RHIZOPHORACEAE ALKALOIDS

Studies in the synthesis of Gerrardine

by

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CONTENTS

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The Council for Scientific and Industrial Research kindly gave a research grant which made this work possible.

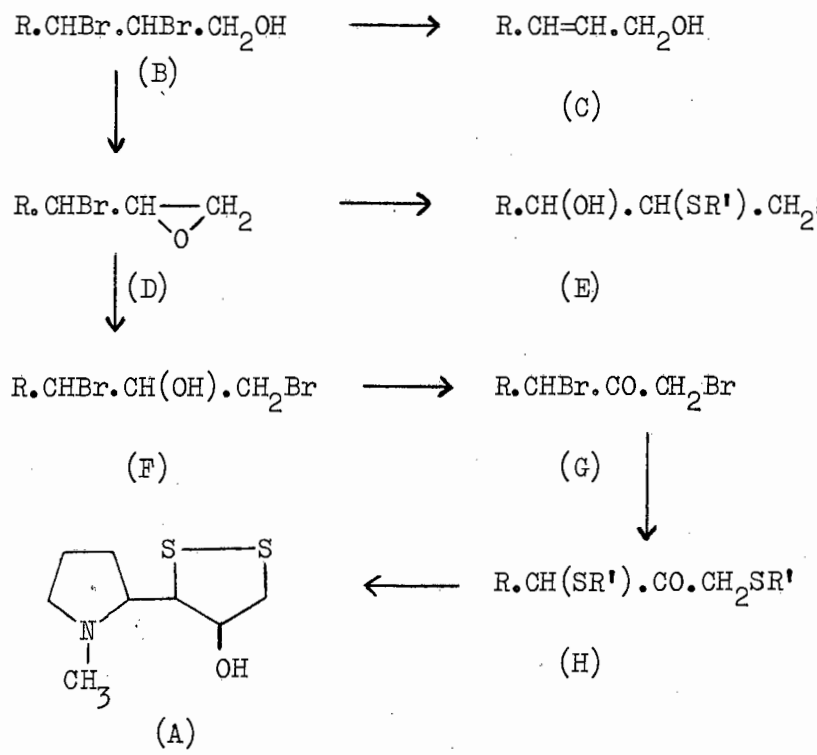
SUMMARY

Gerrardine, an alkaloid isolated from Cassipourea gerrardii was previously established as 1-methyl-2,5-bis-(4'-hydroxy-1',2'-dithiolan-3'-yl)-pyrrolidine. The aim of the present research was to study the ways in which 1-methyl-2-(4'-hydroxy-1',2'-dithiolan-3'-yl)-pyrrolidine, as a model compound could be synthesised since it contained asymmetric centres corresponding to those of gerrardine. The work resolved itself into attempts at the synthesis of 3-(1'-methylpyrrolidin-2'-yl)-1,3-dithiolpropan-2-ol since this would be converted into the required dithiolane by mild oxidation.

The reaction of toluene-ω-thiol as its sodium salt with 3-substituted 2,3-dibromopropanols (B) under varying conditions gave 3-substituted allyl alcohols (C). Prior conversion of the dibromides to 3-substituted 3-bromo-1,2-epoxypropane (D) and the reaction with toluene-ω-thiol under acid and alkaline conditions has been studied. The principal product was 3-substituted 1,2-dithiopropan-3-ol (E).

Conversion of the epoxide to the 1,3-dibromopropan-2-ol (F) and then to the corresponding ketone (G) is the procedure finally adopted to obtain the final required compound (A). The stereochemistry and the reaction mechanisms involved are discussed in relation to the

structure of the final product.



The compound (B) required for this synthesis was synthesised from proline by way of its methyl ester, prolinol, prolinal, and the Knoevenagel reaction to the 3-substituted acrylic acid which was brominated and then reduced to 3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-2,3-dibromopropanol.

Alternative methods which have been attempted are discussed briefly.

INTRODUCTION

1.1 The structure of Gerrardine

The alkaloid Gerrardine, $C_{11}H_{19}NO_2S_4$, m.p. 180°, isolated in these laboratories by Wright and Warren[39] from Cassipourea gerrardii was shown to have the structure I. Reduction with Raney nickel in methanol gave two products $C_{10}H_{22}O_2$, m.p. 33°, identified as decan-2,9-diol (II) and $C_{12}H_{27}NO_2$ which was assigned the structure 4-dimethylaminodecan-2,9-diol (III) resulting from the reductive methylation of the nitrogen atom.

Confirmation of this structure was obtained by a mass spectrum which showed no mass peak at m/e 325 but a strong band at 100% abundance at m/e 204 corresponding to the molecular ion $(C_8H_{14}NOS_2)^+$ (IV). The cleavage product would thus be radical $C_3H_5OS_2$ (V). It was concluded that the nitrogen atom was the seat of the removal of an electron since the ion and the fission product each contain two sulphur atoms and one oxygen atom. The high percentage abundance of one such fragment suggested that the molecule was symmetrical. Since the i.r. spectrum showed no double bonds in the alkaloid, the fragments in the mass spectrometer must have had ring structures. The group $C_3H_5OS_2$ is best represented as 1,2-dithiolan-4-ol since any other arrangement would involve a semiacetal or acetal which would be much more unstable.

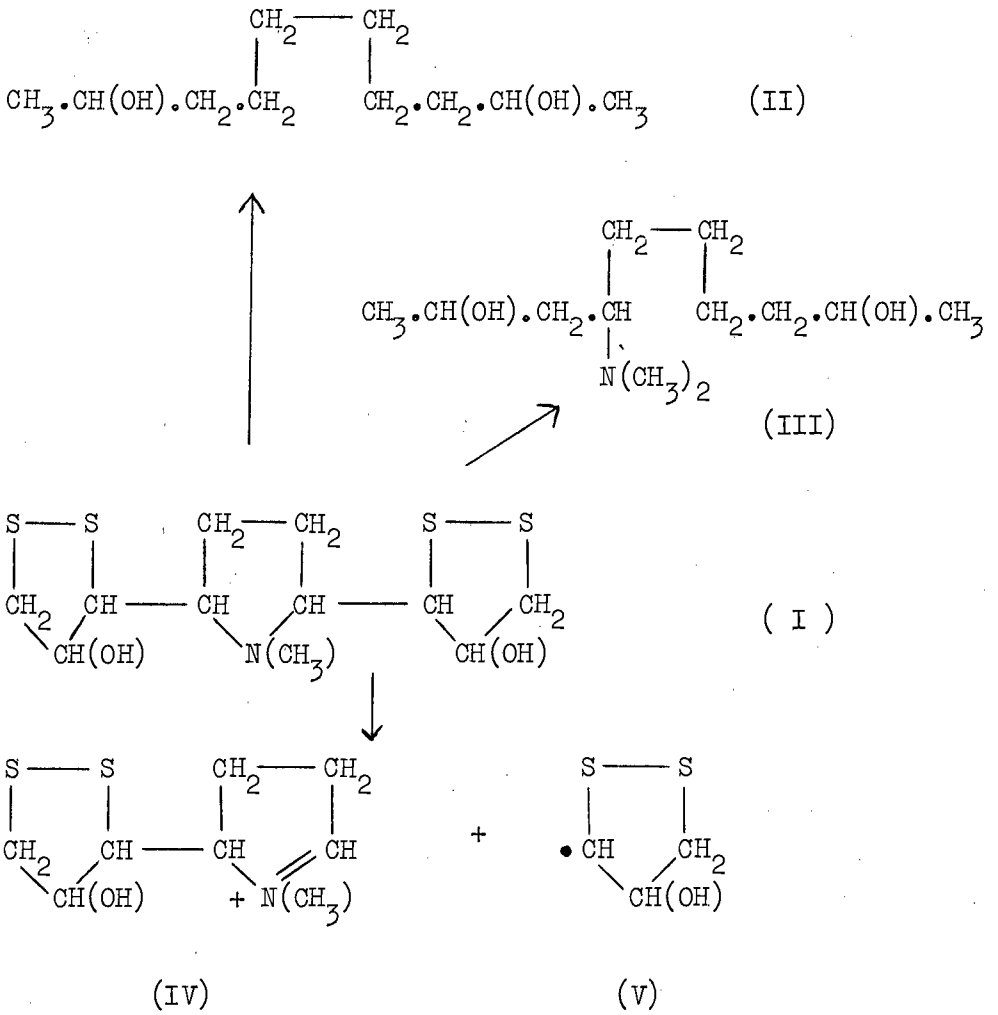
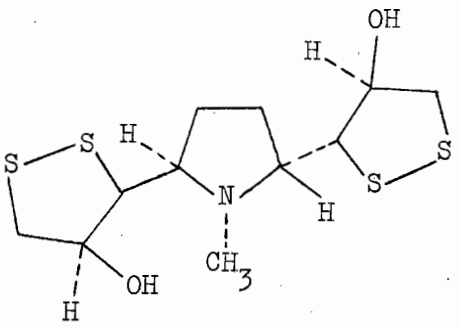


