secondary amines usually occur[65] in the similar frequency range 1650 - 1550 cm.$^{-1}$. The tautomeric form (LXVI) of the base possesses a secondary nitrogen atom. As secondary amines are stronger bases than tertiary amines, it is proposed that the vibrations at 1547, 1540, and 1547 cm.$^{-1}$ in the infrared spectra of the free base, and of its hydrochloride and perchlorate, respectively, are due to the N-H deformation frequencies of the secondary amine, and that this nitrogen atom is the point of attachment of the proton of the hydrochloride and of the perchlorate. These salts would therefore possess the structure (LXVII), where A = Cl or ClO_4.



(LXVI)



A = Cl, or ClO_4.

(LXVII)

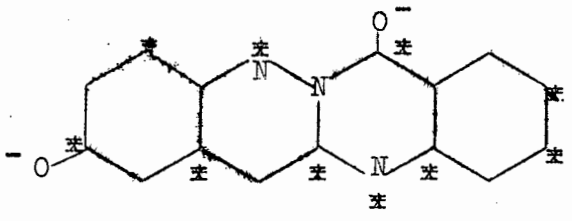
It could be argued that the point of attachment of the proton should be nearer the carbonyl group of the lactam because of the shift to a higher frequency of the lactam carbonyl absorption in the spectra of the hydrochloride and of the perchlorate. However, to draw an analogy once again from the carbonyl absorption in amino-acid hydrochlorides[59], the carbonyl absorption frequency was increased in the infrared spectra of the hydrochlorides of β, γ, and higher homologue amino-acids as well as in the spectra of hydrochlorides of α-amino- and α-amido-acids.

The N-H vibrations found in the infrared spectra of the

free base and of its hydrochloride (in potassium chloride) and of its perchlorate (in nujol) in the region 2300 - 3650 cm.$^{-1}$ supported the assignment of the proton to the nitrogen atom indicated above. The spectra showed absorption maxima at 3412, 3412, and 3477 cm.$^{-1}$, respectively, assigned to the N-H stretching vibrations of secondary amines. The spectra of the hydrochloride and of the perchlorate showed an additional strong absorption at 2739, and 2740 cm.$^{-1}$, respectively, assigned to the $\rangle NH_2^+$ vibrations. The $\rangle NH^+$ vibrations in $C{=}NH^+$ are lower[66], in the region 2500 - 2325 cm.$^{-1}$.

Canonical forms of the base.

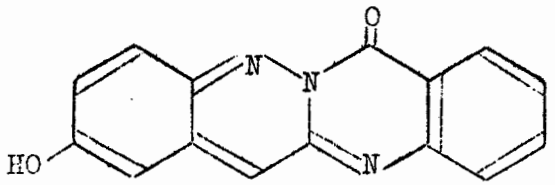
The dark red colour of the base suggested the presence of many charged canonical forms, with a large distribution of charge across the molecule. This was supported by the absence of any melting point in the base, or in its hydrochloride or perchlorate below 300°, although the base charred at 170°. In structure (LXVIII), "*" indicates the possible positions of the positive charge, many of which produce completely planar structures. The high degree of resonance also accounts for the great stability of the compound.



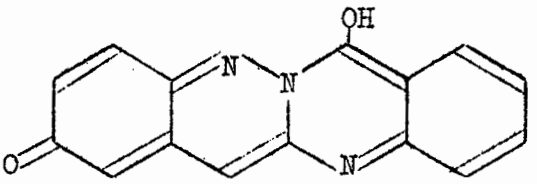
(LXVIII)

Tautomeric forms of the base.

Many stable tautomeric forms were found to be possible, e.g. structure (LXVI) above, and structure (LXIX), and the "enol" form (LXX), below. Structures (LXIX) and (LXX) possess highly



(LXIX)



(LXX)

conjugated systems. Models ("Dreiding") of the free base (XII) showed that it is a planar molecule.

There was considerable evidence for the existence of these tautomeric forms, (a) the deep colours of the free base, the hydrochloride, and the perchlorate, (b) spectroscopic evidence, (c) the solubility properties of the free base and of the hydrochloride, and (d) chemical evidence.

(a) Colour.

The free base was dark red, the hydrochloride existed as bright red needles, and the perchlorate was orange-red. Colour is usually associated with a long conjugated system, and especially when oscillation of charge in this system can occur. The tautomeric forms (LXIX) and (LXX) produce highly conjugated systems in which oscillation of charge can occur. The frequency of absorption of light would be lowered causing the compounds to have colour. The insolubility of the free base and of the hydrochloride in neutral organic solvents, e.g. acetone, chloroform, and ether, indicated the charged nature of the free base.

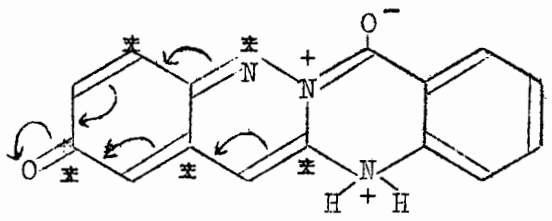
(b) Spectroscopic evidence.

The spectroscopic evidence for the existence of the tautomer (LXVI) has been outlined above in the assignment of the proton in the hydrochloride and in the perchlorate of the base to the secondary nitrogen atom in this tautomer, (page 38).

(c) Solubility properties.

The free base and the hydrochloride were found to be soluble in pyridine and in glacial acetic acid, giving red solutions. They were sparingly soluble in dilute hydrochloric acid, dilute nitric acid and in water, orange solutions being obtained. The change in colour could be attributed to the lower solubility of the base in the latter solvents rather than to a hypsochromic shift. The limiting solubility of the base and of the hydrochloride in the aqueous solvents would be expected because of the large size of the molecules.

In the acid media, the base would probably exist as the protonated structure (LXXI). Although highly conjugated with

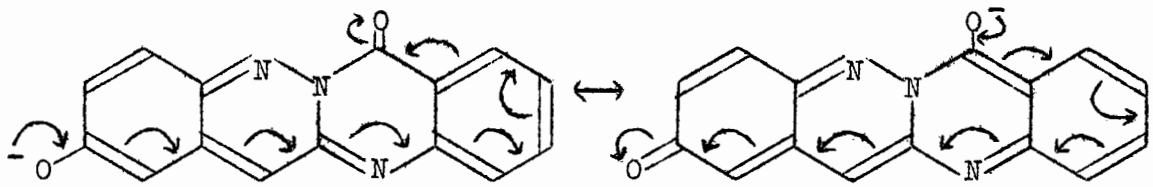


(LXXI)

charge distribution across the molecule, the oscillation of these charges across the molecule is prevented by the nature of the charges. Protonation of the quinone-imine carbonyl group would be repressed by the positive charge already present on the protonated secondary amino nitrogen atom. Oscillation of charge between the starred positions as a result of the flow of electrons shown in structure (LXXI) would therefore be diminished. The base would be expected to absorb in the visible region of the spectrum, but at a high frequency. Hence there is absorption in the region of 490 mμ and therefore the orange colour of the solution. However, a bathochromic shift was observed when the base was dissolved in dilute ammonia or sodium hydroxide. The visible colour of the alkaline solutions of the base was purple.

The ready solubility of the base in the alkaline

solvents indicated the ready formation of the tautomer (LXIX). This would exist in the alkaline solution as the anion (LXXII). Ready oscillation of the negative charge across the molecule indicated by the arrows in the two extreme forms (LXXII) and (LXXIII) would result in the solution absorbing light of a low



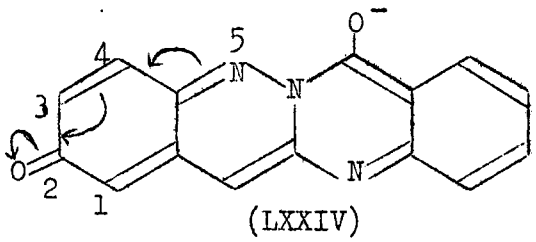
(LXXII) (LXXIII)

frequency. The visible colour would be at a long wavelength, and hence the deep purple colour of the solution in the alkaline media.

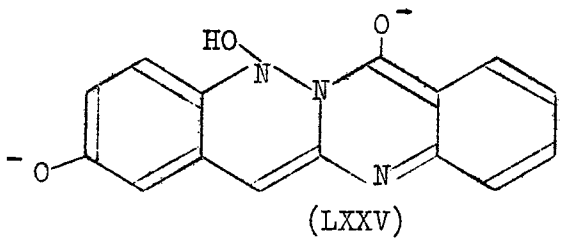
As had occurred with the alkaline solutions of the quinazolinone (LVIII), the alkaline solutions of the base (XII) faded on standing. The sodium hydroxide solution faded to yellow after a few hours, and the ammonia solution faded to green after a few days. Heat rapidly increased the rate of fading. The fading to yellow of the purple solutions occurred equally well in the dark and therefore could not be a light-induced reaction. Nevertheless this fading in the alkaline solvents indicated a reaction. Although the fading of the sodium hydroxide solution of the quinazolinone (LVIII) from purple to yellow was attributed to oxidation, the quinoneimine (XII), under discussion, is already in an oxidised state.

This hypsochromic shift would indicate the disappearance of the long conjugated system, shown in structures (LXXII) and (LXXIII), across which the negative charge can oscillate. The solution was still coloured which indicated that there was still a long conjugated chain present. If another series of electron shifts could compete with the system shown by the arrows in structure (LXXIII), the charge oscillation shown in this structure could be

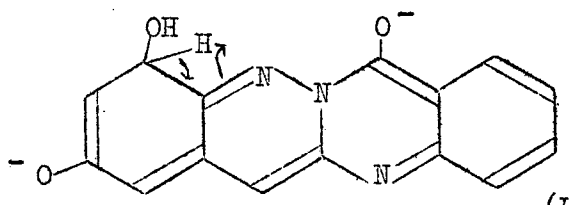
destroyed. Such a system is present and is shown by the arrows in structure (LXXIV). A strong nucleophile could possibly attack the molecule at position 4 or position 5 of this structure. Hydroxyl ions in the alkaline solution may enhance this flow of electrons and a product containing either structure (LXXV) or structure (LXXVI)



(LXXIV)

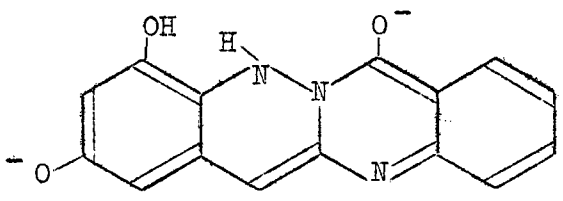


(LXXV)

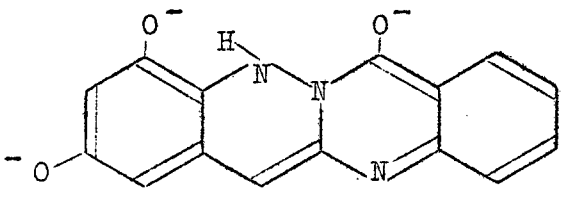


(LXXVI)

may result. If this latter structure (LXXVI) formed, it would tautomerise to the more stable structure (LXXVII). In the alkaline solution this would exist as the anion (LXXVIII). The resonance



(LXXVII)

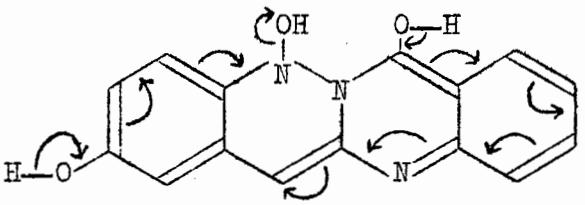


(LXXVIII)

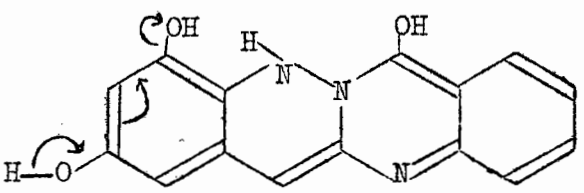
possibilities in the molecule would now be altered. Oscillation of the negative charge across the molecule would now no longer be possible in a system such as structure (LXXV) or structure (LXXVIII). The possible formation of the anion (LXXV) or the anion (LXXVIII) in the alkaline solution would therefore explain the hypsochromic shift

from purple to yellow which was observed.

When the yellow sodium hydroxide solution of the base (XII) was acidified with hydrochloric acid, the hydrochloride of the base (XII) was recovered. If this alkaline solution contained the anion (LXXV) or the anion (LXXVIII), acidification of the alkaline solution would liberate a trihydroxy compound containing either structure (LXXIX) or structure (LXXX). The trihydroxy

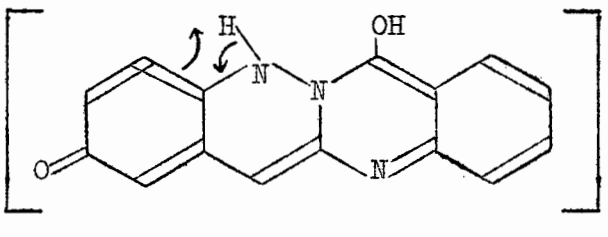


(LXXIX)



(LXXX)

compound (LXXIX) could lose water and tautomerise to form the base (XII). This is shown by the flow of electrons indicated by the arrows in the trihydroxy structure (LXXIX). However, the trihydroxy compound (LXXX) would not lose water as readily. Loss of water as shown by the flow of electrons in structure (LXXX) would form the intermediate (LXXXI). This would have to tautomerise as shown by the flow of electrons in this structure to form the base (XII).



(LXXXI)

Therefore loss of water in the structure (LXXX) is impossible and the anion structure (LXXVIII) in the alkaline solution is eliminated. Hence, if the hypsochromic shift observed in the alkaline solution is due to a nucleophilic attack by an hydroxyl ion, it could be at position 5 and a compound containing the structure (LXXV) may result.

This hydroxylation is supported by the findings of James et al.[63] who studied the oxidation of various hydroquinones in alkaline solution. The products of the oxidation of the hydroquinones, hydrogen peroxide and the corresponding quinones, reacted together to form hydroxyquinones.

Attempted isolation of the sodium salt of the anion present in the yellow sodium hydroxide solution.

An attempt was made to isolate the yellow material, obtained after the purple sodium hydroxide solution of the base (XII) had faded to yellow, from the solution. The envisaged structure, i.e. the sodium salt of the anion (LXXV), for this material could then be investigated.

The base was heated with dilute sodium hydroxide. On cooling the solution, yellow needles crystallised from the solution. The product was very soluble in water, sparingly soluble in ethanol and insoluble in non-polar organic solvents. These solubility properties indicated that the compound possessed an ionic structure and could be the disodium salt of the anion (LXXV). An infrared spectrum of the yellow needles in nujol showed no bands in the carbonyl absorption region. As the carbonyl stretching vibrations of the δ-lactam and of the α,β-α',β'-unsaturated ketone systems of the base were absent in the spectrum of the yellow needles, these groups were no longer present in the yellow product. There was a broad band at 3335 - 3180 $cm.^{-1}$ in the spectrum. This could be due to the stretching vibration of the O-H group present in the anion (LXXV). However, this hydroxy group could arise from any sodium hydroxide contaminating the yellow needles. The band at 1594 $cm.^{-1}$ and the shoulder at 1611 $cm.^{-1}$ in the infrared spectrum of the yellow needles could be assigned to aromatic C=C in-plane stretching vibrations. The band at 1536 $cm.^{-1}$ could be assigned to the cyclic α,β-unsaturated C=N stretching vibration.

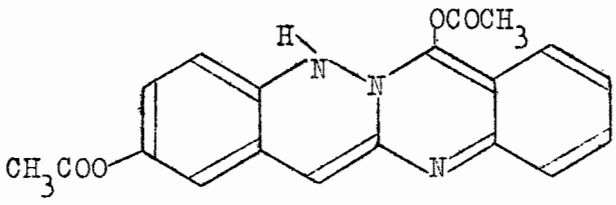
The yellow needles could not be recrystallised. However, the product was dissolved in hot ethanol and benzene added to the solution. Concentration of the solution yielded yellow-green micro-needles. Sodium hydroxide is also sparingly soluble in ethanol. Addition of benzene would also precipitate sodium hydroxide from the solution. As the compound was so dark, it was not possible to conclude whether it was pure or not. Therefore analysis would not indicate much, and in fact did not give any final answer to the problem. The sodium in the compound, when sulphated, gave 38.6% instead of 43.7% expected for the disodium salt of the anion (LXXV). However, analysis did indicate that the product was a sodium salt. The carbon, hydrogen and nitrogen analyses were even less conclusive and are given in the experimental (page 162), for interest.

An infrared spectrum on the yellow-green micro-needles was similar to the spectrum of the yellow needles. The bands in the spectrum of the yellow needles referred to above were at 3400 - 3240 (O-H), 1602 (C=C), 1592 (C=C), and 1515 (C=N) $cm.^{-1}$ in the spectrum of the yellow-green micro-needles. This indicated that the change in colour of the product from yellow to the much darker yellow-green did not alter the structure of the material.

(d) Chemical evidence.

Reductive acetylation product of the base.

Reductive acetylation of the base (XII) yielded a compound which analysed for a diacetate. The acetyl groups were shown to be O-acetyl by their ease of hydrolysis with sodium ethoxide at -3°, and hence the compound was assigned the structure (LXXXII). The C=O absorption bands at 1768, and 1720 $cm.^{-1}$ in the infrared spectrum of the compound in nujol were in the region of the C=O absorption frequencies of the tetra-acetate (LXIV) at 1770, and 1728 $cm.^{-1}$, (see Table 4, page 34). These two peaks were



(LXXXII)

therefore also assigned to the C=O stretching vibrations of the phenolic and vinyl esters as shown in Table 6. The frequencies

Table 6.

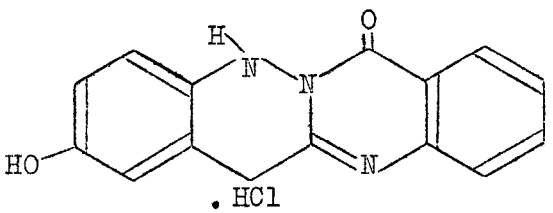
		Diacetate (LXXXII)
		cm.$^{-1}$
N-H stretching vibration of secondary amines		3400
C=O stretching vibrations:	of phenolic ester	1768
	of vinyl ester	1720
Quinazoline I band		1622 sh.
Quinazoline II band		1568
Aromatic C=C in-plane stretching vibrations		1610, 1497

were far higher than the frequency range where amido carbonyl groups absorb. In addition, the band at 3400 cm.$^{-1}$ was assigned to the N-H stretching vibration of the secondary amine group. This indicated that no N-acetyl group was present in the diacetate, supporting the structure (LXXXII) assigned to this compound. The interpretation of the remaining bands in the infrared spectrum is included in Table 6.

The formation of this diacetate (LXXXII) therefore also indicated the ready formation of the tautomeric "enol" form (LXX) of the base, isolated as the diacetate.

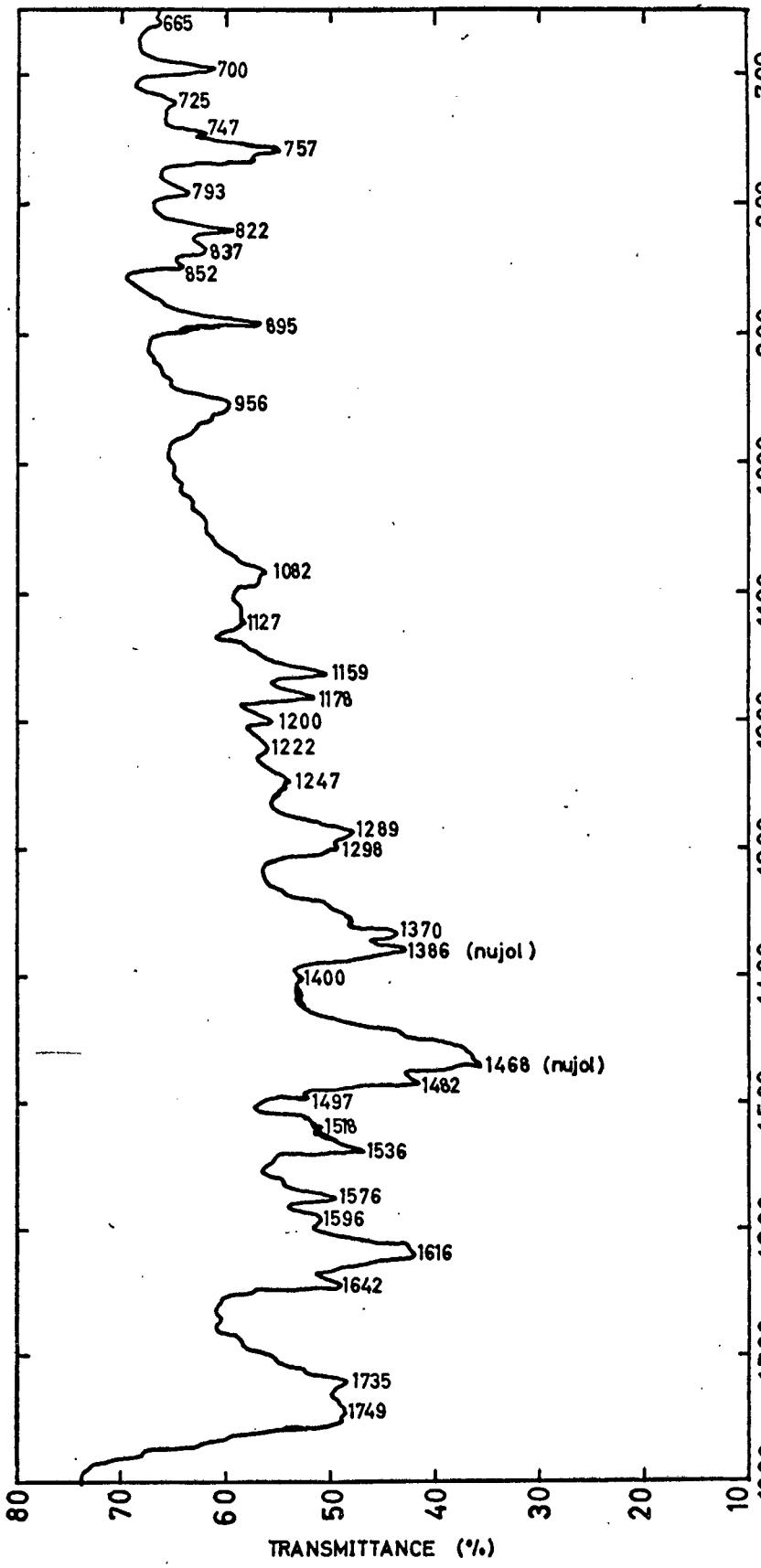
The structure of the deacetylation product.

The product obtained from the sodium ethoxide hydrolysis of the diacetate at -3° was isolated as the hydrochloride. It exhibited the same solubility properties as the hydrochloride of the base (XII) and could not be recrystallised for analysis. An attempt was made to synthesise this product in purer form by an alternative method. Zinc was added to a suspension of the base (XII) in dilute hydrochloric acid and the suspension was warmed on a boiling water-bath. The reduction product was removed from suspension by filtration. However, as neither the base nor the reduction product were very soluble in the dilute hydrochloric acid, complete reduction had not occurred and an impure product resulted. A comparison of the infrared spectra of the deacetylation product (Spectrum A, page 50) and of the reduction product (Spectrum B, page 51) showed that the two compounds were very similar. It is therefore proposed that the same product was obtained from the deacetylation and from the reduction and that it possessed the structure (LXXXIII).



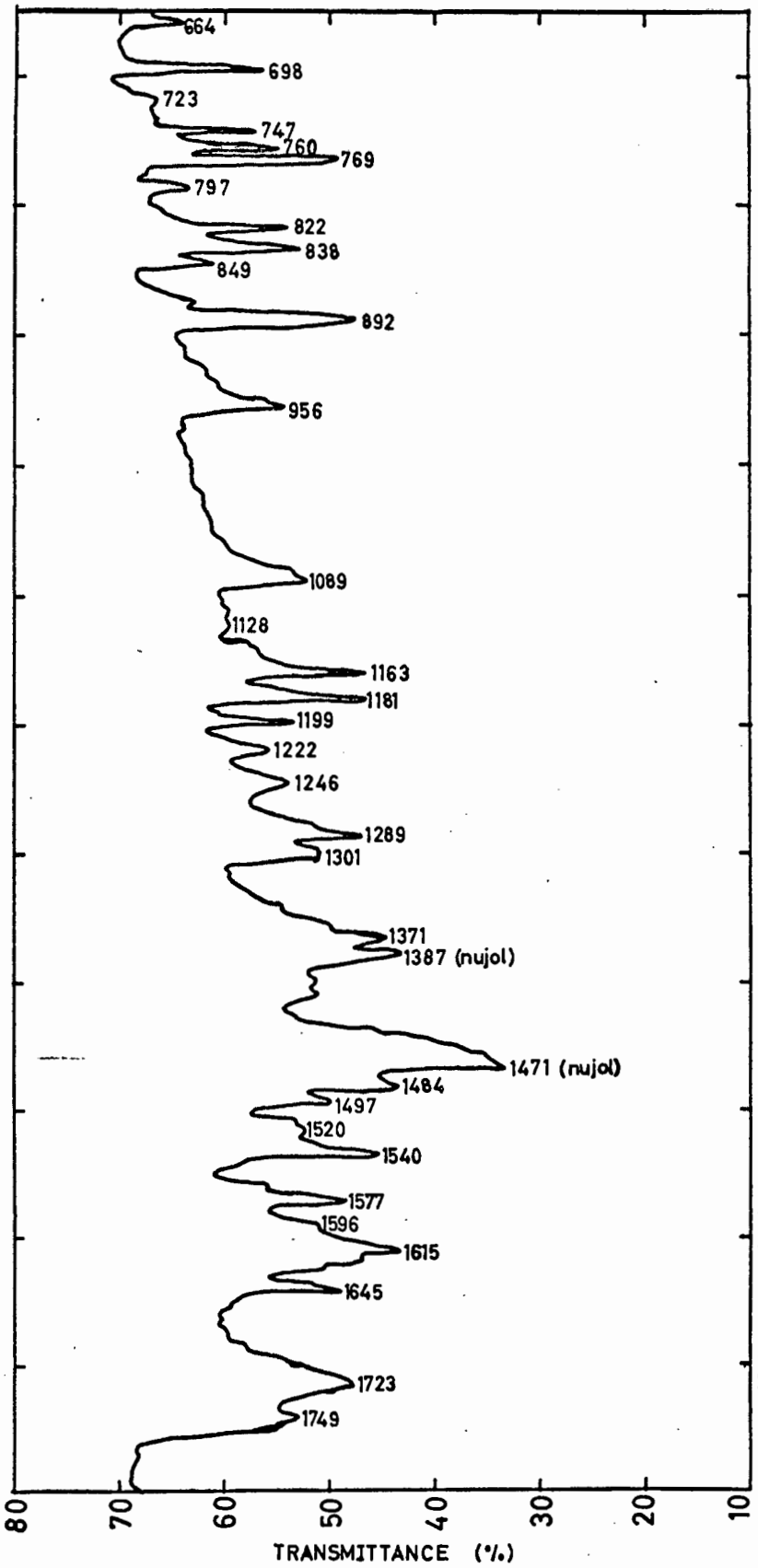
(LXXXIII)

The infrared spectra of the deacetylation product (Spectrum A) and of the reduction product (Spectrum B) were also similar to the infrared spectrum of the hydrochloride of the base (XII) (Spectrum C, page 52). This indicated incomplete reduction of the base to the hydroxy compound (LXXXIII). It also indicated that in the deacetylation to the hydroxy compound (LXXXIII) in the alkaline medium, some oxidation of this hydroxy compound to the base (XII) had occurred. This would occur via the anion (LXXXIV) present in the alkaline solution. The oxidation of compounds by molecular oxygen in alkaline solution is not confined to hydroquinones alone,



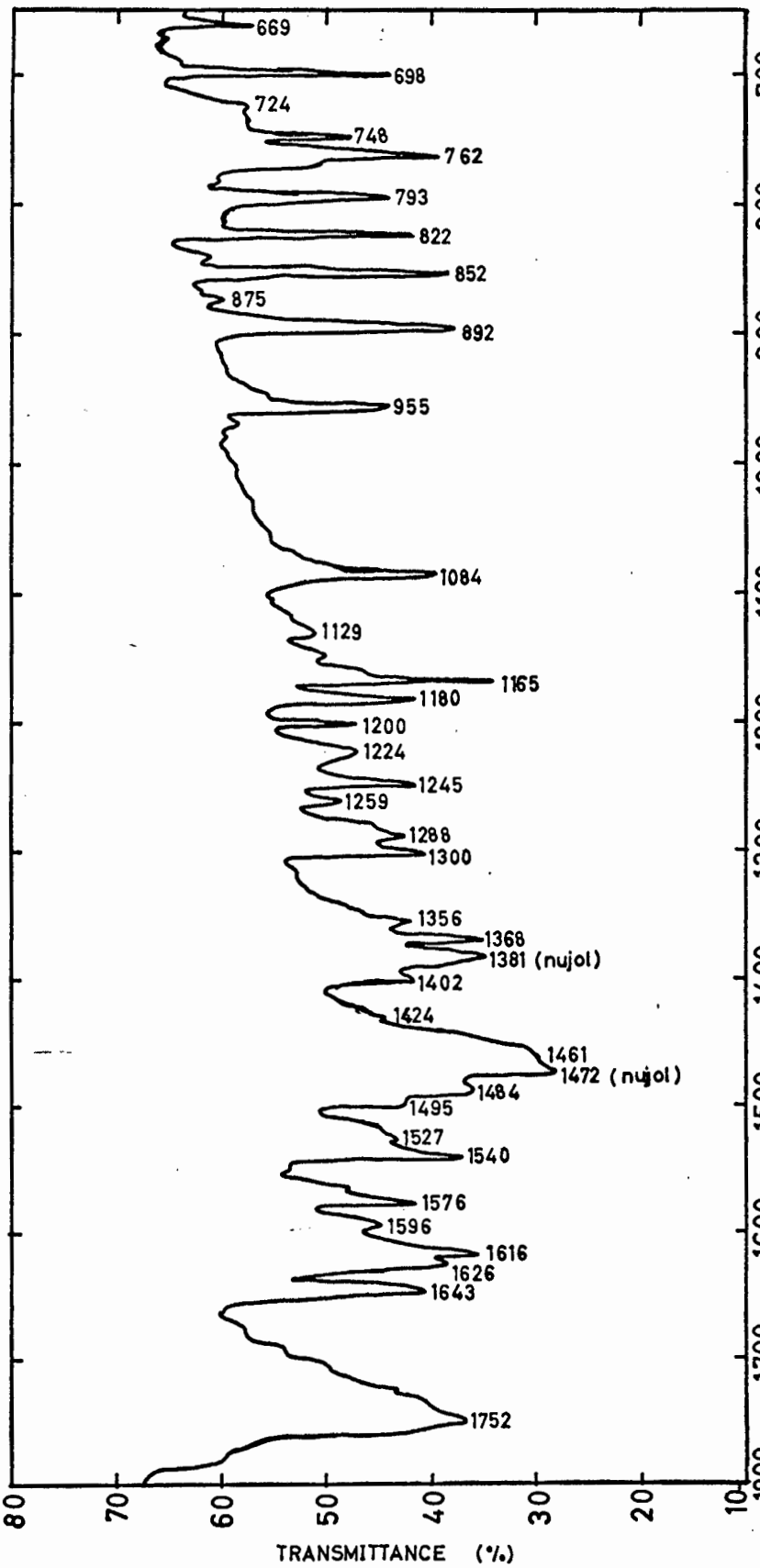
DEACETYLATION PRODUCT (LXXXIII)

SPECTRUM A



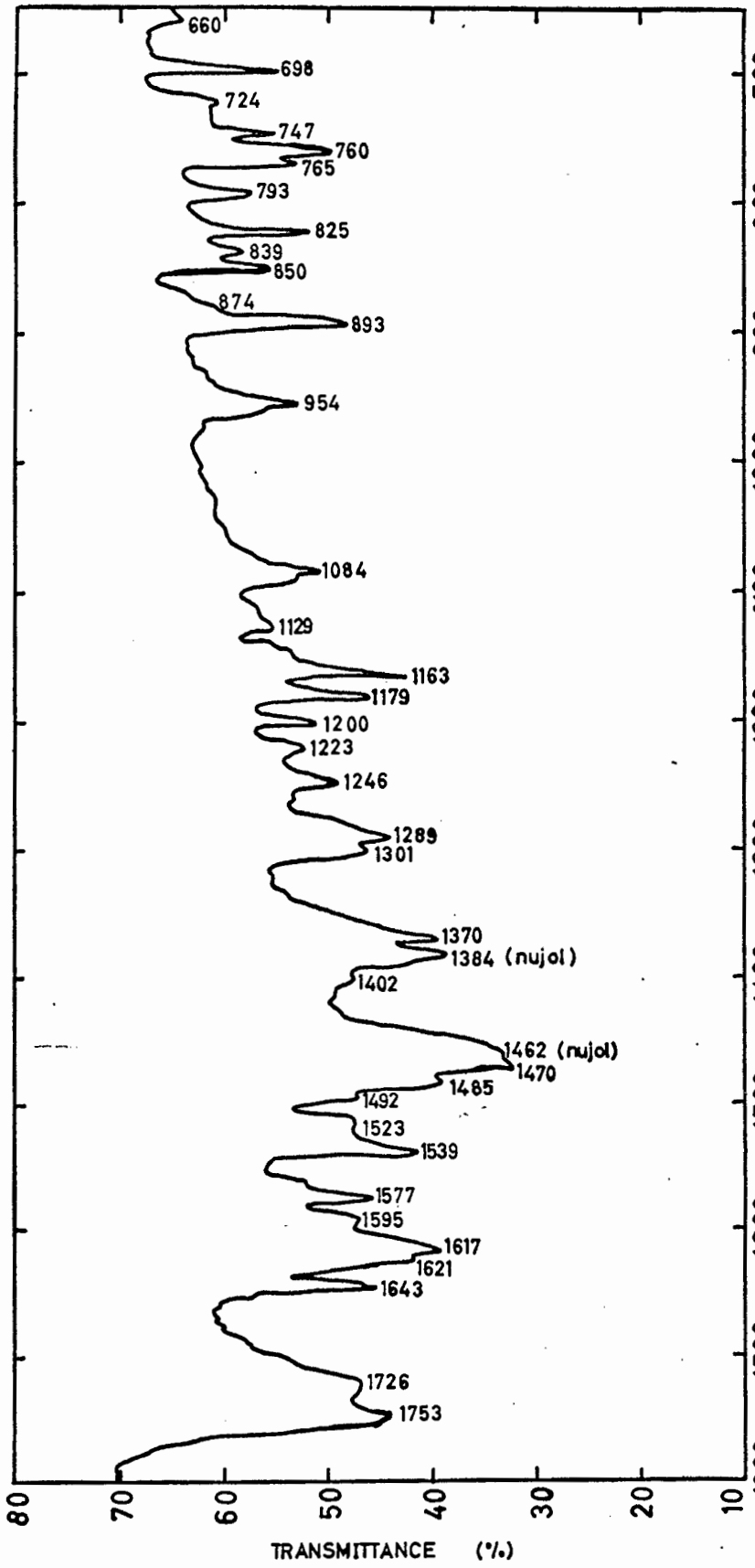
REDUCTION OF THE BASE (XII)

SPECTRUM B



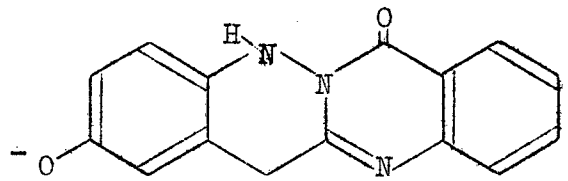
HYDROCHLORIDE OF THE BASE (XII)

SPECTRUM C



DEACETYLATION PRODUCT TREATED WITH SODIUM HYDROXIDE

SPECTRUM D



(LXXXIV)

but is found with many substances, particularly those containing phenolic groups[61].

To test whether any oxidation had occurred in the alkaline medium, the hydroxy compound (LXXXIII) was dissolved in warm, dilute sodium hydroxide and the solution acidified with dilute hydrochloric acid. An infrared spectrum (Spectrum D, page 53) of the red crystals obtained was still similar to the infrared spectrum of the deacetylation product (Spectrum A), but compared more favourably with the spectrum of the hydrochloride of the base (XII) (Spectrum C). This indicated that further oxidation had occurred in the warm sodium hydroxide solution. Consequently, when the diacetyl derivative (LXXXII) was treated with hot aqueous sodium hydroxide, hydrolysis and complete oxidation occurred. The hydrochloride of the base (XII) and not the hydrochloride of the reduced product (LXXXIII) was isolated.

Hence the hydroxy compound (LXXXIII) must have formed on deacetylation of the diacetate, but ready oxidation of the hydroxy compound to the base (XII) could occur in the alkaline medium.

The interpretation of the bands in the infrared spectrum of the hydroxy compound (LXXXIII) is summarised in Table 7. Further discussion on the interpretation of the bands in the spectrum is given on page 76.

Table 7.

	Hydroxy compound (LXXXIII)
	cm.$^{-1}$
C=O absorption of the ring-fused δ-lactam	1749
N-H deformation vibration of secondary amines	1642
Quinazoline I band	1616
Quinazoline II band	1576
Quinazoline III band	1482
Aromatic C=C in-plane stretching vibrations	1596, 1518
Combination of C=C and C=N stretching vibrations in heterocyclic aromatic compounds	1536
C-O stretching and O-H in-plane deformation vibrations of the phenol	1400
O-H deformation vibration	1370
C-N stretching vibrations of secondary amines	1298
Amide III band	1289
O-H stretching frequency intramolecularly hydrogen bonded	3460
N-H stretching vibration of secondary amines	3315
$\rangle NH_2^+$ vibrations	2735

Thiele acetylation of the base.

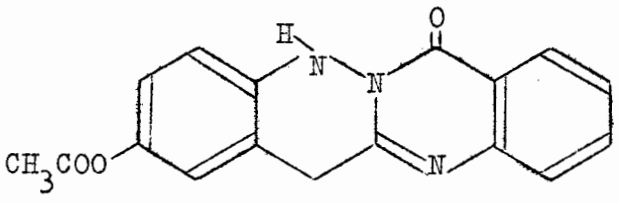
Thiele[51] acetylation of the base (XII) yielded red needles. The product did not melt, but charred at 230°. Analysis suggested that a mono-acetate had formed. An infrared spectrum of the product in potassium chloride showed a band at 1766 cm.$^{-1}$. This was near the frequency of the C=O stretching vibration of the phenolic ester in the diacetate (LXXXII) (at 1768 cm.$^{-1}$), and in the tetra-acetate (LXIV) (at 1770 cm.$^{-1}$). This band at 1766 cm.$^{-1}$ was therefore assigned to this vibration. Similarly, a band at

1721 cm.$^{-1}$ was near the band at 1718 cm.$^{-1}$ in the infrared spectrum of the base (XII) assigned to the C=O stretching vibration of the ring-fused δ-lactam. Therefore the band at 1721 cm.$^{-1}$ was assigned to this vibration. The band at 3440 cm.$^{-1}$ was near the frequencies of the bands in this range in the spectra of the base (XII), and of its hydrochloride and perchlorate (Table 5, page 38), and in the spectrum of the diacetate (LXXXII) (Table 6, page 48). This band was therefore assigned to the N-H stretching vibration of secondary amines. The interpretation of the bands in the spectrum is summarised in Table 8.

Table 8.

		Mono-acetate (LXXXV)
		cm.$^{-1}$
C=O stretching vibrations:	of phenolic esters	1766
	of ring-fused δ-lactam	1721
N-H stretching vibration of the secondary amine		3440
N-H deformation frequency of the secondary amine		1637
Aromatic C=C in-plane stretching vibrations		1594, 1520, 1469
C=N stretching vibrations in the heterocyclic aromatic compound OR: Quinazoline II band		1543
C-H stretching vibrations		1456, 1386
C-N stretching vibrations:	of tertiary aromatic amines	1351
	of secondary aromatic amines	1342

Because of the presence of the phenolic ester and the δ-lactam carbonyl absorptions, and the N-H stretching frequency bands in the spectrum of the mono-acetate, the structure (LXXXV) has been assigned to the product of the Thiele acetylation.



(LXXXV)

Visible and ultraviolet absorption spectra of the base and of its hydrochloride.

(i) Measurement of the spectra.

The visible and ultraviolet absorption spectra of the base and of its hydrochloride were measured for very dilute sodium hydroxide solutions, and for very dilute hydrochloric acid solutions (obtained by acidifying the sodium hydroxide solutions with hydrochloric acid). The spectra were measured for a freshly prepared purple solution of the hydrochloride in sodium hydroxide (Spectrum A), and after the solution had faded completely to yellow, (Spectrum B). The spectra were also measured for a yellow sodium hydroxide solution of the base (Spectrum C). Finally, the spectra were measured for the hydrochloride (Spectrum D), and for the free base (Spectrum E) in dilute hydrochloric acid.

The values of $\lambda_{max.}$ in mμ and $\log \varepsilon$ obtained in the five spectra are shown in Table 9, below.

(ii) Comparison of (a) the spectra obtained for the acid solutions, and (b) the spectra obtained for the alkaline solutions.

The visible and ultraviolet absorption spectra of the base and of its hydrochloride in (a) hydrochloric acid, and (b) dilute sodium hydroxide, should be identical in each solvent system, and the same molar extinction coefficients should be obtained. This was indeed observed. Spectrum D and Spectrum E of the hydrochloride and of the base, respectively, in the hydrochloric acid solutions (i.e. both as the hydrochlorides), were identical. Spectrum B and

Table 9.

Visible and ultraviolet absorption spectra of the base (XII).

No.	Description.	Values.
A	Hydrochloride in sodium hydroxide, purple solution.	$\lambda_{max.}$ 548, 391, 293, 228, 209, 206 log ε 3.76, 4.06, 4.71, 4.43, 4.33, 4.36
B	Hydrochloride in sodium hydroxide, yellow solution.	$\lambda_{max.}$ 546, 366, 298, 261, 239, 202 log ε 2.61, 3.91, 4.45, 4.26, 4.29, 4.47
C	Free base in sodium hydroxide, yellow solution.	$\lambda_{max.}$ 546, 366, 298, 261, 239, 205 log ε 2.60, 3.91, 4.45, 4.26, 4.29, 4.39
D	Hydrochloride in hydrochloric acid, orange solution.	$\lambda_{max.}$ 483, 351, 336, 281, 248, 224 log ε 3.62, 3.84, 3.90, 4.63, 4.22, 4.35
E	Free base in hydrochloric acid, orange solution.	$\lambda_{max.}$ 483, 351, 336, 281, 248, 224 log ε 3.61, 3.83, 3.90, 4.63, 4.22, 4.35

Spectrum C of the compounds in the yellow sodium hydroxide solutions, i.e. as the bases, were also identical.

Hence if one considered either the base, or the hydrochloride as the standard, and the other as a compound of unknown molecular weight, a rapid calculation based on the ultraviolet spectroscopic data would give the molecular weight of the unknown. This gave added support for the structure of the base.

(iii) Identification of the bands in the spectra.

As mentioned above, [(c) Solubility properties, page 42], the purple sodium hydroxide solution of the base (XII) was attributed to the formation of the tautomer (LXIX), present as the anion (LXXII) in the alkaline solution. The fading in colour of the solution from purple to yellow was attributed to the possible formation of the

anion structure (LXXV). Spectrum A would therefore be the spectrum of the anion (LXXII) and Spectrum B may be the spectrum of the anion (LXXV).

As the hydrochloride of the base (XII) could be recovered from the acidified sodium hydroxide solution of the base, the spectrum of the acidified sodium hydroxide solution (Spectrum D, or E) would be the spectrum of the base (XII).

Theoretically, it should be possible to identify the bands in the spectra of the base and of the hydrochloride due to the substituted quinazolinone group[67,68,69], and bands due to the substituted quinone-imine group[70,71]. However, this is only possible where the two groups are isolated, i.e. not joined by conjugation. Identification was not possible, the anion structures (LXXII) and (LXXV) are highly conjugated. In addition, the tautomeric structures (LXVI), (LXIX), and (LXX) of the base (XII) are also highly conjugated.

Oxidation of the quinazolinone (LVIII) in sodium hydroxide solution and the visible and ultraviolet absorption spectra of the quinazolinone.

As mentioned earlier, page 32, the quinazolinone (LVIII) was soluble in dilute sodium hydroxide, the purple solution obtained fading to yellow on standing. Visible and ultraviolet absorption spectra were measured for solutions of the quinazolinone in ethanol (Spectrum A'), hydrochloric acid (Spectrum B'), a freshly prepared sodium hydroxide solution which was purple (Spectrum C'), and after this solution had faded to yellow (Spectrum D'). The purple sodium hydroxide solution of the quinazolinone was acidified with dilute hydrochloric acid and the spectra measured for this solution (Spectrum E'). The faded yellow sodium hydroxide solution of the quinazolinone was similarly acidified and Spectrum F' obtained for this solution.

The values of $\lambda_{max.}$ in mμ and log ε obtained in the six spectra are shown in Table 10.

Table 10.

Visible and ultraviolet absorption spectra of the quinazolinone (LVIII).

No.	Description.	Values.
A'	Red-purple ethanol solution.	$\lambda_{max.}$ 398, 382, 364, 295, 278, 260, log ε 2.71, 2.75, 2.62, 4.14, 4.13, 4.10 $\lambda_{max.}$ 254, 248, 222 log ε 4.13, 4.16, 4.61
B'	Pale orange hydrochloric acid solution.	$\lambda_{max.}$ 480, 282, 227 log ε 2.39, 3.95, 4.36
C'	Purple sodium hydroxide solution.	$\lambda_{max.}$ 549.5, 391.5, 293, 230 log ε 3.92, 4.26, 4.82, 4.50
D'	Yellow sodium hydroxide solution.	$\lambda_{max.}$ 546, 365.5, 298, 260, 238 log ε 2.58, 3.97, 4.48, 4.30, 4.32
E'	Dark orange hydrochloric acid solution. (From acidified purple solution).	$\lambda_{max.}$ 483, 351.5, 337, 278, 246, 223 log ε 3.90, 3.94, 3.95, 4.78, 4.29, 4.44
F'	Dark orange hydrochloric acid solution. (From acidified yellow solution).	$\lambda_{max.}$ 483, 351, 337, 278, 246.5, 223 log ε 3.81, 3.89, 3.91, 4.76, 4.24, 4.41

The spectra obtained from the acidified sodium hydroxide solutions (Spectrum E' and Spectrum F') were the same. In addition, they were the same as the spectrum obtained for the acidified yellow sodium hydroxide solution of the base (XII) (Spectrum E, Table 9, page 58). The spectrum for the yellow sodium hydroxide solution of

the quinazolinone (Spectrum D') and the spectrum for the yellow sodium hydroxide solution of the base (Spectrum C, Table 9, page 58) were the same except for the band at 205 mμ in Spectrum C which was absent in Spectrum D'. Finally, the spectrum for the purple solution of the quinazolinone in aqueous sodium hydroxide (Spectrum C') and the spectrum for the purple solution of the base in this solvent (Spectrum B, Table 9, page 58) compared most favourably.

These visible and ultraviolet absorption spectra therefore indicated that the quinazolinone (LVIII) was oxidised to the base (XII) in the alkaline solution. A reaction had occurred because the spectra for the acidified sodium hydroxide solutions of the quinazolinone (Spectrum E' and Spectrum F') were different from the spectrum for the quinazolinone in hydrochloric acid (Spectrum B').

It therefore appeared that as the quinazolinone dissolved in dilute sodium hydroxide, the hydroquinone group in the quinazolinone was oxidised to a p-benzoquinone group, forming the quinone (X). Ring closure immediately followed and the purple solution obtained was in effect a solution of the base (XII). The fading of the solution from purple to yellow indicated the possible formation of the anion (LXXV) in the alkaline solution. However, acidification of the alkaline solution again formed the base (XII) as has been described earlier (page 45).

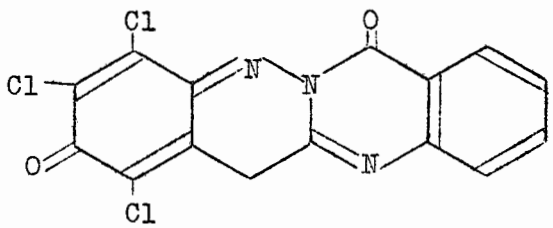
Confirmation that this oxidation had indeed occurred was readily obtained by warming the quinazolinone with dilute sodium hydroxide. When the solution was acidified with dilute hydrochloric acid, red crystals precipitated from the solution. An infrared spectrum of this material was superimposable on an infrared spectrum of the hydrochloride of the base (XII). Oxidation of the quinazolinone and subsequent ring closure had therefore occurred in the alkaline solution.

Identification of the bands in the spectra of the quinazolinone.

It should be possible to identify the bands in the spectra for the ethanol and hydrochloric acid solutions of the quinazolinone (Spectra A' and B', respectively) due to the substituted quinazolinone group[67,68,69], and bands due to the hydroquinone group[70]. However, again, the quinazolinone could possess tautomeric structures which are highly conjugated. Two tautomers are shown in the quinazolinone hydrochloride structures (LXI) and (LXII). The quinazolinone group and the hydroquinone group in the quinazolinone (LVIII) would therefore be joined by conjugation and make identification of individual bands in the spectra impossible.

§ 8. Second method of oxidation.

When the quinazolinone (LVIII) in an ethanolic hydrochloric acid solution was oxidised with hydrogen peroxide, a red solution and red crystals, which could not be isolated in pure form, soon formed. On further oxidation, with heating, the solution subsequently turned yellow, the red crystals slowly dissolved, and within 45 minutes, yellow needles formed in good yield. The product had no ionic chlorine and was thus not a hydrochloride. Analysis nevertheless indicated that three chlorine atoms were present in the molecule. The product had one active hydrogen atom (Zerewitinoff)[72], and on the basis of the above, the analysis, and the infrared spectrum, structure (LXXXVI) has been assigned to this product.



(LXXXVI)

Infrared spectroscopic data.

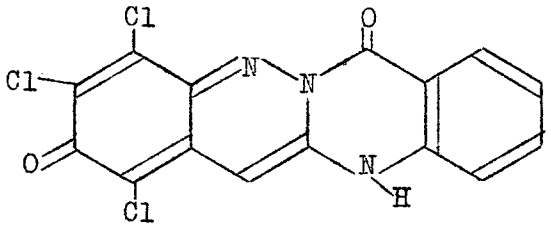
The strong absorption at 1721 $cm.^{-1}$ in the infrared spectrum of the trichloro compound in nujol was at the same frequency range as the band at 1718 $cm.^{-1}$ in the spectrum of the base (XII) and was therefore also assigned to the C=O absorption of the ring-fused δ-lactam system. Although the frequency of the band at 1701 $cm.^{-1}$ in the infrared spectrum of the trichloro compound was 72 $cm.^{-1}$ higher than the frequency of the band at 1629 $cm.^{-1}$ in the spectrum of the base (XII), the band was also assigned to the carbonyl stretching vibration of the α,β-α',β'-unsaturated ketone system. The increase in the frequency of absorption was attributed to the presence of the α,α'-chlorine atoms. Halogen substitution in the immediate vicinity of a carbonyl group is known[73] to cause a high-frequency shift of the carbonyl absorption. The interpretation of the bands in the infrared spectrum of the trichloro compound is summarised in Table 11.