Fig. 1 The degradation of gerrardine.

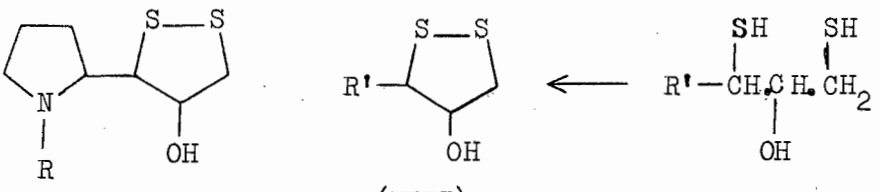
The final stereochemistry, but not the absolute configuration was established as (VI) by X-ray crystallography of a single crystal.

The study of possible routes to the synthesis of gerrardine form the subject of this thesis.

Gerrardine (I) is a symmetrical molecule and it was decided to study the synthesis of the partial structure (VII), which possesses three asymmetric centres.



(VI)

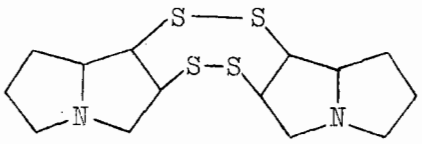


(VII) (VIII) (IX)

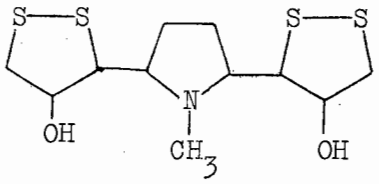
The actual synthesis necessitated a study of the formation of 3-substituted 4-hydroxydithiolane (VIII) which would result from ring closure of 1,3-dithiol-2-hydroxy-3-substituted open chain compound (IX).

1.2 Approaches to the synthesis of sulphur containing Rhizophoraceae alkaloids

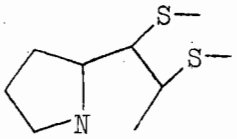
The structure of the two alkaloids, cassipourine (X) and gerrardine (I) reveal a 2-n-propyl pyrrolidine structure with sulphur substituents at the 2,3 (XI) and 1,3 (XII) positions.



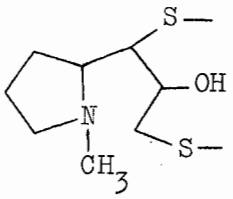
Cassipourine (X)



Gerrardine (I)

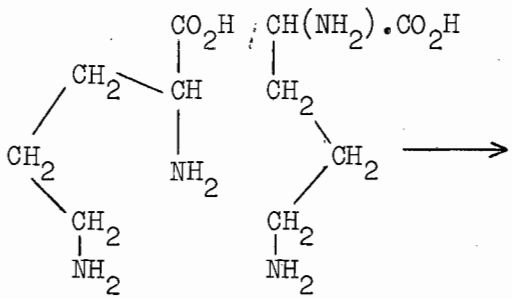


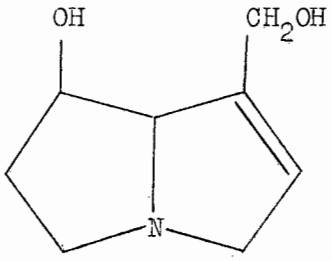
(XI)



(XII)

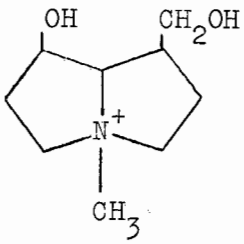
The pyrrolizidine ring system is known to be derived from two ornithine molecules viz.





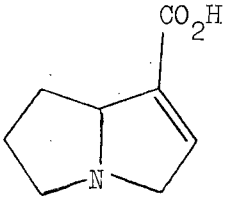
Retronecine

The quarternary alkaloid which occurs with gerrardine has been tentatively assigned the structure (XIII)



(XIII)

It is tempting to speculate that cassipourine arises from the addition of sulphur to the 1,2-dehydro pyrroli zidine or its 1-carboxylic acid derivative (XIV)

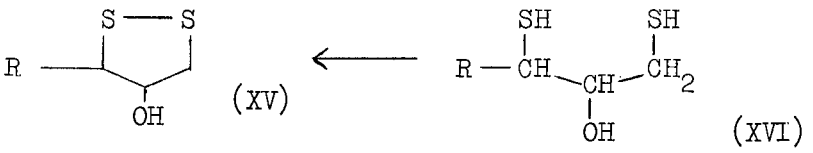


(XIV)

and the approach to the synthesis of cassipourine might be attempted by this route.

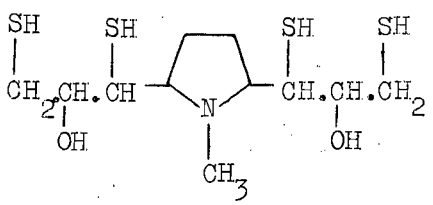
Alternatively, if the biosynthesis occurs by way of intermediate (XI) we might envisage common starting materials for both gerrardine (I) and cassipourine (X).