Table 11.

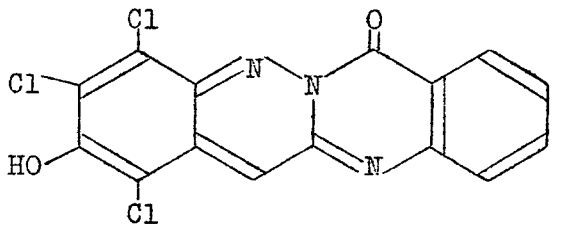
	Trichloro compound (LXXXVI)
	$cm.^{-1}$
C=O stretching vibration of the ring-fused δ-lactam	1721
C=O stretching vibration of the α,β-α',β'-unsaturated ketone	1701
C=N stretching vibration	1659
Aromatic C=C in-plane stretching vibrations	1611, 1575
Quinazoline I band	1620
Quinazoline II band	1558
Quinazoline III band	1511

The active hydrogen atom.

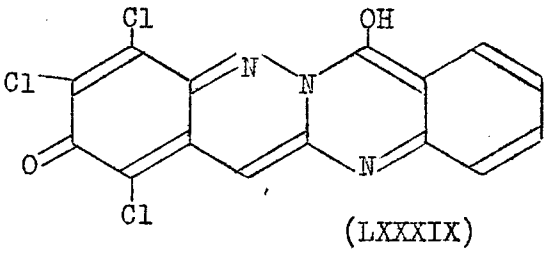
One active hydrogen atom is present in each of the three tautomeric forms (LXXXVII), (LXXXVIII), and the "enol" form (LXXXIX).



(LXXXVII)



(LXXXVIII)

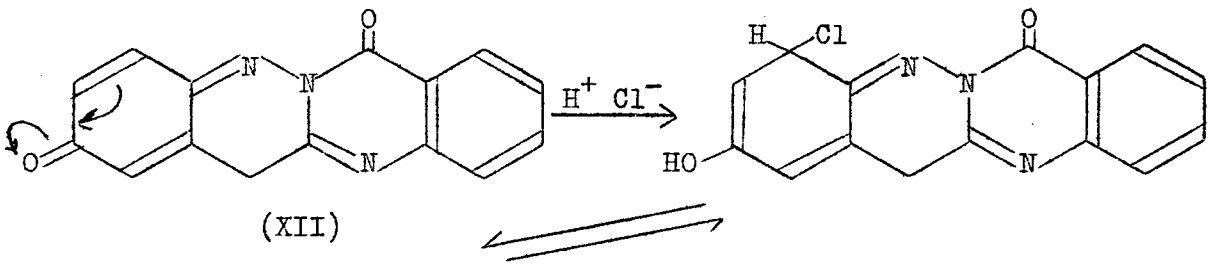


(LXXXIX)

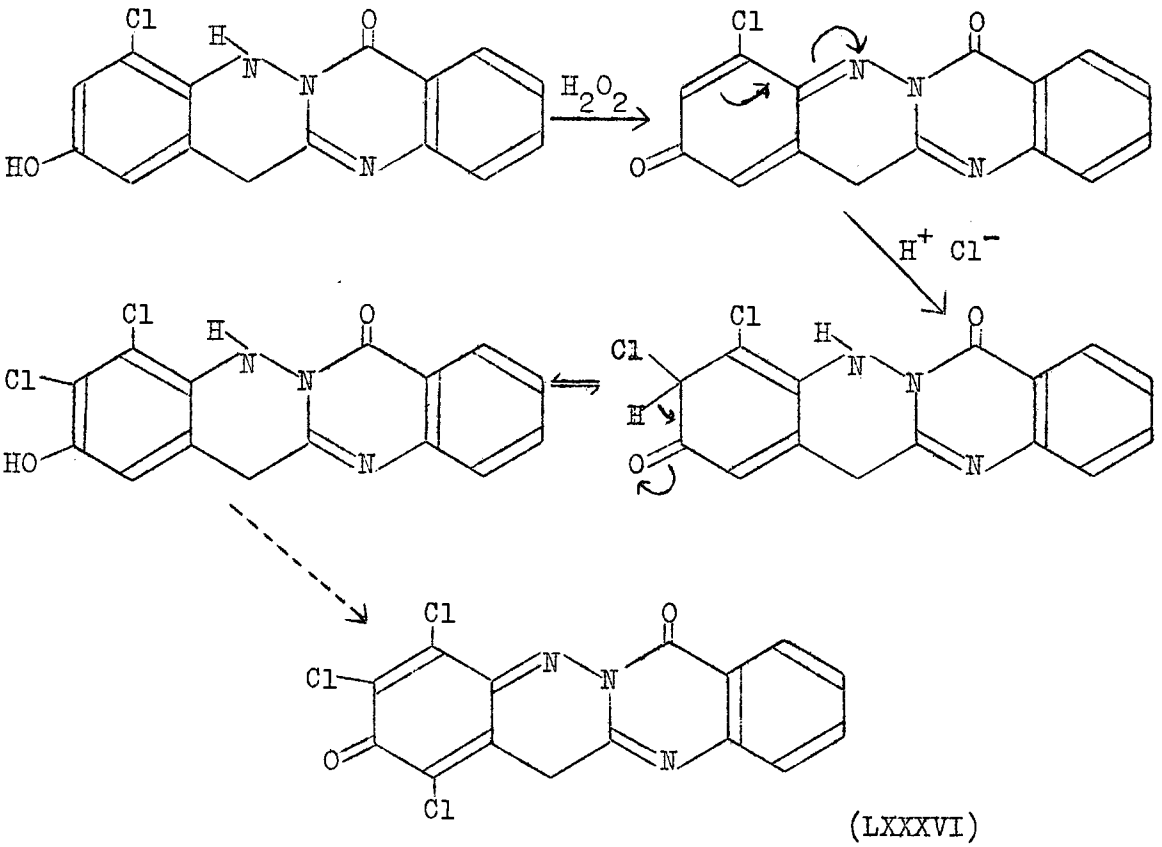
The slightly low value for the active hydrogen obtained supported the theory that this active hydrogen atom arose from a tautomeric structure.

Mechanism of the addition of the chlorine atoms.

The chlorine atoms in the trichloro compound could have entered the molecule by 1,4-addition to the quinone-imine compound (XII), which would be an intermediate in the reaction, as is shown in the following reaction sequence:



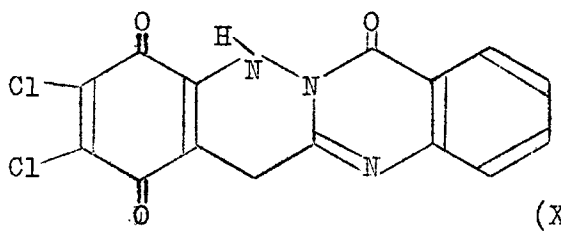
(XII)



(LXXXVI)

This mechanism was supported by the fact that a suspension of the base (XII) in ethanolic hydrochloric acid yielded the same trichloro compound (LXXXVI) on warming with hydrogen peroxide. The elements of hydrochloric acid are known to add to p-benzoquinone by 1,4-addition[74], and chloranil may be prepared by the action of hydrochloric acid and hydrogen peroxide on p-benzoquinone in excellent yield[75,76].

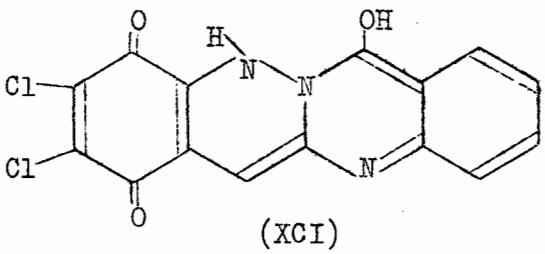
Elimination of a product containing the structure (XC).



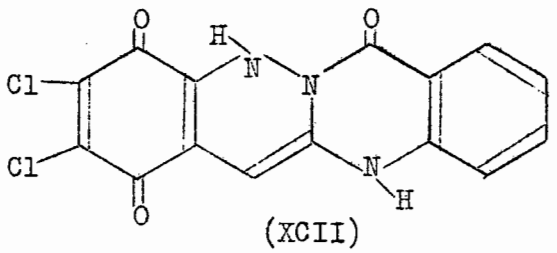
(XC)

A product possessing the structure (XC) which would have been obtained if the reaction had proceeded by an internal 1,4-addition of the amino group to the quinone group, was ruled out by the analysis figures obtained and by the infrared evidence. Only two bands appeared in the carbonyl absorption frequency region of the infrared spectrum of the trichloro compound. If the compound possessed the structure (XC), three bands would be expected.

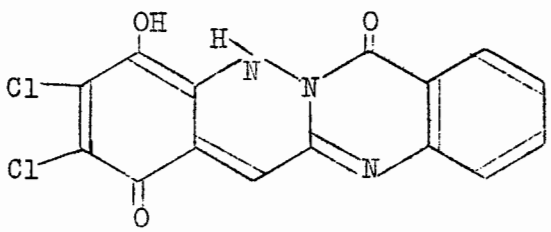
The tautomeric forms (XCI), (XCII), and (XCIII) of the structure (XC) would each possess two active hydrogen atoms. Only one active hydrogen atom was found in the trichloro compound obtained on ring closure.



(XCI)



(XCII)



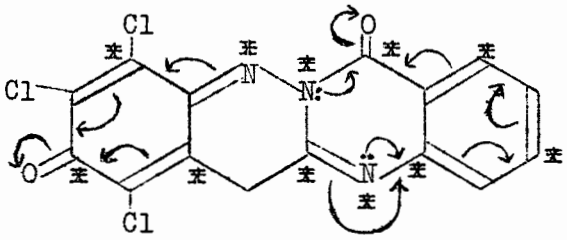
(XCIII)

Basicity of the trichloro compound.

The trichloro compound (LXXXVI) was not as strong a base as the compound (XII). It was not formed as the hydrochloride, and failed to form a picrate, a picrolonate, or a perchlorate. A molecular weight determination in non-aqueous medium (acetic acid) was attempted using acetous perchloric acid and methyl violet indicator. The trichloro compound showed no basic reaction whatsoever.

Stability of the trichloro compound.

The trichloro compound (LXXXVI) was found to be soluble in chloroform, acetone, and acetic acid; and very sparingly soluble in ethanol, forming yellow solutions. Oscillation of charge between the starred positions in structure (XCIV) of the trichloro compound, resulting from the flow of electrons indicated by the arrows, could occur. This may result in absorption in the visible region of the



(XCIV)

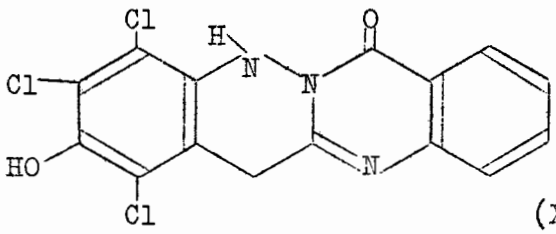
spectrum and this would explain the yellow colour observed for the solutions of the trichloro compound in the different solvents.

However, the solutions of the trichloro compound, and the solid itself, turned red when exposed to light. Thin layer chromatography (TLC) of the trichloro compound on silica gel also indicated the sensitivity of the trichloro compound to light. Single yellow spots were obtained in various solvents when the chromatograms were run in the dark. However, additional pink or purple streaks were obtained when the chromatograms were run in light. On exposure to light the yellow spots darkened to orange. On longer exposure to light, the orange spots and the pink and the purple streaks faded to a uniform yellow-brown. The change in colour of the spots and the streaks on long exposure to light was not due to any acidity in the silica gel as similar results were obtained when a kieselguhr medium was used. (Experimental page 170.)

A red solution was obtained when the yellow solution of the trichloro compound in chloroform/ethanol was exposed to light. TLC on this red solution revealed three spots, a faster moving yellow spot, a purple spot, and a yellow spot at the origin. The

R_F values of these three spots were different from that of the original trichloro compound. On exposure of the chromatogram to light, the purple spot faded and the yellow spots darkened to a uniform yellow-brown. In two-dimensional TLC of these three yellow-brown spots none of the spots moved in either a chloroform or in an ethanol solvent system. The TLC results therefore indicated that the red material obtained from the photolysis of the trichloro compound was itself light sensitive, a yellow compound being formed.

If the trichloro compound was recrystallised by dissolving it in chloroform and adding ethanol, darker and less pure needles were obtained. However, if drops of hydrogen peroxide and concentrated hydrochloric acid were added to the ethanol first, bright yellow needles crystallised from the solution. When the trichloro compound was added to ethanol, although only very sparingly soluble in ethanol, the supernatant solution turned red, immediately in direct sunlight and in ultraviolet light. The red colour became more intense as the yellow trichloro compound slowly dissolved. Tetrachlorohydroquinone has been obtained from chloranil by the effect of sunlight on an absolute ethanol solution[77]. It was therefore possible that the compound in the red solution obtained in sunlight, and in the pink and in the purple streaks in the thin layer chromatograms, could possess the hydroxy structure (XCV).



(XCV)

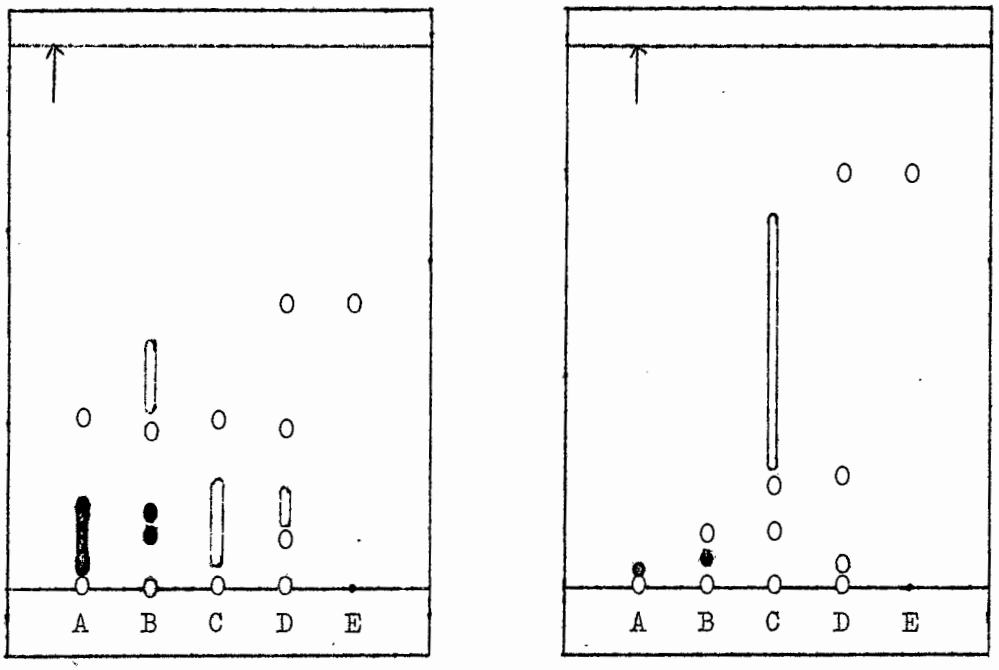
A brief investigation was undertaken to determine whether this photolysis of the trichloro compound was indeed a reduction and/or a loss of halogen atom(s). Samples of the red solution obtained from the photolysis of the trichloro compound

were treated with either hydrochloric acid and/or hydrogen peroxide and the resulting solutions chromatographed on silica gel in two different solvent systems. The different solutions chromatographed are shown in Table 12 and the chromatograms obtained are reproduced in Figure 1. The R_F values of, the colours of, and the effect of

Table 12.

Red solution from the photolysis of the trichloro compound.				Trichloro compound.
Solution A	Solution B	Solution C	Solution D	Solution E
Water added.	Dilute hydrochloric acid added.	Hydrogen peroxide added.	Dilute hydrochloric acid and hydrogen peroxide added.	(In chloroform).

Figure 1.



In chloroform. In ethyl acetate : petroleum ether.

O = yellow spots; ● = purple spots.

light on the spots in the chromatograms are given in the Experimental, page 173.

The chromatograms reproduced in Figure 1 indicated that both hydrochloric acid and hydrogen peroxide were necessary to reform the trichloro compound after the photolysis had occurred. However, it appeared that only the purple material was reconverted to the trichloro compound; the final yellow product of the photolysis was not reconverted to the trichloro compound. Hence it appeared that, initially, both reduction and loss of chlorine had occurred in the photolysis of the trichloro compound.

The different spots obtained in the chromatograms reproduced in Figure 1 indicate the complexity of the products obtained from the photolysis of the trichloro compound. The constitution of the products of the photolysis was therefore not further investigated.

Visible and ultraviolet absorption spectra of the trichloro compound.

The ultraviolet and visible absorption spectra of the trichloro compound were measured in chloroform, great care having been taken to exclude light from the solution, which remained yellow under such conditions. A suspension of the trichloro compound in ethanol was shaken in sunlight to produce a bright red solution, and the visible and ultraviolet absorption spectra were determined for this solution.

The values of $\lambda_{max.}$ in mμ and $\log \varepsilon$ in the visible and ultraviolet absorption spectra for the chloroform and ethanol solutions of the trichloro compound are summarised in Table 13, below.

There are highly conjugated systems in the tautomeric forms (LXXXVII), (LXXXVIII), and (LXXXIX) of the trichloro compound, similar to the tautomeric forms of the base (XII). This again made identification of individual bands due to the quinone-imine system

Table 13.
Visible and ultraviolet absorption spectra.

Description.	Values.
Trichloro compound, in chloroform. Yellow solution.	$\lambda_{max.}$ 370, 330sh., 285sh., 262 log ε 4.09, 3.89, 4.32, 4.39
Trichloro compound, in ethanol. Red solution.	$\lambda_{max.}$ 538, 385plat., 370plat., 285, 222.5 log ε 3.71, 3.91, 4.06, 4.27, 4.49
Chloranil in ethanol. Yellow solution.	$\lambda_{max.}$ 348, 280 log ε 2.59, 4.03
p-Benzoquinone in ethanol. Yellow solution.	$\lambda_{max.}$ 357, 289, 248.5, 229 log ε 2.75, 3.40, 3.80, 3.75
sh. = shoulder, plat. = plateau.	

and the quinazolinone system in the visible and ultraviolet absorption spectra of the trichloro compound impossible. In addition, no favourable comparison could be made between the visible and ultraviolet absorption spectra of the trichloro compound and of the base (XII) (Table 9, page 58) because the spectra were measured for solutions of the two compounds in different solvents. Tautomeric changes of the base probably occurred in the alkaline solution, tautomers (LXIX) and (LXX) predominating, and, in the acid solution, tautomer (LXVI) containing the secondary nitrogen atom predominating. Also the chlorine atoms present in the trichloro compound but absent in the base, could result in markedly different visible and ultraviolet absorption spectra for the two compounds. Indeed, spectra for ethanolic solutions of chloranil and p-benzoquinone were found to be different. The absorption maxima were at different wavelengths in the two spectra and there were additional bands in the ultraviolet absorption spectrum of p-benzoquinone. The values of $\lambda_{max.}$ in mμ and log ε obtained in the visible and ultraviolet absorption spectra of chloranil and of p-benzoquinone are included in Table 13.

Differences between the properties of the trichloro compound (LXXXVI) and of the base (XII).

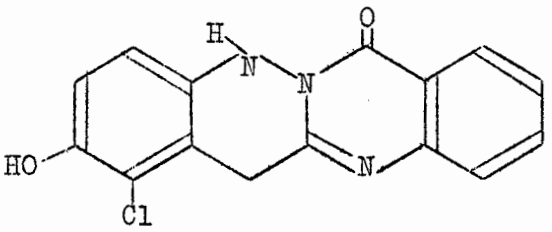
The ability of the trichloro compound to dissolve in chloroform as opposed to the failure of the base (XII) to dissolve in this solvent was attributed to the presence of the three chlorine atoms.

The failure of the trichloro compound to form salts could be attributed to the greater predominance of the tautomers (LXXXVIII) or (LXXXIX) rather than the tautomer (LXXXVII) containing the secondary nitrogen atom. The tautomer (LXXXVIII) could be stabilised by hydrogen bonding of the hydroxyl group with the α-chlorine atoms. Although tertiary nitrogen atoms would still be present in these tautomers and in the predominant structure (LXXXVI), it would appear that they were not sufficiently basic to form salts in this compound. The presence of the tautomer (LXXXVIII) was supported by the presence of the band at 3420 $cm.^{-1}$ in the infrared spectrum of the trichloro compound in potassium chloride. This band could be assigned to the O-H stretching frequency, intramolecularly hydrogen bonded.

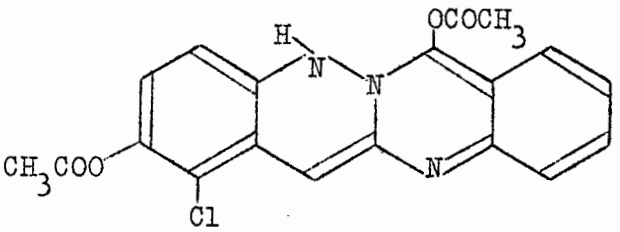
Reductive acetylation of the trichloro compound.

The trichloro compound readily underwent reductive acetylation to give a compound which analysed for a diacetate. Analysis however, indicated that two chlorine atoms had been lost in the reductive acetylation. The bands in the infrared spectrum of the compound at 1776, and 1718 $cm.^{-1}$ were assigned to the C=O stretching vibrations of the phenolic ester and the vinyl ester, respectively, as had been done with the bands at 1768, and 1720 $cm.^{-1}$ in the infrared spectrum of the diacetate (LXXXII) (Table 6, page 48). These acetyl groups were shown to be O-acetyl by their ease of hydrolysis by sodium methoxide in methanol at 0° to yield the hydrochloride of the base (XCVI), when the solution was acidified

with hydrochloric acid. On the basis of this evidence, the diacetate was assigned the structure (XCVII).



(XCVI)



(XCVII)

The infrared spectrum of this diacetate was similar to the infrared spectrum of the diacetate (LXXXII) (Table 6, page 48). The interpretation of the bands in the spectrum of the diacetate (XCVII) is summarised in Table 14.

Table 14.

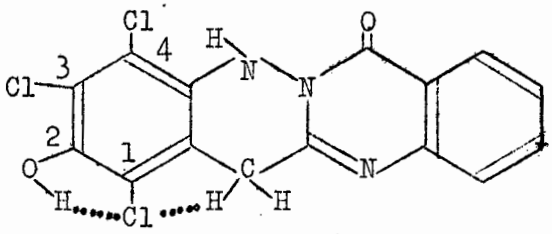
		Diacetate (XCVII)
		cm.$^{-1}$
N-H stretching vibration of the secondary amine		3540
C=O stretching vibrations	of phenolic ester	1776
	of vinyl ester	1718
Quinazoline I band		1628
Quinazoline II band		1574
Aromatic C=C in-plane stretching vibration		1610

The loss of the chlorine atoms.

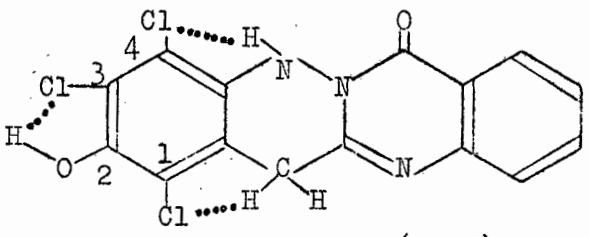
The position of the remaining chlorine atom was established from the nuclear magnetic resonance spectrum of the diacetate recorded[78] on a Varian A-60 spectrometer. The diacetate was dissolved in dimethylsulphoxide and tetramethylsilane was used

as internal reference (τ 10.0). The spectrum showed an AB quartet centred at τ 2.16, (J_{AB} = 8 c./sec. and $\Delta\nu$ = 43.7 c./sec.). This indicated ortho-hydrogen coupling[79]. The remaining four aromatic protons indicated by the hydrogen integral spectrum fell in the range τ 1.9 - 2.4 as a poorly resolved multiplet. The spectrum should also be measured at 40 Mc./sec. to confirm that the AB quartet indicated did arise from ortho-coupling as the coupling constant J_{AB} = 8 c./sec. should therefore remain unchanged. However, this could not be done because a 40 Mc./sec. spectrometer was not available.

The preferential loss of the chlorine atoms in positions 3 and 4 during reduction could possibly be explained by hydrogen bonding in the intermediate. This would stabilise the chlorine atom in position 1 as shown in figure (XCVIII) whereas the chlorine atoms in positions 3 and 4 would be hydrogen bonded as in figure (XCIX).



(XCVIII)



(XCIX)

Chlorine is considered to enter into hydrogen bonds[80] and the hydrogen from C-H can take part in hydrogen bridges but such bonds are generally weak[81].

Instances of replacement of chlorine by hydrogen in the reduction of polychloro-p-benzoquinones are reported in the literature. Dimroth et al.[82] obtained both 2,3-dichlorohydroquinone and chlorohydroquinone when they reduced 2,3-dichloro-p-benzoquinone. Reductive acetylation of chloranil using the conditions used in the reductive acetylation of the trichloro compound (LXXXVI) produced both tetrachlorohydroquinone diacetate and trichlorohydroquinone diacetate.

Reduction of the trichloro compound.

Reduction of the trichloro compound (LXXXVI) with zinc and hydrochloric acid in acetone produced the same hydrochloride that was obtained by the hydrolysis of the diacetate. The free base (XCVI) was again liberated from the hydrochloride as pure purple crystals merely by washing the hydrochloride well with water.

§ 9. The base (XCVI).

An attempt was made to obtain the molecular weight of the base (XCVI) by a similar non-aqueous titration as had been used for the base (XII). Again, the colour of the methyl violet indicator was masked by the deep purple colour of the acetic acid solution of the compound being investigated. The base (XCVI) also gave an orange solution in hydrochloric acid and a purple solution in alkaline solvents. It was again attempted to use this base as its own indicator in the non-aqueous titration. The colour of the solution of the base containing an excess of acetous perchloric acid was dark orange-red, but only a gradual colour change from dark scarlet-red to orange-red at the theoretical end-point was noted. Values of 311.7 and 293.8 were obtained for the equivalent weight. The molecular weight of the base (XCVI) would be 299.8. The titration had to be performed in a hot solution because of the low solubility of the base in glacial acetic acid. After adding an excess of acetous perchloric acid to the solution and allowing it to cool, dark red crystals of the perchlorate formed.

The analyses of the free base, of the hydrochloride, and of the perchlorate supported the structure (XCVI) assigned to this base.

Infrared spectroscopic data of the base (XCVI) and of its hydrochloride and perchlorate.

In the carbonyl absorption frequency range in the infrared spectrum of the base (XCVI) in potassium chloride, only one band at 1739 $cm.^{-1}$ was found. This band could only be due to the C=O stretching vibration of the ring-fused δ-lactam. The δ-lactam C=O stretching vibration was at 1718, and at 1721 $cm.^{-1}$ in the spectra of the base (XII) (Table 5, page 38) and of the trichloro compound (LXXXVI) (Table 11, page 63), respectively, where two rings were fused to the δ-lactam system. In the quinazolinone (LVIII), where only one ring was fused to the δ-lactam system, this C=O absorption was at 1687 $cm.^{-1}$ (Table 3, page 31). In the compounds (XII) and (LXXXVI) a second carbonyl absorption band is present. However, in the base (XCVI) only the one carbonyl group is present. As the structure of the quinazolinone (LVIII) has been conclusively established, and the base (XCVI) was formed from it after a ring-closure, an interesting deduction may be made. Although fusion of one ring to the δ-lactam system does not appear to cause sufficient strain to increase the frequency of the carbonyl absorption[58], it appears that fusion of a second ring has induced strain and the carbonyl absorption frequency is raised considerably.

The carbonyl absorption frequency was again raised in the infrared spectra of the hydrochloride and of the perchlorate of the base (XCVI), as had been observed with the quinazolinone (LVIII) and the base (XII). The interpretation of the infrared spectra of the base (XCVI), and of its hydrochloride and perchlorate is summarised in Table 15 below.

It will be noted that the only difference between the structures of the base (XCVI) and of the dihydroxy compound (LXXXIII) is the presence of the chlorine atom in the former structure. The bands in the infrared spectrum of the dihydroxy compound (LXXXIII) were therefore assigned to the vibrations shown in Table 7, page 55, after a study of the ranges[48,49] in which the various groups absorb,

Table 15.

	Free base* (XCVI)	Hydrochloride	Perchlorate
	$cm.^{-1}$	$cm.^{-1}$	$cm.^{-1}$
C=O stretching vibration of the ring-fused δ-lactam	1739	1772	1768
N-H deformation vibration of secondary amines	1642	1648	1640
Quinazoline I band	1616	1633	1618
Quinazoline II band	1579	1580	1576
Quinazoline III band	1483	1488	1484
Aromatic C=C in-plane stretching vibrations	1600 sh.	1599, 1447	1598, 1450 sh.
Combination of C=C and C=N stretching vibrations in heterocyclic aromatic compounds	1528	1518	1523
C-O stretching and O-H in-plane deformation vibrations of the phenol	1415	1404	1401 sh.
O-H deformation vibration	1371	1365	1368
C-N stretching vibrations of tertiary amines	1320	1347	1354
C-N stretching vibrations of secondary amines	1291	1300 sh.	1296 sh.
Amide III band	1284	1284	1289
O-H stretching frequency intramolecularly hydrogen bonded.	3420	3414*	
N-H stretching vibration of secondary amines.	3300	-	
NH_2^+ vibrations	——	2781*	
Aromatic =C-H stretching vibrations	3100, 3080	3068*	

* Bands obtained in infrared spectra of the compounds in potassium chloride.

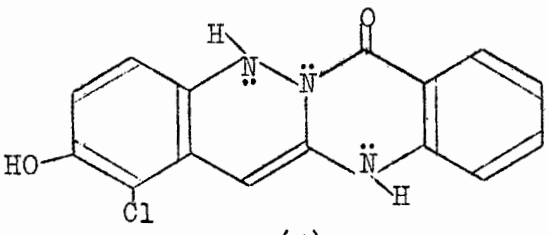
in conjunction with a study of the infrared spectra of the base (XCVI),,(Table 15, page 77), and of the base (XII), (Table 5, page 38).

Chemical properties of the base (XCVI).

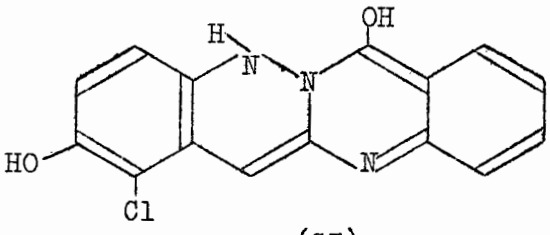
The base (XCVI) could be re-oxidised to the trichloro compound (LXXXVI) by treating a suspension in alcoholic hydrochloric acid with hydrogen peroxide. Acetylation of the base using the conditions used in the reductive acetylation of the trichloro compound (LXXXVI) produced the same diacetate (XCVII).

Tautomeric and canonical forms of the base (XCVI).

Similar tautomeric forms to those present in the base (XII) and in the trichloro compound (LXXXVI) would be possible with this base, viz. structures (C) and (CI).



(C)

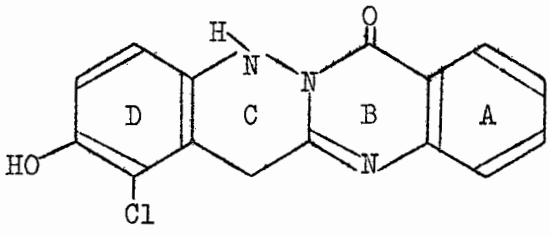


(CI)

In the tautomeric structure (C), there would be two secondary amino groups. Although the point of attachment of the proton in the hydrochloride and in the perchlorate of the base (XCVI) is probably on one of these nitrogen atoms, it is not possible to assign it definitely to either nitrogen atom. The similar solubility properties and deep red colours of the hydrochlorides of the bases (XCVI) and (XII) may indicate the same point of attachment of the proton, but there is no other evidence. The base does not

form a dibasic salt, although there are two secondary amino groups.

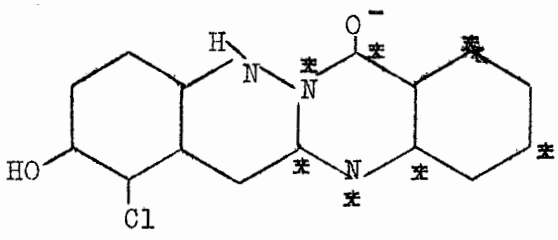
Rings A, B, and D in the base (XCVI), as represented in structure (CII), would be planar. Owing to the tervalent nitrogen and the quaternary carbon atoms in ring C, this ring would be buckled.



(CII)

Rings B and C in the tautomeric structure (C) would both be buckled due to the tervalent nitrogen atoms in these rings. The tautomer (CI) would be highly conjugated and would be planar. Models ("Dreiding") of the three tautomers confirmed these observations. The model of the tautomer (C) was buckled, but could assume a planar structure in one of its conformers.

The dark purple colour of the base suggested considerable contribution from many charged canonical forms with a large distribution of charge across the molecule. This inference was supported by the absence of any melting point in the base, or in its hydrochloride or perchlorate salts below 360°. In structure (CIII), the starred positions indicate the possible positions of the positive charge.

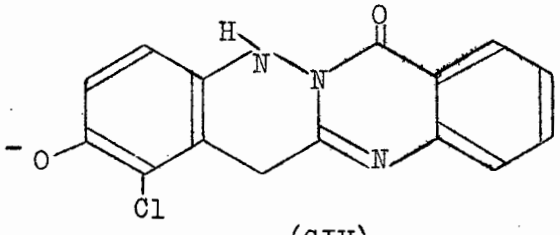


(CIII)

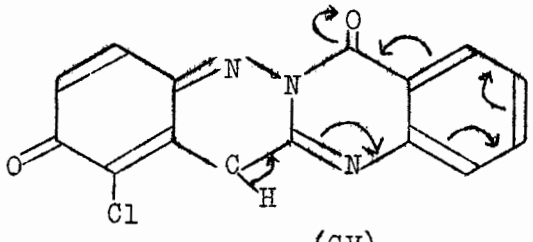
Solubility properties of the base (XCVI).

As in the case of the base (XII), the base (XCVI) and its hydrochloride were also soluble in pyridine, acetic acid, and ethanol, giving red solutions, indicating absorption near 500 mμ. They were sparingly soluble in water giving a purple-red solution and gave orange solutions in dilute nitric acid and dilute hydrochloric acid. The change in colour is again attributed to the lower solubility of the base in the aqueous acidic solvents rather than to a hypsochromic shift. The low solubility in the aqueous solvents would again be expected because of the size of the molecule of the base. This base could have either structure (XCVI) or the tautomeric di-amino structure (C) in the acidic solvents. Although this tautomeric structure possesses a high degree of conjugation, there would be little charge oscillation in the protonated form, and the absorption would be expected to be at a high frequency.

However, dissolution of the base (XCVI) in dilute sodium hydroxide or in dilute ammonia gave a bathochromic shift. Absorption at 562 mμ imparted a purple colour to the solutions. The solubility of the base in the alkaline solvents would be due to the phenolic group present in the base. In the alkaline solvents, the base would be present as the anion (CIV). This anion would be oxidised readily by molecular oxygen in the alkaline solution and the compound (CV)



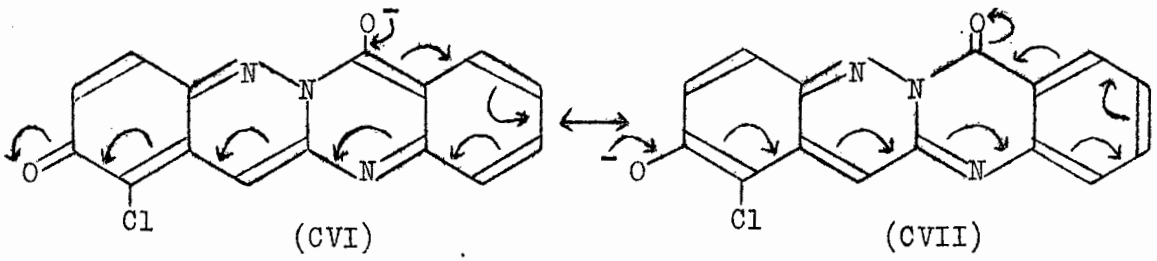
(CIV)



(CV)

would result. It has already been noted that phenolic compounds are readily oxidised in alkaline medium[61] and that the quinazolinone (LVIII) (page 59) and the base (LXXXIII) (page 54) were both

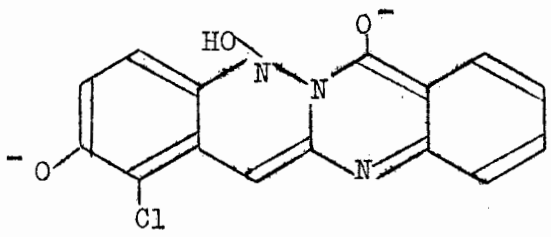
oxidised to the base (XII) in alkaline solution. The structure (CV) is analogous to the structure of the base (XII). Because of the system indicated by the arrows in structure (CV), in the alkaline solution the hydrogen atom on the methylene group can be removed giving the structure (CVI). Ready oscillation of the negative charge across the molecule indicated by the arrows in the two extreme forms structures (CVI) and (CVII), would result in the



(CVI) (CVII)

solution absorbing light at a low frequency and hence the purple colour of the solution observed.

As in the case of the quinazolinone (LVIII) and of the base (XII), the alkaline solutions of the base (XCVI) faded on standing. The ammonia solution faded to yellow-green and the sodium hydroxide solution to yellow. The fading occurred equally readily in the dark as in light and was promoted by heat. This fading could possibly be attributed to the same hydroxylation of the quinone-imine group, contemplated for the base (XII), (page 44). If hydroxylation occurred the compound (CVIII) would result. Again oscillation of



(CVIII)

the negative charge across the molecule would no longer be possible, and the hypsochromic shift observed would result.

Visible and ultraviolet absorption spectra of the base (XCVI).

The visible and ultraviolet absorption spectra of the base (XCVI) and of its hydrochloride for dilute sodium hydroxide and hydrochloric acid solutions were measured in the same way as the spectra of base (XII) (page 57). The values of $\lambda_{max.}$ in mμ and log ε obtained in the five spectra are summarised in Table 16.

Table 16.

Visible and ultraviolet absorption spectra of the base (XCVI).

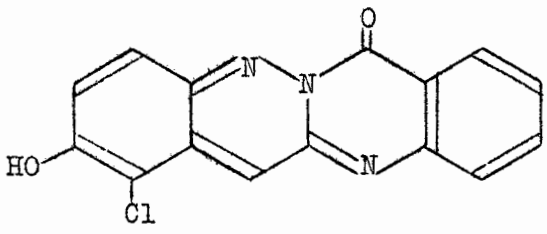
No.	Description.	Values.
A"	Hydrochloride in sodium hydroxide, purple solution.	$\lambda_{max.}$ 562, 389.5, 297, 226, 209, 205.5 log ε 3.67, 4.06, 4.66, 4.47, 4.48, 4.50
B"	Hydrochloride in sodium hydroxide, yellow solution.	$\lambda_{max.}$ 551, 379, 300, 271sh., 212, 202 log ε 2.90, 3.86, 4.45, 4.36, 4.32, 4.35
C"	Free base in sodium hydroxide, yellow solution.	$\lambda_{max.}$ 551, 379, 300, 271sh., 212, 204 log ε 2.94, 3.85, 4.46, 4.39, 4.36, 4.44
D"	Hydrochloride in hydrochloric acid, orange solution.	$\lambda_{max.}$ 443, 349, 332, 281, 246, 234, 214 log ε 3.17, 3.70, 3.96, 4.18, 4.16, 3.91, 3.87
E"	Free base in hydrochloric acid, orange solution.	$\lambda_{max.}$ 441, 349, 333, 281, 244, 234, 216 log ε 3.20, 3.76, 3.96, 4.19, 4.18, 3.92, 3.91

As with the base (XII), the visible and ultraviolet absorption spectra of the base (XCVI) and of its hydrochloride in (a) hydrochloric acid (Spectrum E" and Spectrum D", respectively), and (b) dilute sodium hydroxide (Spectrum C" and Spectrum B", respectively), were identical in each solvent system. In addition, the same molar extinction coefficients were obtained.

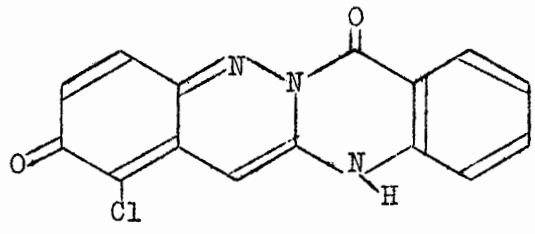
A comparison of the spectra of the base (XCVI) with the spectra of the base (XII) (Table 9, page 58); (a) Spectrum A" and Spectrum A, (b) Spectrum B" and Spectrum B, and (c) Spectrum D"

and Spectrum D, respectively, reveals a close similarity between the two compounds. This spectroscopic evidence strongly indicates that the two bases have the same chromophore in the purple sodium hydroxide solution, and gives strong support to oxidation of the base (XCVI) to the quinone-imine structure (CV), similar to the oxidation of the base (LXXXIII) to the base (XII) observed in alkaline medium (page 54). Although the only difference between the structure (CV) and the structure of the base (XII) is the presence of the chlorine atom in the former compound, this chlorine atom may cause a slight change in the visible and ultraviolet absorption spectra of the two compounds. As shown in Table 13, page 71, the visible and ultraviolet absorption spectra of p-benzoquinone and chloranil are not the same.

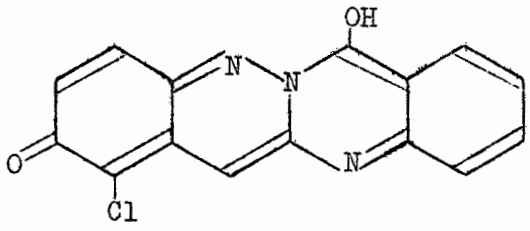
It was not possible to identify either the bands in the spectra due to the substituted quinazolinone group[67,68,69] or those bands due to the substituted quinone-imine group[70,71]. As with the base (XII) and the quinazolinone (LVIII), the groups would be conjugated in the different tautomeric structures for the quinone-imine (CV), shown in structures (CIX), (CX), and (CXI).



(CIX)



(CX)



(CXI)

Attempted isolation of the sodium salt of the anion present in the yellow sodium hydroxide solution.

An attempt was made to isolate the substance in the yellow sodium hydroxide solution of the base (XCVI) to investigate its envisaged structure, i.e. the sodium salt of the anion (CVIII). As in the case of the base (XII), the base (XCVI) was heated with dilute sodium hydroxide. The product obtained could not be recrystallised and was also precipitated from ethanol solution with benzene. Dark green micro-crystals were obtained. The product exhibited the same solubility properties as the material obtained from the base (XII). It was very soluble in water, sparingly soluble in ethanol and insoluble in less polar organic solvents. Hence this material could also be a sodium salt. The infrared spectrum of the material obtained from the base (XCVI) was very similar to the infrared spectrum of the material obtained from the base (XII). There was again a broad band at 3395 - 3230 $cm.^{-1}$ which may have been due to the stretching vibration of the O-H group present in a structure such as the anion (CVIII), but may have arisen from any sodium hydroxide contaminating the product. There was again no band in the carbonyl absorption region of the infrared spectrum. The δ-lactam carbonyl group was therefore no longer present in the product. Bands at 1595 and 1534 $cm.^{-1}$ in the infrared spectrum of the dark green material were in the regions where aromatic C=C in-plane stretching vibrations and cyclic α,β-unsaturated C=N stretching vibrations, respectively, are found.

Because the product may have been contaminated with sodium hydroxide, analysis was inconclusive. However, the sodium residue obtained indicated that the product may have been a sodium salt.

As with the base (XII), it was not possible to give a final answer to the structure of the material isolated from the sodium hydroxide solution.

§ 10. Third method of oxidation.

A third method of oxidation of the quinazolinone (LVIII) in ethanol was attempted. Hydrogen peroxide was again used, but dilute sulphuric acid was used in place of hydrochloric acid to obtain a compound free of chlorine, either in the ring system, or present in ionic form. The ethanolic solution obtained was dark red and scarlet crystals crystallised from the solution. Analysis of the product, however, even after repeated crystallisation, left a residue, and the product was not further investigated.

§ 11. Summary.

The ring closure has been shown to occur in the quinone (X) by the condensation of the amino group with the quinonyl carbonyl group, and not by 1,4-addition of the amino group to the quinone nucleus. The structures of the quinazolino[3,2-b]cinnolines formed have been conclusively established, and some of their properties and reactions have been investigated.

D I S C U S S I O N

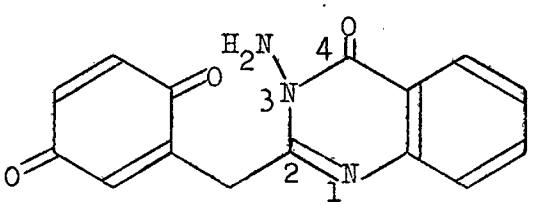
S E C T I O N II

S E C T I O N I I

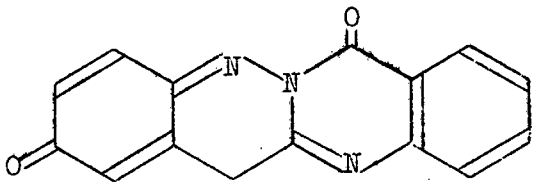
THE SYNTHESIS AND RING-CLOSURE OF 3-AMINO-2-(1,4-NAPHTHAQUINON-5-YL)QUINAZOLIN-4(3H)-ONE.

§ 1. Introduction.

As the quinone (X) was obtained and its ring-closure to the base (XII) demonstrated, it was considered to be of interest to

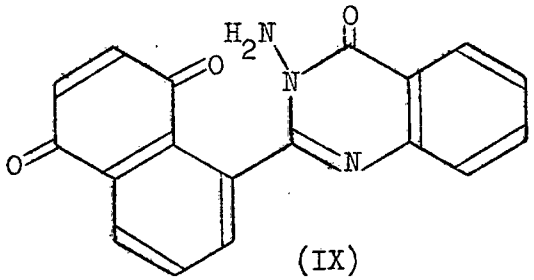


(X)

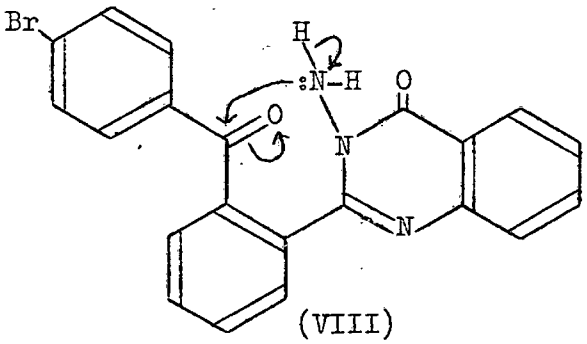


(XII)

attempt the synthesis of the quinone (IX), and to investigate its ring-closure. If ring-closure occurred, it would be by the mechanism outlined in the postulated intermediate (VIII) of Lamchen's work[9]

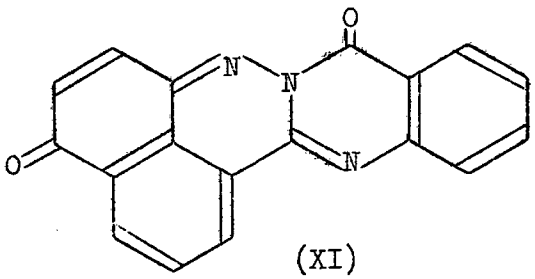


(IX)



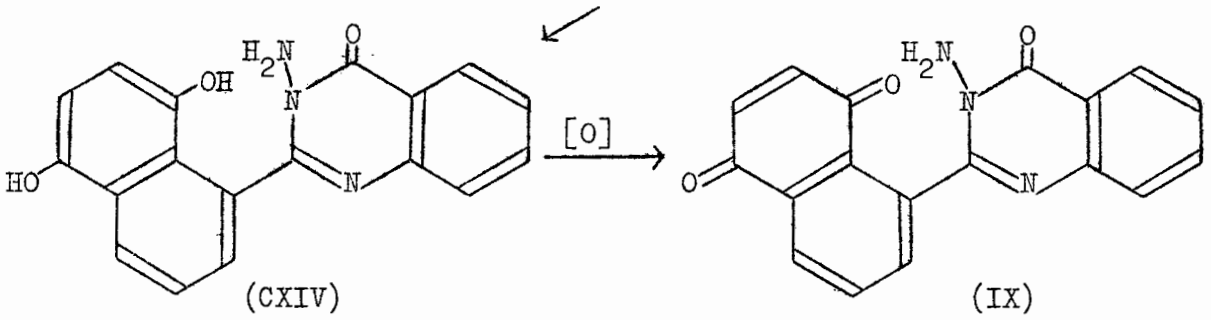
(VIII)

and as had been observed in the quinone (X) discussed in Section I. A product having the structure (XI) would be expected as 1,4-addition of the amino-group to the -C=C-C=O system of the quinone group would



(XI)

(CXII) $\xleftarrow{H_2N-\ddot{N}H_2}$ (CXIII) $CH_3O-C(=O)$



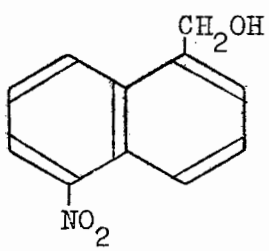
(CXIV) (IX)

§ 2. 1,4-Naphthaquinon-5-ylcarboxylic acid (CXII).

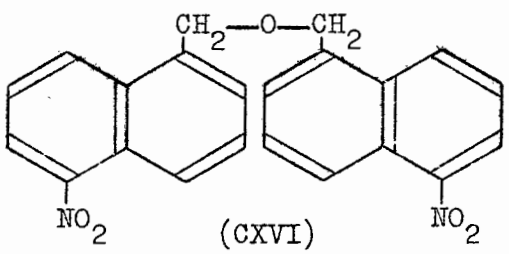
Willstätter et al.[83] obtained 1,4-naphthaquinon-5-ylcarboxylic acid (CXII) by oxidation of the sulphate salt[84] of 5-amino-1-naphthoic acid with lead(IV) peroxide and sulphuric acid. Short and Wang[85] synthesised 5-amino-1-naphthoic acid from 1-nitronaphthalene. Chloromethylation of 1-nitro-naphthalene yielded 5-nitro-1-chloromethylnaphthalene which they hydrolysed to 5-nitro-1-hydroxymethylnaphthalene (CXV) with aqueous sodium carbonate solution. Chromic acid oxidation of this hydroxy compound gave 5-nitro-1-naphthaldehyde and 5-nitro-1-naphthoic acid. Short and Wang reduced this nitro-acid to the required 5-amino-1-naphthoic acid.

It was decided to use the procedure outlined above to obtain the naphthaquinonylcarboxylic acid (CXII).