The synthesis of gerrardine might be considered as a synthesis of 3-substituted 4-hydroxy dithiolane (XV),



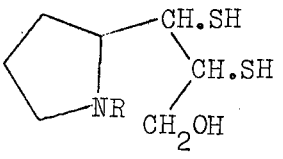
(XV) (XVI)

by cyclisation of the appropriate dithiol (XVI) and it was decided to study this route initially using a method which might be adopted for the incorporation of two dithiolanes from compound (XVII)

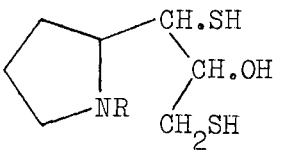


(XVII)

The synthesis of cassipourine and the half structure of gerrardine could then be envisaged as



(XVIII)



(XIX)

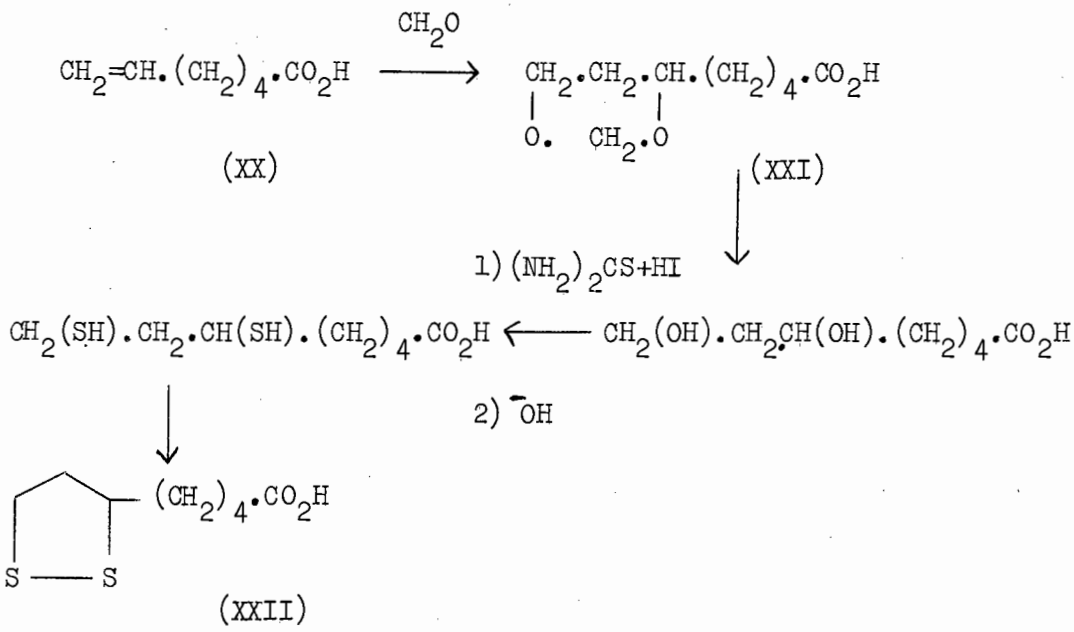
proceeding via structures (XVIII) and (XIX) respectively.

1.3 Possible applications of the synthesis of lipoic acid to gerrardine

Syntheses of both a 3-substituted dithiolane and a 3-substituted 4-hydroxy-dithiolane have been previously reported in the synthesis of lipoic acid.

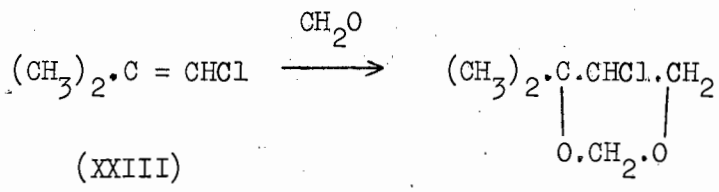
1.3.1 Braude, Linstead and Wooldridge[2] have synthesised lipoic acid (XXII) by way of the Prins condensation of hept-6-enoic acid (XX) with formaldehyde yielding the m-dioxane (XXI).

Sulphur was introduced with thiourea and after several steps yielded lipoic acid in 20 - 30% overall yield.



(XX) (XXI) (XXII)

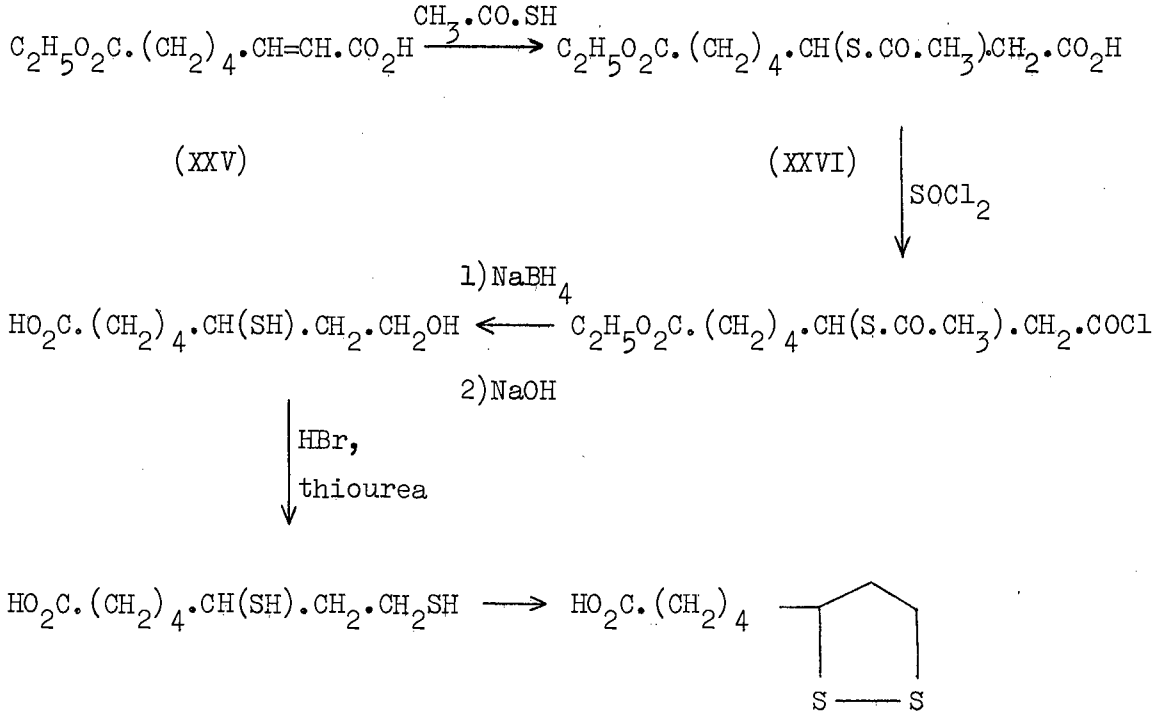
Arundale and Mikeska [1] have carried out a synthesis where isocrotyl chloride (XXIII) was converted into 4,4-dimethyl-5-chloro-m-dioxane (XXIV)



(XXIII) (XXIV)