In the hydrolysis of 5-nitro-1-chloromethylnaphthalene to 5-nitro-1-hydroxymethylnaphthalene[85], the yields of Short and Wang were enhanced and a by-product was isolated in 14.3% yield. This material melted 38° higher than the hydroxy-compound. On the basis of the analysis obtained, a structure such as the ether (CXVI) was



(CXV)



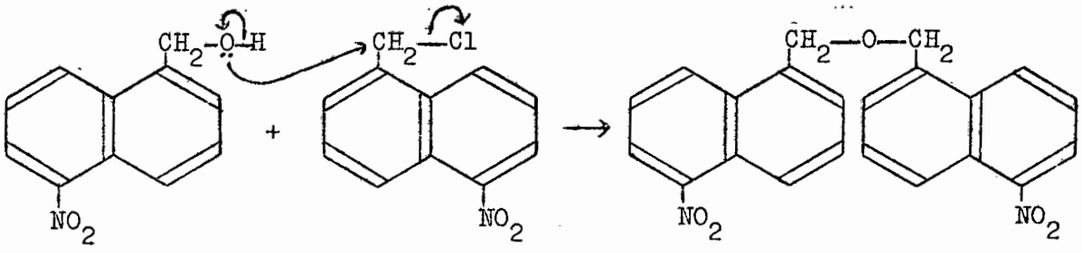
(CXVI)

proposed for this compound. This structure was supported by the infrared spectrum of the by-product in nujol. The interpretation of the bands in the infrared spectra of the ether (CXVI) and of the hydroxy compound(CXV) is shown in Table 17 for comparison. It can be

Table 17.

	Ether (CXVI)	Hydroxy-compound (CXV)
	cm.$^{-1}$	cm.$^{-1}$
Asymmetric aromatic NO_2 stretching vibrations	1525	1526
Symmetric aromatic NO_2 stretching vibrations	1341	1344
C-H out-of-plane deformations of 1,2,3-trisubstituted benzene rings	787	787
O-H stretching vibration, intermolecularly hydrogen bonded	—	3295
C-O stretching vibration of the ether group	1139	—

seen that there is no band at 3295 cm.$^{-1}$ in the spectrum of the ether, but that there is a band at 1139 cm.$^{-1}$ which could be due to the C-O stretching vibration of the ether group. It is proposed that the ether had formed during the hydrolysis of 5-nitro-1-chloromethyl-naphthalene by condensation of the product of the hydrolysis, 5-nitro-1-hydroxymethylnaphthalene (CXV), with unhydrolysed starting material; illustrated as follows:



(CXV) (CXVI)

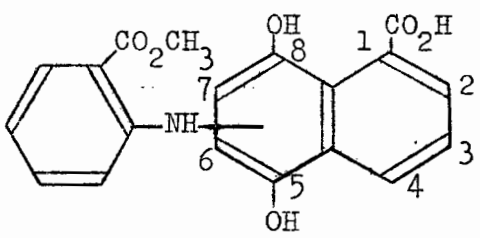
contained no nitrogen and the infrared spectrum, in potassium chloride, confirmed that it was a quinone-acid. The carbonyl absorption bands of the carboxylic acid and of the quinone groups appeared at 1698 and 1676 cm.$^{-1}$, respectively. The interpretation of the infrared spectrum of the quinone-acid is summarised in Table 18.

Table 18.

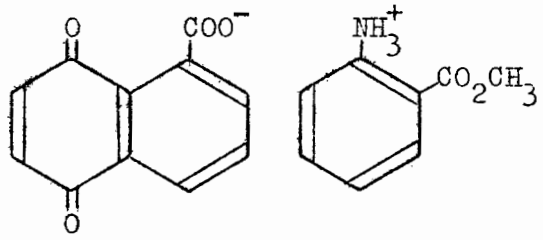
		Quinone-acid (CXII)
		cm.$^{-1}$
C=O stretching vibration:	of carboxylic acid	1698
	of quinone	1676
Free O-H stretching vibration		3420
Aromatic =C-H stretching vibrations		3075, 3045
Aromatic C=C in-plane stretching vibrations		1610, 1582, 1476, 1447
Combination band of C-O stretching and O-H in-plane deformation vibrations		1412

Fusion of the quinone-acid (CXII) with methyl anthranilate.

As Willstätter et al.[83] had mentioned no instability of the naphthaquinonylcarboxylic acid, its fusion with methyl anthranilate was attempted. Combustion analyses of the red needles obtained indicated the formation of either the hydroxy-acid structure (CXVII) or the isomeric compound, the salt (CXVIII) of the quinone and methyl anthranilate. The solubility of the product in dilute



(CXVII)



(CXVIII)

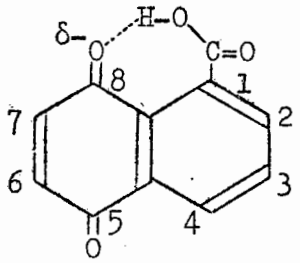
sodium hydroxide (purple solution) and in aqueous sodium bicarbonate (orange solution) suggested the presence of phenolic and carboxyl groups. In addition, the solubility of the product in dilute nitric acid giving an orange solution suggested the presence of an amino group. Finally, the deep red colour of the product and the colours of the solutions of the product indicated the presence of a highly conjugated system in which oscillation of charge could occur. The colour and the solubility properties of the product therefore supported the formation of the hydroxy-acid (CXVII). Confirmation that this had indeed formed was obtained from infrared spectroscopic data. The infrared spectrum of the compound in nujol showed only two absorption maxima in the carbonyl absorption frequency range, at 1746 and at 1697 cm.$^{-1}$. The band at 1676 cm.$^{-1}$ in the spectrum of the quinone-acid (CXII) (assigned to the C=O stretching vibration of the quinone group) was absent in the spectrum of the fusion product thus eliminating the salt structure (CXVIII) for this compound. The band at 1746 cm.$^{-1}$ in the spectrum of the fusion product (CXVII) was in the range[48] where aryl esters absorb. The

band was therefore assigned to the C=O stretching vibration of the aryl ester group. The carbonyl absorption at 1697 cm.$^{-1}$ in the spectrum of the fusion product was near the band at 1698 cm.$^{-1}$ in the spectrum of the quinone-acid (CXII). Hence this band at 1697 cm.$^{-1}$ was also assigned to the C=O stretching vibration of the carboxyl group. The interpretation of the infrared spectrum of the hydroxy-acid is summarised in Table 19 below.

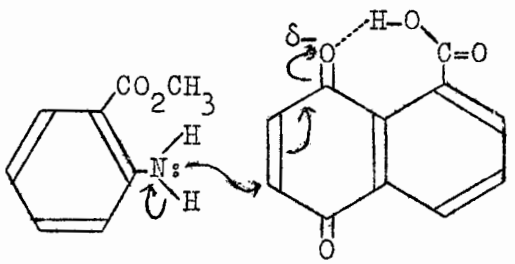
Table 19.

		Hydroxy-acid (CXVII)
		cm.$^{-1}$
C=O stretching vibrations:	of aryl ester	1746
	of aryl acid	1697
N-H stretching vibration of the secondary amine		3275
O-H stretching vibration, intramolecularly hydrogen bonded		3185
Aromatic C=C in-plane stretching vibrations		1624, 1573
N-H deformation vibration		1540
Combination band of C-O stretching and O-H in-plane deformation vibrations of the acid or phenol		1452shoulder
C-H deformation vibration of the methyl group		1354
C-N stretching vibrations of the secondary aromatic amine		1294
C-O stretching vibrations of the benzoate		1280

The hydroxy-acid (CXVII) would be obtained by 1,4-addition of methyl anthranilate to the quinone. The o-methoxycarbonylanilino group could be in position 6 or 7 of the naphthalene nucleus. Possible hydrogen bonding in 1,4-naphthaquinon-5-ylcarboxylic acid as shown in structure (CXIX) would cause the 1,4-addition shown in the intermediate (CXX) giving 5,8-dihydroxy-6-(o-methoxycarbonylanilino)-1-naphthoic acid. However, the structure of the hydroxy-acid was not



(CXIX)



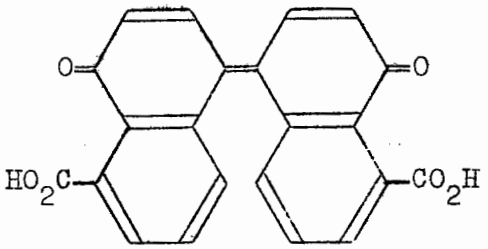
(CXX)

further investigated as the amide (CXIII) was required and not a 1,4-addition product.

Reduction of the quinone (CXII).

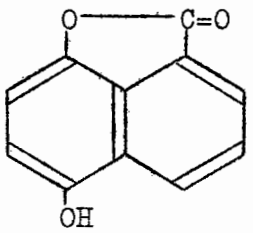
To avoid 1,4-addition to the quinone nucleus, the quinone could be reduced with zinc and hydrochloric acid. Fusion of the resulting hydroxy-acid with methyl anthranilate and treatment of the product with hydrazine should result in the product (CXIV) which was required.

Willstätter et al.[83] stated that 1,4-naphthaquinon-5-yl-carboxylic acid on reduction, for example with zinc dust and acetic acid or hydriodic acid with red phosphorus or with zinc dust, showed characteristic quinone behaviour; the deep-yellow colour which originally appeared showed condensation, probably to a diketo-dinaphthalene-dicarboxylic acid. The diketo-dinaphthalene-dicarboxylic acid (CXXI) referred to was neither isolated nor investigated by Willstätter et al.



(CXXI)

A solution of the quinone (CXII) in ethanol was treated with zinc and hydrochloric acid. The solution did darken to brown as Willstätter *et al*. had observed, but subsequently faded to yellow. The solution was concentrated and, on cooling, clusters of brown needles crystallised from the solution. Combustion analysis of this material fitted the compound (CXXI). The lactone (CXXII) would



(CXXII)

require the same combustion analysis figures. The infrared spectrum of the product, in nujol, strongly supported the formation of the lactone. The strong absorption at 1737 $cm.^{-1}$ was at too high a frequency for the C=O stretching vibration of a carboxyl group and was assigned to the carbonyl absorption of the α,β-unsaturated γ-lactone. The interpretation of the bands in the infrared spectrum of the lactone (CXXII) is summarised in Table 20 below.

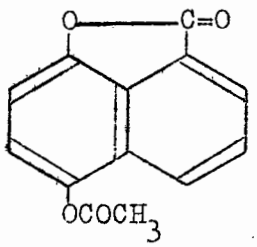
When the reduction of the quinone with zinc and hydrochloric acid was repeated, gums were obtained and vacuum sublimation of the dried gums did not yield any lactone. A different method of reduction was therefore investigated.

Reduction of the quinone-acid (CXII) with sodium borohydride in aqueous sodium bicarbonate solution and with sodium in *n*-propanol using the conditions used by Wheeler and Wheeler[87] for 8-oxodecahydronaphthoic acid was attempted. Gums, from which neither the dihydroxy compound nor its lactone could be isolated, were obtained. Reduction with zinc in acetic acid gave a very low yield of the lactone. However, reductive acetylation of the quinone-acid using the conditions used for the reductive acetylation of

Table 20.

	Lactone (CXXII)	Acetate (CXXIII)
	cm.$^{-1}$	cm.$^{-1}$
O-H stretching frequency intermolecularly hydrogen bonded	3317	——
C=O stretching vibration of the phenolic ester	——	1788
C=O stretching vibration of the α,β-unsaturated γ-lactone		1760
C=O stretching vibration of the α,β-unsaturated γ-lactone, hydrogen bonded	1737	
Conjugated C=C stretching vibrations of alkenes (?)	1652	1654
Aromatic C=C in-plane stretching vibrations	1609,1520, 1485	1604, 1500
C-H deformation vibration of the C-CH_3 group	——	1461

p-benzoquinone[51] readily afforded the lactone of 5-acetoxy-8-hydroxy-1-naphthoic acid (CXXIII) in 78% yield. The compound was assigned this structure on the basis of its analysis and of its infrared



(CXXIII)

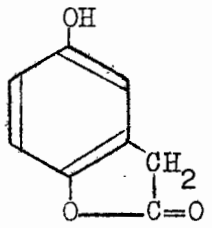
spectrum. There were no bands in the O-H stretching frequency region but strong absorptions in the C=O stretching vibration region at 1788 and at 1760 cm.$^{-1}$. The absorption at 1788 cm.$^{-1}$ was in the range where the carbonyl group of phenolic esters absorbs. This band was therefore assigned to the C=O stretching vibration of a phenolic

ester group. The other band in the carbonyl absorption frequency region, at 1760 cm.$^{-1}$, was assigned to the C=O stretching vibration of the α,β-unsaturated γ-lactone system. The lower frequency of this C=O absorption at 1737 cm.$^{-1}$ in the spectrum of the lactone (CXXII) was attributed to hydrogen bonding of the lactone carbonyl group. The O-H stretching vibration of the lactone at 3317 cm.$^{-1}$ supported intermolecular hydrogen bonding and Searles et al.[88] observed shifts of up to 15 cm.$^{-1}$ in γ- and δ-lactones from this cause. The interpretation of the bands in the infrared spectrum of the acetate (CXXIII) is summarised in Table 20. The interpretation of the bands in the infrared spectrum of the lactone (CXXII) is included in this table for comparison.

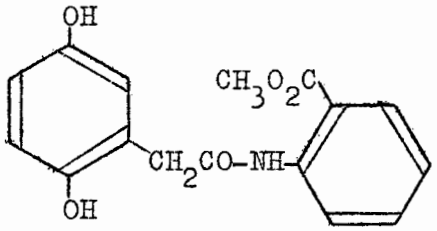
The acetate (CXXIII) was found to be insoluble in cold dilute sodium hydroxide but dissolved on heating the suspension. Addition of hydrochloric acid gave a yellow precipitate, supporting the presence of an acetyl and of a lactone group.

§ 3. Treatment of the acetate (CXXIII) with methyl anthranilate to form the amide.

The lactone of homogentisic acid, (XLIX) readily underwent nucleophilic attack by methyl anthranilate to form the amide (XLVIII),



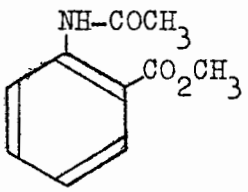
(XLIX)



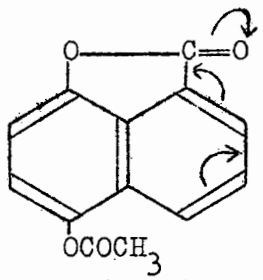
(XLVIII)

[Experimental, page 146, preparation (b)]. However, in the fusion of the acetate (CXXIII) with methyl anthranilate no amide formed. Trans-acetylation occurred as the lactone (CXXII) was obtained in 84.6%

yield and gas-liquid chromatographic analysis of the reaction mixture revealed the presence of methyl o-acetamidobenzoate (CXXIV). The resistance of the aromatic lactone to nucleophilic attack by methyl anthranilate was attributed to the decreased electrophilic reactivity of the carbonyl carbon atom owing to the electron flow shown in structure (CXXV) of the acetate (CXXIII).

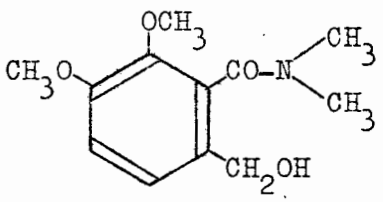


(CXXIV)

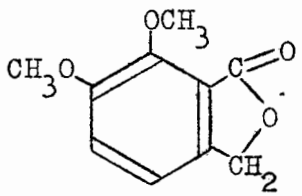


(CXXV)

In another reaction, the lactone ring was also found to be stable to ring-opening. Whereas Blair et al.[89] readily prepared the amide (CXXVI) from meconin (CXXVII) and dimethylamine, treatment



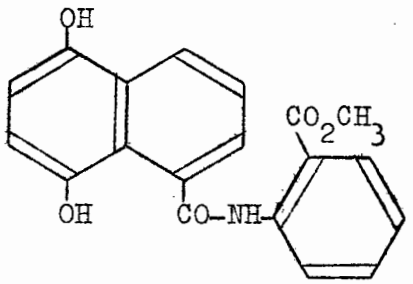
(CXXVI)



(CXXVII)

of the acetate (CXXIII) with methyl anthranilate using the same conditions did not give any opening of the lactone ring. The starting product was recovered almost quantitatively.

It was therefore necessary to open the lactone ring with strong alkali. The dihydroxy-acid which would be obtained could then be fused with methyl anthranilate to obtain the amide (CXXVIII). However, this was not attempted because of the results of the following investigation.

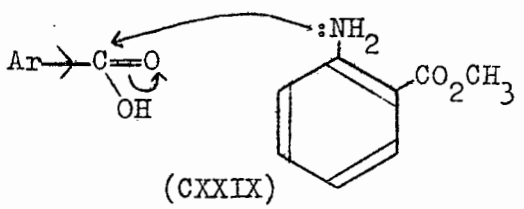


(CXXVIII)

Attempted fusion of several aromatic acids with methyl anthranilate.

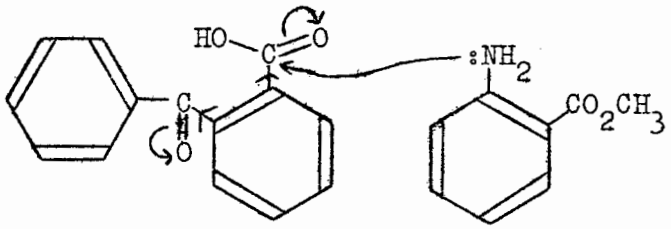
It was found that no amide formed on heating 5-nitro-1-naphthoic acid, 5-acetamido-1-naphthoic acid[90], 1-naphthoic acid, 2,5-dihydroxybenzoic acid (the preparation of which will be described in Section III), or benzoic acid with methyl anthranilate using the conditions of the successful fusion of homogentisic acid with methyl anthranilate described in Section I, [Experimental, page 145, preparation (a)]. In all the attempted fusions, the percentage recovery of the starting acid was between 72.5% and 98%. The fusions were shown to have been unsuccessful by mixed melting points of the products obtained with the starting acids or by a comparison of their infrared spectra.

As a result of the flow of electrons from the aromatic nucleus, the carboxyl group would resist the nucleophilic attack shown in structure (CXXIX), where Ar represents the 5-nitro-1-naphthyl, 5-acetamido-1-naphthyl, naphthyl, 2,5-dihydroxyphenyl, or phenyl groups. Lamchen and Abramowitz[6] successfully obtained several aromatic amides by fusion of o-benzoylbenzoic acid and its derivatives with methyl anthranilate, but far more vigorous conditions were used.



(CXXIX)

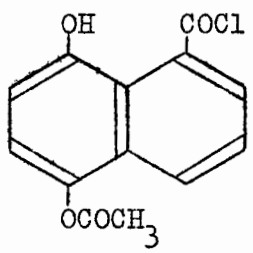
In addition, there is a second electron withdrawing group in o-benzoylbenzoic acid and the carboxyl group would be more susceptible to the nucleophilic attack shown in structure (CXXX).



(CXXX)

Formation of the acid chloride of the acetate (CXXIII).

As amides were not readily formed from aromatic acids, it was decided to form the amide from an acid chloride. The formation of the acid chloride (CXXXI) would not be possible owing to the

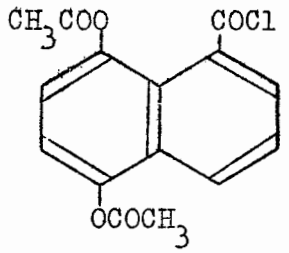


(CXXXI)

favourable position of the hydroxyl group for immediate lactone formation. A German patent[91] describes the formation of 3-hydroxy-2-naphthoyl chloride and its use in the synthesis of an amide. However, Rodionov et al.[92] investigated the stability of this acid chloride and proposed its slow transformation into an inner ester on standing. The formation of this highly strained β-lactone would certainly indicate formation of the γ-lactone from the acid chloride (CXXXI) if it could be formed.

Conversion of the lactone (CXXIII) to the acid chloride was therefore attempted with thionyl chloride in the presence of

acetyl chloride. This should acetylate the free hydroxyl group as it was formed, yielding the acid chloride (CXXXII). The excess of acetyl chloride and the excess of thionyl chloride were completely removed



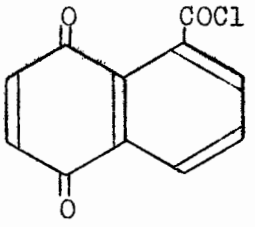
(CXXXII)

from the reaction mixture and methyl anthranilate was added to the yellow solid remaining without attempting to isolate the acid chloride. No heat was evolved, suggesting that no reaction had occurred and the starting lactone (CXXIII) was recovered in good yield.

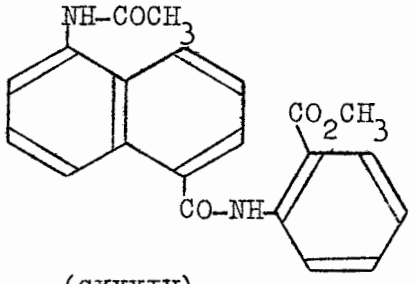
§ 4. Alternative approaches to the synthesis of the amide function.

Treatment of 1,4-naphthaquinon-5-ylcarboxylic acid (CXII) with thionyl chloride to form the acid chloride (CXXXIII) was undesirable due to the susceptibility of the quinone group to 1,4-addition.

The use of 5-acetamido-1-naphthoyl chloride would give the di-amide (CXXXIV) with methyl anthranilate. Before this di-amide

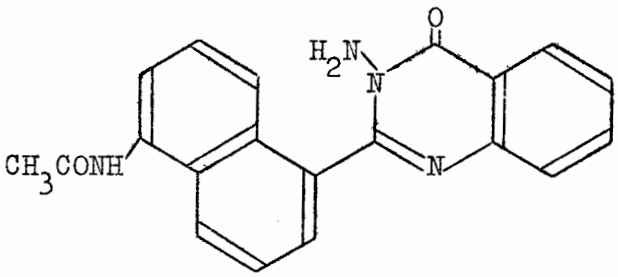


(CXXXIII)

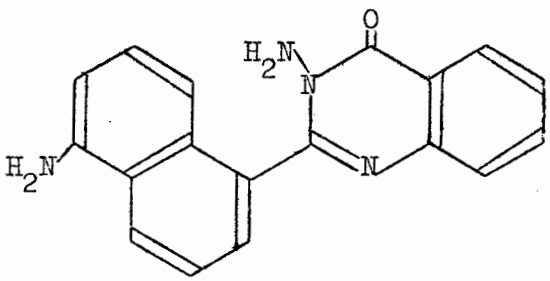


(CXXXIV)

could be oxidised to the quinone (CXIII), the N-acetyl group would have to be removed but hydrolysis would possibly break the other amide link as well. This difficulty could perhaps be avoided by converting the di-amide to the quinazolinone (CXXXV) with hydrazine, as hydrolysis of this quinazolinone might have removed the acetyl group without affecting the quinazolinone group. The quinazolinone (CXXXVI) which would be obtained on hydrolysis could then be submitted

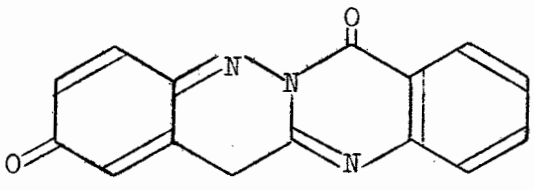


(CXXXV)



(CXXXVI)

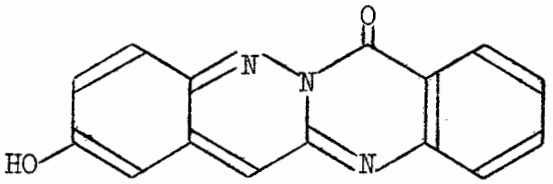
to oxidation to obtain the quinone (IX). However, the oxidation methods usually used, e.g. lead(IV) dioxide and dilute sulphuric acid[83] or a dichromate salt and sulphuric acid[63], being very vigorous, might affect the quinazolinone group. Moreover, if the quinazolinone group was unaffected by the oxidation, ring closure of the quinone to the polycyclic product (XI) could possibly occur. Great difficulty might have been encountered in isolating the polycyclic compound from the oxidation medium if a lead(IV) dioxide slurry were used. The quinazolino[3,2-b]cinnoline (XII) described in Section I was found to be insoluble in neutral organic solvents and very sparingly soluble in acidic solvents. Although the



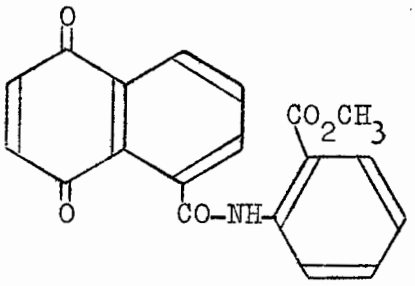
(XII)

quinazolino[3,2-b]cinnoline dissolved in dilute sodium hydroxide, this was attributed to its dissolution as the tautomer (LXIX), and no such hydroxy tautomer could form in the polycyclic structure (XI). In addition, lead dioxide would also be soluble in dilute sodium hydroxide, as sodium plumbate.

Because of the difficulties envisaged in the use of either the acid chloride (CXXXIII) or 5-acetamido-1-naphthoyl chloride for the synthesis of the amide group, it was decided to attempt the following synthesis of the amide (CXIII).

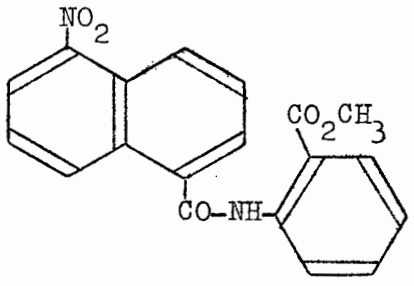


(LXIX)

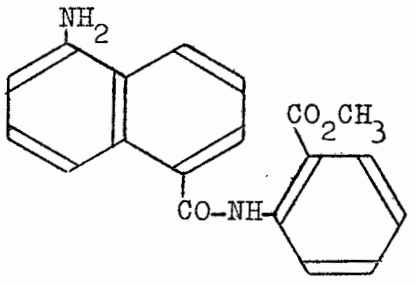


(CXIII)

As Blicke and Parke[93] have converted 5-nitro-1-naphthoic acid to the acid chloride, this acid chloride could be treated with methyl anthranilate to form the amide (CXXXVII). Reduction of the amide with stannous chloride in acetic acid, the method used by Blicke and Parke[93] on their nitro-esters, should give the amino-compound (CXXXVIII). Oxidation of the amino-compound should form the quinone (CXIII).



(CXXXVII)



(CXXXVIII)

Synthesis of the nitro-amide (CXXXVII).

Thionyl chloride treatment of 5-nitro-1-naphthoic acid yielded the acid chloride in good yield[93]. Its condensation with methyl anthranilate gave an excellent yield of a product, the analysis of which fitted the amide (CXXXVII). The infrared spectrum of the compound, in nujol, supported the structure assigned to this compound. Two bands would be expected in the carbonyl absorption frequency range in the infrared spectrum of the compound and two bands were indeed found, occurring at 1697 and 1683 $cm.^{-1}$. The interpretation of the infrared spectrum of the nitro-amide (CXXXVII) is summarised in Table 21 below.

Table 21.

		Nitro-amide (CXXXVII)
		$cm.^{-1}$
C=O stretching vibrations:	of the ester	1697
	of the amide	1683
Bonded N-H stretching frequency of the secondary amide		3230
Aromatic C=C in-plane stretching vibrations		1611, 1595, 1432
Amide II band		1539
C-NO_2 vibrations		1525, 1333
Amide III band		1300
C-O stretching vibrations of benzoates		1276
C-N stretching vibrations		1262

Synthesis of the amino-amide (CXXXVIII).

In the reduction of the nitro-amide with stannous chloride dihydrate in acetic acid, an insoluble tin salt addition product formed as fine white crystals which were insoluble in water. Addition

of dilute sodium hydroxide dissolved the tin salt and liberated the amine as a yellow solid, very sparingly soluble in the alkaline solution. The amine was therefore obtained by continuous ether extraction of a suspension of the tin salt addition product in dilute sodium hydroxide. Analysis of the product indicated the formation of the amino-amide (CXXXVIII). An infrared spectrum of the product, in nujol, supported such a structure. The interpretation of the infrared spectrum of the amino-amide is summarised in Table 22. The bands were

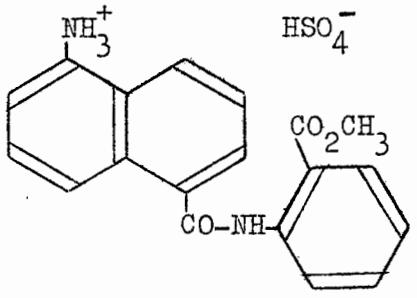
Table 22.

		Amino-amide (CXXXVIII)	Hydrochloride	Bisulphate (CXXXIX)
		cm.$^{-1}$	cm.$^{-1}$	cm.$^{-1}$
N-H stretching frequency of the amino group		3349, 3255	——	——
$-NH_3^+$ stretching and deformation vibrations		——	3285, 3269	3229
Asymmetric $-NH_3^+$ deformation vibrations		——	(?)	1569
Symmetric $-NH_3^+$ deformation vibrations		——	1322	1321
Bonded N-H stretching frequency of the secondary amide		3205	Obscured by other bands at ca. 3200 (?)	
C=O stretching vibrations	of the ester	1695	1691	1697
	of the amide	1669	1665sh.	1661
Aromatic C=C in-plane stretching vibrations		1609, 1589, 1518, 1454	1608, 1594, 1518, 1434	1611, 1590, 1520, 1421
Amide II band		1536	1541	1541
Amide III band		1300	1303	1292
C-O stretching vibration of the benzoate		1277	1287	1278
C-N stretching vibration		1260	1246	1257

assigned these vibrations after a study of the ranges[48,49] in which

the various groups absorb, in conjunction with a study of the infrared spectrum of the nitro-amide (CXXXVII) (Table 21, page 104). The bands at 1525 and 1333 cm.$^{-1}$ in the spectrum of the nitro-amide, assigned to the C-NO_2 vibrations, were absent in the spectrum of the amino-amide. However, two new bands occurred at 3349 and 3255 cm.$^{-1}$ in the spectrum of the amino-amide. These bands were assigned to the N-H stretching frequency of the amino group.

The amine readily formed salts with hydrochloric acid and with sulphuric acid. The analyses of the salts showed that they were the hydrochloride and the bisulphate (CXXXIX), respectively. The



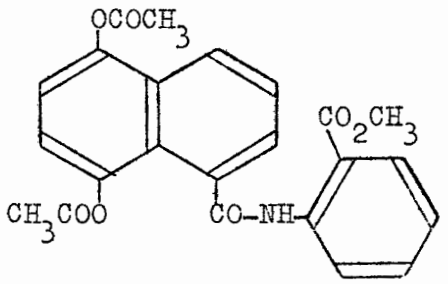
(CXXXIX)

interpretation of the infrared spectra of the hydrochloride and the bisulphate is included in Table 22 for comparison with the infrared spectrum of the amino-amide. It will be seen that the spectra of the salts resemble the spectrum of the amino-amide. Nevertheless, the various $-NH_3^+$ vibrations in the spectra of the hydrochloride and of the bisulphate, detailed in Table 22 were found to be absent in the spectrum of the amino-amide. Although an increase in the frequency of the amido carbonyl absorption was observed when the substituted quinazolinones discussed in Section I were converted to their hydrochlorides, [the quinazolinone (LVIII) (Table 3, page 31), the base (XII) (Table 5, page 38), and the base (XCVI) (Table 15, page 77)], no such increase was observed in the spectra of the amino-amide (CXXXVIII) and of its salts. However, the carbonyl group in the substituted quinazolinones is in a δ-lactam system whereas the carbonyl

group in the amino-amide (CXXXVIII) is in the amide function.

Oxidation of the amino-amide (CXXXVIII) to the quinone (CXIII).

When the ferric chloride oxidation in acid medium used by Smith and Denyes[94] on diaminodurene was applied to the amino-amide (CXXXVIII) the amine was not affected and was recovered as its hydrochloride. However, the use of dilute sulphuric acid and either lead(IV) dioxide or potassium dichromate as the oxidant yielded a dark red powder. Yellow crystals were isolated from this red powder by extraction with cyclohexane and analysis indicated that the quinone (CXIII) had formed. The quinone readily underwent reductive acetylation and the product obtained was assigned the diacetate structure (CXL). The infrared spectra of the quinone and the diacetate obtained from it supported the quinone structure (CXIII) and the diacetate structure (CXL) assigned to these two compounds. The interpretation of the bands in the spectra of the two compounds is



(CXL)

summarised in Table 23 below. The bands were assigned these vibrations after a study of the ranges[48,49] in which the various groups absorb, in conjunction with a study of the infrared spectra of the nitro-amide (CXXXVII) (Table 21, page 104), and the amino-amide (CXXXVIII) (Table 22, page 105). The band at 1672 cm.$^{-1}$ in the spectrum of the quinone, assigned to the C=O stretching vibration of the quinone group, was absent in the spectrum of the diacetate.

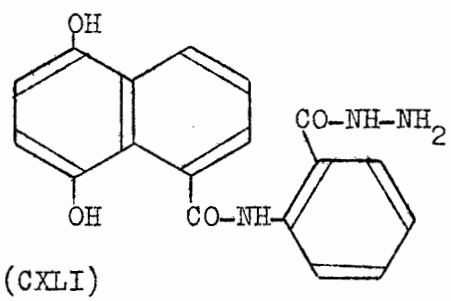
However, additional bands were present at 1780 (shoulder), and 1773 $cm.^{-1}$ in the spectrum of the diacetate and were assigned to the C=O stretching vibrations of the phenolic acetate groups.

Table 23.

		Quinone (CXIII)	Diacetate (CXL)
		$cm.^{-1}$	$cm.^{-1}$
Bonded N-H stretching frequency of the secondary amide		3312	3265
C=O stretching vibrations :	of phenolic esters	——	1780sh.,1773
	of the aryl ester	1720	1702
	of the amide	1688	1687
	of the quinone	1672	——
Aromatic C=C in-plane stretching vibrations		1613,1594, 1515	1608, 1592, 1516
Amide II band		1537	1532
Amide III band		1300	1298
C-O stretching vibration of the benzoate		1282	1285

§ 5. Formation of the quinazolinone (CXIV).

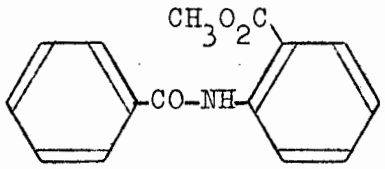
Treatment of the quinone (CXIII) with an excess of hydrazine should both reduce the quinone group and form the hydrazide group resulting in a compound containing the structure (CXLI). Ring-closure of this compound would be expected and the quinazolinone



(CXLI)

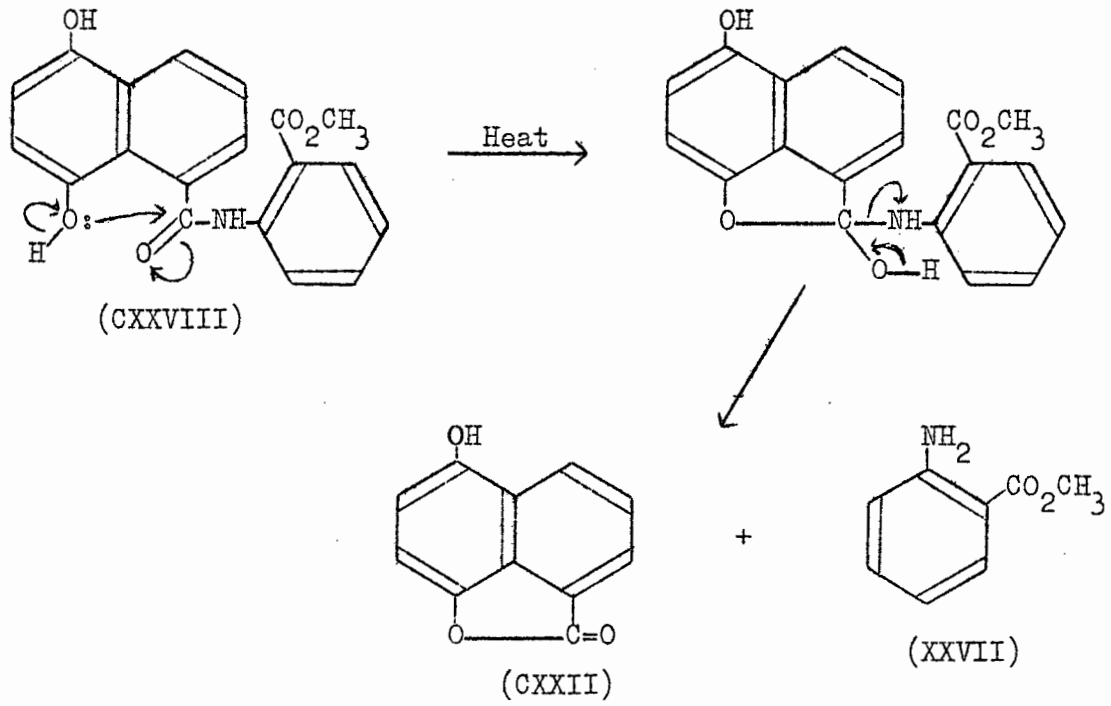
(CXIV) should result. However, when the treatment of the quinone with hydrazine was attempted, severe decomposition appeared to occur and a very low yield of yellow crystals was obtained. Combustion analyses gave no indication as to the identity of the product. The band at 1689 $cm.^{-1}$ in the infrared spectrum of the product was near the band at 1687 $cm.^{-1}$ in the spectrum of the quinazolinone (LVIII) (Table 3, page 31) and may have been due to the carbonyl absorption of the amide I band of a ring-fused δ-lactam, but there was no other evidence that the quinazolinone (CXIV) had formed.

It was therefore decided to reduce the quinone (CXIII) to the dihydroxy-amide (CXXVIII) first, and then to treat this compound with hydrazine to form the quinazolinone (CXIV), to obtain the quinazolinone in better yield and perhaps in purer form. Various quinones have been reduced to the corresponding dihydroxy compounds with zinc dust and acetic acid[95,96] and to determine whether such reduction would affect the ester group in the quinone (CXIII), a model compound, methyl o-benzamidobenzoate (CXLII), was treated with zinc dust and acetic acid under reflux. As the amide (CXLII) was



(CXLII)

recovered, unchanged, in good yield, the quinone was also treated with zinc and acetic acid under reflux. Reduction occurred but the lactone (CXXII) was obtained and no dihydroxy-amide (CXXVIII) was isolated. The dihydroxy-amide must have formed but, similar to the ready decomposition of the amide (XLVIII) to the lactone (XLIX) shown on page 24, the hydroxy group and the amido carbonyl group in the dihydroxy-amide (CXXVIII) would be favourably placed for the nucleophilic attack and attendant decomposition shown below:



The alternative approach to the synthesis of the quinazolinone (CXIV) could therefore not be continued.

No further investigation was performed on the product of the reaction of hydrazine with the quinone (CXIII). As the quinazolinone (CXIV) was not isolated, its oxidation to the quinone (IX) could not be achieved and the ring-closure of this quinone could not be examined.

DISCUSSION

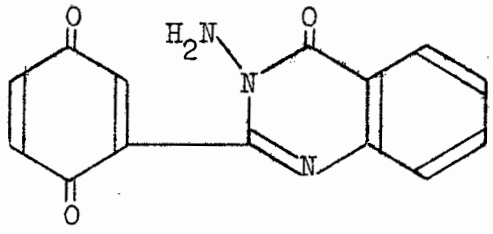
SECTION III

S E C T I O N III

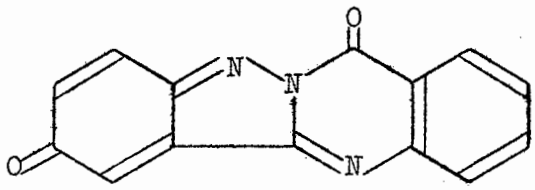
THE SYNTHESIS AND RING-CLOSURE OF 3-AMINO-2-(1,4-BENZOQUINONYL)QUINAZOLIN-4(3H)-ONE.

§ 1. Introduction.

If ring-closure occurred in the quinone (XIII) discussed in this Section, it could proceed by the nucleophilic attack encountered in Section I to give a compound of structure (XIV) or by

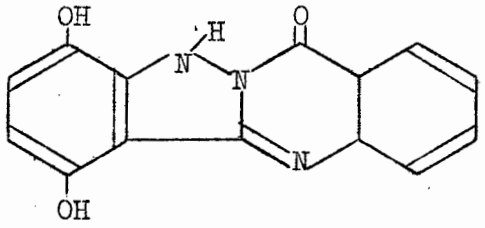


(XIII)

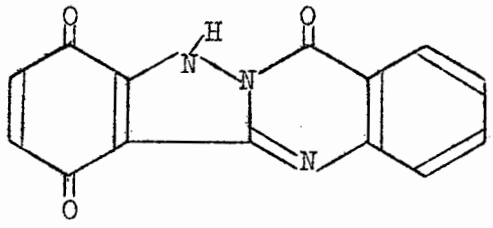


(XIV)

1,4-addition to yield the dihydroxy compound (XXV). An excess of oxidising agent could oxidise the dihydroxy compound to the quinone (CXLIII). It was considered to be of interest to determine whether this fused five-membered ring system would indeed form.

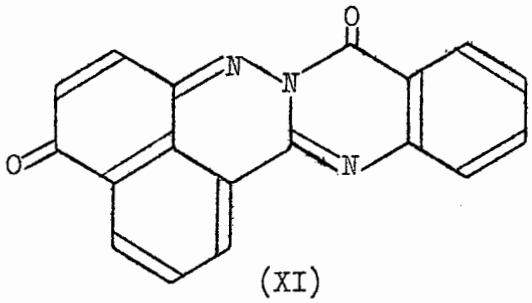


(XXV)

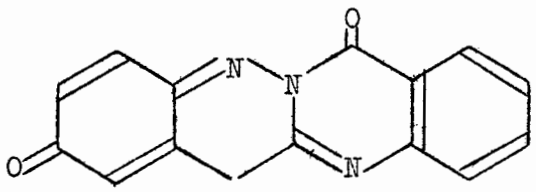


(CXLIII)

Because the compound (XI), which could possess no tautomeric structure had not been obtained, its properties could not be compared with those of the base (XII) where tautomeric structures were possible. However, if the highly conjugated compound (XIV) resulted from the oxidation of the quinone (XIII), again no tautomeric structure would be possible and it could be compared with the base (XII).

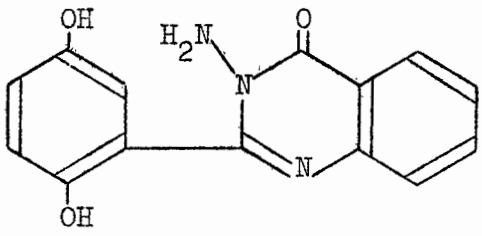


(XI)

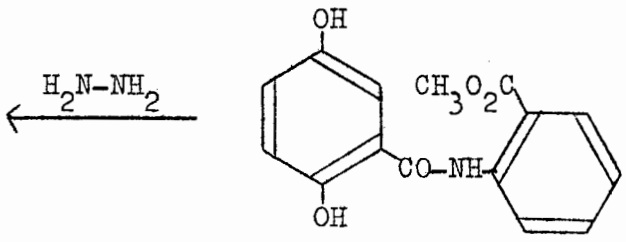


(XII)

The quinone (XIII) being investigated in this Section could best be synthesised by oxidation of the quinazolinone (CXLIV) obtained by the reaction of hydrazine on the amide (CXLV).



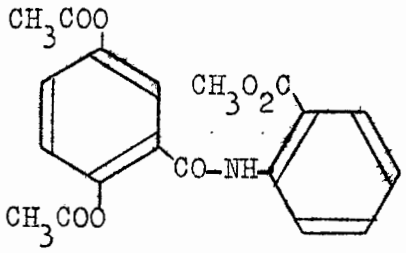
(CXLIV)



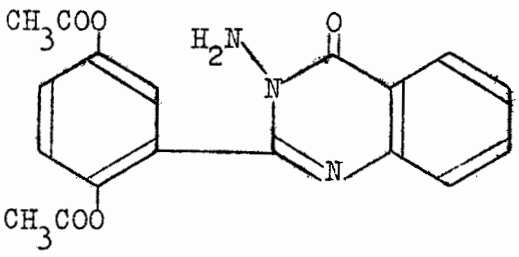
(CXLV)

§ 2. Proposed synthesis of 3-amino-2-(2,5-dihydroxyphenyl)quinazolin-4(3H)-one (CXLIV).

Owing to the difficulty encountered in the fusion of aromatic acids with methyl anthranilate to form amides (Section II, page 99), the amide function in structure (CXLV) would have to be synthesised from an acid chloride. To form the acid chloride of 2,5-dihydroxybenzoic acid, the hydroxyl groups would have to be protected. Hence 2,5-diacetoxybenzoyl chloride would have to be treated with methyl anthranilate to form the amide (CXLVI). Treatment of the amide with hydrazine should form the quinazolinone (CXLVII). Removal of the two acetyl groups from this compound by acid hydrolysis should yield the required quinazolinone (CXLIV).



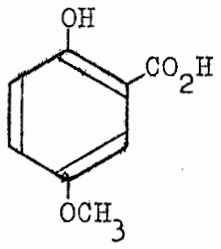
(CXLVI)



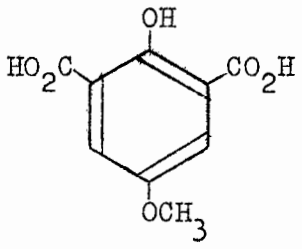
(CXLVII)

Synthesis of 2,5-diacetoxybenzoyl chloride.

2,5-Diacetoxybenzoyl chloride was readily obtained[97] from 2,5-diacetoxybenzoic acid which was synthesised[98] in good yield by acetylation of 2,5-dihydroxybenzoic acid. This acid was obtained by the synthesis of Villani and Lang[99] who demethylated 2-hydroxy-5-methoxybenzoic acid (CXLVIII) which they obtained by a Riemer-Tiemann reaction on 1-hydroxy-4-methoxybenzene. In repeating Villani and Lang's synthesis of 2-hydroxy-5-methoxybenzoic acid (CXLVIII), Shimizu and Maki[100] isolated an additional compound, 2-hydroxy-5-methoxyisophthalic acid, (CXLIX). In the present investigation, both



(CXLVIII)



(CXLIX)

the mono-carboxylic acid (CXLVIII) and the dicarboxylic acid (CXLIX) were isolated. 1-Hydroxy-4-methoxybenzene used in the synthesis of the carboxylic acids was obtained by the method of Robinson and Smith[101]. The purity of the hydroxymethoxybenzene was established by gas-liquid chromatography.

Synthesis of the dihydroxy-amide (CXLV) and its diacetate (CXLVI).

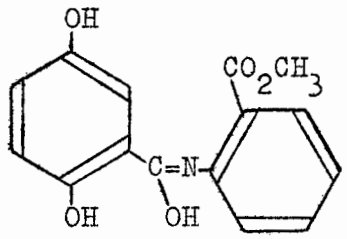
Kloetzel et al.[97] proceeded with their experiments without isolating the 2,5-diacetoxybenzoyl chloride from the reaction mixture. In the present investigation, the acid chloride was therefore dissolved in anhydrous benzene without purification, and methyl anthranilate was added to the solution. A very vigorous reaction ensued and an immediate white precipitate formed. Removal of benzene in vacuo yielded a solid residue consisting of the product and methyl anthranilate hydrochloride. Sodium carbonate solution was added to the solid residue to liberate methyl anthranilate from its hydrochloride. The oily solid obtained was filtered off from the suspension and washed with ethanol to remove the excess of methyl anthranilate. During the formation of the amide, or in its isolation from the reaction mixture, deacetylation must have occurred. The white crystals obtained were sparingly soluble in ethanol, indicating a dihydroxy compound, and its analysis suggested the dihydroxy-amide structure (CXLV). The infrared spectrum of the product, in nujol, supported such a structure.

The product assigned the dihydroxy-amide structure (CXLV) was treated with acetic anhydride and concentrated sulphuric acid as catalyst, the reagents used to acetylate hydroquinone[46]. A different compound was obtained and its analysis indicated the formation of the diacetate (CXLVI), the infrared spectrum of the compound supporting this structure. The formation of this diacetate confirmed that the compound obtained from the acid chloride and methyl anthranilate possessed the dihydroxy structure (CXLV).

Infrared spectroscopic data of the dihydroxy-amide (CXLV) and of its diacetate (CXLVI).

In the infrared spectrum of the dihydroxy-amide (CXLV), there were absorption maxima at 3380, 1762, and 1693 $cm.^{-1}$. These bands were in the ranges where intermolecularly hydrogen bonded O-H

stretching frequencies and carbonyl stretching vibrations are found[48]. The bands were therefore assigned to the O-H stretching frequency at 3380 cm.$^{-1}$ and to the C=O stretching vibrations of the ester and the secondary amide functions at 1762 and 1693 cm.$^{-1}$, respectively. The strong absorption at 1667 cm.$^{-1}$ in the infrared spectrum of the dihydroxy-amide (CXLV) could possibly be due to the C=N stretching vibration. This group would be present in the tautomeric structure (CL) of the amide (CXLV). This tautomer would be stabilised by the



(CL)

completely conjugated system it would produce. The absorption at 1693 cm.$^{-1}$, weaker than that usually found for the C=O absorption of amides supported this tautomeric structure. The interpretation of the infrared spectrum of the dihydroxy-amide (CXLV) is summarised in Table 24 below.

The band at 3380 cm.$^{-1}$, assigned to the O-H stretching frequency, intermolecularly hydrogen bonded, in the spectrum of the dihydroxy-amide (CXLV), was no longer present in the infrared spectrum of the diacetate (CXLVI). In addition to the two bands in the carbonyl absorption range in the infrared spectrum of the dihydroxy-amide (CXLV), two more bands occurred in the infrared spectrum of the diacetate. The four bands occurred at 1774, 1758, 1701, and 1678 cm.$^{-1}$. The assignment of these bands to the carbonyl absorptions shown in Table 24 was made after a study of the ranges where carbonyl absorptions of different carbonyl functions appear. In addition, the infrared spectrum of the diacetate (CXLVI) was compared with the infrared spectrum of the diacetate (L) (Table 2, page 25)

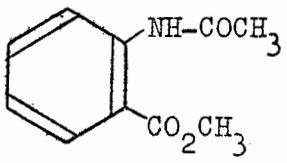
Table 24.

		Dihydroxy-amide (CXLV)	Diacetate (CXLVI)
		cm.$^{-1}$	cm.$^{-1}$
O-H stretching frequency intermolecularly hydrogen bonded		3380	——
N-H stretching frequency of the secondary amide		3259	3255
C=O stretching vibrations :	of phenolic esters	——	1774,1758
	of aryl ester	1762	1701
	of secondary amide	1693	1678
Aromatic C=C in-plane stretching vibrations		1612, 1598, 1497	1612,1589, 1533,1492
Amide II band		1554	1517
Amide III band		1308	1303
C-N stretching vibrations		1332	1323
C-O stretching vibration of the benzoate		1271	1271
C-O stretching vibrations of the phenolic acetates		——	1210,1203
C=N stretching vibration (?)		1667	—
C-H stretching vibrations of the C-CH_3 group		——	1458

where the carbonyl stretching vibrations occurred at 1764 (phenolic ester), 1705 (ester), and 1695 (amide) cm.$^{-1}$. The interpretation of the remaining bands in the infrared spectrum of the diacetate (CXLVI) is included in Table 24 above.

Mechanism of the formation of the dihydroxy-amide (CXLV).