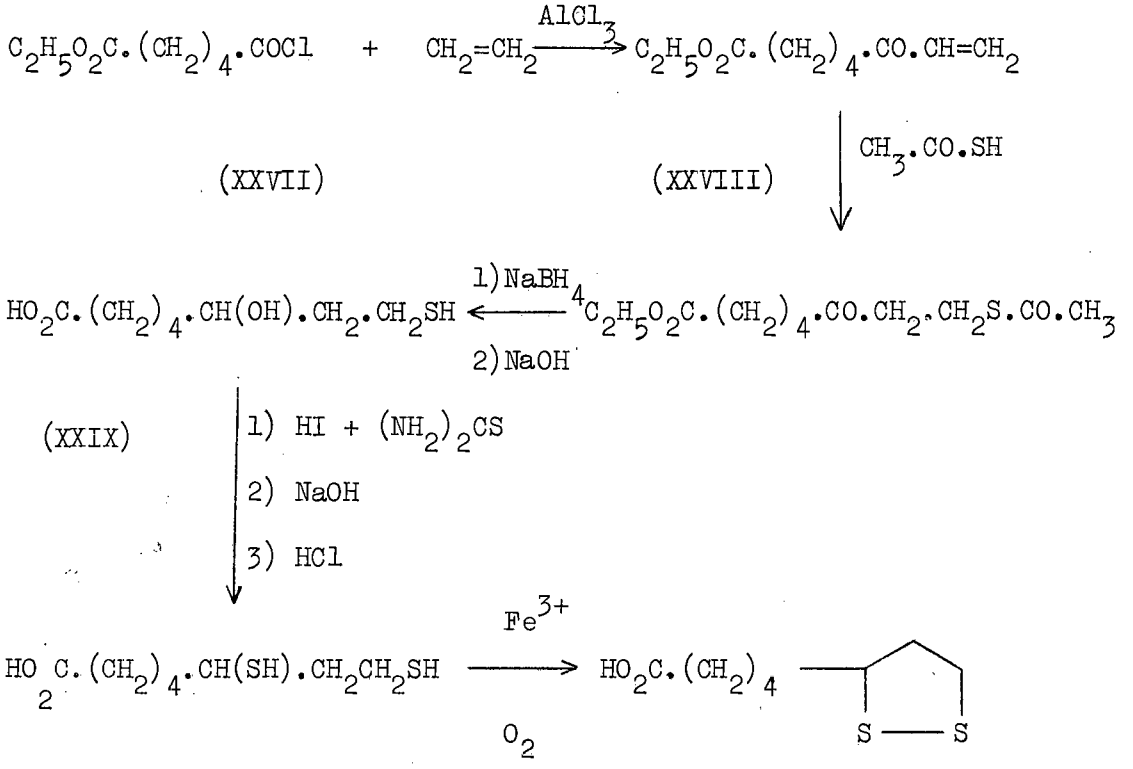
The details of the U.S. patent were not immediately available. Unsuccessful attempts were made by us to effect the condensation with isopropenyl acetate and but-1-en-1-ol acetate.

1.3.2 Addition of thiolacetic acid to 7-carbethoxy-2-heptenoic acid (XXV) yielded 3-acetylthio-7-carbethoxyheptanoic acid (XXVI). Walton, Wagner, Bachelor, Peterson, Holly and Folkers [35] completed their synthesis by reduction of the carbonyl group followed by conversion into the dithiol.



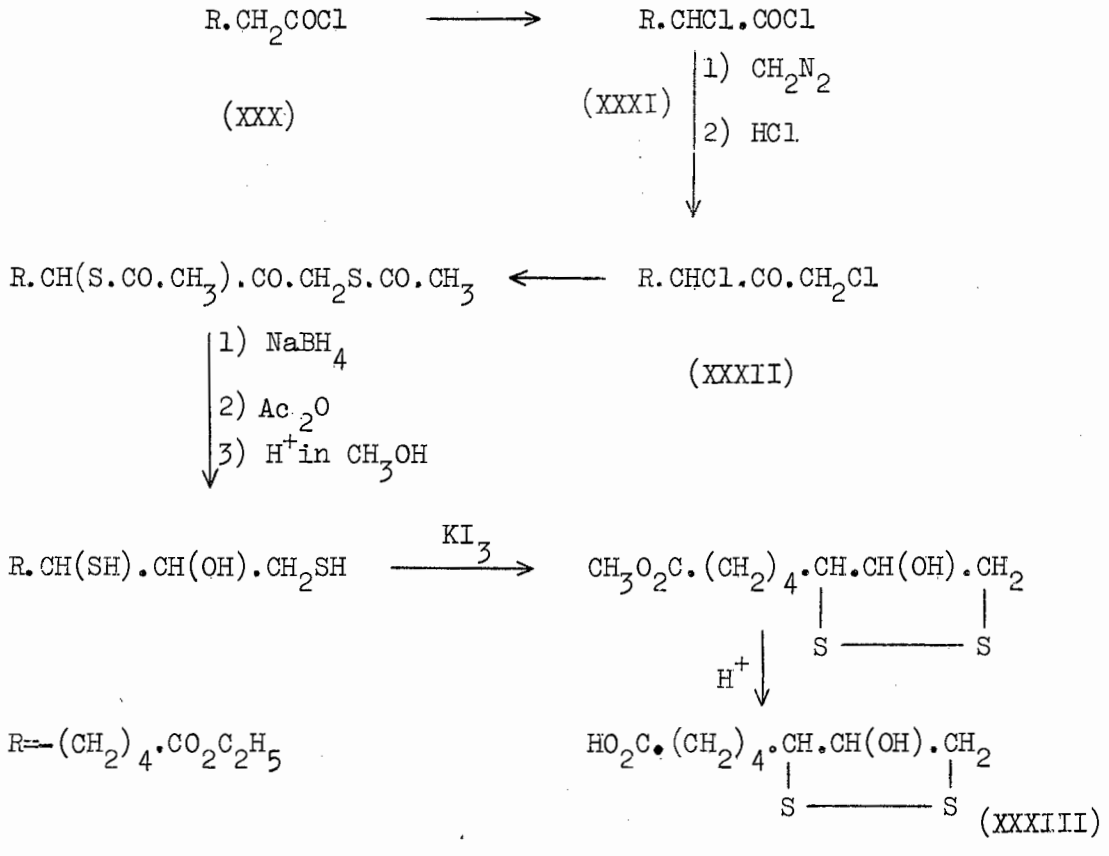
1.3.3 A novel synthesis employed by Bullock, Brockman, Patterson, Pierce, von Saltza, Sanders and Stokstad [3] consisted of the addition of the acid chloride of the monoethyl ester of adipic acid (XXVII) to ethylene in the presence of aluminium chloride to yield on distillation ethyl 6-oxo-

oct-7-enoate (XXVIII). The addition of thiolacetic acid to the vinyl ketone followed by reduction and hydrolysis yielded the alcohol (XXIX). Conversion of the alcohol into the dithiol by means of thiourea and oxidation of the dithiol yielded DL-α-lipoic acid in 8% overall yield.



The addition of ethylene to the acid chloride of the monoethyl ester of adipic acid has been employed by other groups (Soper 1954; Reed 1955)[31] in similar syntheses of DL-α-lipoic acid.

1.3.4 The synthesis of 7-hydroxylipoic acid (XXXIII) has been successfully undertaken by Schmidt, Grafen and Goedde[30]. The ethyl ester of pimelic acid chloride (XXX) on boiling with sulphuryl chloride yielded 2-chloro-6-carbethoxy-capryl chloride (XXXI). This was allowed to react with diazomethane and decomposition of the diazoketone with hydrochloric acid gave ethyl 6,8-dichloro-7-oxo-octanoate (XXXII). The halogen atoms were substituted by thiolacetate, the ketone reduced and the resulting alcohol acetylated. Hydrolysis followed by ring closure of the dithiol with iodine and hydrolysis of the ester yielded the product (XXXIII).



The sequence described above was adopted by the author in his M.Sc. thesis. See section 1.5.

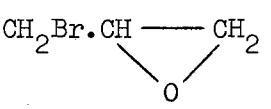
Several more methods for the synthesis of lipoic acid are available but position $C_{(4)}$ of the dithiolane ring in them remains unavailable for further substitution. We rejected the synthesis of Schmidt and Grafen[29] utilising the addition of acetylene to the acid chloride of the monoethyl ester of adipic acid since large quantities of polymeric material would have been produced.

1.4 Preparation of sulphides by bromine replacement

Johary and Owen [14] showed that 2,3-dibromopropanol (XXXIV) on treatment with the sodium salt of toluene-ω-thiol in ethanol gave 1,3-bisbenzylthiopropan-2-ol (XXXV) :-

$CH_2Br.CHBr.CH_2OH \longrightarrow CH_2(SCH_2.C_6H_5).CH(OH).CH_2S.CH_2.C_6H_5$

(XXXIV) (XXXV)



(XXXVI)

The reaction of thio compounds (thiourea, thiocyanate ions, etc.) on vicinal dibromo compounds is known to result in debromination to give the ethylenic derivative. However, the reaction mechanism proposed for the conversion of (XXXIV) to (XXXV) is by way of the epoxide (XXXVI) and once (XXXVI) is formed the debromination would be inhibited.

Accordingly the reaction was attempted on a number of model compounds once it was found that 2,3-dibromobutanol gave thio compounds in moderate yield although the structure was uncertain (see section 3.2.3.)

$$CH_3.CHBr.CHBr.CH_2OH \longrightarrow CH_3.CH(SCH_2.C_6H_5).CH(OH).CH_2SCH_2.C_6H_5$$

+/or

$$CH_3.CH(OH).CH(SCH_2.C_6H_5).CH_2SCH_2.C_6H_5$$

+

$$CH_3.CH(SCH_2.C_6H_5).CH(SCH_2.C_6H_5).CH_2OH$$

The 2,3-dibromo-4-methylpentan-1-ol(XXXVIIb) yielded no detectable substitution product. However, 2,3-dibromopentan-1-ol gave only a 6% yield of sulphur derivative and 54% unsaturated derivative (XXXVIIIa).

The 2,3-dibromo-4-methylpentan-1-ol gave only unsaturated derivative (XXXVIIIb).

$$R.CHBr.CHBr.CH_2OH \longrightarrow R.CH{=}CH.CH_2OH \text{ (principal product)}$$

(XXXVII) (XXXVIII)

a, $R = C_2H_5-$

b, $R = (CH_3)_2.CH -$

The varying yields of sulphur derivatives , although small, indicated that the debromination reaction was favoured under the conditions of the experiments. Accordingly it was decided to carry out the reaction stepwise, first effecting the epoxide formation followed by reaction with hydrogen bromide to give the 1,3-dibromo-2-ol derivative.

$$R.CHBr.CHBr.CH_2OH \longrightarrow R.CHBr.CH - CH_2 \longrightarrow R.CHBr.CH(OH).CH_2Br$$

(O)

Any attempt to substitute this bromocompound would immediately result in epoxide formation and it was therefore decided to oxidise the secondary alcohol to the ketone before substitution.

$R.CHBr.CH(OH).CH_2Br \longrightarrow R.CHBr.CO.CH_2Br$

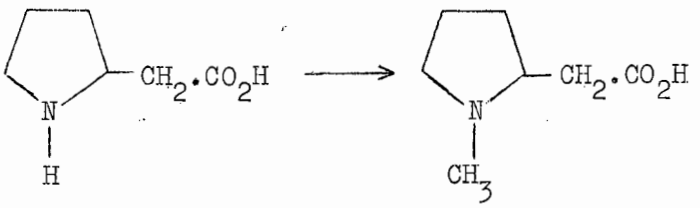
(XXXIX)

The nature of the compound is similar to that used successfully in the synthesis of lipoic acid. (XXXIX, R= $-(CH_2)_4.CO_2C_2H_5$. See section 1.3.4.).

DETAILS OF SYNTHESIS

2.1 Substituents on the nitrogen atom

In the synthesis it was necessary to convert the pyrrolidinyl group, as supplied by (-)-proline, to the 1-methylpyrrolidinyl group in gerrardine. N-Methylation could be carried out in high yield using a formaldehyde, formic acid mixture (Eschweiler-Clarke method), as was shown in the synthesis of hygric acid (XLI) from homoproline (XL) by Marušić[21].



(XL) (XLI)

Since amino-acids are difficult to extract from polar solutions, proline was first reduced to prolinol followed by methylation of the pyrrolidine nitrogen giving the product as a colourless oil in moderate yield. Unsuccessful attempts were made to oxidise the product to 1-methylprolinal using (a) dimethyl sulphoxide and ortho-phosphoric acid, (b) dimethyl sulphoxide and acetic anhydride, (c) Oppenauer oxidation employing aluminium isopropoxide, and (d) passing the vapour over cupric oxide at 300°. The product obtained was a red, viscous tar.

A group attached to the nitrogen atom which would remove its basic properties and could easily be

converted into the N-methyl group was sought since the observed polymerisation yielding the oil was undoubtedly caused by the basic N-methyl group. Nitrogen protection by the formyl group has the advantage that mild reduction by a metal hydride will reduce it to the methyl group. Attempts were made at the formylation of proline using the method of King, Clarke-Lewis and Wade [17] for the introduction of the formyl group.

Unsuccessful attempts were made to induce crystallisation of the colourless oil and attempted distillation led to decomposition. Reduction employing lithium aluminium hydride yielded l-methylprolinol as an oil which formed a picrate identical with the product obtained by N-methylation of proline. Among the main disadvantages of N-formyl protection are its ease of cleavage in acid solution and that many of the compounds are non-crystalline oils. This protective group was rejected since extraction of the acidic product by acidification of the basic solution after completion of the Knoevenagel condensation would cause cleavage of the N-formyl group.

Since oxidation of prolinol to prolinal can be brought about by a solution of dimethyl sulphoxide and acetic anhydride, the amino protection by the acetyl group was employed. Lithium aluminium hydride reduction of

proline to prolinol was followed by acetylation of the amino group yielding a colourless oil which was purified by distillation. Oxidation of 1-acetylprolinol was carried out using a dimethyl sulphoxide and acetic anhydride mixture again gave a viscous oil which showed the characteristic aldehyde peak in its infra-red spectrum. The Knoevenagel condensation gave no tractable product. The main disadvantages of the N-acetyl group are its instability to basic hydrolysis, as happened during the Knoevenagel reaction and most of its derivatives are oils.

To overcome the disadvantages quoted an amino protective group was sought which was (i) formed easily and in high yields, (ii) stable to hydrolysis in basic as well as acidic solutions, (iii) gave crystalline products, and (iv) stable to oxidation and also reduction with lithium aluminium hydride and (v) finally removable. The N-p-toluenesulphonyl protective group satisfied the above requirements and was employed in the described synthesis.