In addition to isolating the dihydroxy-amide (CXLV) from the reaction mixture, both unreacted 2,5-diacetoxybenzoic acid and methyl o-acetamidobenzoate (CXXIV) were obtained. Although 2,5-diacetoxybenzoyl chloride was not isolated, it must have been

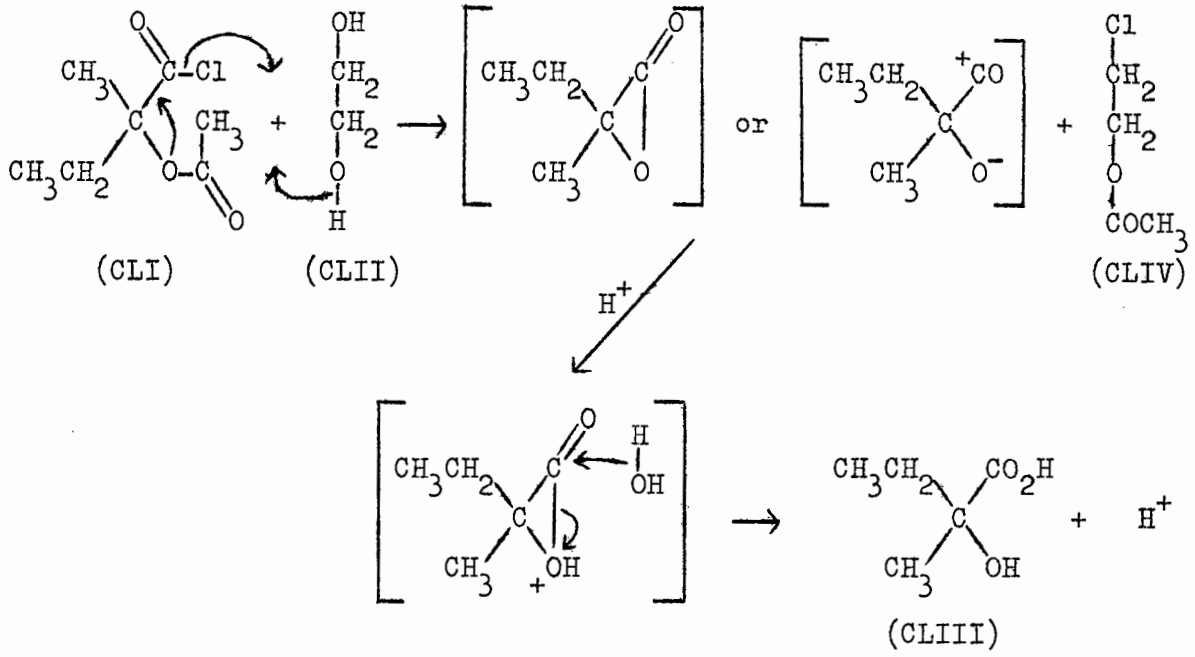


(CXXIV)

present when methyl anthranilate was added to the reaction mixture; if deacetylation had already occurred and 2,5-dihydroxybenzoyl chloride was the substrate, esters would have been obtained. However, no esters were isolated and, based on unrecovered 2,5-diacetoxybenzoic acid, the hydroxy-amide (CXLV) was obtained in excellent yield (97.7%). Hence the acetyl groups must have been present in the dihydroxybenzoyl chloride during the addition of methyl anthranilate. It is unlikely that the mild sodium carbonate solution treatment used in the isolation of the dihydroxy-amide (CXLV) caused hydrolysis of the acetyl groups. Indeed, when the diacetate (CXLVI) was triturated with cold aqueous sodium carbonate for 10 minutes, 90% of the diacetate was recovered on filtration of the suspension. In addition, unreacted diacetoxybenzoic acid and not the deacetylated dihydroxybenzoic acid was recovered from the reaction mixture. For the same reason, deacetylation by methyl anthranilate could also be discounted.

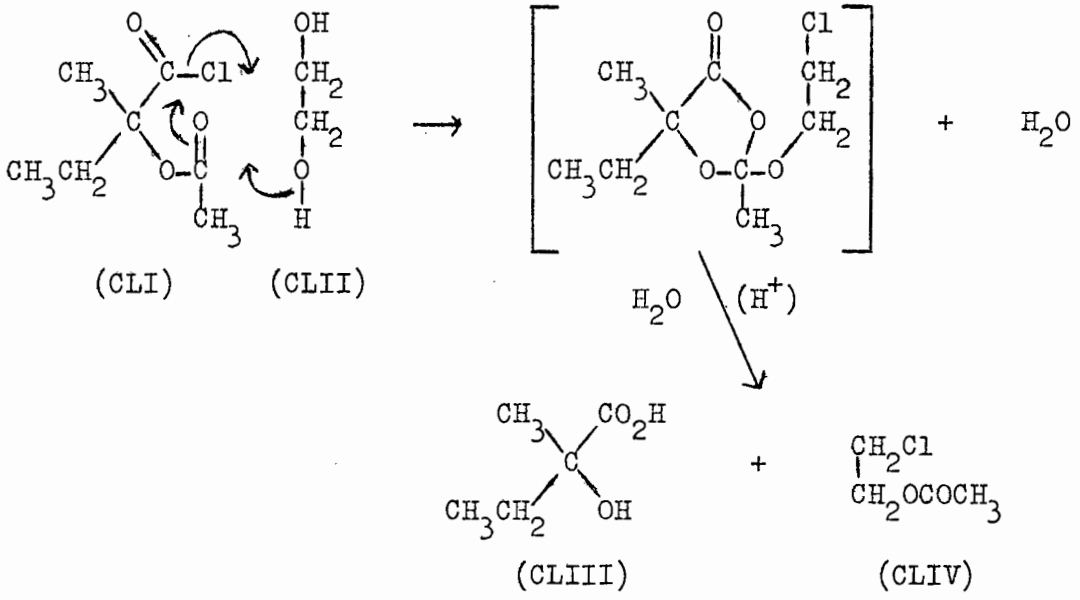
Mattocks[102] found that α-acetoxy-α-methyl-butyryl chloride (CLI) and ethylene glycol (CLII) reacted rapidly at room temperature to give α-hydroxy-α-methylbutyric acid (CLIII) (90%), and 2-chloroethyl acetate (CLIV) ($\lesssim$ 82%). On the basis of further experimental evidence, he proposed the two mechanisms outlined in Scheme 1 and Scheme 2 below, favouring the first.

It is therefore suggested that a similar reaction occurred in the formation of the dihydroxy-amide (CXLV) and methyl o-acetamidobenzoate (CXXIV) from 2,5-diacetoxybenzoyl chloride (CLV) and methyl anthranilate (XXVII) by the mechanism illustrated in Scheme 3 below, page 120.



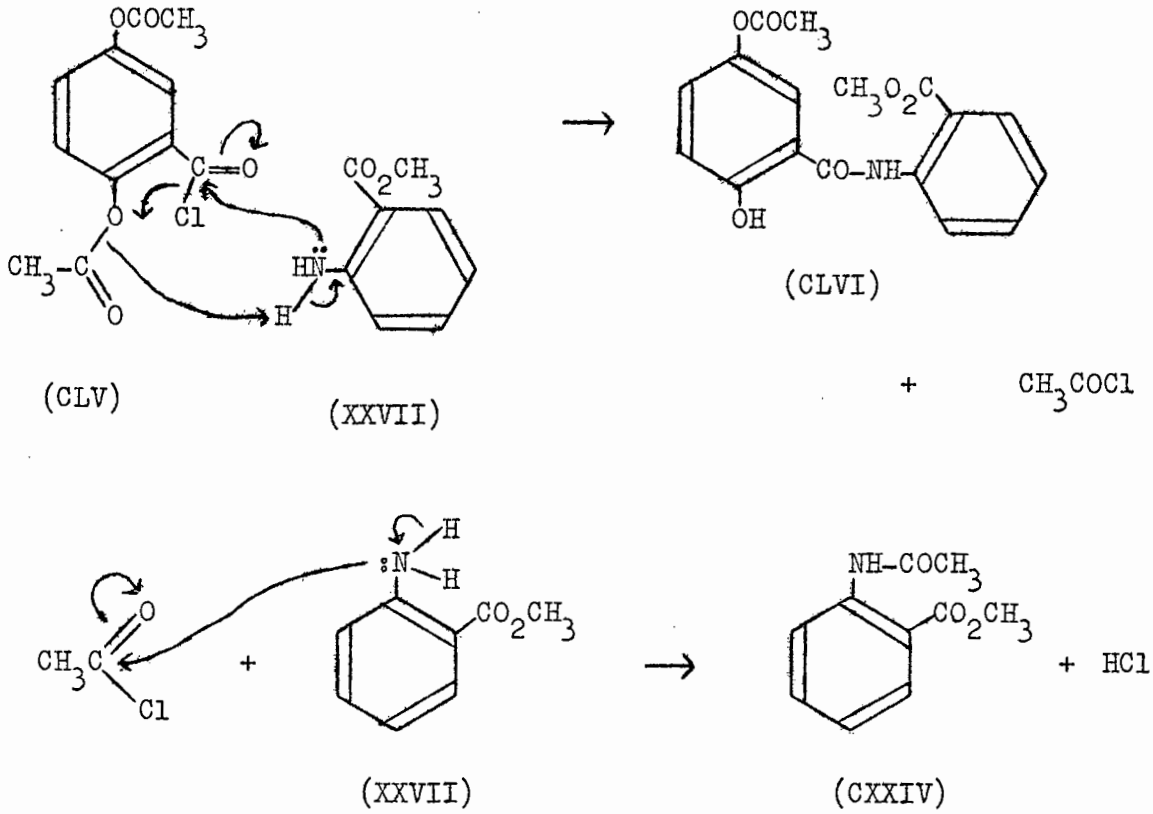
(CLI) (CLII) (CLIV) (CLIII)

Scheme 1.



(CLI) (CLII) (CLIII) (CLIV)

Scheme 2.



Scheme 3.

The mono-acetyl product (CLVI) would possibly have been deacetylated by the mild sodium carbonate conditions used when isolating the product of the reaction.

§ 3. Formation of the quinazolinone (CXLIV).

Heating a suspension of the amide (CXLV) in ethanol with hydrazine produced the expected quinazolinone (CXLIV) which readily formed a hydrochloride. The analyses and infrared spectra of the quinazolinone and its hydrochloride, in nujol, supported the structure (CXLIV) assigned to the quinazolinone. In the infrared spectrum of the quinazolinone, the only band in the carbonyl absorption frequency range was at 1653 $cm.^{-1}$. This absorption was at a lower frequency than the position reported[57] for the C=O stretching

vibration of the amide I band of cyclic amides larger than β- and γ-lactams which is situated at about 1680 cm.$^{-1}$. However, this band at 1653 cm.$^{-1}$ was assigned to the C=O stretching vibration of the

Table 25.

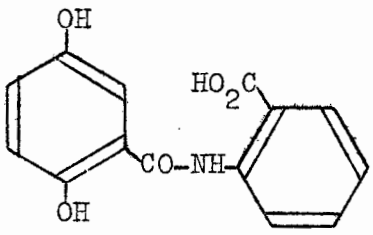
	Quinazolinone (CXLIV)	Hydrochloride
	cm.$^{-1}$	cm.$^{-1}$
N-H stretching frequency of the primary amine	3252	——
$-NH_3^+$ stretching and deformation frequencies	——	3300, 3235
Aromatic =C-H stretching frequency	3068	3060
O-H stretching frequency, intramolecularly hydrogen bonded	2600, (band)	2562sh., 2528
C=O stretching vibration of the amide I band of the ring-fused δ-lactam	1653	1723
C=N stretching vibration	1634	1635
Aromatic C=C in-plane stretching vibrations	1608, 1495	1594, 1533
Quinazoline I band	1612	-
Quinazoline II band	1580	1569
Quinazoline III band	1517	1517
C-N stretching vibration	-	1350
Combination of C-O stretching and O-H in-plane deformation vibrations	1344sh., 1340	1343
$-NH_3^+$ vibrations	——	1296
Amide III band	1272	1274

amide I band of the ring-fused δ-lactam. It was found in Section I that the carbonyl absorption of the δ-lactam in the infrared spectrum of the hydrochloride (LIX) was at a higher frequency than the frequency of the same absorption in the infrared spectrum of the quinazolinone (LVIII) (see Table 3, page 31). In the infrared spectrum of the hydrochloride of the quinazolinone (CXLIV), the C=O

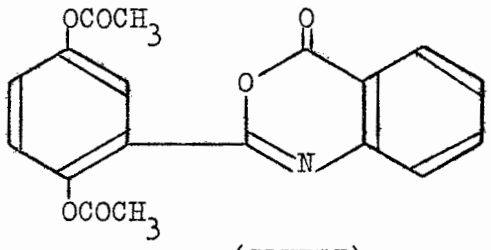
stretching vibration at 1723 cm.$^{-1}$ was again at a higher frequency. The band at 3252 cm.$^{-1}$ in the spectrum of the quinazolinone (CXLIV) was assigned to the N-H stretching frequency of the primary amine group. This band was replaced by the more complex bands at 3300 and 3235 cm.$^{-1}$ in the infrared spectrum of the hydrochloride. These bands were assigned to the $-NH_3^+$ stretching and deformation frequencies. The interpretation of the infrared spectra of the quinazolinone and its hydrochloride is shown in Table 25 above for comparison.

Hydrolysis of the quinazolinone (CXLIV).

In the formation of the hydrochloride of the quinazolinone (CXLIV) by recrystallising the quinazolinone from dilute hydrochloric acid, a yellow insoluble material was also obtained. Crystallisation from ethanol yielded pale yellow crystals. The same product could be obtained by treating the hydroxy-amide (CXLV) with dilute hydrochloric acid and analysis indicated that it was the acid (CLVII). Acetylation of this product with acetic anhydride and sulphuric acid produced the benzoxazinone (CLVIII).

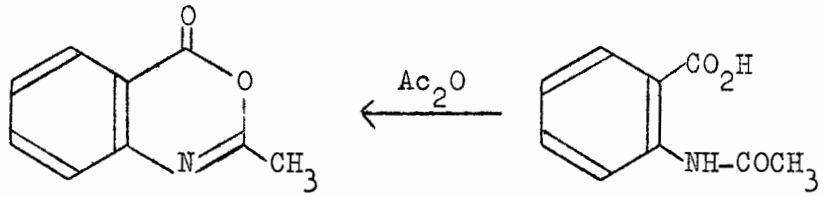


(CLVII)



(CLVIII)

The formation of substituted 3,1-benzoxazin-4-ones by the action of acetic anhydride on N-acetyl- and N-benzoylanthranilic acids has been shown by many workers[103,104,105,106]. This is illustrated by the formation[105,106] of 2-methyl-3,1-benzoxazin-4-one (CLIX) from N-acetyl-anthranilic acid (CLX):



(CLIX) (CLX)

The infrared spectra of the acid (CLVII) and the benzoxazinone (CLVIII) supported these structures assigned to the two compounds.

Infrared spectroscopic data of the acid (CLVII) and of the benzoxazinone (CLVIII).

Bands at 3375 and 3272 cm.$^{-1}$ in the spectrum of the acid were near the bands at 3380 and 3259 cm.$^{-1}$ in the spectrum of the dihydroxy-amide (CXLV) (Table 24, page 117) and were also assigned to the O-H and N-H stretching frequencies, respectively. The band at 1683 cm.$^{-1}$ in the spectrum of the acid was near the band at 1693 cm.$^{-1}$ in the spectrum of the dihydroxy-amide (CXLV) and was also assigned to the C=O stretching vibration of the secondary amide group. The shift of 10 cm.$^{-1}$ observed was attributed to hydrogen bonding of the amido carbonyl group with the O-H of the carboxylic acid group; the O-H stretching vibration of the carboxylic acid group at 2660 cm.$^{-1}$ in the spectrum of the acid (CLVII) was in the range where bonded O-H stretching vibrations occur. The band at 1762 cm.$^{-1}$ (C=O of aryl ester) in the spectrum of the dihydroxy-amide (CXLV) was replaced by the band at 1651 cm.$^{-1}$ in the spectrum of the acid (CLVII). As this band was in the range[48] where the C=O stretching vibration of aryl acids internally hydrogen bonded occur, the band was assigned to this vibration. The interpretation of the infrared spectrum of the acid (CLVII) is summarised in Table 26 below.

The infrared spectrum of the benzoxazinone (CLVIII) showed no bands in the region where O-H and N-H stretching

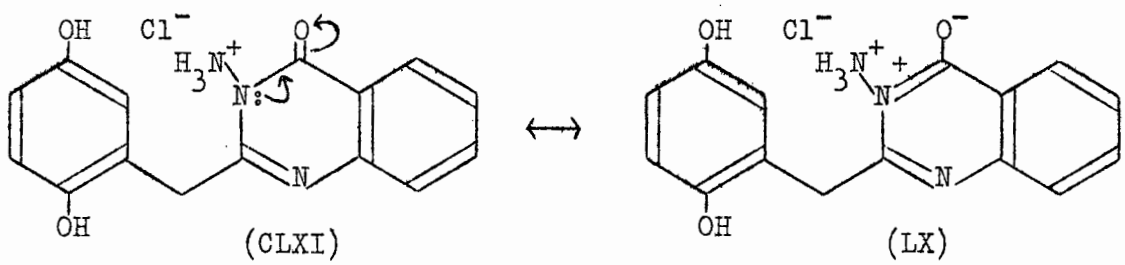
Table 26.

		Acid (CLVII)	Benzoxazinone (CLVIII)
		cm.$^{-1}$	cm.$^{-1}$
O-H stretching frequency, intermolecularly hydrogen bonded		3375	——
N-H stretching frequency of the secondary amide		3272	——
Bonded O-H stretching vibrations of the carboxylic acid		2660	——
C=O stretching vibrations :	of phenolic esters	——	1769, 1760sh.
	of α,β-unsaturated δ-lactone	——	1733
	of secondary amide	1683	——
	of aryl acid, internally hydrogen bonded	1651	——
Aromatic C=C in-plane stretching vibrations		1611, 1591, 1522, 1459	1618, 1608, 1499
C=N stretching vibration		-	1577
Amide II band		1549	——
=C-H stretching vibration		3081 sh.	3081

frequencies occur, and the C=O stretching vibrations of the secondary amide (at 1683 cm.$^{-1}$) and of the aryl acid (at 1651 cm.$^{-1}$) present in the spectrum of the acid (CLVII) were also absent in the spectrum of the benzoxazinone. However, there were three bands in the C=O absorption range. Two of these bands, at 1769 and 1760 (shoulder) cm.$^{-1}$, were near the bands at 1774 and 1758 cm.$^{-1}$ in the spectrum of the diacetate (CXLVI) and were also assigned to the C=O stretching vibrations of phenolic esters. The remaining band in the C=O absorption region, at 1733 cm.$^{-1}$, was in the range where C=O stretching vibrations of α,β-unsaturated δ-lactones absorb and was therefore assigned to this vibration. The interpretation of the infrared spectrum of the benzoxazinone is included in Table 26.

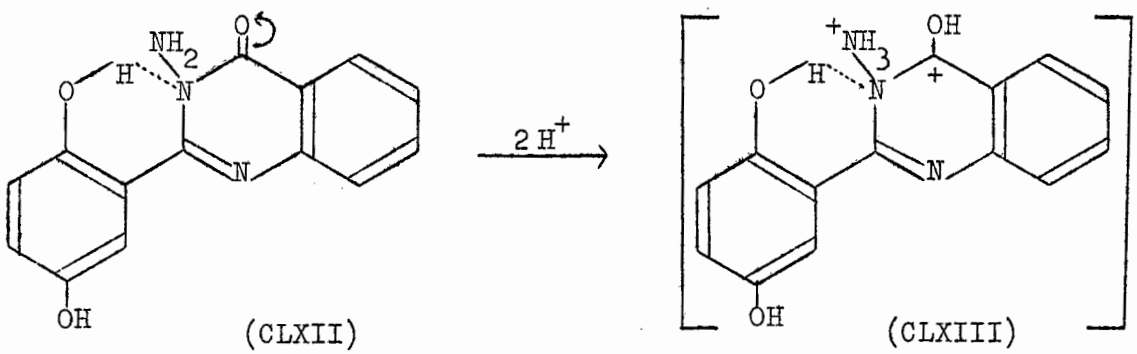
Mechanism of the hydrolysis of the quinazolinone (CXLIV).

The ready hydrolysis of the quinazolinone (CXLIV) in contrast to the stability of the quinazolinone (LVIII) may possibly be explained by hydrogen bonding in the former compound. In the acid solution the flow of electrons shown in structure (CLXI) of the quinazolinone (LVIII) may occur forming the stable canonical form (LX), (see page 29). However, if hydrogen bonding occurred in the



(CLXI) (LX)

quinazolinone (CXLIV) forming the six-membered ring shown in structure (CLXII), the flow of electrons shown in this structure in the acid medium would produce the structure (CLXIII) which would be

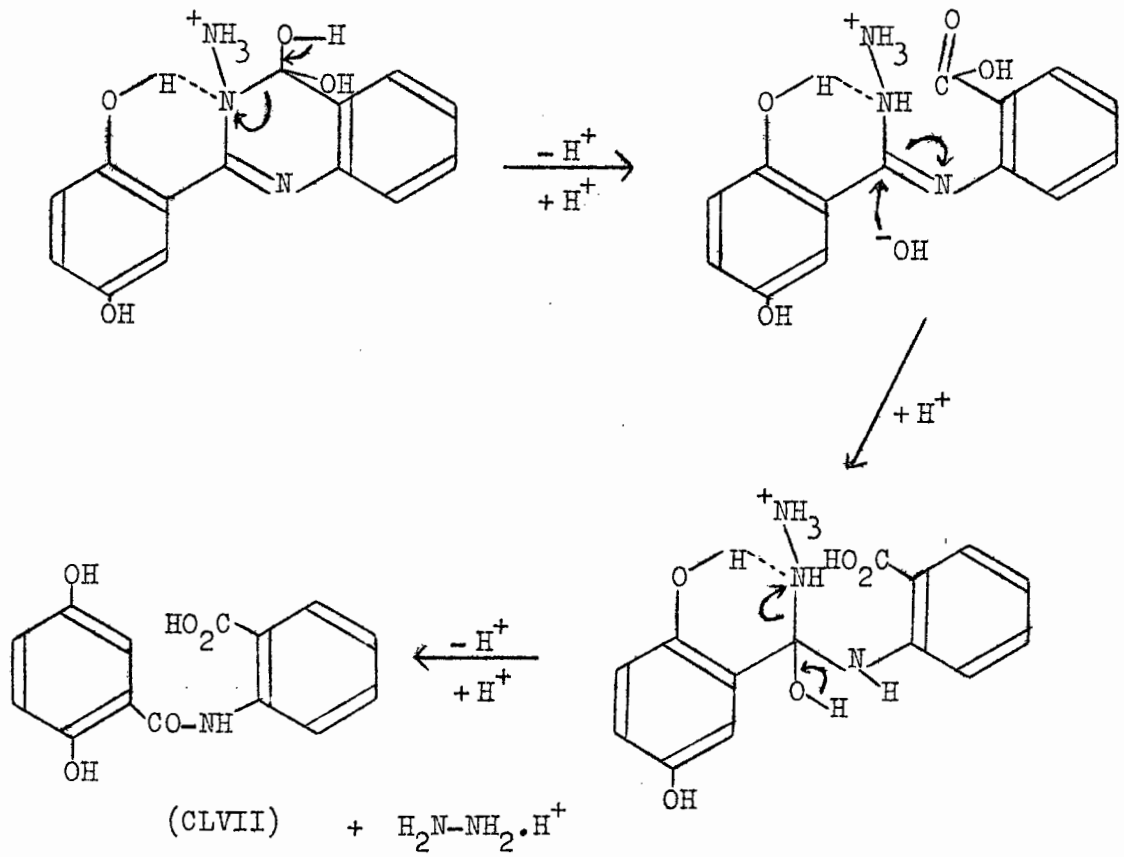


(CLXII) (CLXIII)

readily attacked by a nucleophile, e.g. an hydroxyl ion, with the attendant hydrolysis of the usually stable quinazolinone system shown in Scheme 4 below.

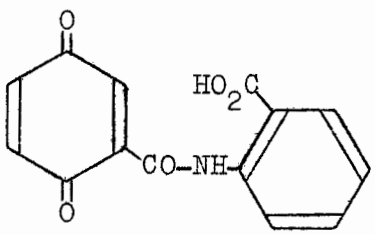
Treatment of the quinazolinone (CXLIV) with dilute sodium hydroxide.

Hydrolysis occurred when the quinazolinone (CXLIV) was treated with dilute sodium hydroxide at room temperature or heated under reflux, the acid (CLVII) again being obtained. The ready



Scheme 4.

hydrolysis of the quinazolinone in the alkaline solution could again possibly be attributed to the hydrogen bonding described above. The isolation of the acid (CLVII) instead of the quinone-acid (CLXIV)



(CLXIV)

from the alkaline medium may be due to the presence of the hydrazine which would also be formed on hydrolysis of the quinazolinone.

Sodium sulphite inhibits the autoxidation of hydroquinone in alkaline solution[26,107] and hydrazine may do the same, especially as hydrazine reduces quinones to the corresponding hydroquinones[17].

The quinazolinone (CXLIV) was therefore not oxidised to the quinone (XIII) in the alkaline medium but was hydrolysed to the acid (CLVII).

Visible and ultraviolet absorption spectra of the quinazolinone (CXLIV).

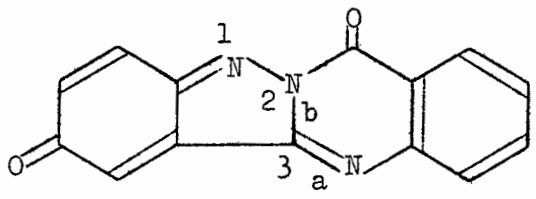
The visible and ultraviolet absorption spectra of the quinazolinone were measured for the solutions of the compound in ethanol and dilute hydrochloric acid. The individual bands due to the substituted quinazolinone group[67,68,69], and the bands due to the hydroquinone group[70] could not be determined because these two groups are conjugated in the quinazolinone (CXLIV). The absorption spectra were also measured for a solution of the quinazolinone in dilute sodium hydroxide. However, these spectra may be the absorption spectra of the sodium salt of the acid (CLVII) and not of the quinazolinone (CXLIV) owing to the ready hydrolysis of the quinazolinone in dilute sodium hydroxide at room temperature. The spectra for the acid were not measured to confirm this.

§ 4. Oxidation of the quinazolinone (CXLIV).

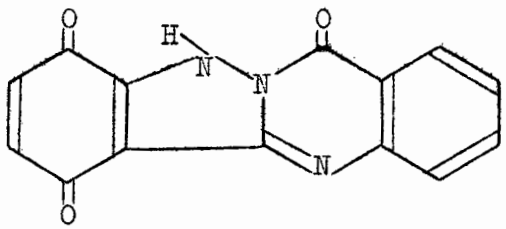
The quinazolinone was oxidised with ferric chloride and with hydrogen peroxide.

In the ferric chloride oxidation in ethanol and hydrochloric acid, a dark brown product, Compound A, containing no chlorine either in the compound or in ionic form, was obtained. Although it could not be recrystallised single spots were obtained in TLC chromatograms in the solvent systems attempted, but the combustion analyses were inconclusive and as a result the structure

of A could not be established. Although the quinazolinone was unstable to acid (and alkali), the high nitrogen content of A shown by analysis indicated that the quinazolinone system had not been affected and the quinazolinone (CXLIV) had probably been oxidised to the quinone (XIII). Subsequent ring-closure had possibly occurred but whether this yielded the indazolo[3,2-b]quinazolinone (XIV) or the dihydroxy compound (XXV), by 1,4-addition, with subsequent oxidation of this to the quinone (CXLIII) could not be ascertained.



(XIV)



(CXLIII)

The infrared spectrum of the product in nujol indicated that ring-closure had possibly occurred, the band at 1730 $cm.^{-1}$ possibly arising from the C=O stretching vibration of the δ-lactam system fused to two rings. This vibration was at 1718 $cm.^{-1}$ in the infrared spectrum of the base (XII) and the increase of 12 $cm.^{-1}$ observed could be due to extra strain imposed on the δ-lactam system by the five-membered ring present in Compound A. However, whether A possessed structure (XIV) or the quinone structure (CXLIII) could not be deduced from the spectrum. The bands in the spectrum could be assigned to vibrations of the groups in either structure as is shown in Table 27 below. The identity of Compound A is therefore not known.

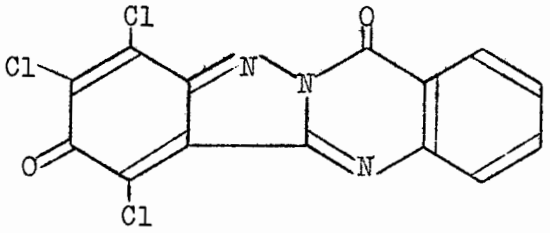
Hydrogen peroxide oxidation.

When the hydrogen peroxide oxidation of the quinazolinone was performed in ethanol and hydrochloric acid a low yield of yellow-brown material was obtained. Because crystallisation from

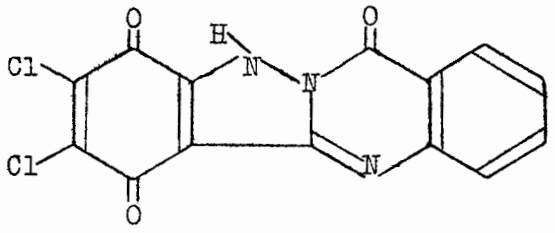
Table 27.

Compound A		
Indazolo[3,2-b]quinazolinone (XIV) (?)	Quinone (CXLIII) (?)	$cm.^{-1}$
C=O absorption of the ring-fused δ-lactam		1730
?	C=O absorption of the quinone (high)	1682
C=O absorption of the α,β-α',β'-unsaturated ketone	C=O absorption of the quinone	1669
C=N stretching vibrations		1635
Aromatic C=C in-plane stretching vibrations		1577, 1516

acetic acid containing hydrogen peroxide and hydrochloric acid produced yellow crystals, the oxidation was performed in acetic acid and concentrated hydrochloric acid and a better yield of yellow crystals, Compound B, was obtained. Compound B was found to be pure by TLC in the solvent systems attempted but was very sensitive to light. Combustion analyses were again inconclusive and no structure could be proposed for Compound B. B contained chlorine atoms and the high nitrogen content shown by the analysis indicated that the quinazolinone group had not been affected (at least not completely) by the acetic acid - hydrochloric acid used in the oxidation. As Compound B could also be obtained from Compound A by oxidation with hydrogen peroxide in acetic acid - hydrochloric acid, the two compounds probably possessed the same basic structure, Compound B containing chlorine atoms by 1,4-addition of hydrogen chloride (and subsequent oxidation). It is therefore possible that Compound B may possess the trichloro structure (CLXV) or the quinone structure (CLXVI). A molecular weight determination[108] indicated the former; the visible and ultraviolet absorption spectra were inconclusive, both structures being highly conjugated, and the solubility properties of Compound B confused the issue. Compound B was soluble in dilute sodium hydroxide



(CLXV)



(CLXVI)

with effervescence and in dilute sodium bicarbonate without effervescence, but insoluble in water and dilute hydrochloric acid.

The infrared spectrum of Compound B in nujol again indicated ring-closure, the band at 1715 cm.$^{-1}$ possibly arising from the C=O stretching vibration of the ring-fused δ-lactam system. However, the band at 1701 cm.$^{-1}$ in the spectrum of the trichloro compound (LXXXVI) assigned to the C=O stretching vibration of the α,β-α',β'-unsaturated ketone, was either obscured by the strong absorption at 1715 cm.$^{-1}$ or absent in the spectrum of Compound B. Bands at 1638 and 1605 cm.$^{-1}$ in the infrared spectrum of Compound B could be assigned to C=N and aromatic C=C in-plane stretching vibrations, respectively. However, the band at 1654 cm.$^{-1}$ was at too low a frequency for the C=O absorption of halogen-substituted α,β-α',β'-unsaturated ketones or the C=O absorption of halogen-substituted quinones.

To help elucidate its structure, Compound B was submitted to reductive acetylation, forming Compound C (which was also light sensitive), and to reduction with zinc and hydrochloric acid, forming Compound D. These two compounds were again shown to be pure by TLC in the solvents attempted but combustion analyses were again inconclusive, and their infrared spectra ambiguous. The structures of Compound C and Compound D were therefore not established and hence gave no indication of the constitution of Compound B from which they were derived. As had occurred with the trichloro compound (LXXXVI), the reductive acetylation and reduction appeared to have removed chlorine atom(s) from Compound B.

§ 5. Summary.

The structures of the oxidation products of the quinazolinone (CXLIV), Compound A and Compound B, and of the products obtained from the latter, viz. Compound C and Compound D were not established at the time of writing this thesis. The ring-closure and method of ring-closure of the quinone (XIII) were therefore not determined.

EXPERIMENTAL

SECTION I

EXPERIMENTAL

Notes:

Ultraviolet and visible absorption spectra were measured with a Beckman DB recording spectrophotometer, and the infrared data were obtained on a Unicam S.P. 100 infrared spectrophotometer. Some of the infrared spectra (those marked "†") were obtained on a Perkin-Elmer 237 Grating infrared spectrophotometer.

The visible and ultraviolet absorption spectra were measured for solutions of the various compounds in 0.0039N-sodium hydroxide. Except where otherwise detailed, the hydrochloric acid solutions of the compounds were made by taking aliquots (15 ml.) of these sodium hydroxide solutions and adding 0.26N-hydrochloric acid (10 ml.). Any necessary dilutions of the acid solutions were made with water.

In the data from the infrared spectra of the various compounds in nujol, no mention has been made of the bands due to the solvent (nujol) in the regions of 1468, and 1384 $cm.^{-1}$, or of the bands in the fingerprint area.

The Spectra reproduced on pages 50 - 53 were obtained on a Perkin-Elmer 237 Grating infrared spectrophotometer but the values of $\nu_{max.}$ were obtained on a Unicam S.P. 100 infrared spectrophotometer.

Abreviations used in the spectroscopic data were:

(sh.) = shoulder; v.s. = very strong intensity;
s. = strong intensity; m. = medium intensity;
w. = weak intensity; v.w. = very weak intensity.

All melting points are uncorrected.

Paper chromatograms were run on Whatman no. 1 paper in the four solvent systems:

n-Butanol : acetic acid : water, 4 : 1 : 5 (System 1),

n-Butanol : hydrochloric acid : water, 5 : 1 : 4 (System 2),

n-Butanol : ammonia : water, 5 : 4 : 1 (System 3),

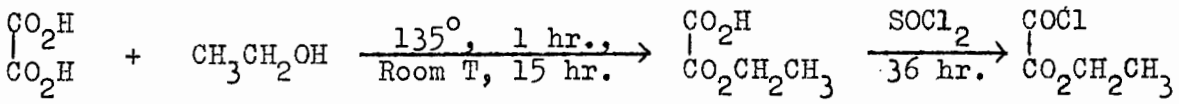
and n-Butanol : pyridine : water, 5 : 3 : 2 (System 4).

Where the spots obtained were elongated, R_F, was measured, which was the R_F of the leading edge of a spot, instead of the usual centre of the spot.

Silica gel G according to Stahl* was used for the thin-layer chromatography plates.

Preparation of mono-ethyl oxalyl chloride (XXXII).

The method of Diels and Nawiasky[32] was used.



(XXXII)

Percentage yield mono-ethyl oxalate: 17.1%, b.p. 118-122°/23 mm. (Diels and Nawiasky obtained 16.8%, b.p. 109°/11-12 mm.).

Percentage yield mono-ethyl oxalate based on unrecovered oxalic acid was 53%.

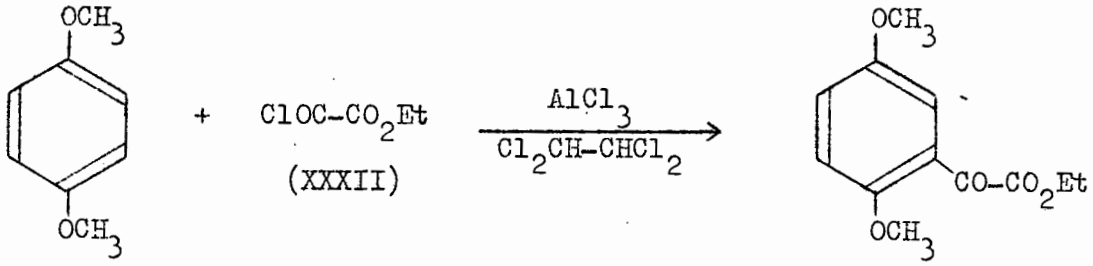
Percentage yield mono-ethyl oxalyl chloride (XXXII), b.p. 130-135°/760 mm., was 76%. (Diels and Nawiasky obtained 78%, b.p. 133-135°/760 mm.).

---

* A product of E. Merck, Darmstadt, Germany.

Preparation of 2,5-dimethoxyphenylglyoxylic acid, ethyl ester (XXXIV).

A method based on that of Kauffmann and Grombach[33] was used.



(XXXIII) (XXXIV)

Anhydrous aluminium chloride (12 g.) was added (0.5 hr.) to a cooled suspension of p-dimethoxybenzene (12 g.) and ethyl oxalyl chloride (10 g.) in tetrachloroethane (10 ml.). The solution turned dark purple with strong evolution of hydrogen chloride. The solution was maintained at room temperature (4 hr.), at 40° (1.5 hr.) and again at room temperature (14 hr.). Evolution of hydrogen chloride ceased and the aluminium chloride complex was decomposed with ice. Unreacted p-dimethoxybenzene and tetrachloroethane were removed by steam distillation. A red-black gum and a yellow-brown aqueous layer were obtained. Ether extraction of the aqueous layer yielded no product. The gum was extracted into ether (900 ml.) leaving a brown powder. The ethereal solution was washed with 0.5N-sodium hydroxide (3 x 50 ml.) and with water (3 x 50 ml.), and dried (Na_2SO_4). Removal of the ether yielded a black-red gum. Distillation, b.p. 120°/22 mm., and recrystallisation (petroleum ether, b.p. 100 - 120°) yielded the ester (XXXIV) (0.26 g.), m.p. 36 - 38°.

The brown powder obtained after ether extraction of the gum, was extracted into petroleum ether (b.p. 100 - 120°). Removal of the solvent yielded a yellow oil which crystallised from petroleum ether as orange crystals (1.9 g.), m.p. 35 - 38°. The products (0.26 g. and 1.9 g.) were combined and crystallised from petroleum ether as

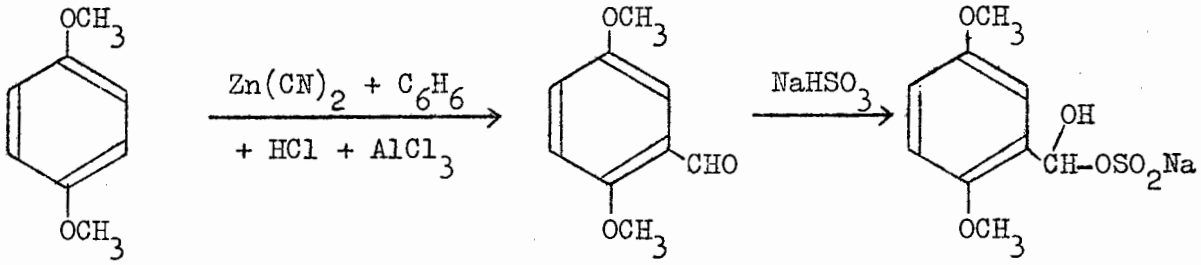
yellow needles of the ester (XXXIV) (1.22 g., 9%), m.p. 37 - 39°. (Kauffmann and Grombach reported a melting point of 38° and gave no quantity for the yield they obtained).

Preparation of zinc cyanide[38].

$$ZnCl_2 + 2\,NaCN \xrightarrow{H_2O} Zn(CN)_2 + 2\,NaCl$$

Zinc cyanide was obtained in 66% yield. Adams and Levine[38] reported no weight or percentage yield.

Preparation of 2,5-dimethoxybenzaldehyde (XXXVII)[36], and preparation of the sodium bisulphite addition compound (XXXVIII)[36,39].



(XXXIII) (XXXVII) (XXXVIII)

Three modifications to the method of Gulland and Virden[36] were used.

(a) The stirred reaction mixture was saturated with hydrogen chloride for 7.5 hr. and not for 24 hr. as Gulland and Virden had done. In addition, instead of adding the aluminium chloride immediately, as was done by Gulland and Virden, the reaction was first left overnight.

(b) On standing, the steam distillate deposited white needles of the aldehyde. The crystals were filtered off from the

suspension and then the additional aldehyde, which was dissolved in the steam distillate, was extracted into ether. Gulland and Virden mentioned no crystalline deposit of the aldehyde.

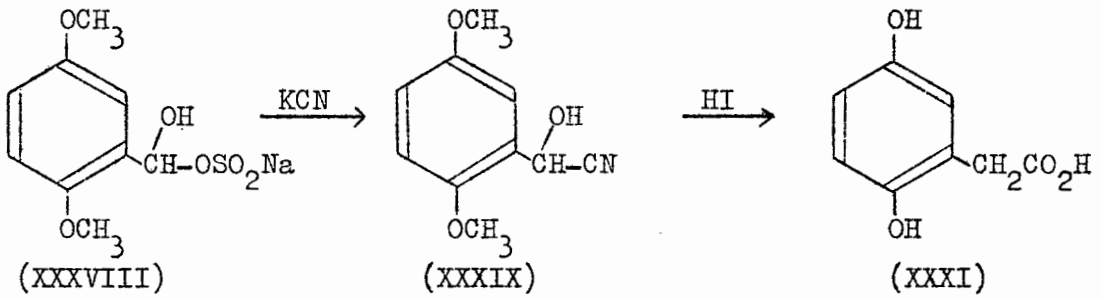
(c) As the bisulphite addition compound was required, the aldehyde was not liberated from the addition compound as Gulland and Virden had done.

These modifications yielded the aldehyde (XXXVII) (5.92 g.), m.p. 47 - 49°, and the sodium bisulphite addition compound (XXXVIII) (8.89 g. equivalent to 5.44 g. of the aldehyde). (Tiemann and Müller[109] report a melting point of 51° for the aldehyde). This amounted to a total yield of 38% of the aldehyde. Saturation of the reaction mixture with hydrogen chloride for 24 hr. (over 3 days) did not improve the yield.

Gulland and Virden obtained the aldehyde in 70% yield.

Attempted preparation of 2,5-dimethoxymandelonitrile (XXXIX) and its reduction with hydriodic acid to 2,5-dihydroxyphenylacetic acid (XXXI).

The method was based on the preparation of o-hydroxyphenylacetic acid by Czaplicki et al.[37].



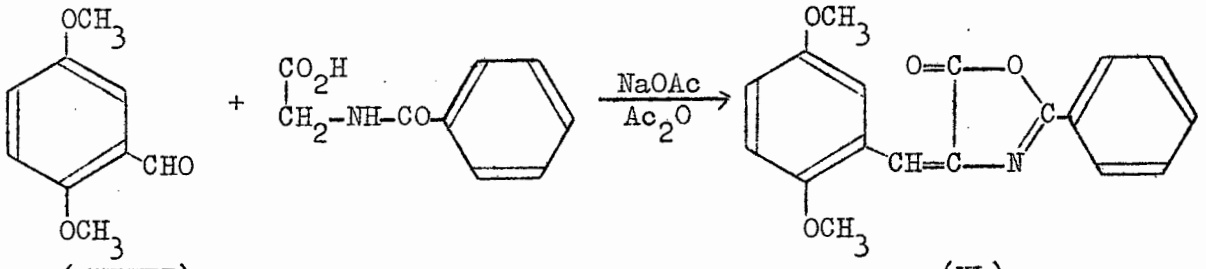
(XXXVIII) (XXXIX) (XXXI)

2,5-Dimethoxybenzaldehyde sodium bisulphite addition compound (XXXVIII) (4.44 g.) was added to a saturated aqueous solution of potassium cyanide (2.23 g.) and the solution stirred for 2.3 hr. A yellow oil which turned deep orange on standing immediately separated from the solution. The solution was extracted with ether

and the ether solution dried (Na_2SO_4). Removal of the solvent yielded a red oil (2.95 g., 93%).

No attempt was made to isolate 2,5-dimethoxymandelonitrile (XXXIX) from this oil. Hydriodic acid (33.5 g., 70%, d = 1.96 g./ml.) was added to the red oil (2.95 g.) and the solution was heated under reflux for 1.5 hr. 5N-Sodium hydroxide was added to the solution to neutralise the hydriodic acid. After ether extraction (3 x 50 ml.) to remove unchanged aldehyde, the sodium hydroxide solution was acidified and again extracted with ether (5 x 100 ml.). Removal of the solvent yielded no homogentisic acid, although the sodium hydroxide solution was dark black before acidifying with hydrochloric acid. The acidified solution was yellow.

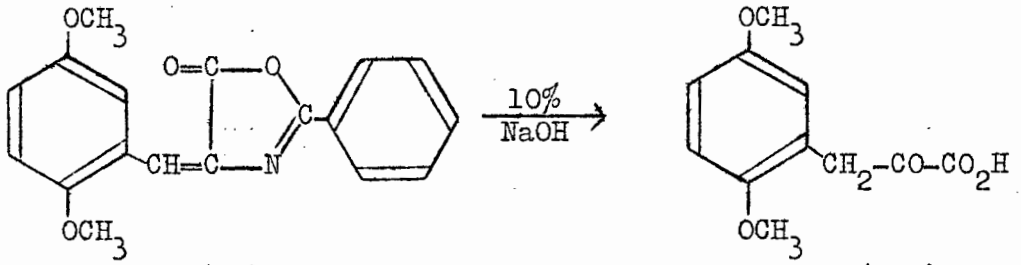
Preparation of 5-keto-2-phenyl-4-(2,5-dimethoxybenzylidine)-5(4H)-oxazole, (azlactone), (XL)[36].



(XXXVII) (XL)

The azlactone (XL), m.p. 170-171° was obtained. Gulland and Virden[36] quoted a melting point of 170-172°.

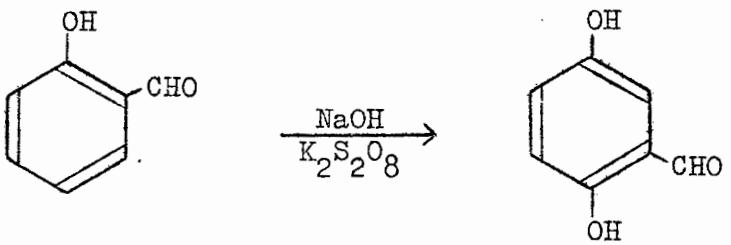
Preparation of 2,5-dimethoxyphenylpyruvic acid (XLI)[36].



(XL) (XLI)

2,5-Dimethoxyphenylpyruvic acid (XLI), m.p. 164 - 168° (decomp.) was obtained in a yield of 10.6%. Gulland and Virden obtained 76%, m.p. 166 - 170° (decomp.).

Preparation of 2,5-dihydroxybenzaldehyde (XLII)[42].



(XLII).

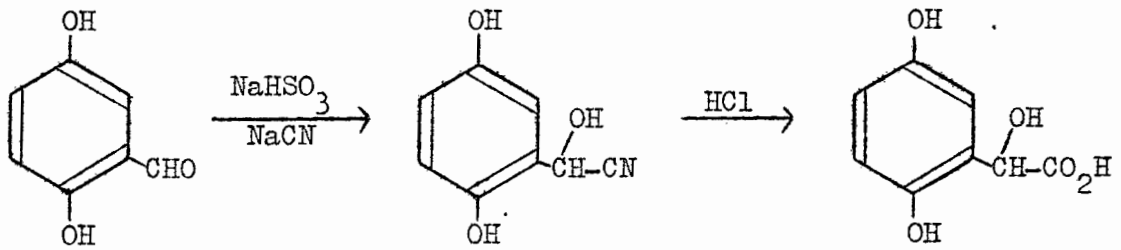
The method of Baker and Brown[42] was used. However, four ether extractions were performed to remove unreacted salicylaldehyde (35%), and not just two extractions as done by Baker and Brown. Removal of ether from the ethereal solution of the product yielded a black gum. Extraction of the gum with hot benzene yielded yellow crystals (24.2%), m.p. 94 - 96°. (Baker and Brown isolated the aldehyde from the gum by distillation).

Recrystallisation from benzene raised the melting point to 97 - 98°. Percentage yield based on unrecovered salicylaldehyde was

37.4%. Baker and Brown reported 24% recovered salicylaldehyde, a 25% yield of 2,5-dihydroxybenzaldehyde (XLII), and a 33% yield, based on unrecovered salicylaldehyde. Hodgson and Beard[110] report a melting point of 98 - 99° for this aldehyde.

Attempted preparation of 2,5-dihydroxymandelonitrile (XLIII) and its hydrolysis to 2,5-dihydroxymandelic acid (XLIV).

The preparation of the nitrile was based on the preparation of o-hydroxymandelonitrile by Ladenburg et al.[40]. The hydrolysis of the nitrile to the acid was based on the hydrolysis[41] of mandelonitrile to mandelic acid.



(XLII) (XLIII) (XLIV)

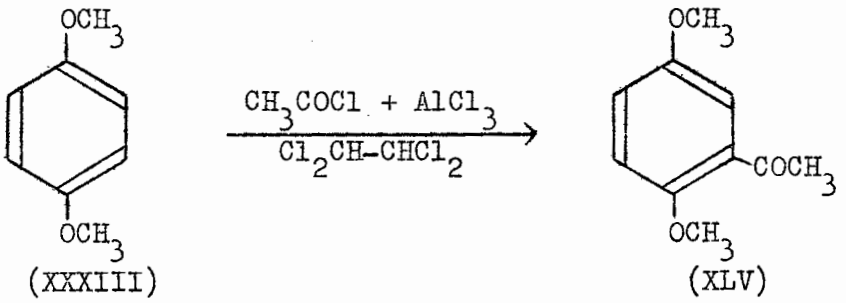
Sodium cyanide (20.5 ml. of 20% aqueous solution) was added slowly to a stirred mixture of 2,5-dihydroxybenzaldehyde (XLII) (5.0 g.) in aqueous sodium bisulphite (37.8 ml. of 10% solution) and ether (25 ml.), cooled to 0 - 5°. After the solution had been stirred for 1 hr., the layers were separated, and the aqueous layer extracted with ether. The combined ether solutions were washed with aqueous sodium bisulphite (2 x 15 ml. of 10% solution), dried (Na_2SO_4) and the ether removed in vacuo at 20°. A black gum was obtained.

Concentrated hydrochloric acid (6 ml.) was added to the black gum, without isolating the nitrile, and the hydrolysis allowed to proceed at room temperature for 12 hr. The solution was extracted with ether (10 x 25 ml.) and the ethereal extract washed once with water (25 ml.). The acid was extracted from the ether into aqueous

sodium bicarbonate (5 x 25 ml. of 10% solution). The sodium bicarbonate solution was acidified with hydrochloric acid and the acidified solution extracted with ether (10 x 40 ml.). The ethereal solution was dried (Na_2SO_4) and removal of the solvent yielded a very small amount of black gum. The gum was soluble in acetone, ethanol and ether; and insoluble in benzene, cyclohexane and petroleum ether, but could not be crystallised.

Preparation of 2,5-dimethoxyacetophenone (XLV).

The method of Abbott and Smith[26] was used. However, tetrachloroethane replaced carbon disulphide as the solvent, and the method was modified accordingly.



(XXXIII) (XLV)

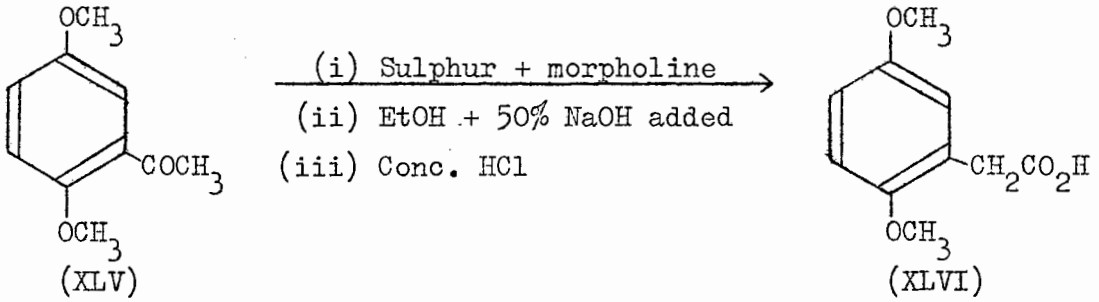
Aluminium chloride (193.1 g.) was added over 1 hr. to a mixture of p-dimethoxybenzene (100 g.), acetyl chloride (68.2 g., 61.7 ml.) and freshly distilled tetrachloroethane (100 ml.) cooled in ice, with shaking. Mechanical stirring was not used as the reaction mixture rapidly set to a hard red-brown tar. The reaction mixture was cooled in ice for 0.5 hr., and then maintained in a water-bath at room temperature for 13 hr. Evolution of hydrogen chloride had ceased, and the aluminium chloride complex was decomposed with concentrated hydrochloric acid (60 ml.) and ice (1000 ml.). Tetrachloroethane was separated from the aqueous layer and dissolved in ether. The aqueous layer was extracted with ether (5 x 50 ml.). The ether extractions and the ethereal solution of

tetrachloroethane were combined, dried (Na_2SO_4), and the ether removed. Tetrachloroethane was removed under reduced pressure, b.p. 40 - 60°/19 mm. The remaining red-black oil was distilled in two fractions, 5.90 g., b.p. 70 - 150°/19 mm., and 97.45 g. (74.6%), b.p. 152 - 179°/19 - 22 mm.

Abbott and Smith obtained 69%, b.p. 141 - 144°/10 mm.

Preparation of 2,5-dimethoxyphenylacetic acid (XLVI).

The method of Abbott and Smith[26] was used.

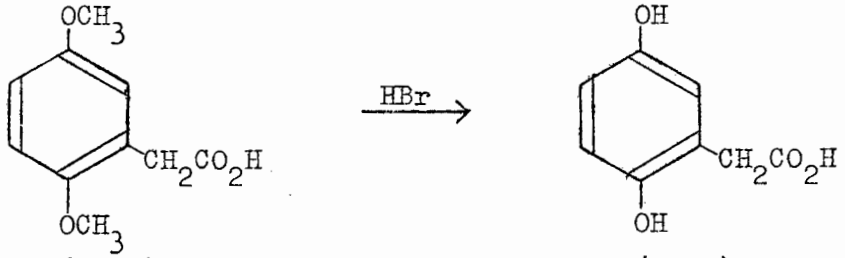


(XLV) (XLVI)

A yield of 45%, m.p. 117 - 119° was obtained. Abbott and Smith obtained 64%, m.p. 121 - 123°.

Preparation of 2,5-dihydroxyphenylacetic acid (homogentisic acid) (XXXI).

The method of Abbott and Smith[26] was used.

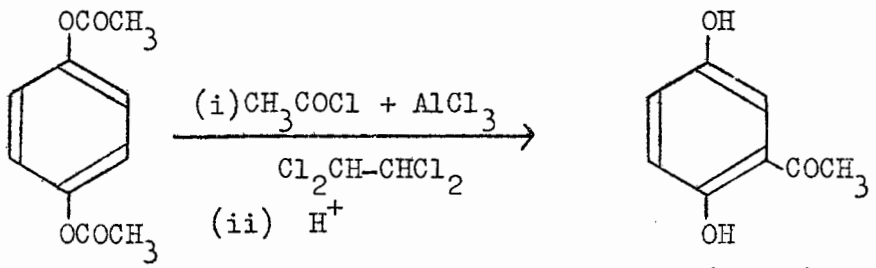


(XLVI) (XXXI)

A yield of 66% pure crystals, m.p. 146 - 148° was obtained. (Yield crude material was 98%). Abbott and Smith obtained 65%, m.p. 148 - 149°, (and a 93% yield of less pure material).

Preparation of 2,5-dihydroxyacetophenone (XLVII).

The Friedel-Crafts reaction of Rosenmund and Lohfert[43] was modified by the use of tetrachloroethane as the solvent instead of nitrobenzene.



(XLVII)

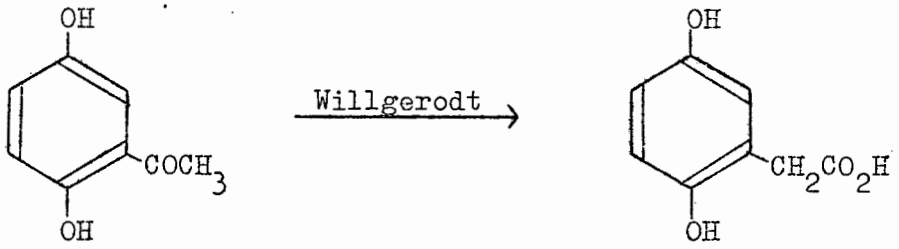
Hydroquinone diacetate[46] (140.5 g.) was dissolved in hot, dry tetrachloroethane (100 ml.) and the solution was rapidly frozen to precipitate the acetate as a fine powder. Acetyl chloride (68.2 g., 61.7 ml.), and aluminium chloride (193.1 g.) were added and the mixture heated on a boiling water-bath for 95 hr. The aluminium chloride complex was decomposed with concentrated hydrochloric acid (60 ml.) and ice (1000 ml.). Tetrachloroethane was removed by steam distillation. The remaining solution was made strongly acid (concentrated hydrochloric acid) and heated under reflux for one hour to hydrolyse any diacetate. On cooling the solution, black crystals were obtained. Repeated crystallisation from dilute methanol and a final crystallisation from a mixture of ethanol and chloroform yielded yellow-green needles (46.7 g., 42%), m.p. 199.5 - 200.5°.

Rosenmund and Lohfert reported a 40% yield of product of

m.p. 202°.

Attempted preparation of 2,5-dihydroxyphenylacetic acid (XXXI).

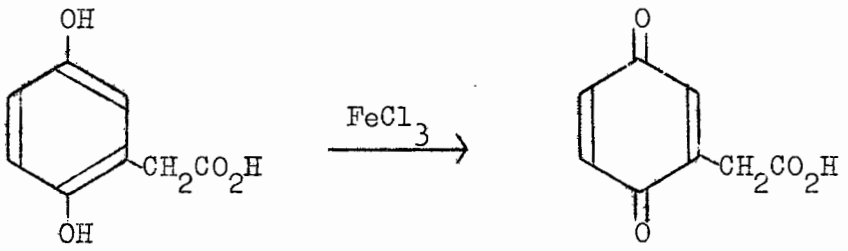
The conditions used by Abbott and Smith[26] for 2,5-dimethoxyphenylacetic acid were employed.



(XLVII) (XXXI)

A mixture of 2,5-dihydroxyacetophenone (XLVII) (10 g.), sulphur (3.2 g.) and morpholine (8.6 g.) were heated under reflux in a hood for 7 hr. The mixture was cooled to room temperature and 95% ethanol (49 ml.) and sodium hydroxide (22 ml. of 50% aqueous solution) were added. After this mixture had been heated under reflux for 45 hr., and ethanol removed by distillation, water (40 ml.) was added to the warm mixture. The mixture was heated to boiling, and the excess of sulphur filtered off from the suspension. The filtrate was placed in an efficient hood and concentrated hydrochloric acid (44 ml.) slowly added to the cooled solution with constant stirring, until the filtrate was acid to Congo-red paper. The suspension was filtered and the yellow aqueous filtrate made strongly acid (hydrochloric acid) and continuously extracted with ether (12 hr.). Removal of solvent yielded cream crystals which melted above 210°. M.p. of 2,5-dihydroxyphenylacetic acid (XXXI)[26] was 148 - 149°.

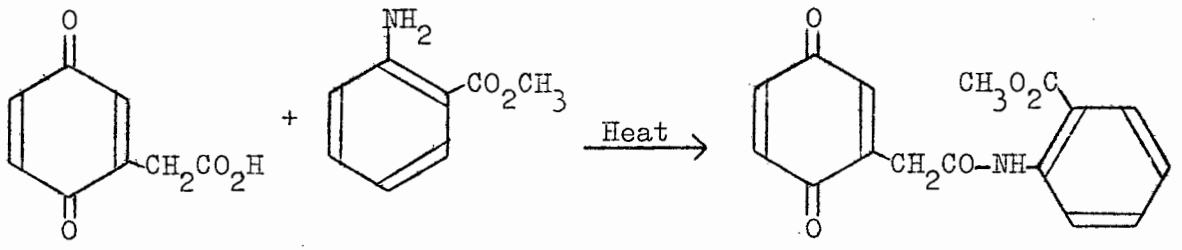
Preparation of p-benzoquinonylacetic acid (XXVI)[23].



(XXXI) (XXVI)

A yield of 91%, m.p. 129.5 - 130° was obtained. Mörner quotes no yield in the ferric chloride oxidation[23] and a 65 - 70% yield of crude material in the acid dichromate oxidation[22]; m.p. pure product[22] was 130°.

Attempted fusion of p-benzoquinonylacetic acid (XXVI) and methyl anthranilate (XXVII) to form methyl o-(α-1,4-benzoquinonylacetamido)-benzoate (XXVIII).



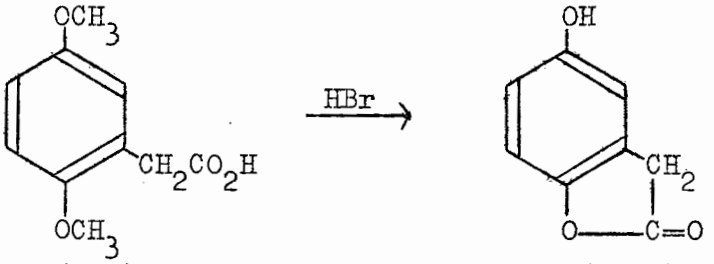
(XXVI) (XXVII) (XXVIII)

p-Benzoquinonylacetic acid (XXVI) (0.5 g.) and methyl anthranilate (2.0 ml.) were heated together slowly to 120° during 50 min. and maintained at 140 - 150° for 1 hr. under slight vacuum to remove water formed in the condensation. The excess of methyl anthranilate was removed below 160° under reduced pressure (15 mm.). The residual black gum was dissolved in ethanol and a small quantity

of black solid, which could not be purified, was obtained.

Preparation of the lactone of 2,5-dihydroxyphenylacetic acid, (XLIX).

The method of Abbott and Smith[26] was used.



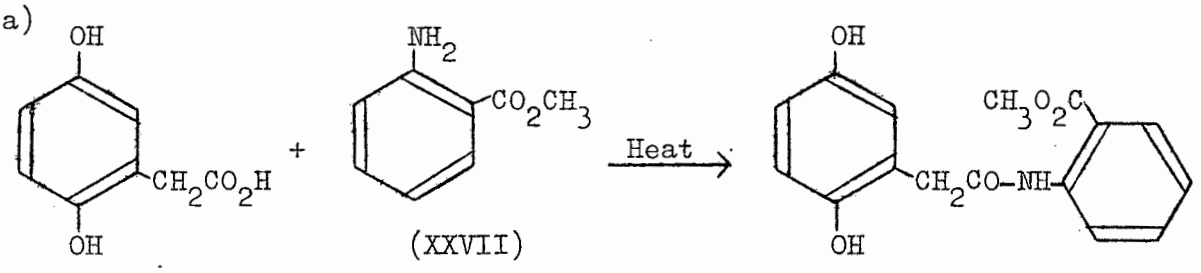
(XLV) (XLIX)

The product obtained melted at 188 - 189°. (The product of Smith and Abbott melted in the same range).

Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 3339v.s., 1792s.(sh.), 1771v.s., 1728s.(sh.), 1642m.; 1612s., 1590m., 1510m., and 1482v.s. cm.$^{-1}$.

Preparation of methyl o-(α-1,4-dihydroxyphenylacetamido)benzoate (XLVIII).

(a)

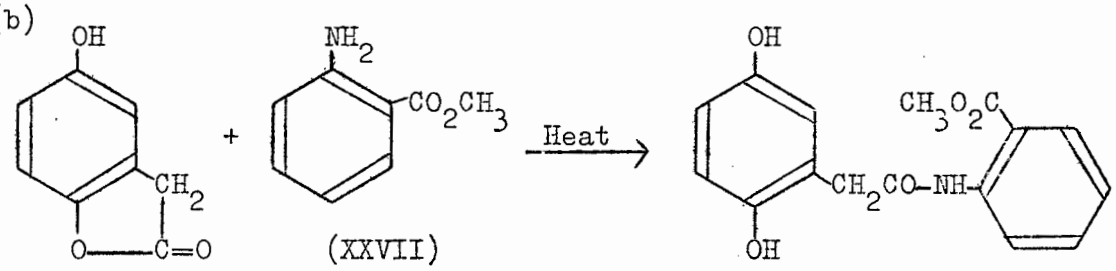


(XXXI) (XXVII) (XLVIII)

2,5-Dihydroxyphenylacetic acid (12.3 g.) and methyl anthranilate (40 ml.) were heated slowly (50 min.) to 140° and

maintained at 140 - 150° for 1 hr. under slight vacuum to remove water formed in the condensation. The excess of methyl anthranilate was removed under vacuum. To the dirty white solid remaining, ethanol (25 ml.) was added, and the solid crushed to a fine powder (18.7 g.). Crystallisation from acetone yielded methyl o-(α-1,4-dihydroxyphenyl-acetamido)benzoate (XLVIII) (17.4 g., 80%) as aggregates of fine white needles, m.p. 213 - 213.5°. Repeated crystallisation from ethanol yielded pink needles, m.p. 224.5 - 225.5°.

(b)



(XLIX) (XXVII) (XLVIII)

The lactone of 2,5-dihydroxyphenylacetic acid, (XLIX) (0.5 g.) and methyl anthranilate (1.0 ml.) were boiled for 3 min. The lactone dissolved and the solution rapidly darkened from green to red to purple. On cooling the solution, white crystals were obtained. The crystals (0.55 g., 55%), m.p. 199 - 200° were removed by filtration and washed with ethanol. Crystallisation from ethanol raised the m.p. to 205 - 206°, which m.p. was not lowered in admixture with the product obtained in (a).

Analysis:	Calculated for $C_{16}H_{15}NO_5$	Found
	C 63.8%	C 64.1%
	H 5.0%	H 5.1%
	N 4.7%	N 4.4%

Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 3270s., 3220s.(sh.), 1694s., 1672s., 1648w., 1604m., 1585s., 1553w., 1528s., 1512s., and 1463m.(sh.) $cm.^{-1}$.

Solubility properties: Fairly soluble in pyridine, tetrahydrofuran, tetrachloroethane, hot ethanol, hot acetone, hot amyl acetate, and hot ethyl acetate.

Sparingly soluble in cold ethanol, cold acetone, cold amyl acetate, and cold ethyl acetate.

Insoluble in water and di-n-butyl ether.

Decomposition in hot tetrachloroethane.

As large volumes of ethanol and acetone were required in the crystallisation of the amide (XLVIII), an attempt was made to recrystallise the compound from tetrachloroethane. Recrystallisation from tetrachloroethane lowered the m.p. from 213 - 213.5° to 179 - 181°, raised by further recrystallisation to 188 - 189°, and not raised by further crystallisation from tetrachloroethane or from ethanol or by heating in vacuo over phosphorus pentoxide at 100° (3 hr.). The low-melting material was shown to be the lactone of 2,5-dihydroxyphenyl-acetic acid, (XLIX) by m.p., mixed m.p., and a comparison of its infrared spectrum with that of authentic material[26].

Thin layer chromatography on silica gel in petroleum ether (b.p. 60 - 80°) : benzene : ethyl acetate : chloroform (2 : 2 : 1 : 1) of the hot tetrachloroethane solution of the amide (XLVIII) revealed the presence of the amide (R_F = 0.10), methyl anthranilate (R_F = 0.69), and the lactone of 2,5-dihydroxyphenylacetic acid, (XLIX) (R_F = 0.22). Methyl anthranilate was identified in ultraviolet light and the remaining spots by spraying the chromatogram with ethanolic sulphuric acid (5%) and charring it.

The acetate (L).

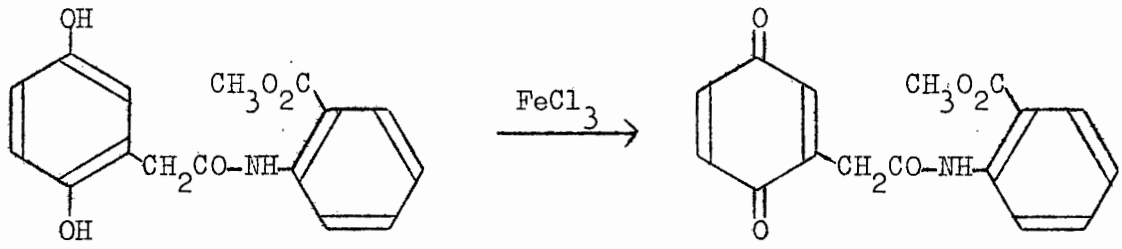
The acetate, methyl o-(α-1,4-diacetoxyphenylacetamido)-benzoate (L), separated from dilute ethanol in clusters of small white needles (78%), m.p. 119 - 121°.

Analysis:	Calculated for $C_{20}H_{19}NO_7$	Found
	C 62.3%	C 62.1%
	H 5.0%	H 5.1%
	N 3.6%	N 3.7%

Spectroscopic data: I.R. (KCl disc): $\nu_{max.}$ were at 3180m., 2961w., 1764v.s., 1705v.s., 1695v.s., 1608s., 1595s., 1539s., 1500s., 1468w.(sh.), 1454s., 1443m., and 1376s. $cm.^{-1}$.

Preparation of methyl o-(α-1,4-benzoquinonylacetamido)benzoate (XXVIII).

This preparation was modelled on Mörner's[23] oxidation of 2,5-dihydroxyphenylacetic acid.



(XLVIII) (XXVIII)

Aqueous ferric chloride (11.44 ml. of 25% solution) was added to a solution of methyl o-(α-1,4-dihydroxyphenylacetamido)-benzoate (XLVIII) (0.5 g.) in concentrated hydrochloric acid (1 ml.) and ethanol (60 ml.). After 45 min., water (110 ml.) was added, and yellow microscopic needles (0.5 g., 100%), m.p. 125 - 126°, crystallised from the solution. Crystallisation by dissolving the quinone (XXVIII) in warm acetic acid and adding water until crystallisation was incipient raised the m.p. to 126 - 128°. Heating the acetic acid solution of the quinone resulted in decomposition of the quinone. The quinone also decomposed on standing.

Analysis:	Calculated for $C_{16}H_{13}NO_5$	Found
	C 64.2%	C 64.6%
	H 4.4%	H 4.8%
	N 4.7%	N 4.6%

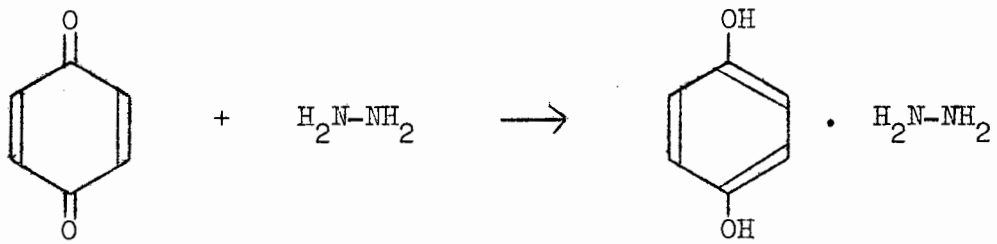
Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 3260w., 1700s., 1684s., 1653v.s., 1602s., 1586s., 1531s., and 1448s. $cm.^{-1}$.

The acetate.

Reductive acetylation modelled on the reductive acetylation of p-benzoquinone[51] produced methyl o-(α-1,4-diacetoxy-phenylacetamido)benzoate (L) (page 147), confirmed by m.p. and mixed m.p. with authentic material.

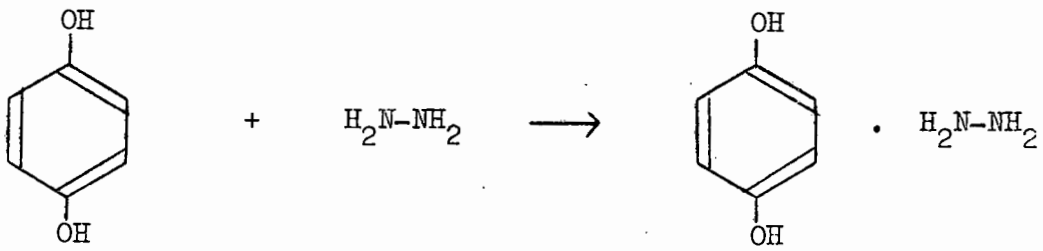
Reaction of (a) p-benzoquinone and (b) hydroquinone with hydrazine.

(a)



Aqueous 95% hydrazine (10 ml.) was very cautiously added to a cooled solution of recrystallised p-benzoquinone (12.1 g.) in ethanol (100 ml.). The solution was heated under reflux (2 hr.). On cooling the solution, pale brown crystals (13.8 g.) were obtained. Crystallisation from 96% ethanol with decolourising charcoal yielded white needles (11.9 g.), m.p. 153 - 153.5° (decomp.). Concentration of the mother liquor of the reaction yielded further white needles (2.1 g.) melting in the same range. Percentage yield was 89%.

(b)

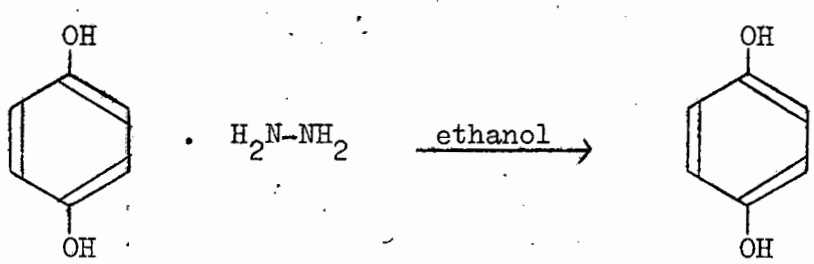


Aqueous 95% hydrazine (1 ml.) was added to a solution of hydroquinone (2 g.) in ethanol (20 ml., 95%). White needles (2.5 g., 96.5%), m.p. 154 - 154.5° (decomp.) precipitated from the solution. The product was the same as the salt prepared in (a) (m.p., and mixed m.p.).

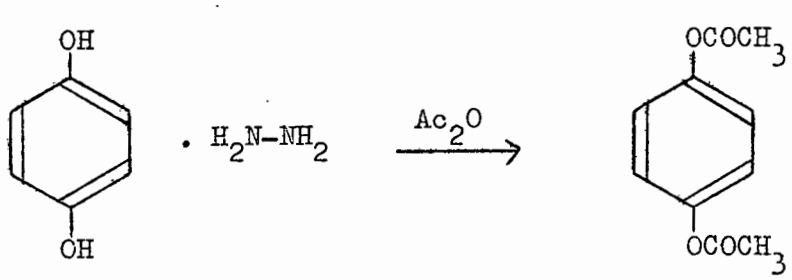
Analysis:	Calculated for $C_6H_{10}N_2O_2$	Found
	C 50.7%	C 50.9%
	H 7.1%	H 7.3%
	N 19.7%	N 19.8%

Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 3320m., 3212m., 2585m. (broad band), and 1627m. $cm.^{-1}$.

Treatment of the hydroquinone + hydrazine salt with ethanol.



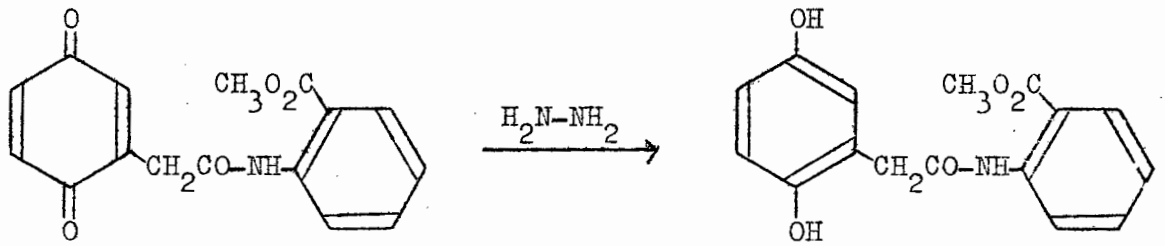
The hydroquinone + hydrazine salt was dissolved in a large excess of ethanol (95%), and the excess of ethanol removed by distillation. More ethanol was added and removed by distillation until addition of concentrated hydrochloric acid (2 drops) to the



A solution of the hydroquinone + hydrazine salt (0.50 g.)

in acetic anhydride (3 ml.) was heated to boiling, cooled, and poured on to ice (30 ml.). White needles (0.38 g., 98.4%), m.p. 110 - 116°, were obtained. Crystallisation from dilute ethanol raised the m.p. to 118 - 119.5°, not lowered in admixture with authentic hydroquinone diacetate[46]. Infrared spectra of the product and of hydroquinone diacetate were identical.

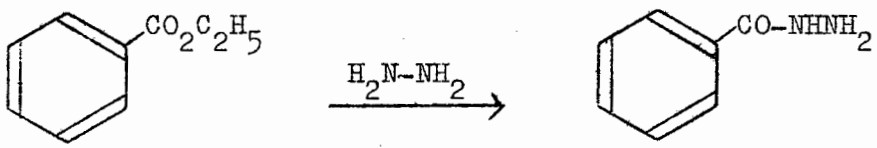
Reaction of methyl o-(α-1,4-benzoquinonylacetamido)benzoate (XXVIII) with hydrazine.



(XXVIII) (XLVIII)

A solution of methyl o-(α-1,4-benzoquinonylacetamido)-benzoate (XXVIII) (0.45 g.) and 95% aqueous hydrazine (8 drops) in ethanol (20 ml.) was heated under reflux for 2 hr. On cooling, white needles (0.3 g.), m.p. 210 - 211°, crystallised from the solution. Mixed m.p. with authentic methyl o-(α-1,4-dihydroxy-phenylacetamido)benzoate (XLVIII) was not lowered.

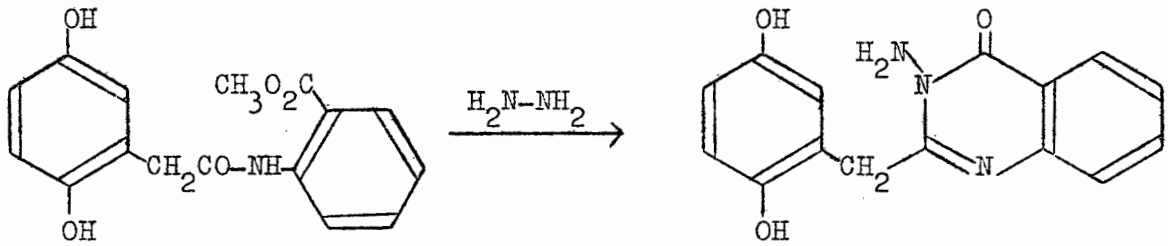
Preparation of benzhydrazide.



(a) Ethyl benzoate (1.0 g.) was heated under reflux with aqueous 95% hydrazine (7 drops) in ethanol (11 ml.) for 2 hr. No crystals formed while heating under reflux or on cooling the solution.

(b) Ethyl benzoate (25 ml.) was heated under reflux with aqueous 95% hydrazine (5 ml.) for 2 hr. Ethanol (5 ml.) was added and white needles (13.3 g.) immediately crystallised from the solution. Crystallisation from ethanol yielded white needles (7.8 g., 33%), m.p. 110 - 113°. (Heilbron's Dictionary of Organic Compounds gives a m.p. of 112.5° for benzhydrazide).

Preparation of 3-amino-2-(2,5-dihydroxybenzyl)quinazolin-4(3H)-one (LVIII) and of its hydrochloride, (LIX).



(XLVIII) (LVIII)

Methyl o-(α-1,4-dihydroxyphenylacetamido)benzoate (XLVIII) (6.6 g.) was heated under reflux (3 hr.) with aqueous 95% hydrazine (5 ml.) in ethanol (35 ml.). The ester slowly dissolved (30 min.) and white needles crystallised from the solution. The excess of hydrazine was removed by distillation with ethanol. The reaction mixture was cooled and the product filtered off from suspension. The crystal mass was washed with a small quantity of ethanol, yielding white crystals (5.5 g.), m.p. 279 - 281°. Concentration of the mother liquor yielded further white crystals (0.4 g.) melting in the same

range. Total yield of the quinazolinone (LVIII) was 95.1%. Crystallisation of the product from ethanol raised the m.p. to 281 - 283°.

Analysis:	Calculated for $C_{15}H_{13}N_3O_3$	Found
	C 63.6%	C 63.2%
	H 4.6%	H 4.5%
	N 14.8%	N 14.3%

Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 3340m., 2730w., 1687s., 1658w., 1614m., 1596s., 1566m., and 1518m. $cm.^{-1}$.

U.V. (Red-purple ethanol solution): $\lambda_{max.}$ were at 398, 382, 364, 295, 278, 260, 254, 248, and 222 mμ (log ε 2.71, 2.75, 2.62, 4.14, 4.13, 4.10, 4.13, 4.16, 4.61).

(Pale orange 0.0256N-hydrochloric acid solution): $\lambda_{max.}$ were at 480, 282, and 227 mμ (log ε 2.39, 3.95, 4.36).

(Purple sodium hydroxide solution): $\lambda_{max.}$ were at 549.5, 391.5, 293, and 230 mμ (log ε 3.92, 4.26, 4.82, 4.50).

(Yellow sodium hydroxide solution): $\lambda_{max.}$ were at 546, 365.5, 298, 260, and 238 mμ (log ε 2.58, 3.97, 4.48, 4.30, 4.32).

(Dark orange hydrochloric acid solution, from acidified purple sodium hydroxide solution): $\lambda_{max.}$ were at 483, 351.5, 337, 278, 246, and 223 mμ (log ε 3.90, 3.94, 3.95, 4.78, 4.29, 4.44).

(Dark orange hydrochloric acid solution, from acidified yellow sodium hydroxide solution): $\lambda_{max.}$ were at 483, 351, 337, 278, 246.5, and 223 mμ (log ε 3.81, 3.89, 3.91, 4.76, 4.24, 4.41).

Solubility properties: Soluble in dilute ammonia (purple solution, fading to green after a few days), dilute sodium hydroxide (purple

solution, fading to yellow after a few hours), dimethylformamide and pyridine (stable purple solutions), acetic acid (red solution) and dilute hydrochloric acid (orange solution).

Sparingly soluble in cold methanol, cold ethanol, hot nitrobenzene, n-butanol, water, tetrachloroethane, amyl acetate, tetrahydrofuran, ethyl acetoacetate, toluene, and ethyl acetate (all pink solutions).

Insoluble in benzene, chloroform, petroleum ether, and ethylene dibromide.

The hydrochloride, (LIX).

The hydrochloride was obtained by dissolving the quinazolinone (LVIII) in the minimum quantity of hot, dilute hydrochloric acid and cooling the solution. Orange cubic crystals, m.p. 245°, formed in good yield. Crystallisation from dilute hydrochloric acid did not raise the melting point.

Large cubic crystals were obtained for X-ray crystallographic studies by allowing the hydrochloride to crystallise slowly from a dilute solution in dilute hydrochloric acid.

Analysis:	Calculated for $C_{15}H_{14}N_3ClO_3$	Found
	C 56.4%	C 56.9%
	H 4.4%	H 4.6%
	N 13.1%	N 13.4%
	Cl 11.1%	Cl 11.2%

Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 3359m., 3290m., 3130m., 2600m.(broad band), 1720s., 1650s., 1614s., 1604s., 1577m., 1546w., and 1512m. $cm.^{-1}$.

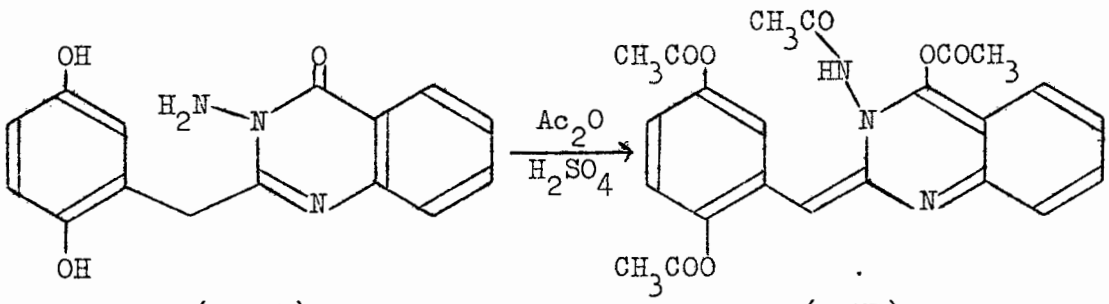
Solubility properties: As for the quinazolinone (LVIII) above in water, the aqueous acid and alkaline solvents, acetic acid, dimethylformamide and pyridine.

Insoluble in neutral organic solvents.

Liberation of the base (LVIII) from the hydrochloride (LIX).

The free base was liberated from the hydrochloride (LIX) by washing a suspension of the hydrochloride with water and filtering off the quinazolinone (LVIII). The identity of the quinazolinone was confirmed by m.p. and mixed m.p. with authentic material.

Acetylation of 3-amino-2-(2,5-dihydroxybenzyl)quinazolin-4(3H)-one (LVIII); formation of 3-acetamido-4-acetoxy-2-(2,5-diacetoxybenzylidene)-2,3-dihydroquinazoline (LXIV).



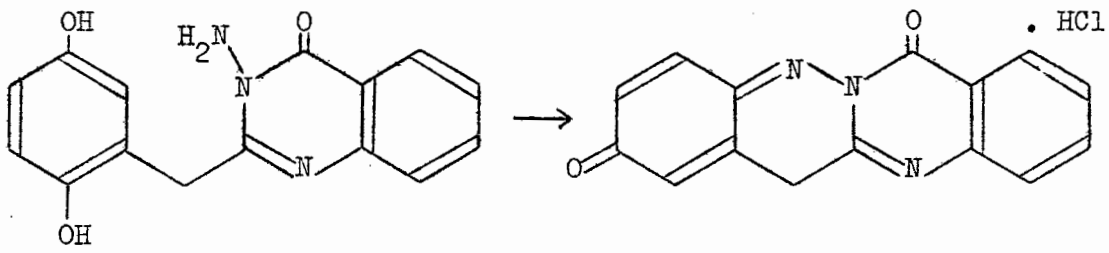
(LVIII) (LXIV)

Concentrated sulphuric acid (1 drop) was added to a suspension of 3-amino-2-(2,5-dihydroxybenzyl)quinazolin-4(3H)-one (LVIII) (0.2 g.) in acetic anhydride (2.5 ml.) and the mixture heated for 3 min. White needles crystallised from the reaction mixture at 0°. Crystallisation from ethanol yielded white needles (0.1 g., 31.4%), m.p. 164.5 - 165°.

Analysis:	Calculated for $C_{23}H_{21}N_3O_7$	Found
C	61.2%	61.2%
H	4.7%	5.6%
N	9.3%	8.8%

Spectroscopic data: I.R. (KCl disc): $\nu_{max.}$ were at 3425m., 3088w., 2955w., 1770s.(sh.), 1758v.s., 1728s., 1697s., 1604s., 1574w., 1498m., 1477m., 1440w., and 1370m. $cm.^{-1}$.

Preparation of quinazolino[3,2-b]cinnoline-2,7(13H)-dione hydrochloride and liberation of the base (XII).



(LVIII)

(a) Aqueous ferric chloride (22.48 ml. of 25% solution) was added to a hot solution of 3-amino-2-(2,5-dihydroxybenzyl)-quinazolin-4(3H)-one (LVIII) (1.0 g.) in 5N-hydrochloric acid (150 ml.). Red needles immediately crystallised from the solution. The solution was cooled and the product (1.06 g., 100%) was filtered off from the suspension. The product charred at 170° and did not melt below 300°. It could not be recrystallised but was washed with dilute hydrochloric acid and dried *in vacuo*.

(b) A solution of 3-amino-2-(2,5-dihydroxybenzyl)-quinazolin-4(3H)-one (LVIII) (0.5 g.) in 5N-sodium hydroxide (25 ml.) was heated under reflux (10 min.). The solution faded from purple to red and finally to yellow-orange. The solution was acidified with 5N-hydrochloric acid (50 ml.) and red micro-crystals precipitated from the solution. The suspension was centrifuged and the aqueous solution decanted by filtration with

suction through a filterstick of porosity 2. The remaining red solid was washed with dilute hydrochloric acid (4 x 100 ml.) by the same centrifuging and decantation procedure until free of sodium ions. The product (0.4 g., 76%) was identical (infrared spectra) with the compound prepared in (a) above.

Analysis:	Calculated for $C_{15}H_{10}N_3ClO_2$		Found	
	C	60.2%	C	60.2%
	H	3.3%	H	3.5%
	N	14.1%	N	13.5%
	Cl	10.7%	Cl	11.3%

Spectroscopic data: I.R. (in Nujol): (Spectrum C, page 52): $\nu_{max.}$ were at 1752s., 1643m., 1626s., 1616s., 1596m., 1576m., 1540m., 1527m.(sh.), 1495m.(sh.), 1484s., 1461s.(sh.), 1424w.(sh.), 1402m., 1368m., 1356w., 1300m., and 1288m. $cm.^{-1}$.

(KCl disc): $\nu_{max.}$ were at 3412m., 3061m., and 2739s. $cm.^{-1}$.

U.V. (Purple sodium hydroxide solution): $\lambda_{max.}$ were at 548, 391, 293, 228, 209, and 206 mμ (log ε 3.76, 4.06, 4.71, 4.43, 4.33, 4.36).

(Yellow sodium hydroxide solution): $\lambda_{max.}$ were at 546, 366, 298, 261, 239, and 202 mμ (log ε 2.61, 3.91, 4.45, 4.26, 4.29, 4.47).

(Orange hydrochloric acid solution, from acidified yellow sodium hydroxide solution): $\lambda_{max.}$ were at 483, 351, 336, 281, 248, and 224 mμ (log ε 3.62, 3.84, 3.90, 4.63, 4.22, 4.35).

Solubility properties: Soluble in pyridine and in acetic acid (red solutions), in dilute ammonia (purple solution, fading to green after a few days), and in dilute sodium hydroxide (purple solution, fading to yellow after a few hours).

Sparingly soluble in dilute nitric acid,

dilute hydrochloric acid, ethanol, and water (orange solutions). Insoluble in non-polar organic solvents.

The base, quinazolino[3,2-b]cinnoline-2,7(13H)-dione, (XII).

A suspension of the hydrochloride in water was washed in a centrifuge bottle. The suspension was centrifuged and the supernatant solution decanted by filtration with suction through a filterstick of porosity 2. The washing procedure was repeated until the washings were free of chloride ions. The base (XII) was obtained almost quantitatively as dark red crystals which did not melt below 300°.

Analysis:	Calculated for $C_{15}H_9N_3O_2$	Found
	C 68.4%	C 68.3%
	H 3.5%	H 3.4%
	N 16.0%	N 16.0%

Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 1718v.s., 1629s., 1616m., 1598s., 1568m., 1547m., 1527s., 1508s., 1487v.s., 1428s., 1327m., 1317m., and 1279s. $cm.^{-1}$.

(KCl disc): $\nu_{max.}$ were at 3412s., and 3080s. $cm.^{-1}$.

U.V. (Yellow sodium hydroxide solution): $\lambda_{max.}$ were at 546, 366, 298, 261, 239, and 205 mμ ($\log \varepsilon$ 2.60, 3.91, 4.45, 4.26, 4.29, 4.39).

(Orange hydrochloric acid solution, from acidified yellow sodium hydroxide solution): $\lambda_{max.}$ were at 483, 351, 336, 281, 248, and 224 mμ ($\log \varepsilon$ 3.61, 3.83, 3.90, 4.63, 4.22, 4.35).

Solubility properties: As for the hydrochloride above.

Paper chromatography: R_F values of quinazolino[3,2-b]cinnoline-2,7(13H)-dione (XII) and of its hydrochloride in the solvent

systems 1, 2, 3, and 4 were identical in each system and were 0.82, 0.63, 0.27, and 0.64, respectively.

The picrate.

Quinazolino[3,2-b]cinnoline-2,7(13H)-dione (XII) (0.2156 g.) was dissolved in hot ethanol (300 ml.) and an ethanolic solution of picric acid (0.1830 g.) was added to the solution. Concentration of the ethanol to 15 ml. yielded red-brown crystals which could not be recrystallised.

Attempted determination of the equivalent weight of quinazolino[3,2-b]-cinnoline-2,7(13H)-dione (XII) by non-aqueous titration; formation of the perchlorate.

An attempt was made to determine the equivalent weight of the base, quinazolino[3,2-b]cinnoline-2,7(13H)-dione (XII) by non-aqueous titration in acetic acid with acetous perchloric acid, using methyl violet as indicator. The colour of the indicator was, however, completely masked by the deep orange colour of the acetic acid solution of the base. The titration was performed using the base as its own indicator but no definite colour change at the theoretical equivalence point was observed.

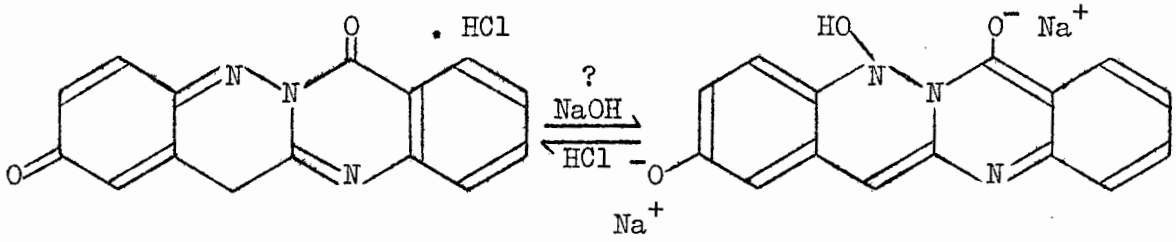
As the base was only soluble in hot acetic acid, the titration was performed at 100°. An excess of perchloric acid was added to the hot solution of the base and the solution was cooled. Orange-red crystals of the perchlorate crystallised from the solution. The perchlorate did not melt below 300°.

Analysis:	Calculated for $C_{15}H_{10}N_3ClO_6$		Found	
	C	49.6%	C	-
	H	2.8%	H	-
	N	11.6%	N	-
	Cl	9.8%	Cl	10.0%

The carbon, hydrogen and nitrogen analyses could not be determined because of the explosive nature of this perchlorate.

Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 3477m., 3300m., 3090m., 2740m., 1737s., 1655m., 1620s., 1594m., 1579m., 1547m., 1518m., 1502m., 1486s., 1415m., 1358m., 1308m., and 1289m. $cm.^{-1}$.

Attempted isolation of the sodium salt formed from quinazolino[3,2-b]-cinnoline-2,7(13H)-dione (XII).



Quinazolino[3,2-b]cinnoline-2,7(13H)-dione (XII) hydrochloride (0.42 g.) was suspended in 5N-sodium hydroxide (10 ml.) and the solution boiled for 10 min. The red crystals turned purple and slowly dissolved. The purple solution obtained rapidly turned yellow on heating. On cooling, yellow needles (0.50 g.) crystallised from the clear solution.

Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 3335 - 3180m. (band), 1611s.(sh.), 1594s., and 1536m. $cm.^{-1}$.

Solubility properties: Very soluble in water.
Sparingly soluble in ethanol.
Insoluble in chloroform, acetone, benzene, and petroleum ether (b.p. 80 - 100°).

The yellow needles could not be recrystallised. However, the product (0.38 g.) was dissolved in hot ethanol (60 ml.), benzene

(80 ml.) added, and the solution concentrated. Yellow-green micro-needles (0.28 g.), m.p. above 300°, formed. The treatment with ethanol and benzene was repeated twice more.

Analysis:	Calculated for $C_{15}H_9N_3Na_2O_3$	Found
	C 55.4%	C 45.0%
	H 2.8%	H 4.7%
	N 12.9%	N 10.0%
	Na_2SO_4 43.7%	Na_2SO_4 38.6%

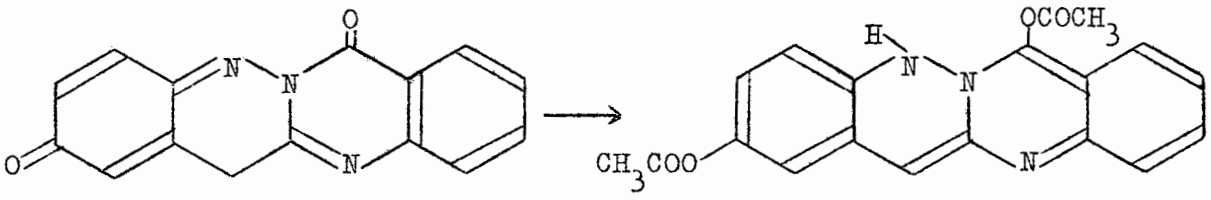
Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 3400 - 3240m. (band), 1602s.(sh.), 1592s., and 1515s. $cm.^{-1}$.

Addition of 5N-hydrochloric acid to an aqueous solution of the sodium salt precipitated red needles from the solution. The product was identical with quinazolino[3,2-b]cinnoline-2,7(13H)-dione (XII) hydrochloride (infrared spectra).

Reductive and Thiele acetylation of quinazolino[3,2-b]cinnoline-2,7(13H)-dione (XII).

Formation of (a) 2,7-diacetoxy-5H-quinazolino[3,2-b]cinnoline (LXXXII), and (b) 2-acetoxy-5H-quinazolino[3,2-b]cinnolin-7(13H)-one, (LXXXV).

(a) Reductive acetylation.



(XII) (LXXXII)

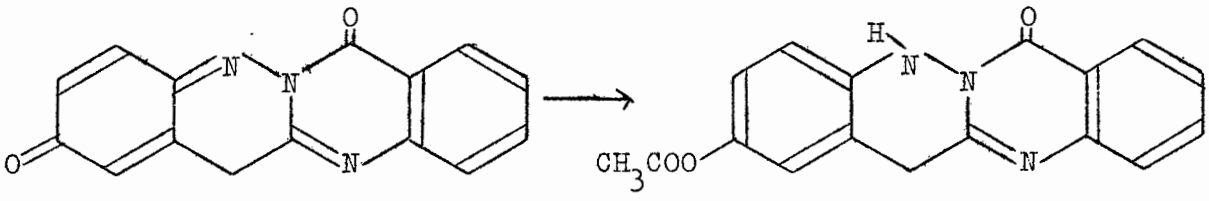
Quinazolino[3,2-b]cinnoline-2,7(13H)-dione (XII) (0.5 g.),

zinc dust (0.5 g.) and anhydrous sodium acetate (0.1 g.) were suspended in acetic anhydride (4 ml.). On gentle heating (15 min.), the red base slowly dissolved and the red solution faded to orange. Zinc and sodium acetate were filtered off from suspension and extracted with hot acetic acid (2 x 4 ml.). The acetic acid washings and the acetic anhydride solution were combined and concentrated to 3 ml. Water was added until precipitation of pink crystals from the solution had ceased. Crystallisation from ethanol yielded pale pink crystals (0.57 g., 86%), m.p. 230 - 231°. Repeated recrystallisation raised the m.p. to 234 - 235°.

Analysis:	Calculated for $C_{19}H_{15}N_3O_4$	Found
	C 65.4%	C 65.3%
	H 4.3%	H 4.5%
	N 12.1%	N 12.1%

Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 3400w., 1768v.s., 1720v.s., 1705v.s., 1685v.s., 1628m.(sh.), 1622s.(sh.), 1610s., 1568w., and 1497s. $cm.^{-1}$.

(b) Thiele acetylation.



(XII) (LXXXV)

Quinazolino[3,2-b]cinnoline-2,7(13H)-dione (XII) (0.2 g.) was triturated with acetic anhydride (3.5 ml.) and concentrated sulphuric acid (1 drop). The dark red solid turned orange. On warming the suspension at 50° (30 min.) followed by heating to boiling, the orange solid dissolved forming a red solution. Ice and

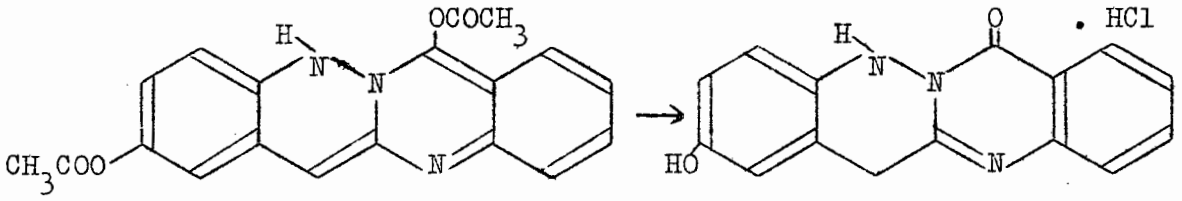
water were added and the solution cooled. Red needles, which did not melt below 270°, but darkened at 220°, formed. Crystallisation from ethanol afforded red needles which did not melt, but charred at 230°.

Analysis:	Calculated for $C_{17}H_{13}N_3O_3$	Found
	C 66.4%	C 66.2%
	H 4.2%	H 4.5%
	N 13.7%	N 13.1%

Spectroscopic data: I.R. (KCl disc): $\nu_{max.}$ were at 3440m., 1766m., 1721s., 1637w., 1594w., 1543m., 1520s., 1469m., 1456s., 1386w., 1351w., and 1342w. $cm.^{-1}$.

Hydrolysis of 2,7-diacetoxy-5H-quinazolino[3,2-b]cinnoline (LXXXII).

(a) Formation of 2-hydroxy-5H-quinazolino[3,2-b]cinnolin-7(13H)-one hydrochloride (LXXXIII).



(LXXXII) (LXXXIII)

Sodium (0.3 g.) in cold anhydrous ethanol (10 ml.) was added to a solution of 2,7-diacetoxy-5H-quinazolino[3,2-b]cinnoline (LXXXII) (0.5 g.) in anhydrous ethanol (50 ml.) cooled to -3°. The colourless solution immediately turned pink, darkening to purple. The solution was maintained at -3° for 1 hr. and the excess of sodium ethoxide destroyed by passing carbon dioxide through the solution. A white precipitate of sodium carbonate formed. Methanol was removed *in vacuo* below 40°. The solid residue obtained was dissolved in water (30 ml.) and insoluble material (A) removed by filtration. Addition

of 5N-hydrochloric acid (30 ml.) to the filtrate precipitated dark red crystals which were removed by filtration and washed with hydrochloric acid. The product, m.p. above 300°, could not be recrystallised for analysis.