2.2 The synthesis

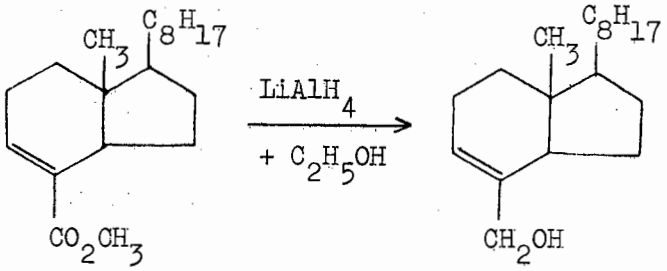
The asymmetry at $C_{(2)}$ of (-)-proline was preserved after (i) introduction of the nitrogen protecting p-toluene-

sulphonyl group, (ii) lithium aluminium hydride reduction to the alcohol, and (iii) oxidation employing dimethyl sulphoxide and dicyclohexyl-carbodiimide yielding the aldehyde. This was established by oxidation of a small quantity of the aldehyde to proline which showed the same optical activity as the starting material.

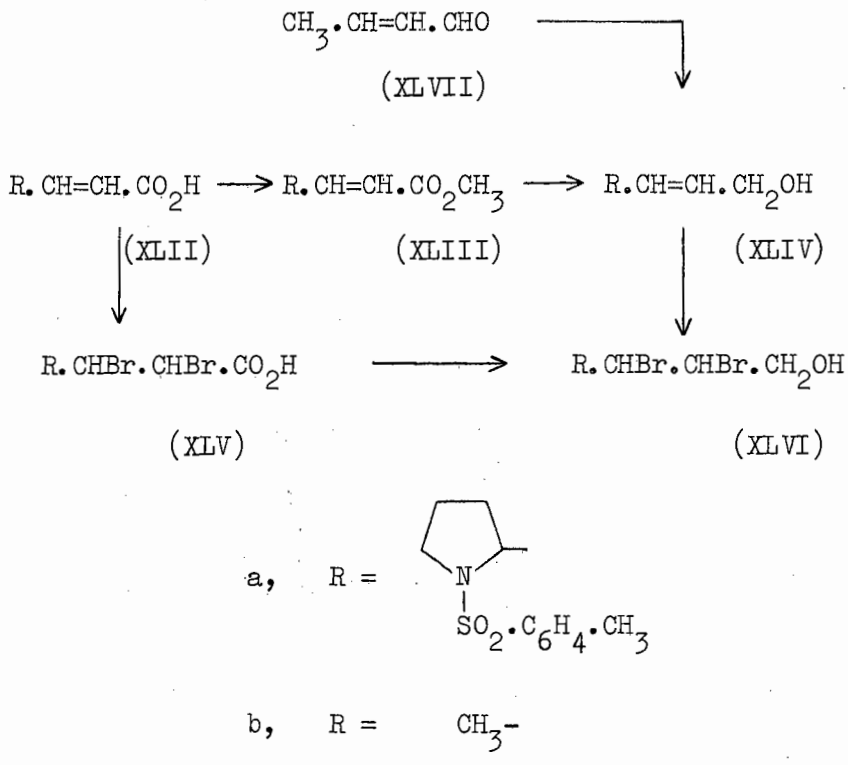
The Knoevenagel condensation (Döbner modification) as employed by Koo, Fish, Walker and Blake [19] was used in an attempt to effect the formation of 3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propenoic acid (XLIIa) under anhydrous conditions employing piperidine as catalyst. When the temperature was raised to 80° over thirty minutes, yields of the order of 20% were obtained. Suspecting that the active complex preceding condensation was being formed to a small extent only, and that decarboxylation of malonic acid was taking place in preference, the temperature of the reaction mixture was raised slowly to 80° over three hours and not above 90°, giving yields higher than 80%.

In order to attempt the rearrangement employed by Johary and Owen[14] the unsaturated acid (XLIIa) had to be converted into the dibromo-alcohol (XLVIa). It seemed that this could most easily be effected by

bromination of the unsaturated alcohol (XLIVa) since most carboxyl reducing agents are very sensitive to halogens. Lithium aluminium hydride being a powerful reducing agent, reduces carboxyl groups and their esters together with alkenes in conjugation with the carboxyl group. This reducing agent after deactivation with ethanol has been employed by Davidson, Günther, Waddington-Feather and Lythgoe [5] in an analogous reduction of the methyl ester of the α,β-unsaturated acid yielding the α,β-unsaturated alcohol.

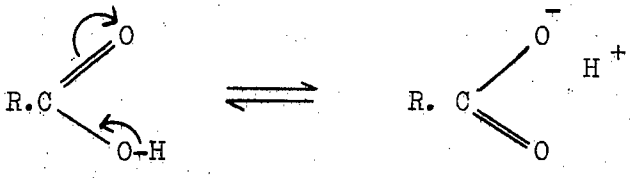


The methyl acrylate (XLIIIa) after reduction and purification by elution from an alumina column gave only a small yield of unsaturated alcohol (XLIVa). The efficiency of this reduction was tested by reduction of methyl crotonate (XLIIIb) to crotyl alcohol (XLIVb).



Purification of the product by distillation gave only 14% yield of unsaturated alcohol. The product exhibited infra-red absorption identical with that of crotyl alcohol, made by reduction of crotonaldehyde (XLVII) with sodium borohydride in neutral aqueous solution, as used by Wolfrom and Wood[37]. This reagent, being a mild reducing agent, afforded high yields of pure product as judged by the narrow boiling point range. Sodium borohydride in neutral solution selectively reduces the carbonyl group when conjugated with an alkene. The reason for it not being possible to reduce acids is possibly because the charge is delocalised over two oxygen atoms as in (XLVIII). In a thiolester

the charge is limited to a greater extent to the carbonyl group. Reduction of benzylthiocrotonate (IL) was attempted employing methanolic sodium borohydride at pH 7. G.l.c. analysis of the product showed no trace of crotyl alcohol.



(XLVIII)

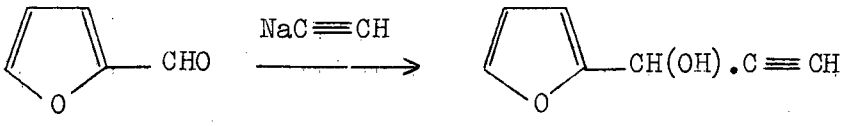
$$CH_3.CH{=}CH.CO.SCH_2.C_6H_5$$

(IL)

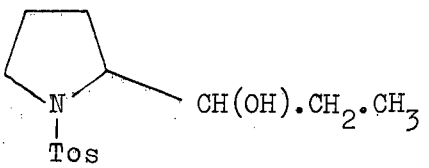
The synthesis of an α,β-unsaturated secondary alcohol can also be effected by the reaction of the sodium salt of acetylene on an aldehyde or ketone followed by reduction with the Lindlar catalyst. This technique was employed by Woodward, Cava, Ollis, Hunger, Daeniker and Schenker [38] in the synthesis of strychnine.

$$R.CO.R' \xrightarrow{NaC{\equiv}CH} R.CR'(OH).C{\equiv}CH \xrightarrow[\text{catalyst}]{\text{Lindlar}} R.CR'(OH).CH{=}CH_2$$

An analogous reaction has been successfully carried out by Jones and McCombie [15] on 2-formylfuran by reaction with the sodium salt of acetylene in liquid ammonia giving a 65% yield of product.