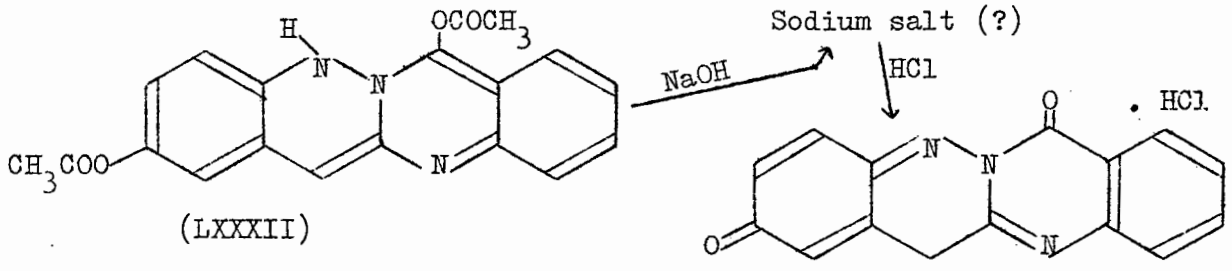
Spectroscopic data: I.R. (in Nujol): (Spectrum A, page 50): $\nu_{max.}$ were at 3460m., 3315m., 2735m., 2585m., 1749m., 1735m., 1642w., 1616s., 1596m., 1576m., 1536m., 1518m., 1497m.(sh.), 1482s., 1400m., 1370s., 1298m., and 1289m. $cm.^{-1}$.

Solubility properties: As for quinazolino[3,2-b]cinnoline-2,7(13H)-dione (XII) hydrochloride.

The insoluble material (A), obtained after filtration of the sodium carbonate solution, was dissolved in warm 5N-sodium hydroxide (20 ml.). The yellow solution obtained was acidified with 5N-hydrochloric acid (30 ml.) and the red crystals which precipitated from the solution were filtered off and washed with 5N-hydrochloric acid.

Spectroscopic data: I.R. (in Nujol): (Spectrum D, page 53): $\nu_{max.}$ were at 3461m., 3310m., 2735m., 2625m., 1753s., 1726s., 1643s., 1621s.(sh.), 1617v.s., 1595s., 1577s., 1539s., 1523s., 1492s.(sh.), and 1485v.s. $cm.^{-1}$.

(b) Formation of the sodium salt from, and the hydrochloride of, quinazolino[3,2-b]cinnoline-2,7(13H)-dione (XII).

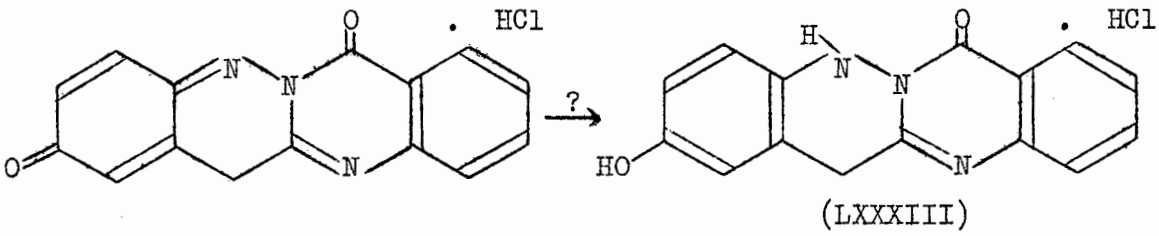


(LXXXII)

2,7-Diacetoxy-5H-quinazolino[3,2-b]cinnoline (LXXXII) (0.5 g.) and 5N-sodium hydroxide (15 ml.) were heated under reflux for 30 min. Part of the white suspension turned purple and within 4 min. a clear yellow solution was obtained. On cooling, yellow needles crystallised from the solution. The product was shown to be the same as the yellow needles obtained from the action of 5N-sodium hydroxide on quinazolino[3,2-b]cinnoline-2,7(13H)-dione (XII) by a comparison of the infrared spectra of the two substances.

Acidification of the filtrate from the yellow needles with 5N-hydrochloric acid precipitated red needles from the solution. The red needles were washed twice with dilute hydrochloric acid by centrifuging and decanting the supernatant washings. The infrared spectrum of this material was identical with the spectrum of authentic quinazolino[3,2-b]cinnoline-2,7(13H)-dione (XII) hydrochloride.

Attempted reduction of quinazolino[3,2-b]cinnoline-2,7(13H)-dione (XII) hydrochloride; formation of 2-hydroxy-5H-quinazolino[3,2-b]-cinnolin-7(13H)-one hydrochloride (LXXXIII) (?).



(LXXXIII)

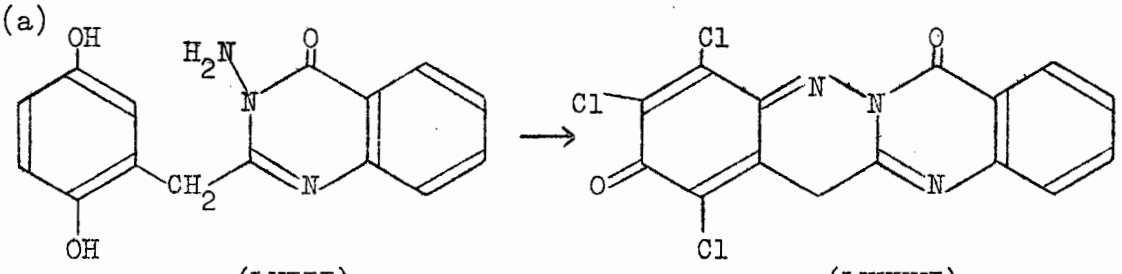
Zinc (1.0 g.) was added to a suspension of quinazolino-[3,2-b]cinnoline-2,7(13H)-dione (XII) hydrochloride (0.2 g.) in 5N-hydrochloric acid (50 ml.). The suspension was warmed on a boiling water-bath until the zinc had dissolved, the suspension was cooled, and the red crystals were filtered off from the suspension and washed with 5N-hydrochloric acid. The product, m.p. above 300°, could not be recrystallised for analysis.

Spectroscopic data: I.R. (in Nujol): (Spectrum B, page 51): $\nu_{max.}$ were at 3465m., 3305m., 2735m., 2560m., 1749m., 1723s., 1645m., 1615s., 1596m.(sh.), 1577m., 1540m., 1520m., 1497m., and 1484s. $cm.^{-1}$.

Solubility properties: As for quinazolino[3,2-b]cinnoline-2,7(13H)-dione (XII) hydrochloride.

Formation of 1,3,4-trichloro-quinazolino[3,2-b]cinnoline-2,7(13H)-dione (LXXXVI) from (a) 3-amino-2-(2,5-dihydroxybenzyl)quinazolin-4(3H)-one (LVIII), (b) quinazolino[3,2-b]cinnoline-2,7(13H)-dione (XII) hydrochloride, and (c) 1-chloro-2-hydroxy-5H-quinazolino-[3,2-b]cinnolin-7(13H)-one (XCVI) hydrochloride.

(a)

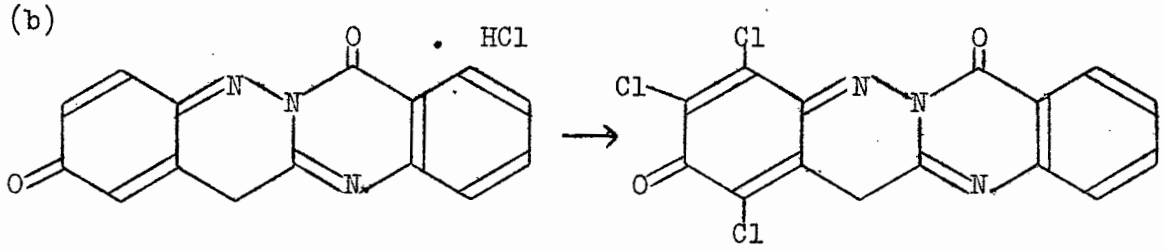


(LVIII) (LXXXVI)

Hydrogen peroxide (5 ml. 30% w./v.) was added to a solution of 3-amino-2-(2,5-dihydroxybenzyl)quinazolin-4(3H)-one (LVIII) (2.0 g.) in 5N-hydrochloric acid (80 ml.) and 96% ethanol (180 ml.). The solution was heated on a boiling water-bath for 45 min., more hydrogen peroxide being periodically added (about 5 x 1 ml.). The solution turned red and red crystals formed. The red product slowly dissolved and yellow needles formed. At the end of the reaction a clear yellow solution and yellow needles were obtained (2.1 g., 77.1%), m.p. 245° (sealed tube, inserted at 240°). The crystals darkened (red) on exposure to light, or on heating. Crystallisation of the yellow needles from chloroform-ethanol or

chloroform - petroleum ether (b.p. 80 - 100°) produced khaki, impure crystals. Crystallisation was attained by dissolving the compound in warm chloroform and adding ethanol containing concentrated hydrochloric acid (1 drop) and hydrogen peroxide (1 drop 30% w./v.). On shaking, yellow needles separated from the solution.

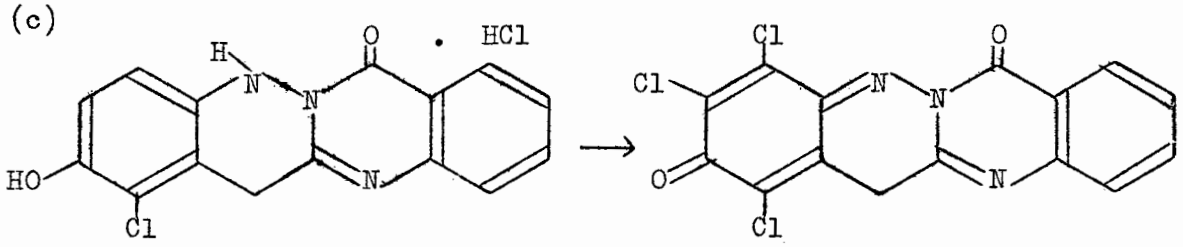
(b)



(LXXXVI)

Quinazolino[3,2-b]cinnoline-2,7(13H)-dione (XII) hydrochloride (0.6 g.), ethanol (55 ml.), 5N-hydrochloric acid (55 ml.), and hydrogen peroxide (5 ml. 30% w./v.) were heated on a hot water-bath for 30 min. The red compound slowly dissolved and yellow crystals (0.6 g., 81.7%) crystallised from the yellow solution. If, during the heating, the solution darkened to red, more hydrogen peroxide was added. The product was identical with the compound prepared in (a) (m.p., mixed m.p., and infrared spectra).

(c)



(LXXXVI)

1-Chloro-2-hydroxy-5H-quinazolino[3,2-b]cinnolin-7(13H)-one (XCVI) hydrochloride (0.2 g.), ethanol (30 ml. 96%), concentrated

hydrochloric acid (4 ml.) and hydrogen peroxide (4 ml. 30% w./v.) were heated under reflux on a water-bath with occasional shaking for 1.5 hr. Yellow needles (0.2 g., 91.8%) crystallised from the solution. The product was identical with the compound prepared in (a) (m.p., mixed m.p., and infrared spectra).

Analysis:	Calculated for $C_{15}H_6N_3Cl_3O_2$	Found
C	49.2%	49.0%
H	1.7%	1.8%
N	11.5%	11.2%
Cl	29.0%	28.5%
Active H	0.27%	[72] Active H 0.24%

Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 1721s., 1701s., 1659m., 1620m., 1611m., 1575m., 1558m., and 1511m. $cm.^{-1}$.

(KCl disc): $\nu_{max.}$ were at 3420s., and 3060m. $cm.^{-1}$.

U.V. (in Chloroform): $\lambda_{max.}$ were at 370, 330sh., 285sh., and 262 mμ ($\log \varepsilon$ 4.09, 3.89, 4.32, 4.39).

*(in Ethanol): $\lambda_{max.}$ were at 538, 385 (plateau), 370(plateau), 285, and 222.5 mμ ($\log \varepsilon$ 3.71, 3.91, 4.06, 4.27, 4.49).

[The ethanol solution was red and was obtained by dissolving the trichloro compound (LXXXVI) in ethanol in sunlight.]

Solubility properties: Soluble in chloroform, acetone, and glacial acetic acid.

Very sparingly soluble in ethanol. (The solutions in these solvents were yellow but turned red on exposure to light.)

Insoluble in water, dilute hydrochloric acid, dilute ammonia and dilute sodium hydroxide, petroleum ether, and ether.

---

* Unicam S.P. 500 spectrophotometer.

Thin layer chromatography: (i) On silica gel:

(a) In the dark: In chloroform: Yellow spot, R_F = 0.52.
In ethyl acetate : petroleum ether (b.p. 80-100°), (1 : 1), (System 5): Yellow spot, R_F = 0.76.
In ethanol: Yellow spot at the origin.

(b) In light: In chloroform: Yellow spot, R_F = 0.52 with a pink "tail" almost to the origin.
In Solvent System 5: Yellow spot, R_F = 0.76 with a pink "tail".
In ethanol: A yellow spot at the origin and a purple streak, $R_{F'}$ = 0.91, from the yellow spot.

(ii) On kieselguhr:

(a) In the dark: In ethanol: Yellow spot, R_F = 0.96.
In chloroform: Yellow spot, R_F = 0.99.

(b) In light: In ethanol: Yellow spot, R_F = 0.96 with a pink "tail".

On exposure of all the chromatograms to light, the yellow spots darkened to orange. On longer exposure (6 - 12 hr.), the orange spots and the pink and the purple streaks faded to yellow-brown.

Proof of the absence of ionic chlorine in the trichloro compound (LXXXVI).

Proof that this compound had not separated from the solution as the hydrochloride was obtained by dissolving the compound in chloroform and rapidly extracting the solution with dilute ammonia. The aqueous layer contained no ionic chlorine. Removal of the chloroform in vacuo in the cold afforded dark yellow material which was crystallised from acetic acid containing hydrogen peroxide (1 drop).

Analysis:	Calculated for $C_{15}H_6N_3Cl_3O_2$	Found
C	49.2%	48.9%
H	1.7%	2.0%
N	11.5%	10.8%
Cl	29.0%	29.1%

Attempted preparation of the picrate and the picrolonate of 1,3,4-trichloro-quinazolino[3,2-b]cinnoline-2,7(13H)-dione (LXXXVI).

(a) A solution of picric acid (625.0 mg.) in chloroform (60 ml.) was added to a solution of the trichloro compound (999.3 mg.) in chloroform (10 ml.). The solution was concentrated to incipient crystallisation (with slight darkening of the solution to red). The yellow clusters of needles obtained proved to be unchanged 1,3,4-trichloro-quinazolino-[3,2-b]cinnoline-2,7(13H)-dione (LXXXVI) by m.p., mixed m.p., and infrared spectra.

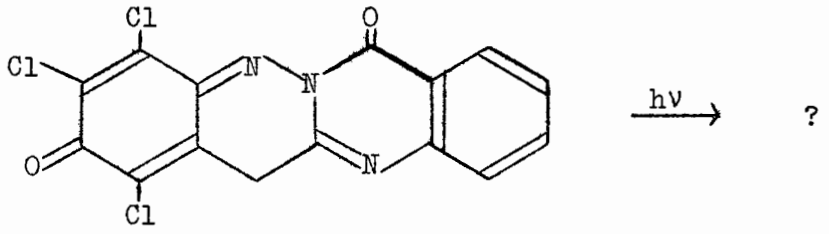
(b) A solution of picrolonic acid (288.56 mg.) in chloroform (20 ml.) was added to a solution of the trichloro compound (LXXXVI) (391.95 mg.) in chloroform (4 ml.) and the mixture worked up as described in (a). The product again proved to be unchanged starting product by m.p., mixed m.p., and infrared spectra.

Attempted determination of the equivalent weight of 1,3,4-trichloro-quinazolino[3,2-b]cinnoline-2,7(13H)-dione (LXXXVI) by non-aqueous titration; and attempted preparation of the perchlorate.

The trichloro compound (LXXXVI) dissolved readily in warm glacial acetic acid giving a red solution. Methyl violet indicator (1 drop) was added giving a purple solution. After 1 drop

of acetous perchloric acid had been added, the solution turned red-yellow again. Addition of a large excess of acetous perchloric acid produced no further colour change. On standing, yellow needles formed. The product proved to be unchanged trichloro compound (LXXXVI) by m.p., mixed m.p., and infrared spectra.

Photolysis of 1,3,4-trichloro-quinazolino[3,2-b]cinnoline-2,7(13H)-dione (LXXXVI).



(LXXXVI)

The trichloro compound (LXXXVI) was dissolved in chloroform, ethanol added, and the solution exposed to direct sunlight (12 hr.). As the solvent evaporated, more ethanol was added as required. A dark red solution was obtained. Thin layer chromatography (TLC) of this red solution on silica gel in chloroform revealed the presence of three spots, a yellow spot (R_F = 0.31), a purple streak from the origin ($R_{F'}$ = 0.15), and a yellow spot at the origin. None of the original trichloro compound remained. On exposure of the chromatogram to light (6 - 12 hr.), the purple spot faded and the yellow spots darkened to yellow-brown. The three resulting yellow-brown spots did not move from the origin in a two-dimensional chromatogram run in either a chloroform or an ethanol solvent system.

The dark red solution obtained from the photolysis of the trichloro compound was divided into four samples, A, B, C, and D, (0.2 ml. each). Water (2 drops) was added to sample A; water (1

drop) and 5N-hydrochloric acid (1 drop) to sample B; water (1 drop) and hydrogen peroxide (1 drop, 30% w./v.) to sample C; and 5N-hydrochloric acid (1 drop) and hydrogen peroxide (1 drop) to sample D. The solutions were heated to boiling and cooled. Sample D turned yellow. Chloroform (2 drops) was added to each sample to extract any trichloro compound formed by this treatment of the four solutions. The chloroform extracts, A, B, C, and D, and a sample of pure trichloro compound in chloroform, sample E, were spotted on TLC plates. The chromatograms were run in chloroform and in solvent System 5 (page 170) in the dark. The resulting chromatograms are reproduced in Figure 1, page 69.

TLC results: In chloroform:

Solution A: A yellow spot (R_F = 0.31), a purple streak ($R_{F'}$ = 0.15), and a yellow spot at the origin were obtained.

Solution B: A yellow streak ($R_{F'}$ = 0.46), a yellow spot (R_F = 0.27), two purple spots (R_F = 0.13 and 0.10), and a yellow spot at the origin were obtained.

Solution C: A yellow spot (R_F = 0.30), a yellow streak ($R_{F'}$ = 0.18), and a yellow spot at the origin were obtained.

Solution D: A yellow spot which immediately darkened to orange in light (R_F = 0.52), a yellow spot (R_F = 0.29), a yellow streak ($R_{F'}$ = 0.16), a yellow spot (R_F = 0.09), and a yellow spot at the origin were obtained.

Solution E: A yellow spot which immediately darkened to orange in light (R_F = 0.52) was obtained.

In solvent system 5:

Solution A: A purple spot (R_F = 0.03) and a yellow spot at the origin were obtained.

Solution B: A yellow spot (R_F = 0.09), a purple spot (R_F = 0.05), and a yellow spot at the origin were obtained.

Solution C: A yellow streak ($R_{F'}$ = 0.70), two yellow spots

(R_F = 0.18 and 0.09), and a yellow spot at the origin were obtained.

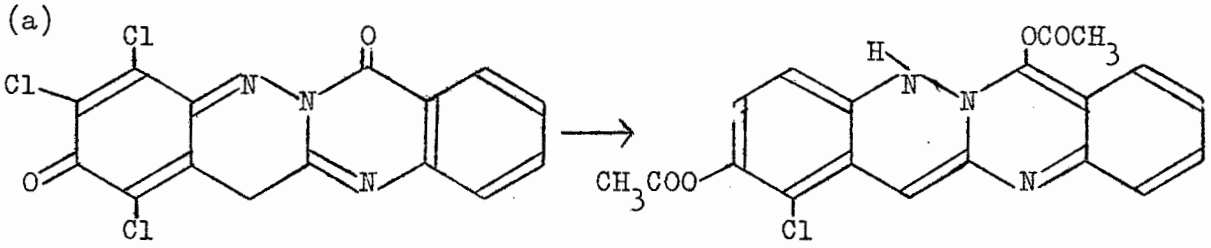
Solution D: A yellow spot which immediately darkened to orange in light (R_F = 0.76), two yellow spots (R_F = 0.20, and 0.05), and a yellow spot at the origin were obtained.

Solution E: A yellow spot which immediately darkened to orange in light was obtained.

On prolonged exposure of the chromatograms to light, the yellow and the orange spots in both chromatograms turned yellow-brown (6 - 12 hr.), and the purple spots faded to yellow-brown (3 hr.).

Formation of 1-chloro-2,7-diacetoxy-5H-quinazolino[3,2-b]cinnoline (XCVII) by reductive acetylation of (a) 1,3,4-trichloro-quinazolino-[3,2-b]cinnoline-2,7(13H)-dione (LXXXVI), and (b) 1-chloro-2-hydroxy-5H-quinazolino[3,2-b]cinnolin-7(13H)-one (XCVI).

(a)

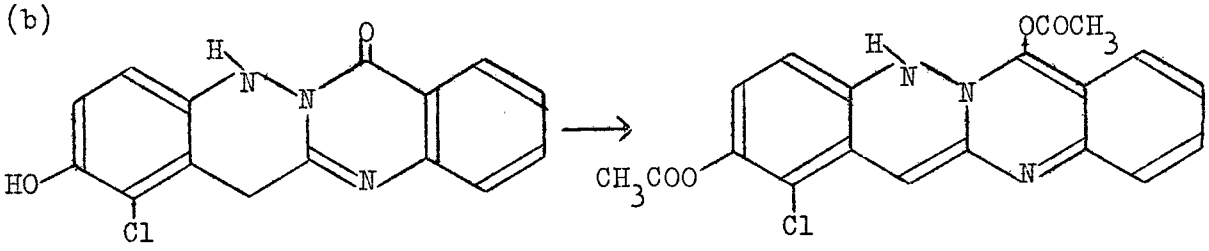


(LXXXVI) (XCVII)

A suspension of 1,3,4-trichloro-quinazolino[3,2-b]-cinnoline-2,7(13H)-dione (LXXXVI) (0.5 g.), anhydrous sodium acetate (0.1 g.), and zinc dust (0.5 g.) in acetic anhydride (3.5 ml.) was warmed at 50° for 5 min. and then gently boiled for 10 min. The greenish-brown solution obtained was filtered free of inorganic material which was extracted with acetic acid (2 x 2 ml.). Water was

added to the combined acetic acid and acetic anhydride solutions until precipitation ceased. White crystals (0.4 g., 76.5%), m.p. 219°, with sintering at 218° were obtained. Crystallisation from dilute acetic acid raised the m.p. to 221.5 - 222°.

(b)



(XCVI) (XCVII)

A suspension of 1-chloro-2-hydroxy-5H-quinazolino[3,2-b]-cinnolin-7(13H)-one (XCVI) (0.7 g.), anhydrous sodium acetate (0.1 g.) and zinc dust (0.5 g.) in acetic anhydride (4 ml.) was heated under reflux for 10 min. The purple solid slowly dissolved forming a green solution. The product was worked up as described under (a) to give white crystals (0.6 g., 67%), m.p. 208.5 - 209.5°, with sintering at 207°. Repeated crystallisation from ethanol and from acetic acid raised the melting point to 219 - 219.5°, with sintering at 218°. The product was identical with the compound obtained in (a) (m.p., mixed m.p., and infrared spectra).

Analysis:	Calculated for $C_{19}H_{14}N_3ClO_4$	Found
C	59.6%	59.3%
H	3.7%	3.9%
N	11.0%	10.9%
Cl	9.3%	9.3%
Acetyl	22.4%	22.7%[111]

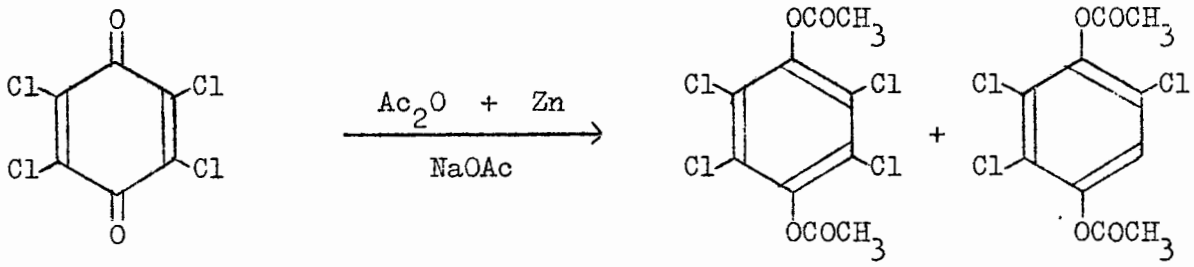
Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 3540m., 1776v.s., 1718v.s., 1696v.s., 1628v.s., 1610s., and 1574m. $cm.^{-1}$.

Solubility properties: Very soluble in dimethylsulphoxide, and pyridine.

Soluble in dimethylformamide, acetic acid, dioxane, ethanol, chloroform, acetone, carbon tetrachloride, and benzene.

Reductive acetylation of chloranil; formation of tetrachlorohydroquinone diacetate and trichlorohydroquinone diacetate.

This preparation was modelled on the reductive acetylation of p-benzoquinone[51].



When acetic anhydride (20 ml.) was added to a mixture of chloranil (5.0 g.), zinc dust (5.0 g.) and anhydrous sodium acetate (0.5 g.), a very vigorous exothermic reaction occurred. More acetic anhydride (10 ml.) was added after the solution had cooled, the mixture was heated to dissolve the white crystals formed, and the pale yellow solution was filtered. On cooling, the filtrate deposited white needles (4.5 g.), m.p. 207 - 217°. Crystallisation from acetic acid yielded pure white needles (2.7 g.), m.p. 231 - 234°. The acetic acid solution was concentrated and addition of water yielded off-white needles, (1.6 g.), m.p. 149 - 165°.

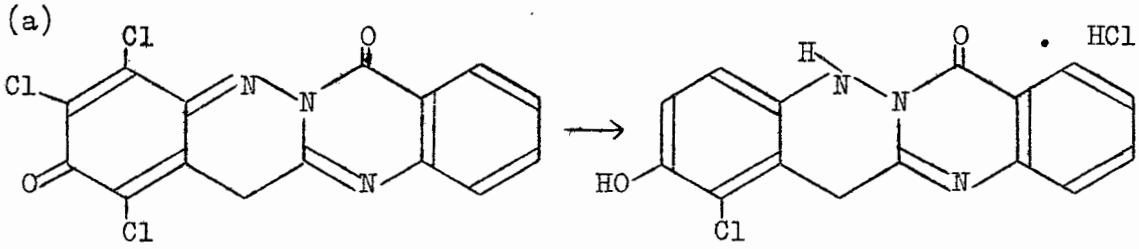
Repeated crystallisation of the pure white needles from acetic acid yielded white needles (1.8 g., 26.6%), m.p. 241 - 241.5°. Graebe[112] reported a melting point of 245° for tetrachlorohydroquinone diacetate.

Repeated crystallisation of the off-white needles yielded white crystals (1.0 g., 16.5%), m.p. 153 - 154°. Graebe[113] reported a melting point of 153° for trichlorohydroquinone diacetate.

Spectroscopic data: I.R. (Tetrachlorohydroquinone diacetate) (in Nujol): $\nu_{max.}$ were at 1780v.s., and 1600v.w. cm.$^{-1}$.
(Trichlorohydroquinone diacetate) (in Nujol): $\nu_{max.}$ were at 1776s., and 1569v.w. cm.$^{-1}$.

Formation of 1-chloro-2-hydroxy-5H-quinazolino[3,2-b]cinnolin-7(13H)-one hydrochloride [and liberation of the base (XCVI)], (a) by reduction of 1,3,4-trichloro-quinazolino[3,2-b]cinnoline-2,7(13H)-dione (LXXXVI), and (b) by hydrolysis of 1-chloro-2,7-diacetoxy-5H-quinazolino[3,2-b]cinnoline (XCVII).

(a)

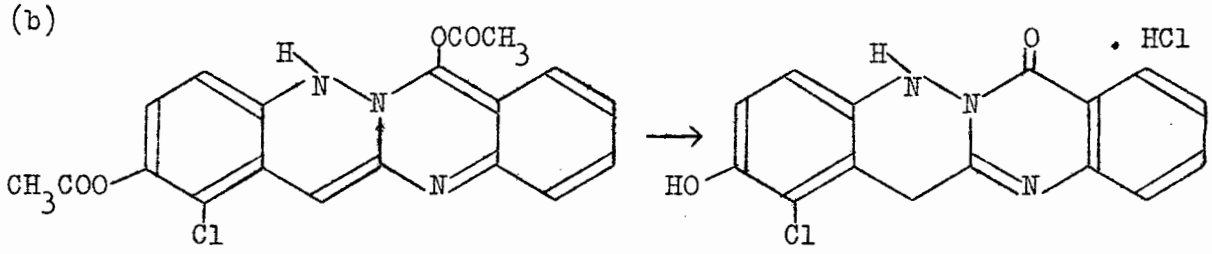


(LXXXVI)

1,3,4-Trichloro-quinazolino[3,2-b]cinnoline-2,7(13H)-dione (LXXXVI) (2.0 g.) was partially dissolved in acetone (200 ml.), and the suspension stirred on a boiling water-bath during addition of granulated zinc (3 x 8 g.) and concentrated hydrochloric acid (3 x 50 ml.) over 3 hr. The yellow compound slowly dissolved and red needles crystallised from the solution. After 1 hr. evolution of hydrogen had ceased, the suspension was centrifuged, and the supernatant solution was decanted by filtration with suction through a filterstick of porosity 2. The crystals were washed with 5N-hydrochloric acid (2 x 200 ml.) until free of zinc ions (negative

test with ammonium mercuric thiocyanate), with acetone (4 x 200 ml.) and with chloroform (30 ml.) by the same centrifuging and decantation procedure. Red needles (1.6 g., 87.1%) which did not melt below 360°, were obtained. The product could not be recrystallised.

(b)



(XCVII)

Sodium (0.1 g.) in cold methanol (5 ml.) was added to a cooled solution of 1-chloro-2,7-diacetoxy-5H-quinazolino[3,2-b]-cinnoline (XCVII) (0.1 g.) in anhydrous methanol (25 ml.) and anhydrous chloroform (3 ml.) at 0°. The yellow solution immediately turned orange, then pink and finally purple, the purple colour darkening very rapidly. The solution was maintained at 0° (1 hr.), the excess of sodium methoxide destroyed by passing carbon dioxide through the solution, and methanol removed in vacuo below 30°. Water was added to the remaining solid and the clear purple solution obtained was filtered. Addition of 5N-hydrochloric acid (10 ml.) precipitated red needles from the solution. The suspension was centrifuged and the product washed with 5N-hydrochloric acid (4 x 100 ml.) by the decantation procedure used in (a) until free of sodium ions. The product was identical with the compound prepared in (a) (infrared spectra).

Analysis:	Calculated for $C_{15}H_{11}N_3Cl_2O_2$	Found
	C 53.6%	C 53.4%
	H 3.3%	H 3.0%
	N 12.5%	N 12.5%
	Cl 21.1%	Cl 21.4%

Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 1772v.s., 1648m., 1633v.s., 1599s., 1580s., 1518m., 1488v.s., 1447v.s., 1404m., 1365s., 1356s., 1347v.s., 1300m.(sh.), and 1284s. $cm.^{-1}$.

(KCl disc): $\nu_{max.}$ were at 3414m., 3068m., and 2781v.s. $cm.^{-1}$.

U.V. (Purple dilute sodium hydroxide solution): $\lambda_{max.}$ were at 562, 389.5, 297, 226, 209, and 205.5 mμ (log ε 3.67, 4.06, 4.66, 4.47, 4.48, 4.50).

(Yellow dilute sodium hydroxide solution): $\lambda_{max.}$ were at 551, 379, 300, 271sh., 212, and 202 mμ (log ε 2.90, 3.86, 4.45, 4.36, 4.32, 4.35).

(Orange hydrochloric acid solution, from acidified yellow sodium hydroxide solution): $\lambda_{max.}$ were at 443, 349, 332, 281, 246, 234, and 214 mμ (log ε 3.17, 3.70, 3.96, 4.18, 4.16, 3.91, 3.87).

Solubility properties: Very soluble in pyridine (bright red solution), dilute ammonia (purple solution, fading to green after a few days), and in dilute sodium hydroxide (purple solution, fading to yellow after a few hours).

Soluble in acetic acid (red-purple solution).

Sparingly soluble in ethanol (red solution), in water (purple-red solution), and in dilute hydrochloric and nitric acids (orange solutions).

Insoluble in neutral organic solvents.

The base, 1-chloro-2-hydroxy-5H-quinazolino[3,2-b]cinnolin-7(13H)-one (XCVI).

The hydrochloride was washed by the centrifuging and decantation procedure used above, with water (5 x 150 ml.) until the washings were free of chloride ions. The base (XCVI) was liberated almost quantitatively as purple micro-crystals. The base was crystallised by dissolving it in a large volume of ethanol, and

concentrating the solution to low volume. Purple needles were obtained. The product did not melt below 360°.

Analysis:	Calculated for $C_{15}H_{10}N_3ClO_2$	Found
	C 60.2%	C 59.7%
	H 3.3%	H 2.6%
	N 14.1%	N 14.2%
	Cl 11.7%	Cl 11.5%
	M.W. 299.8	*M.W.[311.7, 293.8]

Spectroscopic data: I.R. (KCl disc): $\nu_{max.}$ were at 3420s., 3300m., 3100m., 3080m., 1739m., 1642s., 1616s., 1600m.(sh.), 1579s., 1528v.s., 1483v.s., 1415m., 1371m., 1320m., 1291s., and 1284s.(sh.) $cm.^{-1}$.

U.V. (Yellow dilute sodium hydroxide solution): $\lambda_{max.}$ were at 551, 379, 300, 271sh., 212, and 204 mμ (log ε 2.94, 3.85, 4.46, 4.39, 4.36, 4.44).

(Orange hydrochloric acid solution, from acidified yellow sodium hydroxide solution): $\lambda_{max.}$ were at 441, 349, 333, 281, 244, 234, and 216 mμ (log ε 3.20, 3.76, 3.96, 4.19, 4.18, 3.92, 3.91).

Solubility properties: As for the hydrochloride above.

Paper chromatography: R_F values of 1-chloro-2-hydroxy-5H-quinazolino[3,2-b]cinnolin-7(13H)-one (XCVI) and of its hydrochloride were identical in each of the solvent systems 1, 2, 3, and 4 and were 0.75, 0.77, 0.50, and 0.50, respectively.

*Attempted determination of the equivalent weight of 1-chloro-2-hydroxy-5H-quinazolino[3,2-b]cinnolin-7(13H)-one (XCVI) by non-aqueous titration; formation of the perchlorate.

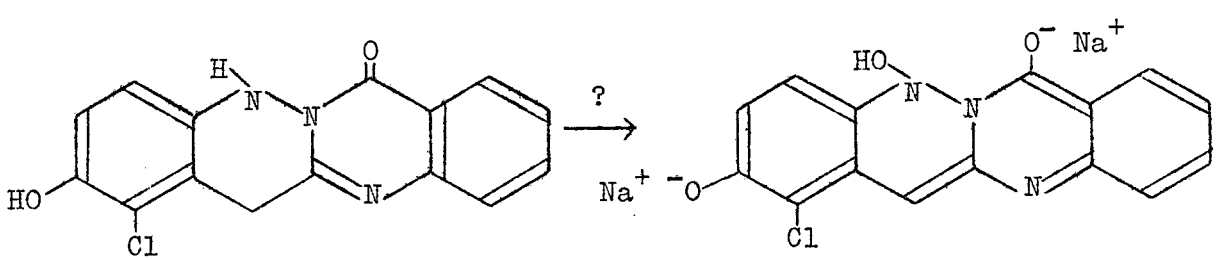
An attempt was made to determine the equivalent weight of the base, 1-chloro-2-hydroxy-5H-quinazolino[3,2-b]cinnolin-7(13H)-

one by non-aqueous titration in acetic acid with acetous perchloric acid, using methyl violet as indicator. The colour of the indicator was, however, completely masked by the dark purple colour of the acetic acid solution of the base. Using the compound as its own indicator gave a gradual colour change from dark scarlet-red to dark orange-red. Values of 311.7 and 293.8 were obtained for the equivalent weight. The base was not very soluble in cold glacial acetic acid and the titration had to be performed at 100°. The solution was cooled and dark red crystals of the perchlorate crystallised from the solution. The product did not melt below 360°.

Analysis:	Calculated for $C_{15}H_{11}N_3Cl_2O_6$	Found
	C 45.0%	C 45.4%
	H 2.8%	H 2.5%
	N 10.5%	N 9.9%
	Cl 17.8%	Cl 18.0%

Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 3242m., 1768s., 1640s., 1618v.s., 1598s., 1576s., 1523s., 1484v.s., 1450s.(sh.), 1401m.(sh.), 1368s., 1354s., 1296m.(sh.), and 1289m. $cm.^{-1}$.

Attempted isolation of the sodium salt formed from 1-chloro-2-hydroxy-5H-quinazolino[3,2-b]cinnolin-7(13H)-one (XCVI).



(XCVI)

A suspension of 1-chloro-2-hydroxy-5H-quinazolino[3,2-b]-cinnolin-7(13H)-one (XCVI) (0.40 g.) in 5N-sodium hydroxide (10 ml.)

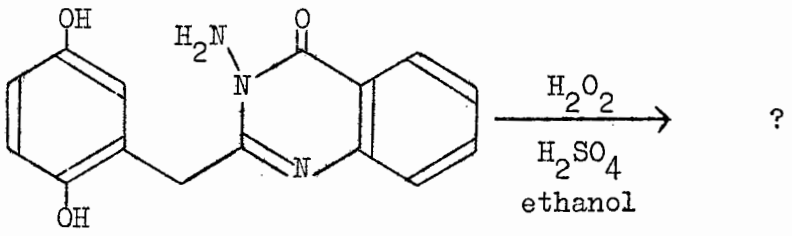
was heated under reflux for 15 min. The solid turned deep purple and rapidly dissolved giving a purple solution which turned yellow-green on heating. Ethanol (80 ml.) was added and the precipitated sodium hydroxide removed by filtration. The solution was evaporated to dryness *in vacuo* and the remaining solid dissolved in water (2 ml.). Ethanol was added until a cloudy suspension formed. The precipitated sodium hydroxide was removed by filtration and the filtrate taken to dryness *in vacuo*. The remaining solid was extracted into hot ethanol and the solution filtered. Benzene was added until precipitation of the dark green micro-crystals which separated from the solution ceased. The product did not melt below 300°.

Analysis:	Calculated for $C_{15}H_8N_3ClNa_2O_3$		Found	
	C	50.1%	C	40.2%
	H	2.2%	H	3.4%
	N	11.7%	N	8.9%
	Cl	9.9%	Cl	7.5%
	Na_2SO_4	39.5%	Na_2SO_4	39.7%

Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 3395 - 3230m. (band), 1595s., and 1534s. $cm.^{-1}$.

Solubility properties: Very soluble in water.
Sparingly soluble in ethanol.
Insoluble in acetone, ether, chloroform, petroleum ether (b.p. 80 - 100°), and benzene.

Attempted oxidation of 3-amino-2-(2,5-dihydroxybenzyl)quinazolin-4(3H)-one (LVIII) with hydrogen peroxide in sulphuric acid and ethanol.



(LVIII)

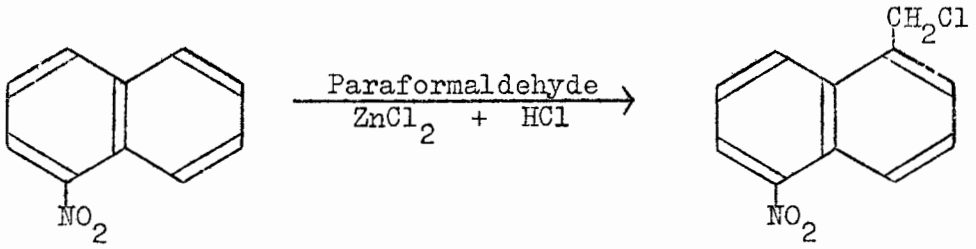
Hydrogen peroxide (2 ml. 30% w./v.) was added to a yellow solution of 3-amino-2-(2,5-dihydroxybenzyl)quinazolin-4(3H)-one (LVIII) (0.6 g.) in 5N-sulphuric acid (10 ml.) and ethanol (10 ml.) and the solution heated under reflux on a boiling water-bath for 4 hr. The solution darkened rapidly to dark red-brown and on cooling, dark scarlet crystals (0.5 g.), no m.p. below 300°, formed. Repeated crystallisation from ethanol failed to give a pure compound: On analysis, a residue was obtained.

EXPERIMENTAL

SECTION II

Preparation of 5-nitro-1-chloromethylnaphthalene.

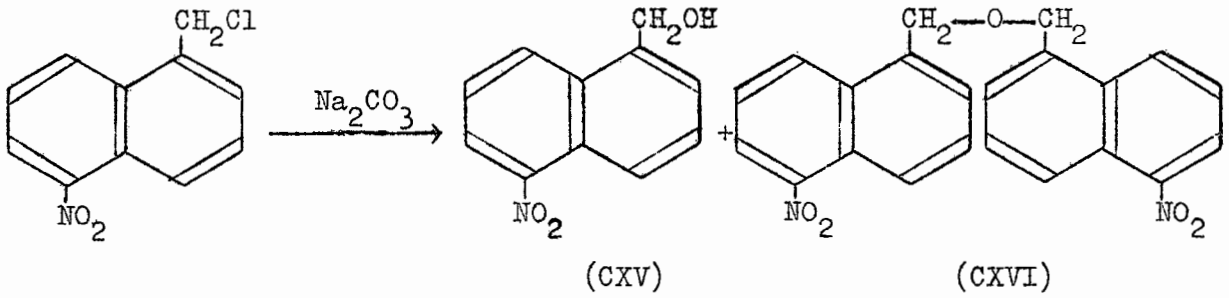
The method of Short and Wang[85] was used.



The compound, m.p. 94 - 96°, was obtained in 64% yield. (Short and Wang obtained 57%, m.p. 96 - 98°).

Preparation of 5-nitro-1-hydroxymethylnaphthalene (CXV) and isolation of bis(5-nitro-1-naphthylmethyl) ether (CXVI).

The method of Short and Wang[85] was used.



(CXV) (CXVI)

5-Nitro-1-hydroxymethylnaphthalene (CXV), m.p. 127 - 127.5°, (chloroform), was obtained in a yield of 75.3%. (Short and Wang obtained 65% yield, m.p. 128 - 129°).

In a repeat preparation, 5-nitro-1-hydroxymethyl-naphthalene, m.p. 128 - 129° (chloroform) was obtained in 56.5% yield. In addition, three crops of yellow crystals, 15.3% m.p. 119 - 120°;

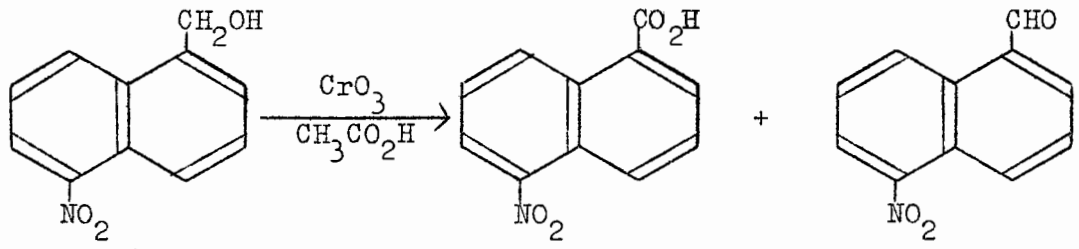
15.8% m.p. 128 - 140°; and 2.3%, m.p. 118 - 129°, were obtained. Repeated crystallisation of these three fractions from chloroform-ethanol or benzene-ethanol mixtures yielded a further 12.6% (total yield 69.1%) 5-nitro-1-hydroxymethylnaphthalene (CXV), m.p. 127 - 128° and a high melting product (14.3%), m.p. 164 - 166°. (Short and Wang isolated no by-product).

Analysis:	Calculated for $C_{22}H_{16}N_2O_5$	Found
	C 68.0%	C 68.1%
	H 4.2%	H 5.0%
	N 7.2%	N 7.6%

Spectroscopic data: I.R. (in Nujol): [Ether (CXVI)]: $\nu_{max.}$ were at 1525s., 1341m., 1326m., 1139m., and 787s. $cm.^{-1}$.
(in Nujol): [5-Nitro-1-hydroxymethyl-naphthalene (CXV)]: $\nu_{max.}$ were at 3295m., 1526s., 1344m., 1328m., 1033m., and 787s. $cm.^{-1}$.

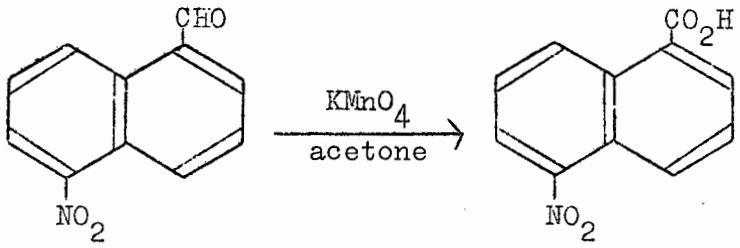
Preparation of 5-nitro-1-naphthoic acid (and 5-nitro-1-naphthaldehyde).

(a) The method of Short and Wang[85] was used.



A yield of 77% 5-nitro-1-naphthoic acid, m.p. 236 - 237° and 20% 5-nitro-1-naphthaldehyde, m.p. 134 - 135° was attained. (Short and Wang obtained 53% nitro-acid, m.p. 237 - 239° and no aldehyde with the conditions used. They reported a melting point of 134 - 136° for the nitro-aldehyde.).

(b) This preparation was modelled on the method of Ruggli and Buckhardt[86].

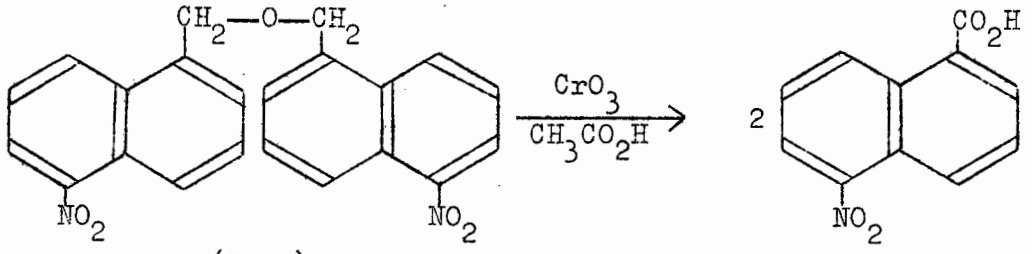


Potassium permanganate (27 g.) was added to a solution of 5-nitro-1-naphthaldehyde (38.7 g.) in acetone (1300 ml.). The solution was heated under reflux on a waterbath for 75 min., and acetone was then removed by distillation. The residue obtained was dispersed in 2N-sodium carbonate and solid suspension filtered off from the solution. When the filtrate was acidified with concentrated hydrochloric acid, buff crystals (37.8 g., 92.6%), precipitated from the solution. The product was identical with the nitro-acid prepared in (a) (m.p., and mixed m.p.). (Ruggli and Buckhardt quoted a melting point of 236 - 237° for the nitro-acid and did not report the yield they obtained.)

The solid material obtained from the sodium carbonate solution by filtration, consisted of 5-nitro-1-naphthaldehyde and manganese dioxide. Manganese dioxide was dissolved in an excess of concentrated hydrochloric acid and the aldehyde (2.4 g.), m.p. 133 - 135° was removed by filtration.

Yield of nitro-acid based on unrecovered nitro-aldehyde was 96.5%.

(c) This preparation was modelled on the oxidation of 5-nitro-1-hydroxymethylnaphthalene by Short and Wang[85].

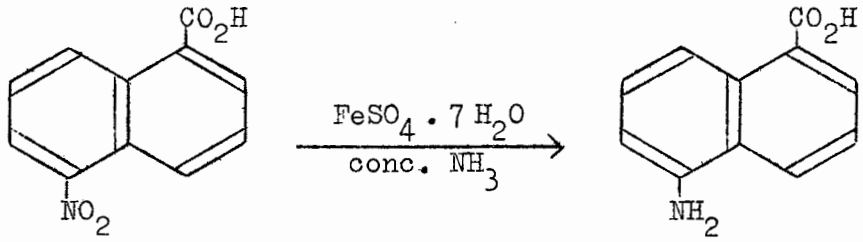


(CXVI)

A solution of chromic anhydride (1.8 g.) in hot acetic acid (55 ml.) was added over 1.5 hr. to a stirred solution of the ether (CXVI) (2.2 g.) in acetic acid (22 ml.). The temperature was maintained at 65 - 70° during the addition and subsequently for an hour. The solution was concentrated to 8 ml. below 80°, and the residue was washed with 5N-hydrochloric acid and with water. Extraction of the residue with 2N-sodium carbonate removed 5-nitro-1-naphthoic acid (1.0 g., 40.7%), m.p. 233 - 235°. Reprecipitation from sodium carbonate solution with 5N-hydrochloric acid yielded the nitro-acid (0.9 g.), m.p. 234 - 235°, unchanged in admixture with the nitro-acid prepared in (a). The residue (0.8 g.), m.p. 144 - 152° consisted of a mixture of 5-nitro-1-naphthaldehyde and starting material, (mixed melting points and positive aldehyde test with Brady's reagent.)

Preparation of 5-amino-1-naphthoic acid.

The method of Short and Wang[85] was used.

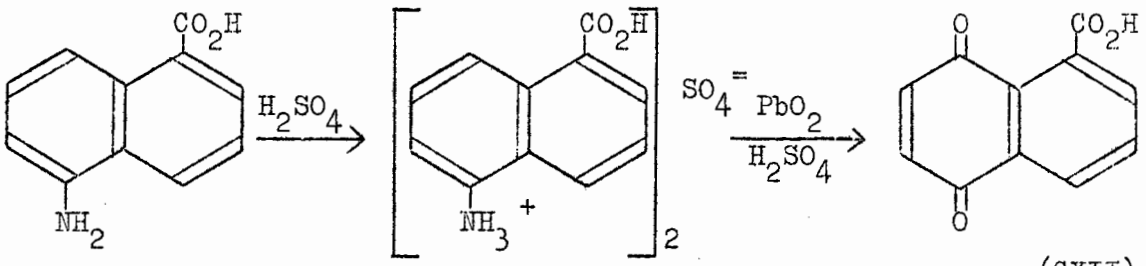


5-Amino-1-naphthoic acid, m.p. 210.5 - 211° was obtained in 88.8% yield. (Short and Wang obtained 82% crude product which on

crystallisation melted at 201 - 202°). Ekstrand[84] found a melting point of 212 - 213° for this amino-acid.

Preparation of 1,4-naphthaquinon-5-ylcarboxylic acid (CXII).

The method of Willstätter et al.[83] was used.



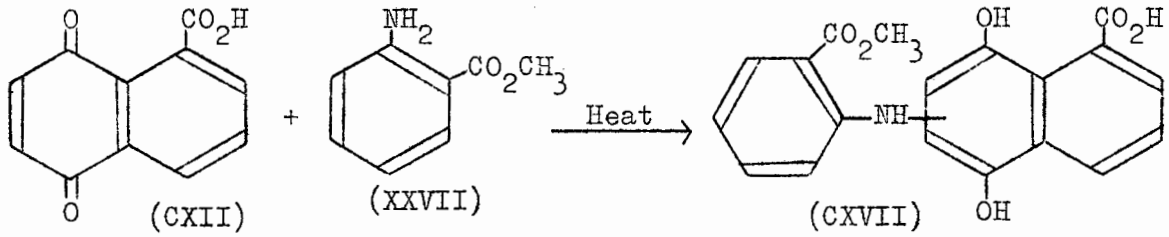
(CXII)

The quinone-acid (CXII) was obtained in 65% yield. It darkened at 155°, blackened at 160 - 174° and melted at 202 - 204° (decomp.). (Willstätter et al. obtained the compound in 62% yield and stated that the compound had no m.p., but turned brown at 164° and from brown to black at 170 - 185°).

The product contained no nitrogen.

Spectroscopic data: I.R. (KCl disc): $\nu_{max.}$ were at 3420s., 3075m., 3045m., 2933m., 1712s.(sh.), 1698s., 1676s., 1610m., 1582m., 1476m., 1447w., and 1412m. $cm.^{-1}$.

Fusion of 1,4-naphthaquinon-5-ylcarboxylic acid (CXII) and methyl anthranilate (XXVII); formation of 5,8-dihydroxy-6-(or-7-)-(o-methoxycarbonylanilino)-1-naphthoic acid (CXVII).



(CXII) (XXVII) (CXVII)

1,4-Naphthaquinon-5-ylcarboxylic acid (CXII) (1.0 g.) and methyl anthranilate (XXVII) (4.0 ml.) were heated slowly to 123° during 45 min. and maintained at 123 - 130° for 1 hr. under slight vacuum to remove any water formed in the condensation. The excess of methyl anthranilate was removed in vacuo below 160°, the black gum obtained was taken up in ethanol (12 ml.) and the solution was cooled (12 hr.). Orange-brown crystals (0.6 g., 34.4%), m.p. 215° were removed from suspension by filtration and crystallised from ethanol to yield red needles (0.3 g.), m.p. 214 - 215° with sintering at 209°.

Analysis:	Calculated for $C_{19}H_{15}NO_6$	Found
	C 64.7%	C 65.0%
	H 4.3%	H 4.3%
	N 4.0%	N 3.9%

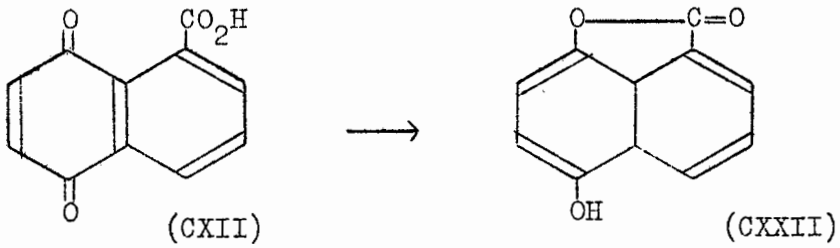
Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 3275m., 3185m., 1746s., 1697s., 1624v.s., 1573v.s., 1540s., 1452s.(sh.), 1354m., 1316m., 1294s., 1280s., and 1268s. $cm.^{-1}$.

Solubility properties: Soluble in hot ethanol, benzene, acetic acid, dilute sodium hydroxide (purple solution), and dilute sodium bicarbonate (orange solution).

Sparingly soluble in dilute nitric acid (red solution).

Insoluble in petroleum ether (b.p. 100 - 120°).

Reduction of 1,4-naphthaquinon-5-ylcarboxylic acid (CXII) to the lactone of 5,8-dihydroxy-1-naphthoic acid, (CXXII).



(CXII) (CXXII)

(a) This preparation was modelled on method (iii) of the reduction of 8-oxodecahydronaphthoic acid by Wheeler and Wheeler[87].

A solution of sodium borohydride (479 mg.) in water (4 ml.) was added to a yellow solution of 1,4-naphthaquinon-5-yl-carboxylic acid (CXII) (405 mg.) and sodium bicarbonate (186 mg.) in water (8 ml.). The solution faded and after standing for 25 hr., it was acidified with 20% sulphuric acid. The solution, which darkened on standing, was extracted with ethyl acetate. The ethyl acetate solution was washed with saturated sodium chloride solution, dried (Na_2SO_4) and the solvent removed. The gum obtained could not be crystallised. Paper chromatography of the gum and of the product obtained in (c) below in solvent systems 1, 2, 3, and 4 (page 133) showed that no lactone (CXXII) had formed.

(b) This preparation was modelled on method (i) of the reduction of 8-oxodecahydronaphthoic acid by Wheeler and Wheeler[87].

Sodium (8 g.) was added during 1.5 hr. to a solution of the quinone (CXII) (414 mg.) in propanol (100 ml.) heated under reflux in a metal-bath. Addition of sodium turned the solution green, the colour darkening rapidly to yellow-brown. After the sodium had dissolved (2 hr.), 5N-hydrochloric acid was added to the solution and the acidified solution was extracted with ethyl acetate. The ethyl acetate solution was washed with saturated sodium chloride solution, dried (Na_2SO_4), and the solvent removed. The dark-brown gum obtained could not be crystallised.

(c) Granulated zinc (2 g.) and concentrated hydrochloric

acid (15 ml.) were slowly added to a solution of 1,4-naphthaquinon-5-ylcarboxylic acid (CXII) (0.5 g.) in ethanol (25 ml.) heated under reflux on a boiling water-bath for 1.5 hr. The solution was concentrated and any black solid which separated from the solution was removed by filtration. The solution was cooled (24 hr.) and clusters of brown needles, m.p. 201 - 208° were filtered off from suspension. Crystallisation from dilute ethanol with decolourising charcoal yielded tan feathers of the lactone (CXXII) (0.3 g., 65.2%), m.p. 231 - 233°. Repeated crystallisation from ethanol-benzene-petroleum ether (b.p. 60 - 80°) mixture raised the m.p. to 241 - 242° with sintering at 239°.

In repeat preparations, gums were obtained. Vacuum sublimation of the dried gums yielded no product.

(d) Zinc dust (0.1 g.) was added to a solution of 1,4-naphthaquinon-5-ylcarboxylic acid (CXII) (0.5 g.) in acetic acid (5 ml.). The light brown solution darkened and was left at room temperature for 5 min. Zinc dust (0.1 g.) was added and the solution heated under reflux for 5 min. The solution turned yellow. Inorganic material was removed by filtration and water was added to the filtrate until crystallisation was incipient. Cooling at 4° (14 hr.) precipitated yellow crystals (0.1 g., 2.2%), m.p. 224 - 230°, from the solution. The melting point was raised to 235 - 236° in admixture with the product prepared in (c).

Analysis:	Calculated for $C_{11}H_6O_3$	Found
	C 70.9%	C 70.5%
	H 3.3%	H 3.2%

Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 3317s., 1737v.s., 1652s., 1639m., 1609w., 1520w., and 1485v.s. $cm.^{-1}$.

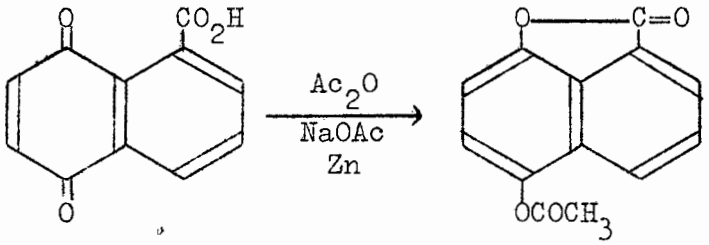
Solubility properties: Soluble in ethanol, chloroform and acetic acid.

Sparingly soluble in benzene.

Insoluble in water and petroleum ether.

Reductive acetylation of 1,4-naphthaquinon-5-ylcarboxylic acid (CXII); formation of the lactone of 5-acetoxy-8-hydroxy-1-naphthoic acid, (CXXIII).

The conditions used for the reductive acetylation[51] of p-benzoquinone were used.



(CXII) (CXXIII)

1,4-Naphthaquinon-5-ylcarboxylic acid (5.0 g.), zinc dust (3.0 g.), anhydrous sodium acetate (0.6 g.) and acetic anhydride (15 ml.) were warmed gently for 6 min. and then boiled for 6 min. The light yellow solution was decanted from the solid which was extracted with acetic acid (2 x 8 ml.). The acetic anhydride and acetic acid solutions were combined and concentrated (10 ml.). Water was added until crystallisation was incipient and on cooling the solution, yellow crystals formed, (4.4 g., 78%), m.p. 121 - 122°. Crystallisation from ethanol with decolourising charcoal yielded pale yellow crystals of the acetate (CXXIII) (3.3 g., 58.5%), m.p. 125 - 126°.

Analysis:	Calculated for $C_{13}H_8O_4$	Found
	C 68.4%	C 68.5%
	H 3.5%	H 3.7%

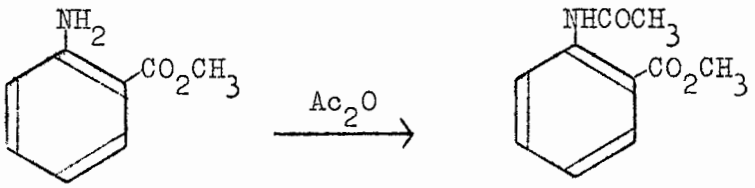
Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 1788v.s.,

1760v.s., 1654m., 1635w., 1604w., 1500w., and 1461v.s. cm.$^{-1}$.

Solubility properties: The product was insoluble in cold dilute sodium hydroxide, but dissolved on heating the suspension. Addition of hydrochloric acid to the solution precipitated yellow material from the yellow-brown solution.

Preparation of methyl o-acetamidobenzoate (CXXIV).

The conditions used for the acetylation of amines[114] were used.



(XXVII) (CXXIV)

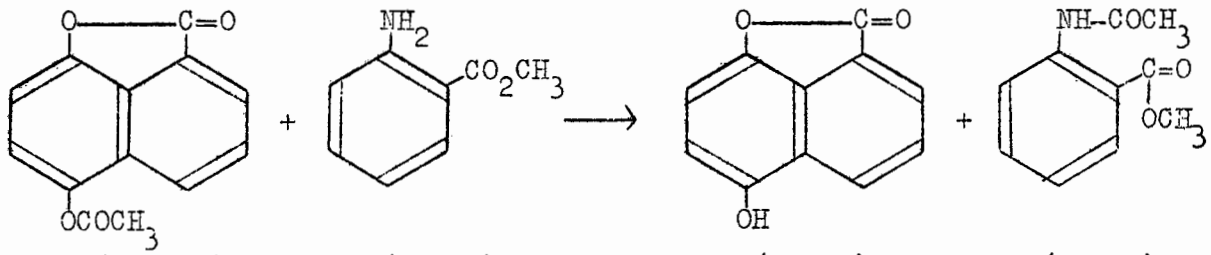
Methyl o-acetamidobenzoate (CXXIV), m.p. 98 - 100°, was obtained in a yield of 75.4% (from 96% ethanol). [Heilbron's Dictionary of Organic Compounds gives a melting point of 101° for the acetate (CXXIV)].

Spectroscopic data: I.R. †(in Nujol): $\nu_{max.}$ were at 3260s., 1688s., 1601s., 1589s., and 1520s. cm.$^{-1}$.

---

† Perkin-Elmer 237 Grating infrared spectrophotometer.

Attempted fusion of the lactone of 5-acetoxy-8-hydroxy-1-naphthoic acid, (CXXIII) with methyl anthranilate (XXVII); formation of the lactone of 5,8-dihydroxy-1-naphthoic acid, (CXXII), and methyl o-acetamidobenzoate (CXXIV).



(CXXIII) (XXVII) (CXXII) (CXXIV)

(a) The lactone of 5-acetoxy-8-hydroxy-1-naphthoic acid, (CXXIII) (0.8 g.) and methyl anthranilate (XXVII) (3 ml.) were heated to 100° during 15 min., to 130° during 1 hr. and maintained at 130 - 135° for 2 hr. The excess of methyl anthranilate was removed in vacuo below 190° and the residue was dissolved in hot ethanol. On cooling the solution, yellow crystals (0.6 g., 84.6%), m.p. 224°, were obtained. Crystallisation from dilute ethanol and from an ethanol-benzene-petroleum ether (b.p. 60 - 80°) mixture raised the melting point to 241 - 242°, with sintering at 238°, not lowered in admixture with authentic lactone of 5,8-dihydroxy-1-naphthoic acid, (CXXII).

(b) The lactone of 5-acetoxy-8-hydroxy-1-naphthoic acid, (CXXIII) (0.5 g.) and methyl anthranilate (XXVII) (2.5 ml.) were boiled for 5 min., and the solution was cooled. A sample of the solution (0.1 ml.) was removed for gas-liquid chromatographic analysis. Benzene (10 ml.) was added to the remaining solution and the crystalline precipitate which formed was filtered off from suspension and washed with benzene. This yielded yellow crystals (0.3 g., 73.5%), m.p. 234 - 236°, not lowered in admixture with authentic lactone of 5,8-dihydroxy-1-naphthoic

acid, (CXXII).

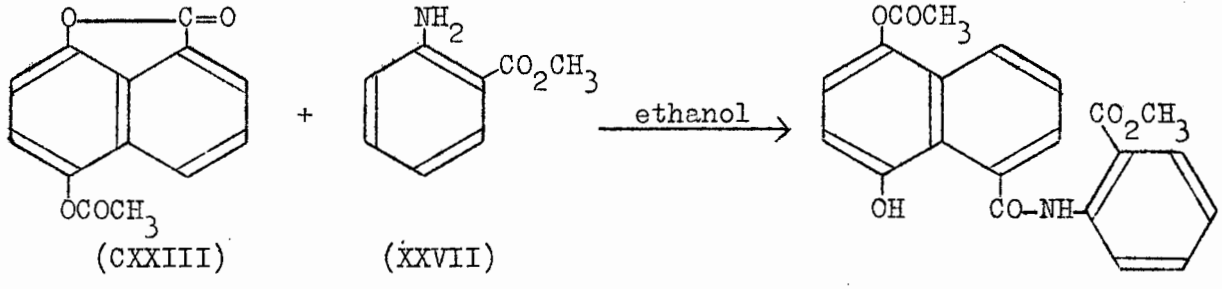
Gas-liquid chromatography on the sample revealed the presence of methyl o-acetamidobenzoate (CXXIV).

Gas-liquid chromatography data: Gas-liquid chromatography was performed on a Beckman GC 2A gas chromatograph, flame ionisation detector, nitrogen carrier gas. The column used was of 3 ft. x 0.25 in. (18 gauge) copper tubing, packed with 6% ethylene glycol succinate polyester on 80 - 100 mesh Gas Chromosorb P: An operating temperature of 155° and an inlet pressure of 20 p.s.i.g. were used.

The retention times were: Methyl anthranilate: 17 min.
Methyl o-acetamidobenzoate: 44.5 min.
Lactone (CXXIII): Above 216 min.
Lactone (CXXII): Above 216 min.

Attempted preparation of 5-acetoxy-8-hydroxy-N-(o-methoxycarbonyl-phenyl)-1-naphthamide.

This preparation was modelled on the amide formation of Blair et al.[89].



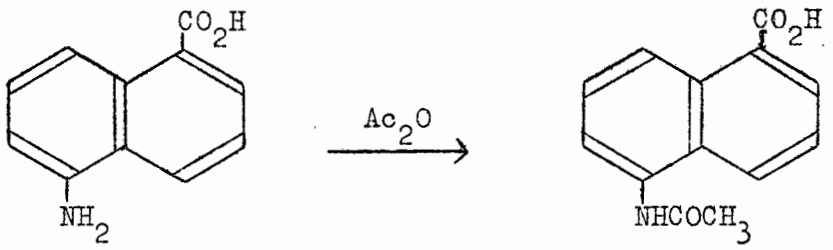
(CXXIII) (XXVII)

Methyl anthranilate (XXVII) (5.8 ml.) was added to a solution of the lactone of 5-acetoxy-8-hydroxy-1-naphthoic acid, (CXXIII) (1.0 g.) in ethanol (52 ml.). The solution was left at room temperature for 108 hr. and the yellow needles which crystallised from

the solution were removed by filtration. This yielded the starting lactone (CXXIII) (0.2 g.), m.p. and mixed m.p. 121 - 123.5°. Concentration of the solution afforded further lactone (CXXIII) as yellow needles, (0.7 g.) melting in the same range. Percentage recovery was 90%.

Preparation of 5-acetamido-1-naphthoic acid.

The method of Ekstrand[90] was used.

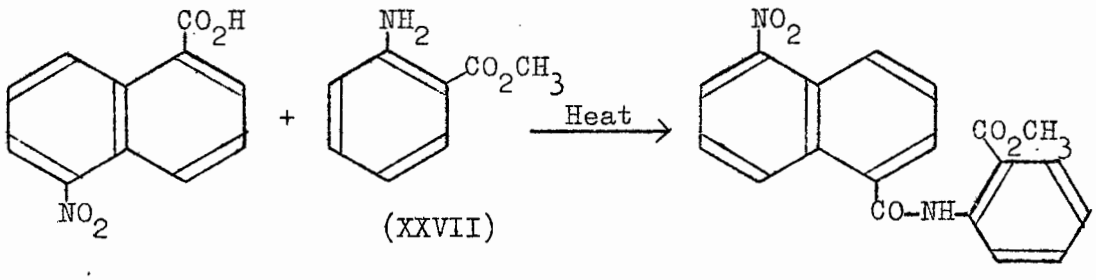


The product obtained (96%) did not melt below 295°. Ekstrand reported the m.p. as above 288° and reported no figure for the yield he obtained.

Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 3265s., 2620m., 1691v.s., 1660v.s., 1629s., 1600m., 1587m., 1545s., 1515v.s., 1472s., 1429m., 1405m., and 1345s. $cm.^{-1}$.

Attempted fusions of (a) 5-nitro-1-naphthoic, (b) 5-acetamido-1-naphthoic, (c) 1-naphthoic, (d) 2,5-dihydroxybenzoic, and (e) benzoic acids with methyl anthranilate (XXVII).

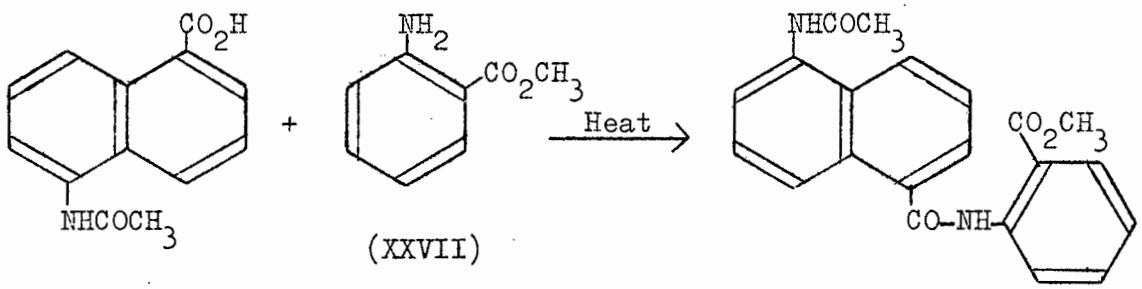
(a)



5-Nitro-1-naphthoic acid (2.4 g.) and methyl anthranilate (XXVII) (16 ml.) were heated together to 200° during 35 min. and maintained at 205 - 210° for 4 hr. under slight vacuum (740 mm.). The excess of methyl anthranilate was removed in vacuo (2.0 mm.) and the black residue was crystallised from ethanol with decolourising charcoal yielding tan crystals of 5-nitro-1-naphthoic acid (1.9 g.), m.p. and mixed m.p. 234-235°. Percentage recovery was 79.2%.

In previous fusions at 140° (2 hr.) and 190° (2 hr.), the percentage recoveries were 93.3% and 89.4%, respectively.

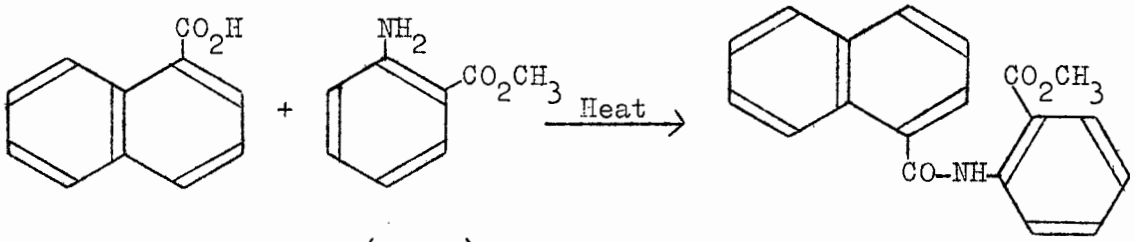
(b)



(XXVII)

5-Acetamido-1-naphthoic acid (3.0 g.) and methyl anthranilate (15 ml.) were heated and worked up as described in (a), considerable decomposition occurring, to give 5-acetamido-1-naphthoic acid (2.2 g.) with the same infrared spectrum. Percentage recovery was 73.3%.

(c)

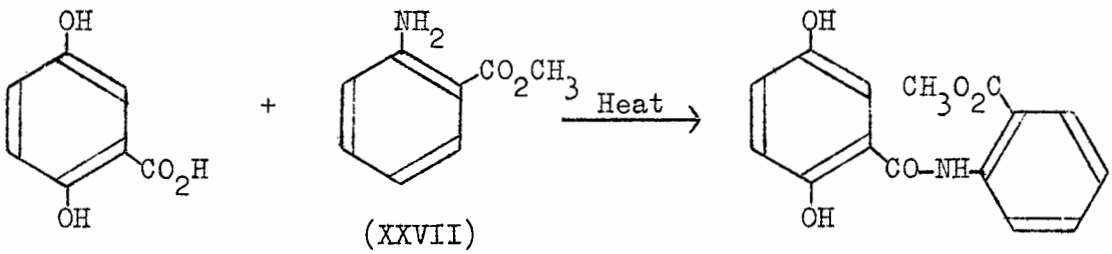


(XXVII)

1-Naphthoic acid (2.0 g.) and methyl anthranilate (8 ml.) were heated together to 170° during 45 min. and maintained at 160-

180° for 1.5 hr. under slight vacuum (740 mm.). The reaction mixture was worked up as described in (a) yielding white crystals (1.5 g.), m.p. 157 - 158°. Recrystallisation from ethanol raised the m.p. to 159 - 160°, which was raised to 160 - 160.5° in admixture with starting material. Percentage recovery was 72.5%.

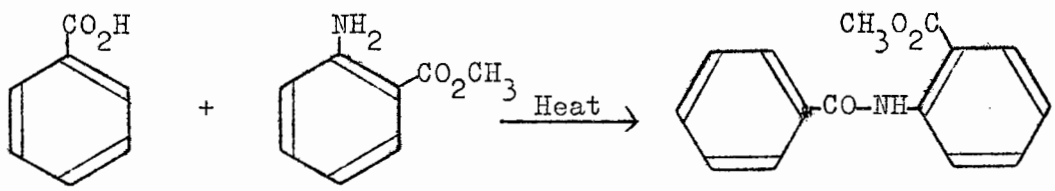
(d)



(XXVII)

2,5-Dihydroxybenzoic acid (5.0 g.) and methyl anthranilate (17.8 ml.) were heated and worked up as described in (c), but benzene was added to the crystalline residue obtained after removal of the excess of methyl anthranilate. Filtration of the suspension yielded off-white crystals (4.9 g.), m.p. 191 - 192° (decomp.), raised to 198 - 199° (decomp.) in admixture with pure starting product. Percentage recovery was 98%.

(e)

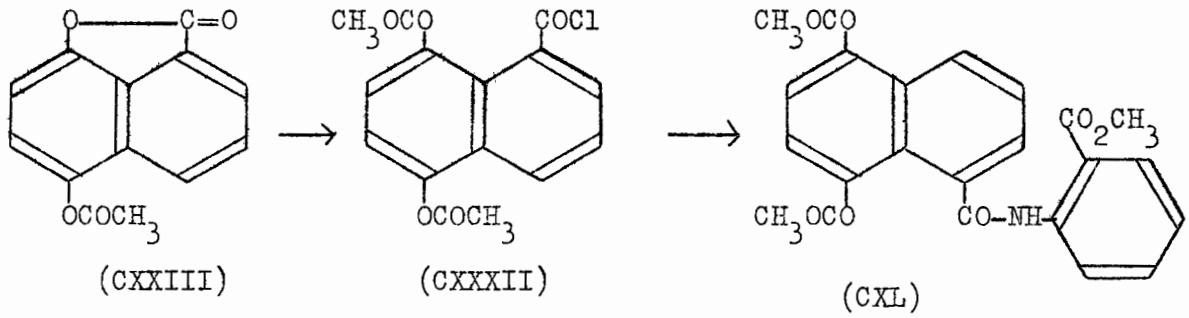


(XXVII)

Benzoic acid (4.1 g.) and methyl anthranilate (10 ml.) were heated to 150° during 45 min. and maintained at 140 - 160° for 1.5 hr. The excess of methyl anthranilate was removed <u>in vacuo</u>. A white solid distilled over with methyl anthranilate. The distillate

was dissolved in ether and extracted with 2N-sodium carbonate solution (3 x 15 ml.). The sodium carbonate extract was washed with ether (2 x 15 ml.) and acidified with 5N-hydrochloric acid. The white precipitate obtained was removed by filtration and washed with water, yielding benzoic acid (3.5 g.), m.p. and mixed m.p. 121.5-122°. Crystallisation of the black residue obtained after removal of methyl anthranilate yielded a further 0.3 g. benzoic acid melting in the same range. Percentage recovery was 92.6%.

Attempted formation of 5,8-diacetoxy-N-(o-methoxycarbonylphenyl)-1-naphthamide (CXL) from the reaction of methyl anthranilate (XXVII) and the acid chloride (CXXXII) from the lactone of 5-acetoxy-8-hydroxy-1-naphthoic acid, (CXXIII).



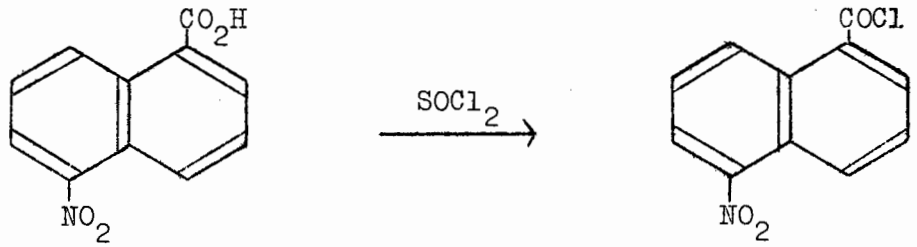
(CXXIII) (CXXXII) (CXL)

The lactone of 5-acetoxy-8-hydroxy-1-naphthoic acid, (CXXIII) (0.8 g.), acetyl chloride (0.8 ml.) and thionyl chloride (0.8 ml.) were heated under reflux for 1 hr. and the excess of thionyl chloride and of acetyl chloride were removed in vacuo. The yellow residue obtained was dissolved in anhydrous benzene and the solvent was removed in vacuo. This treatment with benzene was repeated twice more. The yellow residue was dissolved in methyl anthranilate (1.4 ml.) and after 20 min. ether (20 ml.) was added to the solution. When the solution was cooled yellow crystals formed and were filtered off from the suspension. This yielded yellow

crystals (0.6 g.), m.p. 123 - 125°, raised to 125 - 126° in admixture with authentic lactone of 5-acetoxy-8-hydroxy-1-naphthoic acid, (CXXIII). Percentage recovery was 75%.

Preparation of 5-nitro-1-naphthoyl chloride.

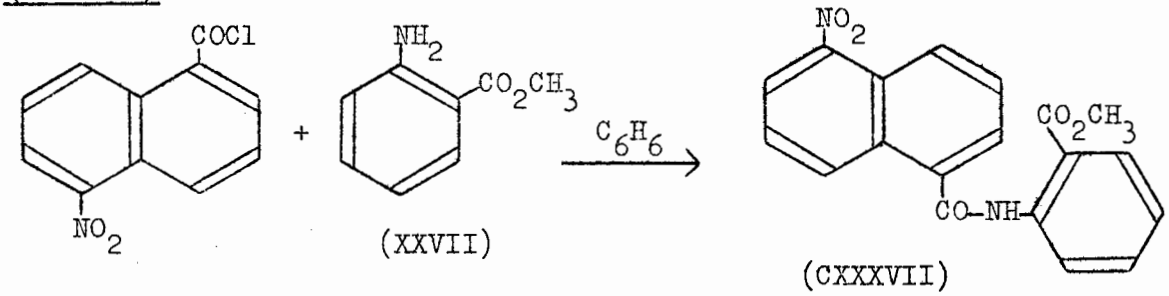
The method of Blicke and Parke was used[93].



The acid chloride (77.5%) obtained melted at 130 - 131°. (Blicke and Parke reported a melting point of 132 - 134° for the acid chloride but no quantity for the yield they obtained.)

Petroleum ether (b.p. 90 - 100°) insoluble material was heated under reflux with 5N-sodium hydroxide (30 ml.) for 30 min. The solution was filtered through animal charcoal and acidified with 5N-hydrochloric acid. The buff precipitate obtained was filtered off from suspension and washed with water yielding 5-nitro-1-naphthoic acid (3.5 g., 14%), m.p. 235 - 237°. Percentage yield acid chloride based on unrecovered nitro-acid was 90.1%.

Preparation of 5-nitro-N-(o-methoxycarbonylphenyl)-1-naphthamide (CXXXVII).



(XXVII)

(CXXXVII)

Anhydrous methyl anthranilate (25 ml.) was added to a warm solution of 5-nitro-1-naphthoyl chloride (18.2 g.) in anhydrous benzene (100 ml.) under reflux. The solution became very hot and an immediate white precipitate formed. The mixture was kept at 100° for 45 min. and benzene was removed in vacuo. The solid residue was pulverised and 2N-sodium bicarbonate solution (35 ml.) was added to the solid to liberate methyl anthranilate from its hydrochloride. The oily white product obtained was filtered off and pressed on the filter-pad to remove methyl anthranilate. The oily solid was suspended in 96% ethanol (50 ml.) and washed. The white solid was filtered off and again washed by suspension in 96% ethanol (40 ml.). Filtration of the suspension yielded white crystals of the nitro-amide (CXXXVII) (25.9 g., 95.3%), m.p. 205 - 206°. Crystallisation from ethanol raised the melting point to 206.5 - 207.5°.

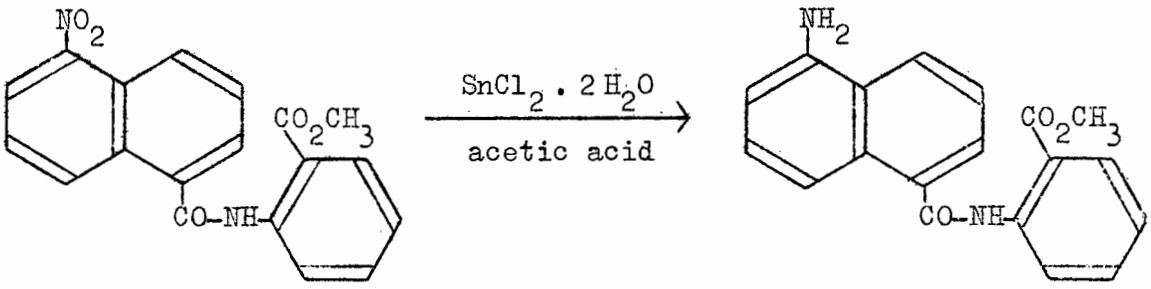
The sodium bicarbonate washings were extracted with ether (3 x 25 ml.) and acidified with concentrated hydrochloric acid precipitating buff crystals of 5-nitro-1-naphthoic acid (0.6 g.), m.p. and mixed m.p. 236 - 237°, from the solution. Percentage yield nitro-amide (CXXXVII) based on unrecovered 5-nitro-1-naphthoic acid was 98.9%.

Analysis:	Calculated for $C_{19}H_{14}N_2O_5$	Found
	C 65.2%	C 65.2%
	H 4.0%	H 4.2%
	N 8.0%	N 8.2%

Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 3230w., 1697s., 1683s., 1611m., 1595m., 1539s., 1525v.s., 1432m., 1357m., 1333m., 1300m., 1276v.s., and 1262s. $cm.^{-1}$.

Preparation of 5-amino-N-(o-methoxycarbonylphenyl)-1-naphthamide (CXXXVIII).

This preparation was modelled on the reduction of nitro-esters by Blicke and Parke[93].



(CXXXVII) (CXXXVIII)

Crushed stannous chloride dihydrate (234 g.) was added to a stirred suspension of 5-nitro-N-(o-methoxycarbonylphenyl)-1-naphthamide (CXXXVII) (27.0 g.) in acetic acid (372 ml.) under anhydrous conditions. Dry hydrogen chloride was passed through the solution maintained at 40 - 60° for 2 hr. The suspension thickened to a paste (7 min.) and subsequently thinned to a slurry (30 - 45 min.) which was saturated with hydrogen chloride. After 12 hr. the fine white crystals of the tin salt addition compound were removed from suspension by filtration and dried in an efficient hood. The acetic acid filtrate was concentrated in vacuo. The concentrated solution with precipitated product, and the dried tin salt addition compound were combined and made strongly alkaline with 5N-sodium hydroxide (4000 ml.). The white solid turned yellow in a yellow aqueous solution. Water (1000 ml.) was added to the suspension to dissolve sodium chlorostannate which had precipitated from the solution and the suspension was continuously extracted with ether until the yellow suspension had dissolved and the ether layer was colourless. Removal of the ether in vacuo yielded tan crystals (18.9 g., 76.6%), m.p.

147 - 149°. Crystallisation from ethanol (450 ml.) yielded yellow crystals of the amino-amide (CXXXVIII) (17.8 g., 72.2%), m.p. 148 - 149° and concentration of the ethanol yielded further yellow crystals (0.7 g., 2.8%), melting in the same range. Repeated crystallisation of the product from ethanol raised the m.p. to 151 - 152°.

Prolonged saturation of the reaction mixture with hydrogen chloride turned the fine white crystals pink, with no detriment to the product.

Analysis:	Calculated for $C_{19}H_{16}N_2O_3$	Found
	C 71.3%	C 71.1%
	H 5.0%	H 4.7%
	N 8.8%	N 8.6%

Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 3349w., 3255w., 3205w., 1695m., 1669m., 1609m., 1589m., 1536m., 1518m., 1454v.s., 1300s., 1277s., and 1260s. $cm.^{-1}$.

The hydrochloride.

The amine was dissolved in ethanol and concentrated hydrochloric acid was added to the solution. The mixture was concentrated and cooled yielding white crystals of 5-amino-N-(o-methoxycarbonylphenyl)-1-naphthamide hydrochloride, m.p. 235.5 - 236.5° (decomp.). Crystallisation from ethanol raised the m.p. to 237 - 238° (decomp.).

Analysis:	Calculated for $C_{19}H_{16}N_2O_3.HCl$	Found
	C 64.0%	C 64.3%
	H 4.8%	H 4.9%
	N 7.9%	N 7.8%
	Cl 10.0%	Cl 10.2%

Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 3285w., 3269w., 1691s., 1665w.(sh.), 1608s., 1594s., 1541s., 1518s., 1468s.(sh.),

1434m., 1322m., 1303s., 1287s., 1272s.(sh.), and 1246m. cm.$^{-1}$.

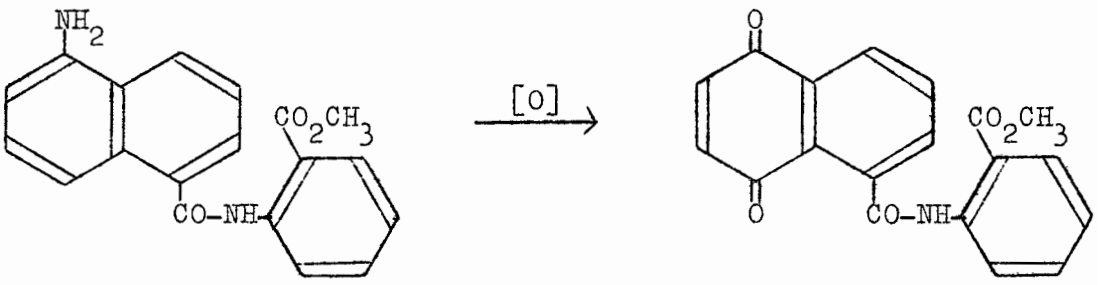
The bisulphate (CXXXIX).

The amine was dissolved in ethanol and dilute sulphuric acid was added to the solution. Pink crystals, m.p. 191 - 192° (decomp.), precipitated from the solution. Crystallisation from ethanol yielded white needles of 5-amino-N-(o-methoxycarbonylphenyl)-1-naphthamide bisulphate (CXXXIX), m.p. 193 - 193.5° (decomp.).

Analysis: Calculated for $C_{19}H_{16}N_2O_3.H_2SO_4$ Found
S 7.7% S 7.9%

Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 3229w., 2638m., 1697s., 1661s., 1611s., 1590s., 1569s., 1541s., 1520s., 1421w., 1321s., 1292v.s., 1278s., and 1257m. cm.$^{-1}$.

Preparation of N-(o-methoxycarbonylphenyl)-1,4-naphthaquinon-5-yl-carboxamide (CXIII).



(CXXXVIII) (CXIII)

(a) This preparation was modelled on the oxidation of diaminodurene with ferric chloride by Smith and Denyes[94].

A solution of ferric chloride (2.0 g.) in water (6.0 ml.) was added to a suspension of 5-amino-N-(o-methoxycarbonylphenyl)-1-naphthamide (CXXXVIII) (0.5 g.) in ethanol (20 ml.) and concentrated

hydrochloric acid (1 ml.). The mixture was shaken for 3 hr. and then left to stand with frequent shaking for 43 hr. Solid material was filtered off from suspension and washed with 5N-hydrochloric acid and with water to yield mauve crystals (0.4 g.), m.p. 235 - 236° (decomp.), darkening at 232°. Crystallisation from ethanol yielded white crystals which melted in the same range, even in admixture with an authentic sample of 5-amino-N-(o-methoxycarbonylphenyl)-1-naphthamide hydrochloride. Percentage recovery of the amine was 72.2%.

(b) This preparation was modelled on the oxidation of 5-amino-1-naphthoic acid to 1,4-naphthaquinon-5-ylcarboxylic acid by Willstätter et al.[83].

5-Amino-N-(o-methoxycarbonylphenyl)-1-naphthamide (CXXXVIII) bisulphate (3.0 g.) was rubbed with lead(IV) dioxide (30 g.) and 25% sulphuric acid (75 ml.) and the suspension was shaken for 15.5 hr. Solid material was filtered off from the suspension and washed with water until free of sulphate ions. The black solid obtained was dried and continuously extracted with ether for 15 hr. in a Soxhlet apparatus. Removal of ether in vacuo yielded dark red material (0.8 g.), m.p. 162 - 167°, with sintering at 155°.

Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 3305w., 3275w., 1720w. (sh.), 1692s.(sh.), 1681s., 1609s., 1590s., and 1524s. $cm.^{-1}$.

Solubility properties: Soluble in benzene, acetone, ether, and ethanol.

Insoluble in petroleum ether (b.p. 80 - 100°), and cyclohexane.

(c) This preparation was modelled on the oxidation of xylidines to dimethylquinones by James, Snell, and Weissberger[63].

A solution of potassium dichromate (40 g.) in water (400 ml.) and concentrated sulphuric acid (40 ml.) was added during 30 min. to a stirred suspension of 5-amino-N-(o-methoxycarbonylphenyl)-1-naphthamide (CXXXVIII) (4.0 g.) in water (400 ml.) and concentrated sulphuric acid (40 ml.). The suspension was stirred for 96 hr. and solid material was filtered off and washed with water until free of inorganic ions. This yielded a dark red powder (3.2 g.) which proved to be identical with the product obtained in (b), (m.p., mixed m.p., and infrared spectra).

Extraction of the red powder with hot cyclohexane yielded yellow-orange crystals of the quinone (CXIII) (1.1 g., 26.3%), m.p. 134 - 137°. Crystallisation from benzene-petroleum ether (b.p. 80 - 100°) yielded yellow crystals, m.p. 138 - 139°.

Analysis:	Calculated for $C_{19}H_{13}NO_5$	Found
	C 68.1%	C 68.5%
	H 3.9%	H 4.1%
	N 4.2%	N 4.1%

Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 3312m., 1720m., 1696m.(sh.), 1688s., 1672s., 1613m., 1594s., 1537s., 1515m., 1337m., 1325m., 1300m., and 1282s. $cm.^{-1}$.

Solubility properties: Soluble in benzene, acetone, and ether. Sparingly soluble in ethanol, cyclohexane, and petroleum ether (b.p. 80 - 100°).

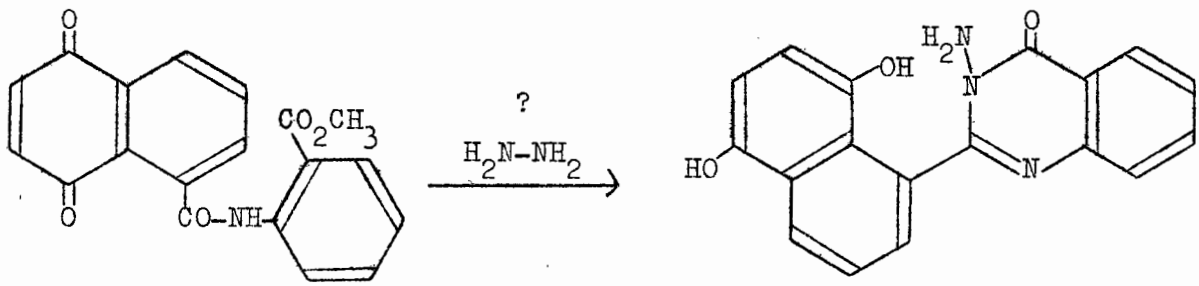
The diacetate (CXL).

Reductive acetylation[51] of N-(o-methoxycarbonylphenyl)-1,4-naphthaquinon-5-ylcarboxamide (CXIII) yielded the diacetate, 5,8-diacetoxy-N-(o-methoxycarbonylphenyl)-1-naphthamide (CXL) (70%) as pale yellow crystals, m.p. 166.5 - 167° (ethanol).

Analysis:	Calculated for $C_{23}H_{19}NO_7$	Found
	C 65.6%	C 65.5%
	H 4.6%	H 4.8%
	N 3.3%	N 3.2%

Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 3265w., 1780s.(sh.), 1773s., 1702s., 1687s., 1608m., 1592m., 1532m., 1516s., 1315m., 1298s., and 1285s. $cm.^{-1}$.

Reaction of N-(o-methoxycarbonylphenyl)-1,4-naphthaquinon-5-yl-carboxamide (CXIII) with hydrazine.



(CXIII) (CXIV)

Aqueous 95% hydrazine (1.5 ml.) was added to a solution of the quinone (CXIII) (0.46 g.) in benzene (4 ml.). A black precipitate immediately formed. Ethanol (10 ml.) was added to the reaction mixture which was then heated under reflux for 4 hr. The solvents were removed by distillation in vacuo; water (20 ml.) was added to the black residue which was then filtered off, washed well with water, and dried to yield a black material (0.23 g.), m.p. above 300°. Crystallisation from ethanol with decolourising charcoal yielded yellow crystals (0.01 g.), m.p. above 300°.

Analysis:	Calculated for $C_{18}H_{13}N_3O_3$	Found
	C 67.8%	C 65.9%
	H 4.1%	H 2.0%
	N 13.2%	N 13.7%

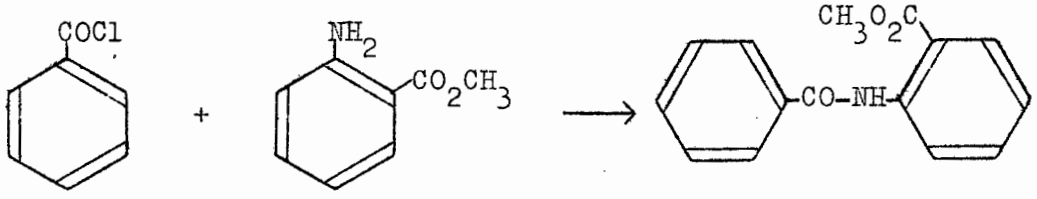
Spectroscopic data: I.R. †(in Nujol): $\nu_{max.}$ were at 3186m., 3142m., 3078m., 3050m., 1689v.s., 1671v.s., 1650v.s., 1618m.(sh.), 1589m., 1576m., and 1552m. $cm.^{-1}$.

Solubility properties: Sparingly soluble in ethanol (yellow solution). Insoluble in water.

TLC results: Chromatograms developed in iodine vapour.
In ethanol: Brown spot (R_F = 0.69) obtained.
In ethyl acetate : petroleum ether (b.p. 80 - 100°) (1 : 1)
(Solvent System 6): Brown spot (R_F = 0.42) obtained.

Preparation of methyl o-benzamidobenzoate (CXLII).

The conditions used for the benzoylation of amines[114] were used.

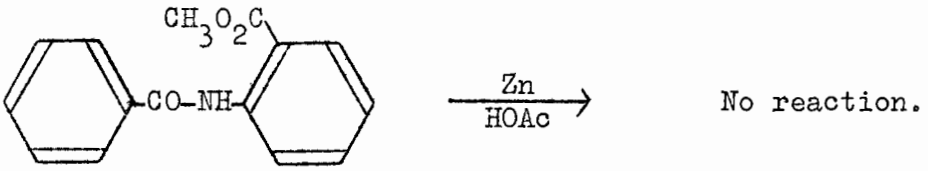


(XXVII) (CXLII)

A quantitative yield of methyl o-benzamidobenzoate (CXLII), m.p. 97 - 99°, (from ethanol) was obtained. [Heilbron's Dictionary of Organic Compounds gives a melting point of 100° for the benzoate (CXLII)].

† Perkin-Elmer 237 Grating infrared spectrophotometer.

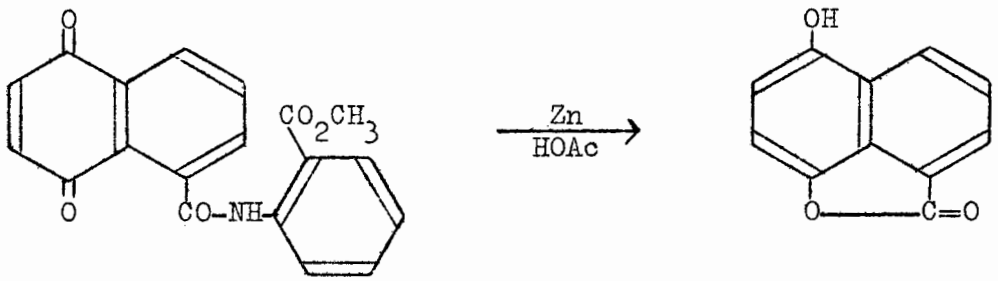
Treatment of methyl o-benzamidobenzoate (CXLII) with zinc and acetic acid.



(CXLII)

A solution of methyl o-benzamidobenzoate (CXLII) (1.0 g.) in acetic acid (30 ml.) and zinc dust (8.0 g.) were heated under reflux for 15 min. The suspension was filtered and the zinc boiled with acetic acid (3 x 10 ml.) which was added to the main solution. The acetic acid solution was diluted with water (200 ml.) and the white crystals obtained were removed by filtration yielding the starting amide (CXLII) (0.94 g.), m.p. and mixed m.p. 96 - 99°. Percentage recovery was 94%.

Reduction of N-(o-methoxycarbonylphenyl)-1,4-naphthaquinon-5-yl-carboxamide (CXIII); formation of the lactone of 5,8-dihydroxy-1-naphthoic acid, (CXXII).



(CXIII) (CXXII)

A solution of the quinone (CXIII) (0.24 g.) in acetic acid (15 ml.) and zinc dust (2 g.) were heated under reflux for 15 min.

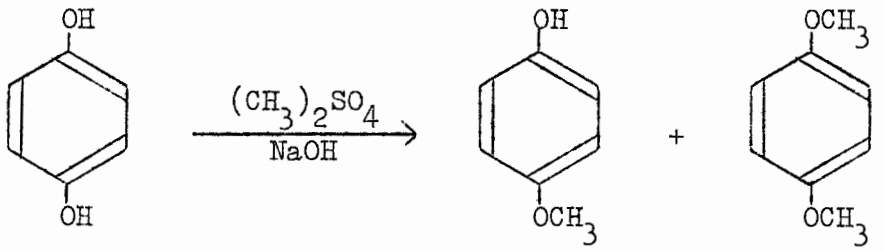
The suspension was filtered and the zinc boiled with acetic acid (5 x 5 ml.) which was added to the main solution. The acetic acid solution was concentrated *in vacuo* to 5 ml. and diluted with water (100 ml.). The yellow material (0.1 g., 75%), m.p. 225 - 228°, which precipitated from the solution was filtered off, dried, and crystallised from dilute ethanol yielding yellow crystals of the lactone (CXXII), m.p. 237 - 239°, not lowered in admixture with authentic lactone. Infrared spectra of the product of this reaction and authentic lactone were identical.

EXPERIMENTAL

SECTION III

Preparation of 1-hydroxy-4-methoxybenzene and 1,4-dimethoxybenzene.

The method of Robinson and Smith[101] was used.

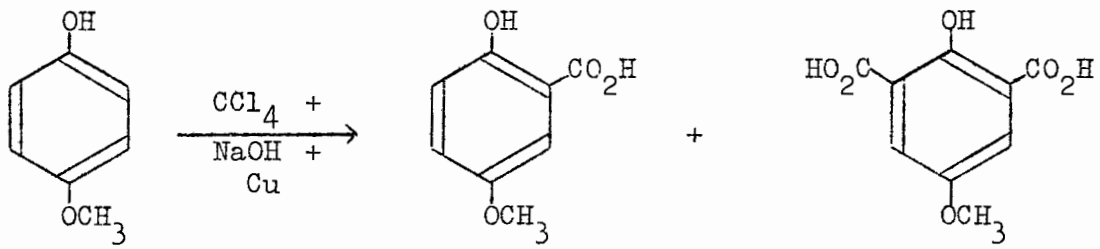


1-Hydroxy-4-methoxybenzene (53.7%), b.p. 242 - 245°, m.p. 55 - 56°, was obtained. The product was shown to be pure by gas-liquid chromatography. (Robinson and Smith obtained 36.2% product, m.p. 52 - 54°, and 24.2% less pure product, m.p. 41 - 46° which after purification had b.p. 243 - 244°, m.p. 56°.)

1,4-Dimethoxybenzene (26.3%), m.p. 52 - 55° was obtained. (Robinson and Smith obtained 23.8%, m.p. 56°.)

Preparation of 2-hydroxy-5-methoxybenzoic acid (CXLVIII) and 2-hydroxy-5-methoxyisophthalic acid (CXLIX).

The method of Villani and Lang[99] was used, in conjunction with the observations of Shimizu and Maki[100] concerning this reaction.