The Grignard reaction of N-(p-toluenesulphonyl)-prolinal and the sodium salt of acetylene dissolved in liquid ammonia yielded a product which polymerised on exposure to light. The reaction repeated in the dark and followed by reduction over palladium oxide yielded the alcohol (L) in only low yield making the synthesis by this route impracticable.



(L)

The failure of this reaction was substantiated by the low yield of product (L) obtained when the aldehyde was allowed to react with ethyl magnesium bromide.

Finally, a successful synthesis of the 3-substituted

allyl alcohol was effected by way of the dibromo-acid. The 2,3-dibromopropanoic acid (XLVa) was readily formed in moderate yield by the slow addition of bromine to an aqueous solution of the sodium salt of the acrylic acid (XLIIa). The dibromo-acid dissolved in dry tetrahydrofuran was added to a solution of diborane and set aside for several days to yield quantitatively the dibromo-alcohol (XLVIa).

2.3 Disubstitution of vicinal dibromides leading to elimination

Johary and Owen [14] obtained quantitative yields of 1,3-bisbenzylthiopropan-2-ol (LII) on reaction of 2,3-dibromopropanol (LI) with the sodium salt of toluene-ω-thiol

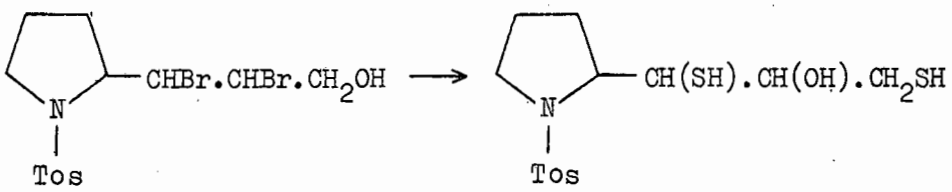
$$CH_2Br.CHBr.CH_2OH \xrightarrow{C_6H_5.CH_2SNa} CH_2(SCH_2.C_6H_5).CH(OH).CH_2(SCH_2.C_6H_5)$$

(LI) (LII)

to yield a product containing sulphides on the terminal carbon atoms.

It was thought that this reaction might be applied to the dibromo-alcohol (LIII) to incorporate the desired

1,2-dithiolane rings of gerrardine by ring closure of the 1,3-dithiol compound (LIV)



(LIII) (LIV)

The reaction product was a colourless mass of oily crystals. The sulphur analysis and infra-red spectrum indicated an unsaturated compound formed by the loss of bromine without the addition of any further sulphide.

The known debromination of 1,2-dibromides with thiourea employed by Ibne-Rasa, Muhammad and Hasibullah [13] led to the study of this reaction with model compounds.

Thompson [32] allowed the salt of the thiol (mainly 1-propanethiol) to reflux with the α,β-dihalogenated ketone for several hours. The product isolated was the corresponding alkene formed by dehalogenation.

2,3-Dibromobutan-1-ol reacted with the sodium salt of toluene-ω-thiol at room temperature under nitrogen in the absence of light to give 58% yield of a mixture of the desired 1,3-dibenzylthiobutan-2-ol (LV) and/or

1,2-dibenzylthiobutan-3-ol (LVI) together with the 2,3-dibenzylthiobutan-1-ol (LVII) in the ratio 7:1 (see fig. 2). The proportion of the primary and secondary alcohols was determined by Johary and Owen's method : debenzylation with sodium in liquid ammonia, desulphurisation by Raney nickel, and g.l.c. analysis using peak areas of the resulting alcohol. The dibenzylthiobutanol mixture was purified by distillation at 100°/1 mm. yielding 58% of the disubstituted mixture. The remaining dibromopropanol could have been converted into but-2-enol (b.p. 121°/754 mm.) by dehalogenation accounting for the remaining 42% of the 2,3-dibromobutan-1-ol and not have been condensed on distillation at low pressure.

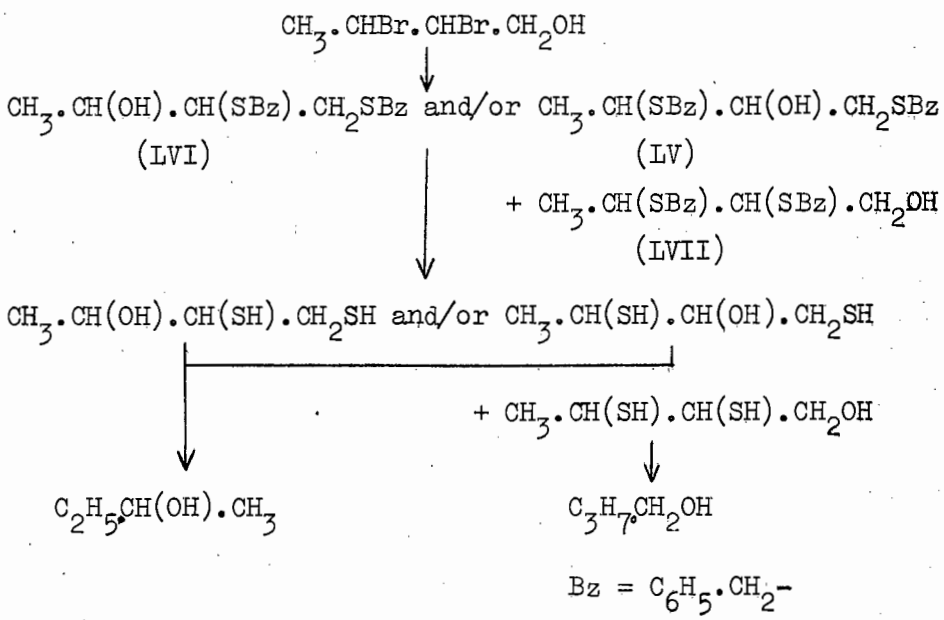


Figure 2. The reaction of 2,3-dibromobutan-1-ol with the sodium salt of toluene-ω-thiol and identification of products.

The reaction was repeated under the same conditions on 2,3-dibromopentanol at room temperature giving only a 6% yield of disubstituted product which, identified as above, consisted mainly of either pentan-2-ol or pentan-3-ol or a mixture of these two together with a small quantity of pentan-1-ol as outlined in figure 3. The other product obtained in 54% yield was pent-2-en-1-ol (LVIII), identified by oxidation to the aldehyde by active manganese dioxide yielding pent-2-enal (LIX) characterised as its 2,4-dinitrophenylhydrazone, m.p. 154 - 155.5°.