(CXLVIII) (CXLIX)

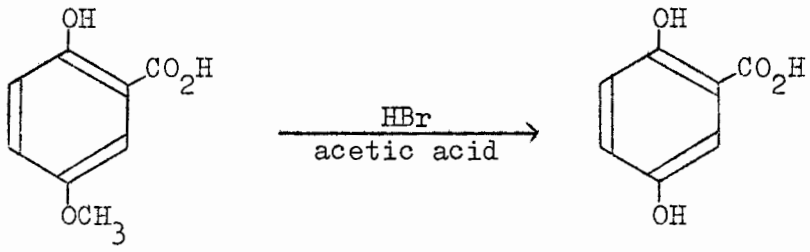
2-Hydroxy-5-methoxybenzoic acid (CXLVIII), m.p. 140 - 141° was obtained in a yield of 29.2%. (Villani and Lang's[99] product melted at 142 - 144°).

2-Hydroxy-5-methoxyisophthalic acid (CXLIX), m.p. 224 - 225° (decomp.) was obtained in a yield of 19.6%. [Shimizu and Maki's[100] product melted at 223 - 225° (decomp.).]

Villani and Lang obtained the monocarboxylic acid (CXLVIII) only, in a yield of 74%. Shimizu and Maki obtained both products but quoted no yields.

Preparation of 2,5-dihydroxybenzoic acid.

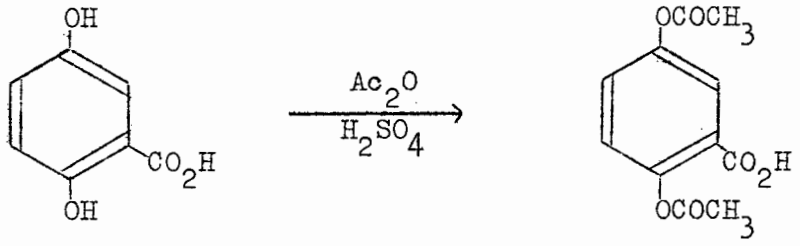
The method of Villani and Lang[99] was used.



2,5-Dihydroxybenzoic acid (60%), m.p. 197 - 198° was obtained. (Villani and Lang obtained 65%, m.p. 189 - 191°; m.p. lit. 196 - 200°.) The product was identical with the product of BDH (m.p. and mixed m.p.).

Preparation of 2,5-diacetoxybenzoic acid.

Klemenc[98] gave no experimental details. The conditions used in the acetylation of hydroquinone[46] were used.



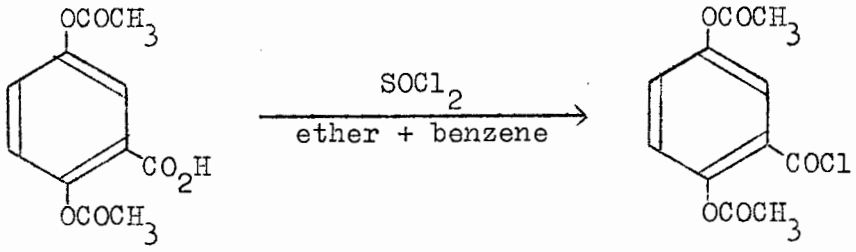
Concentrated sulphuric acid (1 drop) was added to a suspension of 2,5-dihydroxybenzoic acid (47.1 g.) in acetic anhydride (29.7 ml.). A clear solution was obtained on warming the suspension. The solution was cooled at room temperature for 5 min. and poured onto ice (175 ml.). The white crystalline precipitate (50.0 g., 68.8%), m.p. 117 - 119°, was removed by filtration and washed with water. Crystallisation from a mixture of benzene and ligroin yielded white crystals (41.1 g., 56.5%), m.p. 124 - 125°.

Klemenc obtained a quantitative yield but gave no m.p.; Kloetzel et al.[97] obtained 90%, m.p. 119 - 121°.

Spectroscopic data: I.R. †(in Nujol): $\nu_{max.}$ were at 3490s., 3440s., 2590s.(band), 1746v.s., 1740v.s., 1664v.s., and 1618v.s. $cm.^{-1}$.

Preparation of 2,5-diacetoxybenzoyl chloride (CLV).

The method of Kloetzel et al.[97] was used.



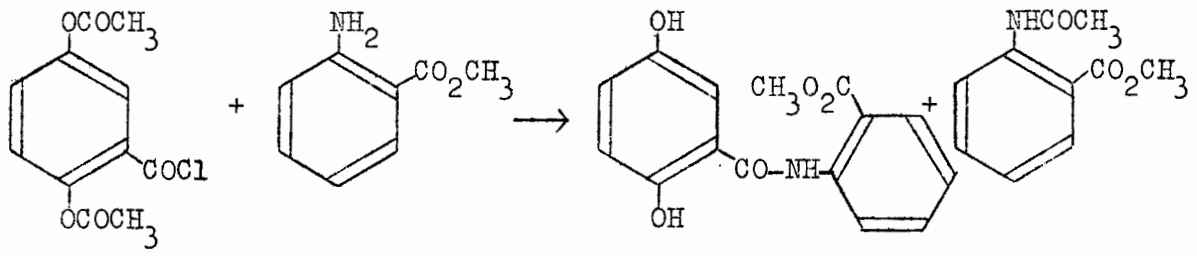
(CLV)

The acid chloride (CLV) was not isolated[97] but was used in the preparation of the amide (CXLV).

---

† Perkin-Elmer 237 Grating infrared spectrophotometer.

Preparation of 2,5-dihydroxy-N-(o-methoxycarbonylphenyl)benzamide (CXLV); and isolation of methyl o-acetamidobenzoate (CXXIV).



(CLV) (XXVII) (CXLV) (CXXIV)

Anhydrous, freshly distilled methyl anthranilate (42 ml.) was added to a solution of the acid chloride (CLV) from 2,5-diacetoxybenzoic acid (29.93 g.) in anhydrous benzene (75 ml.) shaken under reflux. A vigorous reaction ensued and an immediate crystalline white precipitate formed. The mixture was heated under reflux at 90° for 10 min. and benzene was then removed in vacuo. The solid residue was pulverised, 2N-sodium carbonate solution (50 ml.) added and the yellow, oily product removed from the sodium carbonate solution (A) by filtration. The product was washed with water and pressed on the filter-pad to remove methyl anthranilate, and then suspended in 96% ethanol (50 ml.) and washed. The white solid obtained was filtered off and again washed by suspension in 96% ethanol (50 ml.). Filtration of the suspension yielded white crystals of 2,5-dihydroxy-N-(o-methoxycarbonylphenyl)benzamide (CXLV) (25.30 g., 68.5%), m.p. 166 - 168°. Crystallisation from ethanol (2000 ml.) gave white feathers (24.85 g.), m.p. 168 - 169°, not raised by further crystallisation. The ethanol washings were combined and concentrated in vacuo to 15 ml. The off-white crystals obtained were filtered off from the methyl anthranilate-ethanol solution (B) and washed with ether yielding the amide (CXLV) (1.02 g.), m.p. 160 - 163°. (Total yield amide was 71.2%).

The sodium carbonate washings (A) were extracted with

ether (3 x 50 ml.) (C) to remove methyl anthranilate, and acidified with concentrated hydrochloric acid. The buff precipitate (7.59 g., 25.0%), m.p. 115 - 120°, was removed by filtration, washed with water, and dried *in vacuo*. Crystallisation from benzene with decolourising charcoal yielded 2,5-diacetoxybenzoic acid (m.p., mixed m.p., and infrared spectra).

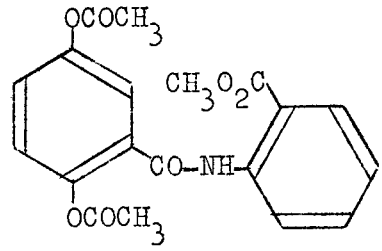
The acidified sodium carbonate solution was extracted with ether (5 x 50 ml.) and the ethereal solution combined with the methyl anthranilate-ethanol solution (B) and the ether solution (C). 2.5N-Hydrochloric acid (500 ml.) was added to the ethereal solution and the mixture stirred to dissolve methyl anthranilate hydrochloride which had precipitated from the solution. The ether layer was dried (Na_2SO_4) and concentrated *in vacuo*. The red oil obtained was dissolved in ether (50 ml.) and washed with 5N-hydrochloric acid (5 x 25 ml.), with water (2 x 25 ml.), with 2.5N-sodium hydroxide (5 x 25 ml.), and finally with water (2 x 25 ml.). The ethereal solution was dried (Na_2SO_4) and the solvent removed *in vacuo*. Crystallisation (dilute ethanol) of the buff precipitate obtained yielded methyl *o*-acetamidobenzoate (CXXIV) (2.15 g.) (m.p., mixed m.p., and infrared spectra).

The amide (CXLV) was therefore obtained in a yield of 97.7% and methyl *o*-acetamidobenzoate (CXXIV) in a yield of 13.0%, both based on unrecovered 2,5-diacetoxybenzoic acid.

Analysis:	Calculated for $C_{15}H_{13}NO_5$		Found	
	C	62.8%	C	62.7%
	H	4.6%	H	4.8%
	N	4.9%	N	4.5%

Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 3380w., 3259w., 1762s., 1693m., 1667s., 1612s., 1598s., 1554s., 1497m., 1332m., 1308m., 1271v.s., 1242v.s., and 1222s. $cm.^{-1}$.

The diacetate, [2,5-diacetoxy-N-(o-methoxycarbonylphenyl)benzamide, (CXLVI)].



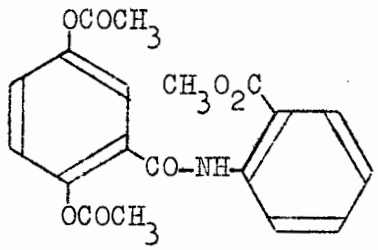
(CXLVI)

The dihydroxy-amide (CXLV) was acetylated with acetic anhydride using sulphuric acid as catalyst. Yellow crystals, m.p. 114 - 120°, were obtained. Crystallisation from dilute ethanol yielded 2,5-diacetoxy-N-(o-methoxycarbonylphenyl)benzamide (CXLVI) as white crystals (77.4%), m.p. 124 - 126°.

Analysis:	Calculated for $C_{19}H_{17}NO_7$	Found
	C 61.5%	C 61.5%
	H 4.6%	H 4.7%
	N 3.8%	N 3.8%

Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 3255w., 1774s., 1758s., 1701s., 1678s., 1612m., 1589m., 1533m., 1517m., 1492m., 1458v.s., 1323m., 1303m., 1280s., 1271s., 1241m., 1210s., and 1203s. $cm.^{-1}$.

Treatment of 2,5-diacetoxy-N-(o-methoxycarbonylphenyl)benzamide (CXLVI) with dilute sodium carbonate solution.

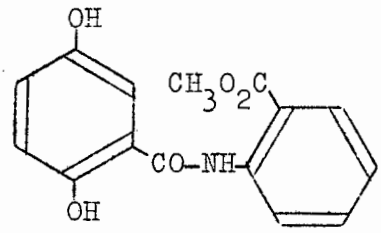


$\xrightarrow[H_2O]{Na_2CO_3}$ No reaction.

(CXLVI)

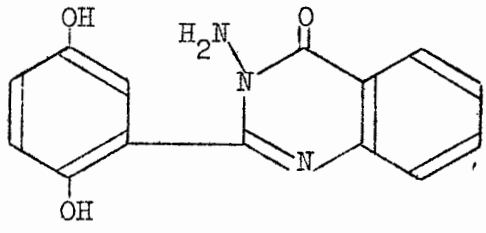
A suspension of 2,5-diacetoxy-N-(o-methoxycarbonylphenyl)-benzamide (CXLVI) (0.1g.) in 2N-sodium carbonate solution (2 ml.) was triturated for 10 min. The solid was filtered off and washed with water yielding white crystals (0.08 g.), m.p. 125 - 126°, of the benzamide (CXLVI) (m.p. and mixed m.p.). Percentage recovery was not less than 80%.

Preparation of 3-amino-2-(2,5-dihydroxyphenyl)quinazolin-4(3H)-one (CXLIV).



(CXLV)

$\xrightarrow[\text{ethanol}]{H_2N-NH_2}$



(CXLIV)

Aqueous 95% hydrazine (5 ml.) was added to a suspension of 2,5-dihydroxy-N-(o-methoxycarbonylphenyl)benzamide (CXLV) (5.0 g.) in ethanol (30 ml.). The ethanol solution immediately turned yellow. The mixture was heated under reflux for 3 3/4 hr., most of the

starting material dissolved (2 hr.) and white needles crystallised from the solution. Ethanol (40 ml.) was added to the reaction mixture and the suspension was dried *in vacuo*. Water (40 ml.) was added to the solid residue obtained and the suspension was filtered yielding white needles of the quinazolinone (CXLIV) (3.7 g., 79.0%), m.p. 277 - 280°, darkening at 263°. Crystallisation from acetic acid lowered the m.p. to 278 - 279.5°.

Analysis:	Calculated for $C_{14}H_{11}N_3O_3$	Found
	C 62.5%	C 62.2%
	H 4.1%	H 4.1%
	N 15.6%	N 15.2%

Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 3252m., 3068m., 2600m.(band), 1653s., 1634m., 1612s., 1608s., 1580s., 1517s., 1495s., 1344s.(sh.), 1340s., 1289w., 1272w., and 1255m. $cm.^{-1}$.

U.V. (Ethanol, pink solution): $\lambda_{max.}$ were at 320, 284, 258sh., 252sh., 246, and 219 mμ (log ε 4.00, 3.98, 4.04, 4.17, 4.27, 4.58).

(Dark orange 0.0256N-hydrochloric acid solution): $\lambda_{max.}$ were at 309, 234, and 203 mμ (log ε 3.95, 4.29, 4.36).

(Dark red 0.0269N-sodium hydroxide solution): $\lambda_{max.}$ were at 366sh., 331, 240, and 226 mμ (log ε 3.98, 4.03, 4.39, 4.39).

Solubility properties: Soluble in dilute sodium hydroxide (yellow solution darkening to red on standing).

Sparingly soluble in dilute hydrochloric acid (orange solution), acetic acid (yellow solution), and ethanol (pink solution).

Insoluble in water.

TLC results: Chromatograms developed in iodine vapour.

In solvent system 6 (page 208): A brown spot (R_F = 0.75) was obtained.

In chloroform : pyridine (4 : 1), (System 7): A brown spot (R_F = 0.81) was obtained.

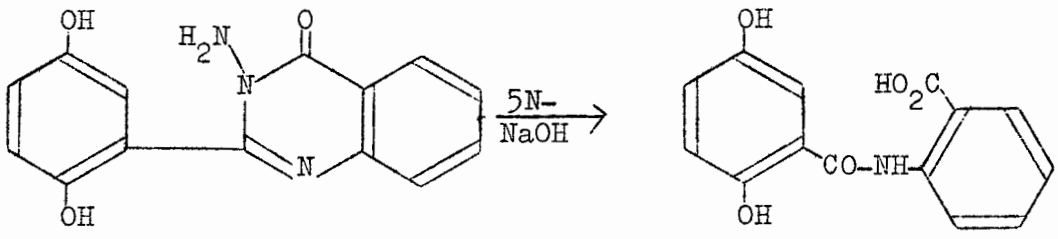
Formation of o-(2,5-dihydroxybenzamido)benzoic acid (CLVII) and 3-amino-2-(2,5-dihydroxyphenyl)quinazolin-4(3H)-one (CXLIV) hydrochloride.

(a) Hydrolysis of the quinazolinone (CXLIV) with sodium hydroxide; formation of the acid (CLVII).

(b) Formation of the acid (CLVII) and the hydrochloride from the quinazolinone (CXLIV) and hydrochloric acid.

(c) Hydrolysis of 2,5-dihydroxy-N-(o-methoxycarbonylphenyl)-benzamide (CXLV); formation of the acid (CLVII).

(a)



(CXLIV) (CLVII)

(i) A solution of 3-amino-2-(2,5-dihydroxyphenyl)-quinazolin-4(3H)-one (CXLIV) (0.5 g.) in 5N-sodium hydroxide (10 ml.) was left at room temperature for 4 hr., the yellow solution rapidly darkening to deep scarlet. The solution was then filtered, acidified with 5N-hydrochloric acid (50 ml.) and water (70 ml.) was added to dissolve sodium chloride which had precipitated from the solution. The brown suspension obtained

was centrifuged and the supernatant liquid was decanted through a filterstick of porosity 2. The remaining brown solid was washed with 5N-hydrochloric acid (5 x 100 ml.) until free of sodium ions by the same centrifuging and decantation procedure and then filtered off and dried. This yielded red-brown crystals (0.2 g.).

Spectroscopic data: I.R. †(in Nujol): $\nu_{max.}$ were at 3380s.(broad band), 1721s.(sh.), 1710s., 1658s., 1642s., 1632s., 1572s., 1482s., and 1450s. $cm.^{-1}$.

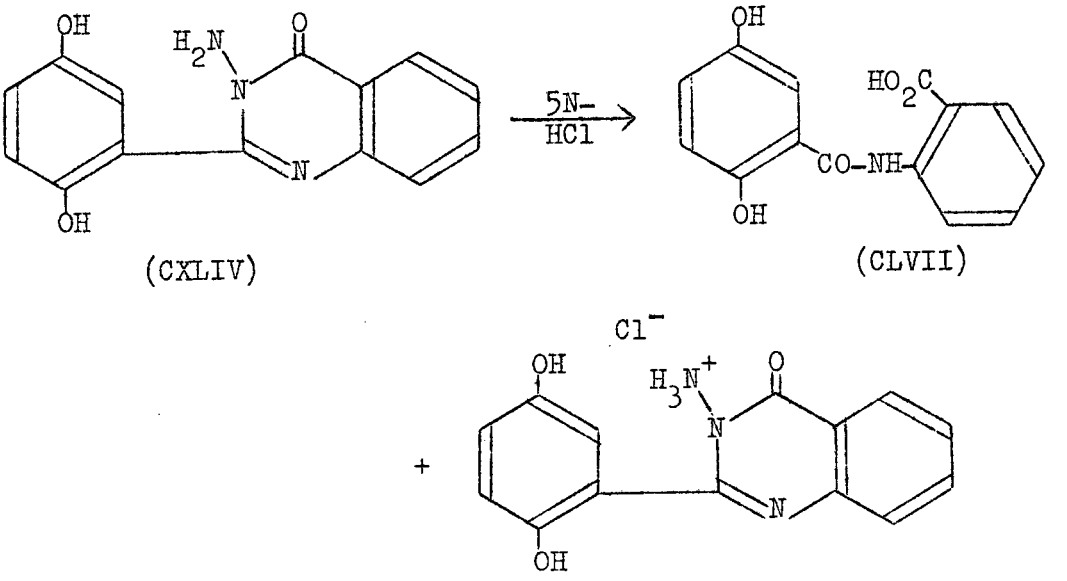
(ii) A solution of 3-amino-2-(2,5-dihydroxyphenyl)-quinazolin-4(3H)-one (CXLIV) (0.5 g.) in 5N-sodium hydroxide (10 ml.) was heated under reflux for 20 min., cooled, and worked up as described under (i), but the brown solid was washed with water (5 x 100 ml.) instead of with hydrochloric acid. The red-brown crystals obtained proved to be identical with the product prepared in (i) (infrared spectra).

(iii) A solution of 3-amino-(2,5-dihydroxyphenyl)-quinazolin-4(3H)-one (CXLIV) (3.20 g.) in 5N-sodium hydroxide (40 ml.) was heated and worked up as described under (ii). The red-brown product obtained was recrystallised from dilute ethanol with decolourising charcoal yielding pale yellow crystals of o-(2,5-dihydroxybenzamido)benzoic acid (CLVII) (0.71 g., 21.9%), m.p. 252 - 253° (decomp.).

---

† Perkin-Elmer 237 Grating infrared spectrophotometer.

(b)

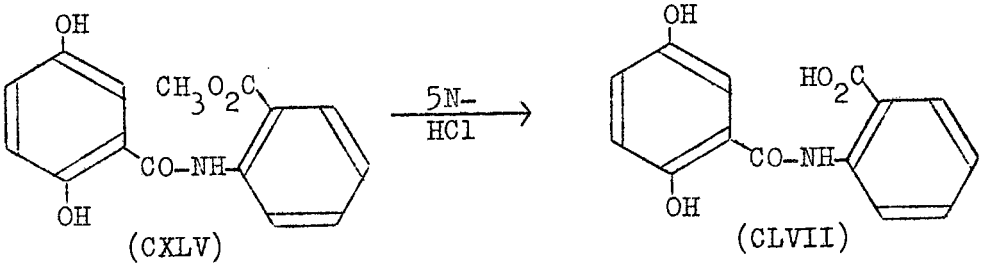


(CXLIV) (CLVII)

3-Amino-2-(2,5-dihydroxyphenyl)quinazolin-4(3H)-one (CXLIV) (3.41 g.) was heated under reflux with 5N-hydrochloric acid (500 ml.) for 10 min. and yellow insoluble crystals (A) of the acid (CLVII) (1.35 g., 39.0%), m.p. 250° (decomp.), filtered off from the suspension. On cooling the filtrate, the hydrochloride crystallised from the solution as yellow needles (2.2 g., 56.9%), m.p. 239 - 241° (decomp.). Recrystallisation twice from 5N-hydrochloric acid raised the melting point to 245 - 246° (decomp.). Insoluble yellow crystals (B) and (C) were again obtained.

(A), (B), and (C) were identical (m.p., mixed m.p., infrared spectra) and were combined and recrystallised from ethanol yielding pale yellow crystals of the acid (CLVII) identical with the product prepared in (a) (iii) (m.p., mixed m.p., infrared spectra and TLC).

(c)



(CXLV) (CLVII)

A suspension of 2,5-dihydroxy-N-(o-methoxycarbonylphenyl)-benzamide (CXLV) (0.25 g.) in 5N-hydrochloric acid (100 ml.) was heated under reflux for 1 hr. The solution was filtered and on cooling the filtrate, white crystals (0.15 g., 63.1%), m.p. 247 - 248°, crystallised from the solution. Crystallisation from dilute ethanol yielded white crystals of the acid (CLVII) identical with the acid prepared in (b) (m.p., mixed m.p., infrared spectra, and TLC).

The acid (CLVII).

Analysis:	Calculated for $C_{14}H_{11}NO_5$	Found
	C 61.6%	C 61.8%
	H 4.1%	H 4.2%
	N 5.1%	N 5.1%

Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 3375s., 3272s., 3081s.(sh.), 2660m., 1683s., 1651s., 1611v.s., 1591s., 1549s., 1522s., and 1459v.s. $cm.^{-1}$.

Solubility properties: Soluble in dilute sodium hydroxide (yellow solution), dilute sodium carbonate with effervescence (yellow solution), and ethanol.

Insoluble in water.

TLC results: Chromatograms developed in iodine vapour.

In ethanol: A brown spot (R_F = 0.77) was obtained.

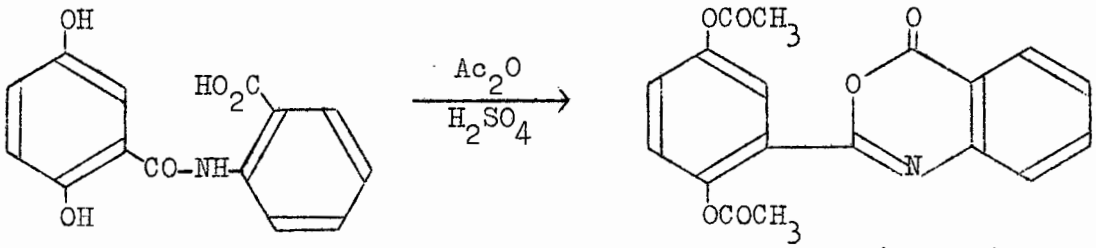
In solvent system 6 (page 208): A brown spot (R_F = 0.09) was obtained.

The hydrochloride.

Analysis:	Calculated for $C_{14}H_{12}N_3ClO_3$	Found
	C 55.1%	C 54.9%
	H 4.0%	H 4.1%
	N 13.8%	N 13.7%
	Cl 11.6%	Cl 11.8%

Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 3300w., 3235m., 3060m., 2562m.(sh.), 2528m., 1723s., 1635s., 1594s., 1569s., 1533m., 1517s., 1350s., 1343s., 1296m., and 1274m. $cm.^{-1}$.

Formation of 2-(2,5-diacetoxyphenyl)-4H-3,1-benzoxazin-4-one (CLVIII).



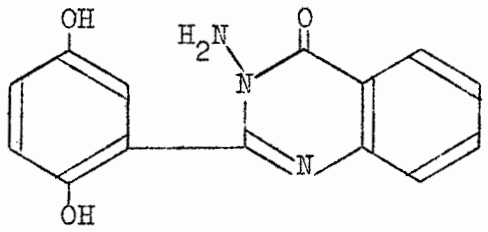
(CLVII) (CLVIII)

Concentrated sulphuric acid (1 drop) was added to a suspension of o-(2,5-dihydroxybenzamido)benzoic acid (CLVII) (0.50 g.) in acetic anhydride (2.0 ml.). The reaction mixture was heated to boiling point and the clear solution obtained was left at room temperature for 10 min. Water (80 ml.) was added to the reaction mixture and the mixture was cooled at 0°. White crystals (0.56 g.), m.p. 170 - 172° with sintering at 165°, crystallised from the solution and were removed by filtration. Crystallisation from ethanol yielded the benzoxazinone (CLVIII) as white needles (0.46 g., 74.1%), m.p. 186 - 187°. Further crystallisation from ethanol raised the m.p. to 186.5 - 187.5°.

Analysis:	Calculated for $C_{18}H_{13}NO_6$		Found	
	C	63.7%	C	64.3%
	H	3.9%	H	3.5%
	N	4.1%	N	4.2%
	Acetyl	25.4%	Acetyl	25.0%

Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 3081m., 1769v.s., 1760v.s.(sh.), 1733s., 1618s., 1608v.s., 1577s., and 1499s. $cm.^{-1}$.

Oxidation of 3-amino-2-(2,5-dihydroxyphenyl)quinazolin-4(3H)-one (CXLIV) with ferric chloride; formation of Compound A.



$\xrightarrow[HCl]{FeCl_3}$ Compound A .

(CXLIV)

(a) Aqueous ferric chloride (47.2 ml. of 25% solution) was added to a filtered solution of 3-amino-2-(2,5-dihydroxyphenyl)quinazolin-4(3H)-one (CXLIV) (2.2 g.) in ethanol (100 ml.) and 5N-hydrochloric acid (40 ml.). The solution darkened through a transient red to a dark brown and a dark brown precipitate formed. After 30 min. the suspension was centrifuged and the supernatant solution was decanted by filtration through a filterstick of porosity 2. The remaining dark brown solid was washed by the same centrifuging and decantation procedure with 5N-hydrochloric acid (4 x 130 ml.) until the washings were free of ferric ions (negative test with ammonium thiocyanate, even when the solution was diluted with water to decompose any $FeCl_6^{3-}$ complex present). The remaining suspension was filtered and the

product was dried yielding dark brown micro-crystals of Compound A (1.67 g.), no m.p. The product could not be recrystallised.

(b) The reaction described in (a) was performed on the quinazolinone (CXLIV) (0.5 g.) and ferric ions were removed in the same way. However, after washing the product with hydrochloric acid, it was washed with water (4 x 100 ml.) by the same decantation procedure until free of chloride ions. The product was filtered off from the remaining suspension and dried yielding Compound A (0.38 g.) identical with the compound prepared in (a) (infrared spectra).

Analysis:	Calculated for $C_{14}H_7N_3O_2$,		$C_{14}H_7N_3O_3$		Found	
	C	67.6%	C	63.5%	C	62.6%
	H	2.8%	H	2.7%	H	3.4%
	N	16.9%	N	15.9%	N	14.7%

Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 3181m., 3141m., 3118m., 3076m., 1730s., 1682s., 1669s., 1635s., 1577s., 1516m., and 1485s. $cm.^{-1}$.

Solubility properties: Soluble in pyridine (dark yellow solution). Sparingly soluble in acetic acid, acetone, ethanol, dilute hydrochloric acid, and hot dilute sodium hydroxide (yellow solutions).

Insoluble in cold dilute sodium hydroxide, water, benzene, and chloroform.

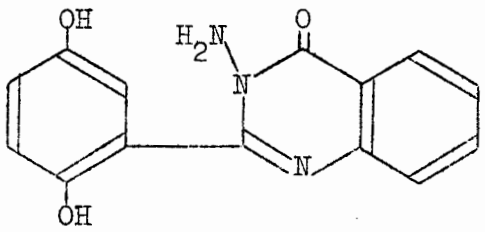
TLC results: Chromatograms developed in iodine vapour.

In ethanol: A brown streak (R_F = 0.41) was obtained.

In solvent system 7 (page 219): A dark brown spot (R_F = 0.02) was obtained.

Oxidation of (a) 3-amino-2-(2,5-dihydroxyphenyl)quinazolin-4(3H)-one (CXLIV) and (b) Compound A with hydrogen peroxide; formation of Compound B.

(a)



(CXLIV)

H_2O_2 + HCl
(i) in ethanol
(ii) in acetic acid

Compound B .

(i) Hydrogen peroxide (5 ml. 30% w./v.) was added to a hot yellow solution of 3-amino-2-(2,5-dihydroxyphenyl)quinazolin-4(3H)-one (CXLIV) (0.5 g.) in ethanol (75 ml.) and 5N-hydrochloric acid (10 ml.), and the solution was heated on a boiling water-bath for 45 min. The solution first went red, yellow-brown crystals formed, and the solution subsequently turned yellow. The crystals did not dissolve on longer heating and were filtered off from suspension. Concentration of the filtrate in vacuo yielded a yellow crystalline solid which was combined with the yellow-brown crystals and recrystallised from acetic acid containing concentrated hydrochloric acid (3 drops) and hydrogen peroxide (5 drops) yielding yellow crystals (0.1 g.), no m.p. below 300°, but charring at 225°.

(ii) Hydrogen peroxide (20 ml. 30% w./v.) was added to a hot solution of the quinazolinone (CXLIV) (5.6 g.) in acetic acid (90 ml.) and concentrated hydrochloric acid (40 ml.) and the solution was heated under reflux. The solution turned bright red and at 5 min. intervals hydrogen peroxide (3 x 5 ml. 30% w./v.) was very cautiously added to the solution as very vigorous effervescence (chlorine) occurred. The solution turned bright yellow and after 5 min. the solution was cooled at 4° in the dark

for 12 hr. to yield yellow crystals of Compound B (3.4 g.). The product was recrystallised from acetic acid containing hydrogen peroxide (1 drop), great care being taken to avoid light falling on the compound which was very unstable to light rapidly darkening to dark green-brown in direct sunlight. The product did not melt, but charred at 240°. A sample of the product was submitted to repeated crystallisation from acetic acid and hydrogen peroxide for analysis.

(b) Compound A $\xrightarrow[\text{acetic acid}]{H_2O_2 + HCl}$ Compound B .

Hydrogen peroxide (1 ml. 30% w./v.) was added to a suspension of Compound A (0.22 g.) in acetic acid (20 ml.) and concentrated hydrochloric acid (1 ml.) and the suspension was triturated at 70° for 10 min. Concentrated hydrochloric acid (1 ml.) and hydrogen peroxide (1 ml.) were added to the suspension and the trituration was continued for 10 min. The brown compound dissolved and an orange-red solution was obtained. Concentrated hydrochloric acid (1 ml.) and hydrogen peroxide (1 ml.) were added to the solution which was then heated in a boiling water-bath for 3 min. The solution was left in the dark and yellow crystals (0.17 g.) crystallised from the solution. The product was recrystallised as described under (a) (i), yielding yellow crystals of Compound B, no m.p., charring at 240°, identical with the compound prepared in (a) (ii) (infrared spectra).

Analysis: Calculated for $C_{14}H_4N_3Cl_3O_2$, $C_{14}H_5N_3Cl_2O_3$ Found

C	47.7%	C	50.4%	C	47.8%
H	1.1%	H	1.5%	H	2.3%
N	11.9%	N	12.6%	N	11.5%
Cl	30.2%	Cl	21.2%	Cl	25.7%
M.W.	352.6	M.W.	334.2	M.W.	348.3

The molecular weight was determined in acetic acid by an ebullioscopic method in a Sucharda-Bobranski-Schmitt apparatus[108].

The product was recrystallised from acetic acid containing hydrogen peroxide and concentrated hydrochloric acid:

Analysis: Found: Cl 25.7%

Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 1715 v.s., 1654s., 1638s., 1605s., and 1546m. $cm.^{-1}$.

U.V. (in Ethanol, yellow solution): $\lambda_{max.}$ were at 352, 308sh., 252sh., 228, and 214 mμ (log ε 4.19, 3.84, 4.23, 4.39, 4.38).

Solubility properties: Very soluble in dilute sodium hydroxide with effervescence (yellow-brown solution).

Soluble in dilute sodium bicarbonate solution (without effervescence), pyridine, acetic acid, chloroform, ethanol, and acetone (yellow solutions).

Sparingly soluble in benzene (yellow solution).

Insoluble in water and dilute hydrochloric acid.

TLC results: In ethanol:

In the dark: A yellow streak ($R_{F'}$ = 0.61) which turned blue in light was obtained.

In light: A blue streak ($R_{F'}$ = 0.61) was obtained.

In solvent system 6 (page 208):

In the dark: A yellow spot which turned blue in light remained at the origin.

In light: A blue spot (R_F = 0.06) and a yellow spot (which turned blue on longer exposure to light) at the origin were

obtained.

In solvent system 7 (page 219):

In the dark: A yellow spot (R_F = 0.04) which turned blue-brown in light was obtained.

In light: A yellow streak ($R_{F'}$ = 0.19) which turned yellow-brown in light was obtained.

Reductive acetylation of Compound B; formation of Compound C.

The reductive acetylation procedure used for p-benzoquinone[51] was used.

$$\text{Compound B} \xrightarrow[Ac_2O]{Zn + NaOAc} \text{Compound C} \quad .$$

Compound B (0.7 g.) was submitted to the reductive acetylation used on p-benzoquinone[51] yielding Compound C (0.5 g.), m.p. 245° with sintering at 210°. Repeated crystallisation from ethanol with decolourising charcoal yielded cream crystals (0.3 g.), m.p. 277 - 278°, with darkening at 262°. The compound was light sensitive.

Analysis:	Calculated for $C_{18}H_{11}N_3Cl_2O_4$,		$C_{20}H_{13}N_3Cl_2O_6$		Found	
	C	53.6%	C	52.2%	C	49.5%
	H	2.7%	H	2.8%	H	3.1%
	N	10.4%	N	9.1%	N	12.3%
	Cl	17.5%	Cl	15.4%	Cl	18.9%
	O-Acetyl	10.7%	O-Ac	18.6%	O-Ac	3.4%

Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 3295w., 3220m., 3140m., 1717s., 1676s., 1654s., 1617m., 1584m., and 1498m. $cm.^{-1}$.

Solubility properties: Soluble in dilute sodium hydroxide, dilute sodium carbonate solution without effervescence (yellow

solutions), pyridine, acetic acid, acetone, and ethanol.

Insoluble in benzene, chloroform, water, and dilute hydrochloric acid.

TLC results: In ethanol:

In the dark: A yellow spot (R_F = 0.09) which turned blue in light was obtained.

In light: A yellow streak ($R_{F'}$ = 0.36) which turned greenish-blue on longer exposure to light was obtained.

In solvent system 6 (page 208):

In the dark: A yellow spot which darkened to blue-green in light remained at the origin.

In light: A yellow spot which darkened to blue-green on longer exposure to light remained at the origin.

In solvent system 7 (page 219):

In the dark: A yellow spot (R_F = 0.04) which darkened to blue-green in light was obtained.

In light: A yellow streak ($R_{F'}$ = 0.27) was obtained.

Reduction of Compound B with zinc and hydrochloric acid; formation of Compound D.

Compound B $\xrightarrow{Zn + HCl}$ Compound D .

Compound B (0.50 g.), granulated zinc (1 g.), concentrated hydrochloric acid (5 ml.) and ethanol (130 ml.) were heated under reflux on a hot water-bath for 1.5 hr. and then more zinc (1 g.) and concentrated hydrochloric acid (5 ml.) were added to the reaction mixture. After 1.5 hr., the clear yellow solution was filtered and concentrated in vacuo to an orange oil. Addition of water precipitated cream micro-crystals of Compound D (0.46 g.), m.p. 258 - 262°, sintering at 228°, from the solution. Repeated

crystallisation from ethanol raised the melting point to 270 - 271°.

Analysis:	Calculated for $C_{14}H_8N_3ClO_2$,		$C_{14}H_8N_3ClO_3$		Found	
	C	59.0%	C	55.9%	C	52.7%
	H	2.8%	H	2.7%	H	4.2%
	N	14.7%	N	14.0%	N	11.7%
	Cl	12.4%	Cl	11.8%	Cl	16.1%

Spectroscopic data: I.R. (in Nujol): $\nu_{max.}$ were at 3290m., 3235m., 3120m., 1745m., 1727m., 1681s., 1665s., 1587m., 1547w., and 1504m. $cm.^{-1}$.

Solubility properties: Very soluble in pyridine and dilute sodium hydroxide (yellow solutions).

Soluble in acetic acid, ethanol (pale yellow solutions), and acetone.

Insoluble in dilute sodium bicarbonate solution, dilute hydrochloric acid, water, benzene, and chloroform.

TLC results: Chromatograms developed in iodine vapour.

In ethanol: A yellow spot (R_F = 0.29) was obtained.

In solvent system 6 (page 208): A yellow spot (R_F = 0.45) was obtained.

In solvent system 7 (page 219): A yellow spot (R_F = 0.13) was obtained.

INDEX TO EXPERIMENTAL

INDEX TO EXPERIMENTAL

The following is an index to the various compounds, the preparation of which is described in this thesis. No inclusion is made in this index of unsuccessful preparations.

INDEX TO TABLES

INDEX TO TABLES

SUMMARY

SUMMARY

The problems investigated in this thesis have been the synthesis of the three quinones, (a) 3-amino-2-(1,4-benzoquinonylmethyl)-, (b) 3-amino-2-(1,4-naphthaquinon-5-yl)- and (c) 3-amino-2-(1,4-benzoquinonyl)quinazolin-4(3H)-one and an investigation of their ring-closure. The precurser to the first quinone, 3-amino-2-(2,5-dihydroxybenzyl)quinazolin-4(3H)-one has been synthesised and its structure conclusively established. Its oxidation with ferric chloride, sodium hydroxide, and hydrogen peroxide to the quinone has been described and the products obtained, quinazolino-[3,2-b]cinnoline-2,7(13H)-dione hydrochloride and 1,3,4-trichloroquinazolino[3,2-b]cinnoline-2,7(13H)-dione, and their derivatives, have been investigated. The ring-closure has been shown to proceed by condensation of the amino-group with the quinonyl carbonyl group and not by 1,4-addition of the amino group to the quinone nucleus.

Various approaches to the synthesis of the second quinone to be investigated have been attempted and discussed but the quinone was not obtained. Its ring-closure could therefore not be investigated.

The synthesis of the precurser, 3-amino-2-(2,5-dihydroxyphenyl)quinazolin-4(3H)-one, to the third quinone investigated and its instability to aqueous acid and alkali have been described. Its oxidation to the third quinone with ferric chloride and hydrogen peroxide has been attempted but the structures of the products obtained have not been established.

It has been shown that fusion of a second ring to a ring-fused δ-lactam system has increased the frequency of the carbonyl infrared absorption.

The effect of hydrazine on the quinone group and various unsuccessful attempts at the synthesis of 2,5-dihydroxyphenylacetic acid have also been described.

A C K N O W L E D G E M E N T S

A C K N O W L E D G E M E N T S

The Author wishes to thank Dr. M. Lamchen, most sincerely, for his unfailing interest, and ever-ready guidance and advice both throughout the course of this work and while this thesis was being written; and also Professors E.C. Leisegang and A.M. Stephen for the facilities of the Chemistry Department.

Thanks are also due to other members of the Chemistry Department, for their helpful suggestions and stimulating discussions; to Messrs. R. von Holdt and E.G. Marshall, and Dr. K.G. Fuhr for the micro-analyses; to Messrs. H.H.D. Holleman and A. Tarr for infrared spectra; and to Mr. W.C. Lewis for his skilful glass-blowing.

Grateful mention must also be made of Professor F.L. Warren, of the University of Natal, for some helpful suggestions and of Dr. K. Pachler, of the National Chemical Research Laboratories, C.S.I.R., for measuring and interpreting the nuclear magnetic resonance spectrum.

Finally, the Author wishes to thank his parents, the Council for Scientific and Industrial Research for financial aid during the earlier part of this research, and Mr. C.R. Maspero and Miss L. Feilman for help in the proof-reading of the final manuscript.

BIBLIOGRAPHY

BIBLIOGRAPHY

1 E.J. Engels, M. Lamchen, and A.J. Wicken, J., 1959, 2694.

2 S. Gabriel, Ber., 1878, 11, 2261.

3 M. Lamchen and A.J. Wicken, J., 1959, 2779.

4 H.R. Ing and R.H.F. Manske, J., 1926, 2348.

5 M. Lamchen and A.J. Wicken, J., 1960, 1857.

6 E. Abramowitz and M. Lamchen, J., 1965, 2165.

7 Idem, ibid., p. 2173.

8 M. Lamchen and (Mrs.) N.E. Taylor, private communication.

9 M. Lamchen, private communication.

10 E.H. Rodd, Chemistry of Carbon Compounds, Vol. III Part B, Aromatic Compounds, Elsevier (London), 1956, p. 714 et seq.

11 H.H. Hodgson and F.H. Moore, J., 1923, 2500.

12 H. Goldschmidt, Ber., 1884, 17, 213; H. Goldschmidt and H. Schmidt, Ber., 1885, 18, 568.

13 R. Nietzki and A.L. Guitermann, Ber., 1888, 21, 429.

14 F. Kehrmann, Ber., 1881, 21, 3319.

15 E.H. Rodd, op. cit., p. 698.

16 R. Willstätter and E. Meyer, Ber., 1904, 56, 2398.

17 T. Akita, Yakugaku Zasshi, 1962, 82, 91-5; C.A., 1962, 57, 9711a.

18 R. Willstätter, Ber., 1907, 40, 1432.

19 J. Thiele and M. Barlow, Annalen, 1898, 302, 314.

20 A.W. Hofmann, J., 1863, 415; E.H. Rodd, op. cit., p. 724.

21 E.H. Rodd, op. cit., p. 724.

22 C.T. Mörner, Z. physiol. Chem., 1912, 78, 307.

23 C.T. Mörner, ibid., p. 325.

24 G. Hahn and W. Stenner, Z. physiol. Chem., 1929, 181, 88-100.

25 E. Baumann and S. Fränkel, Z. physiol. Chem., 1895, 20, 219.

26 L.D.F. Abbott and J.D. Smith, J. Biol. Chem., 1949, 179, 365-8.

27 G. Leaf and A. Neuberger, Biochem. J., 1948, 43, 606-610.

28 W.A. Osborne, J. Physiol., 1903, 29, xiii.

29 O. Neubauer and L. Flatow, Z. physiol. Chem., 1907, 53, 375.
30 S.M. McElvain and H. Cohen, J. Amer. Chem. Soc., 1942, 64, 260.
31 U. Ulfvarson, Acta Chem. Scand., 1958, 12, 1342-3; C.A., 1960, 54, 2246.
32 O. Diels and P. Nawiasky, Ber., 1904, 37, 3678.
33 H. Kauffmann and A. Grombaoh, Annalen, 1906, 344, 68.
34 O. Neubauer and L. Flatow, loc. cit., p. 395.
35 M. Lamchen, unpublished observations.
36 J.M. Gulland and C.J. Virden, J., 1928, 1481.
37 S. Czaplicki, St. v. Kostanecki and V. Lampe, Ber., 1909, 42, 828.
38 R. Adams and I. Levine, J. Amer. Chem. Soc., 1923, 45, 2373.
39 A.I. Vogel, "Practical Organic Chemistry", Longmans, London, 1957, p. 331.
40 K. Ladenburg, K. Folkers, and R.T. Major, J. Amer. Chem. Soc., 1936, 58, 1292.
41 A.I. Vogel, op. cit., p. 774.
42 W. Baker and N.C. Brown, J., 1948, 2306.
43 K.W. Rosenmund and H. Lohfert, Ber., 1928, 61, 2605.
44 G. Wittig, Annalen, 1926, 446, 182.
45 K.W. Rosenmund and H. Lohfert, loc. cit., p. 2606.
46 A.I. Vogel, op. cit., p. 677.
47 C.T. Mörner, Z. physiol. Chem., 1912, 78, 309 et seq.
48 L.J. Bellamy, "The Infra-red Spectra of Complex Molecules", Methuen, London, 1960.
49 A.D. Cross, "Introduction to Practical Infra-red Spectroscopy", Butterworths, London, 1964.
50 M.L. Josien and J. Deschamps, J. Chim. Phys., 1955, 52, 213; L.J. Bellamy, op. cit., p. 150.
51 A.I. Vogel, op. cit., p. 749.
52 A. Purgotti, Gazzetta Chemica Italiana, 1894, 24, I, 582.
53 A. Purgotti, ibid., p. 584.
54 A.I. Vogel, op. cit., p. 722.
55 G. Heller, E. Göring, J. Kloss, and W. Köler, J. prakt. Chem., 1925, (iii), 36-53; C.A., 1926, 20, 206.

56 D. Feil, M. Linck, and J. van Nierop, Physics Department, University of Cape Town. Private communication.

57 L.J. Bellamy, op. cit., p. 205.

58 O.E. Edwards and T. Singh, Can. J. Chem., 1954, 32, 683; L.J. Bellamy, op. cit., p. 213.

59 L.J. Bellamy, op. cit., p. 236.

60 H. Culbertson, J.C. Decius, and B.E. Christensen, J. Amer. Chem. Soc., 1952, 74, 4834.

61 V.K. La Mer and E.K. Rideal, J. Amer. Chem. Soc., 1924, 46, 223.

62 T.H. James and A. Weissberger, J. Amer. Chem. Soc., 1938, 60, 98.

63 T.H. James, J.M. Snell, and A. Weissberger, ibid., p. 2084.

64 A.D. Cross, op. cit., p. 75.

65 L.J. Bellamy, op. cit., p. 249.

66 A.D. Cross, op. cit., p. 71.

67 J.M. Hearn, R.A. Morton, and J.C.E. Simpson, J., 1951, 3326.

68 J.B. Koepfli, J.F. Mead, and J.A. Brockman, J. Amer. Chem. Soc., 1949, 71, 1052.

69 M.L. Sherrill, E. Ortelt, S. Duckworth, and Z. Budenstein, J. Org. Chem., 1954, 19, 704.

70 L.C. Anderson and M.B. Geiger, J. Amer. Chem. Soc., 1932, 54, 3067.

71 J.C.E. Simpson, "The Chemistry of Heterocyclic Compounds", "Condensed Pyridazine and Pyrazine Rings (Cinnolines, Phthalazines, and Quinoxalines)", Interscience Publishers, Inc., New York, 1953, p. 361.

72 R.P. Linstead, J.A. Elvidge, and M. Whalley, "A Course in Modern Techniques of Organic Chemistry", Butterworth Scientific Publications, London, 1955, p. 138.

73 L.J. Bellamy, op. cit., p. 139.

74 C.F.H. Allen and C.V. Wilson, J. Amer. Chem. Soc., 1941, 63, 1756.

75 M. Gallotti, Ann. Chim. appl., 1932, 22, 602; C.A., 1933, 27, 278.

76 R.T. Arnold and C. Collins, J. Amer. Chem. Soc., 1940, 62, 983.

77 H. Klinger, Annalen, 1911, 382, 221.

78 K. Pachler, N. Chem. R.L., C.S.I.R., Pretoria. Private communication.

79 L.M. Jackman, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press, London, 1959, p. 85.

80 G.C. Pimentel and A.L. McClellan, "The Hydrogen Bond", W.H. Freeman and Co., San Francisco, 1960, p. 195.

81 G.C. Pimentel and A.L. McClellan, op. cit., pp. 197 - 203.

82 O. Dimroth, H. Eber, and K. Wehr, Annalen, 1926, 446, 144.

83 R. Willstätter, E. Ulbrick, L. Pogàny, and C. Maimeri, Annalen, 1929, 477, 179.

84 A.G. Ekstrand, J. Prakt. Chem., 1888, 38, 244.

85 W.F. Short and H. Wang, J., 1950, 991 - 4.

86 P. Ruggli and E. Buckhardt, Helv. Chim. Acta, 1940, 23, 441 - 5.

87 D.M.S. Wheeler and M.W. Wheeler, J. Org. Chem., 1962, 27, 3796.

88 S. Searles, M. Tamres, and G.M. Barrow, J. Amer. Chem. Soc., 1953, 75, 71.

89 J. Blair, J.J. Brown, and G.T. Newbold, J., 1955, 708.

90 A.G. Ekstrand, ibid., p. 245.

91 G.P. 888,733/1953; C.A., 1954, 48, 13232e.

92 V.M. Rodionov, B.M. Bogoslovskiĭ, and A.A. Artem'ev, J. Gen. Chem., U.S.S.R., 1946, 16, 443 - 4; C.A., 1947, 41, 747e.

93 F.F. Blicke and H.C. Parke, J. Amer. Chem. Soc., 1939, 61, 1201.

94 L.I. Smith and R.O. Denyes, J. Amer. Chem. Soc., 1936, 58, 304.

95 O.H. Emerson and L.I. Smith, J. Amer. Chem. Soc., 1940, 62, 142.

96 L.I. Smith and J. Nichols, J. Amer. Chem. Soc., 1943, 65, 1742.

97 M.C. Kloetzel, R.P. Dayton, and B.Y. Abidir, J. Org. Chem., 1955, 20, 42.

98 A. Klemenc, Monatsh., 1912, 33, 1243.

99 F.J. Villani and J. Lang, J. Amer. Chem. Soc., 1950, 72, 2301.

100 M. Shimizu and M. Maki, J. Pharm. Soc. Japan, 1951, 71, 961 - 963; C.A. 1952, 46, 8058d.

101 R. Robinson and J.C. Smith, J., 1926, 393.

102 A.R. Mattocks, J., 1964, 1918 et seq.

103 D.T. Zentmyer and E.C. Wagner, J. Org. Chem., 1949, 14, 967.

104 E. Mohr and Fr. Köhler, Ber., 1907, 40, 997; D.T. Zentmyer and E.C. Wagner, loc. cit.

105 M.T. Bogert and H.A. Seil, J. Amer. Chem. Soc., 1907, 29, 529; D.T. Zentmyer and E.C. Wagner, loc. cit.

106 R. Anschütz and O. Schmidt, Ber., 1902, 35, 3473; D.T. Zentmyer and E.C. Wagner, loc. cit.

107 A.L. Lumière and A. Seyewetz, Bull. soc. chim., 1905, 33, [3], 344.

108 J.B. Niederl and V. Niederl, "Micromethods of Quantitative Organic Analysis", John Whiley & Sons, Inc., New York, 1942, p. 213.

109 F. Tiemann and W.H.M. Müller, Ber., 1881, 14, 1986.

110 H.H. Hodgson and H.G. Beard, J., 1927, 2339.

111 E.P. Clark, Ind. Eng. Chem. Anal., 1936, 8, 487; idem, ibid., 1937, 9, 539.

112 C. Graebe, Annalen, 1868, 146, 20.

113 Idem, ibid., p. 28.

114 A.I. Vogel, op. cit., p. 652.