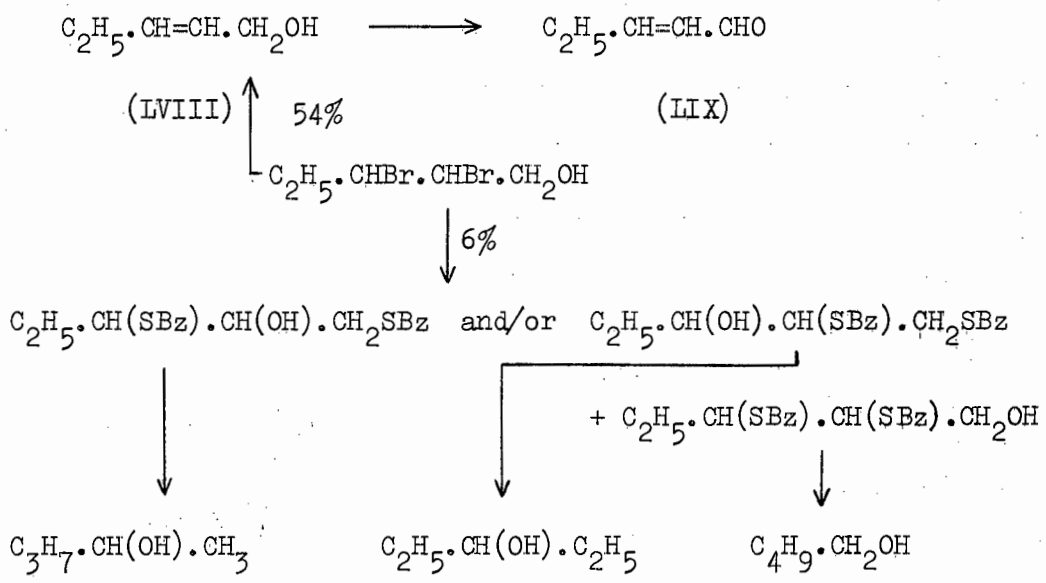


Figure 3. The reaction of 2,3-dibromopentan-1-ol with the sodium salt of toluene-ω-thiol and identification of products.

In order to approach the spatial conditions of the 1-(p-toluenesulphonyl)-pyrrolidin-2-yl group attached to 2,3-dibromopropanol (see formula), the reaction was repeated on 2,3-dibromo-4-methyl-pentan-1-ol (LX) with cooling of the exothermic reaction in a water bath. Only 4-methylpent-2-enol (LXI) was isolated in 43% yield being identified by oxidation to the aldehyde and formation of the 2,4-dinitrophenylhyrazone, m.p. 181°. Dibenzyl disulphide (LXII) isolated accounted for 91% of the toluene-ω-thiol employed.

$$(CH_3)_2.CH.CHBr.CHBr.CH_2OH \quad + \quad 2\ C_6H_5.CH_2SNa$$

(LX)

$$\downarrow$$

$$(CH_3)_2.CH.CH{=}CH.CH_2OH \quad + \quad (C_6H_5.CH_2S)_2 \quad + \quad 2\ NaBr$$

43% 91%

(LXI) (LXII)

The debromination of vicinal dibromo-alcohols yielding the alkenes did not seem immediately applicable. Fairbourne, Gibson and Stephens[9] have shown that substitution on these alcohols proceeds by way of the epoxide and it was thus thought that substitution could be better effected by first conversion into the epoxide.

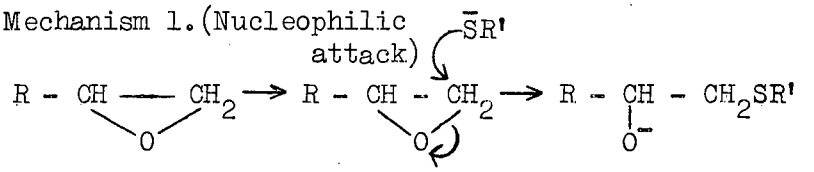
$$R.CHBr.CHBr.CH_2OH \longrightarrow R.CHBr.CH\!-\!O\!-\!CH_2$$

2.4 Alkane substitution by epoxide fission.

Cleavage of an epoxide may take place by two mechanisms. In acid medium, the oxygen would first be protonated followed by the attack of a nucleophilic reagent. Basic media would render the epoxide subject to attack by nucleophilic reagents only. Parker and Isaacs [25] in their review state that "under basic or neutral conditions, the normal isomer (corresponding to attack on the least substituted carbon atom) is nearly always the major or only isolated product".

One would expect ring opening to take place easily in the presence of acids due to protonation of the oxygen followed by ring fission and slower fission in basic solution (see fig. 4)

Mechanism 1. (Nucleophilic attack)



Mechanism 2. (Protonation)

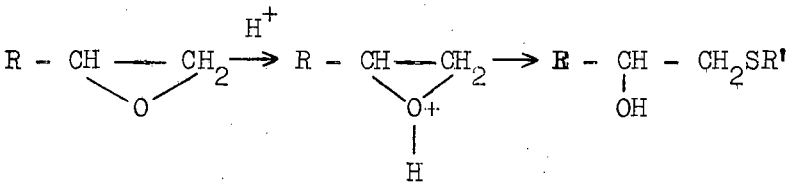
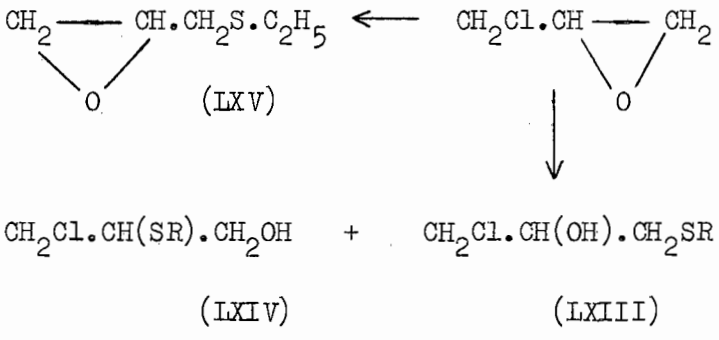
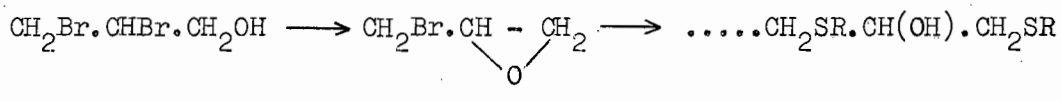


Figure 4. The mechanism of attack of epoxides by nucleophilic reagents.

The reaction of 1-chloro-2,3-epoxypropane with thiols has been studied by Fromm, Kapeller and Taubmann[10] who showed that the product depended on the nature of the addendum : electrophilic attack by acids (RSH) occurs readily to give both addition products (LXIII) and (LXIV) whereas nucleophilic attack by bases (RSNa) necessitated higher temperatures but was more stereo-specific to give terminal addition (LXIII). Nenitzescu and Scarlatescu[23] showed that the potassium salt of ethylthiol on 1-chloro-2,3-epoxypropane gave product (LXV) which was envisaged by the authors as the replacement of the chlorine atom by the thiol.



Johary and Owen[14] pointed out that the reaction



could be explained by the intermediate formation of the

epoxide. Accordingly, and in order to avoid the debromination reaction referred to above, the dibromo-alcohol was first converted by alkali to the bromo-epoxide; and this epoxide was then reacted with the sodium salt of toluene-ω-thiol. Only low yields were obtained. Careful scrutiny of the experimental conditions of the above reaction reveal that the formation of the epoxide (LXVII) from the dibromo-alcohol (LXVI) will generate toluene-ω-thiol together with sodium bromide. The mechanism advanced by Johary and Owen may be explained as shown in fig. 5. The toluene-ω-thiol being nucleophilic would attack the terminal carbon atom of the epoxide giving rise to the substituted bromo-alcohol (LXVIII). The reaction sequence would then be repeated yielding the epoxide followed by the disubstituted product (LXIX).

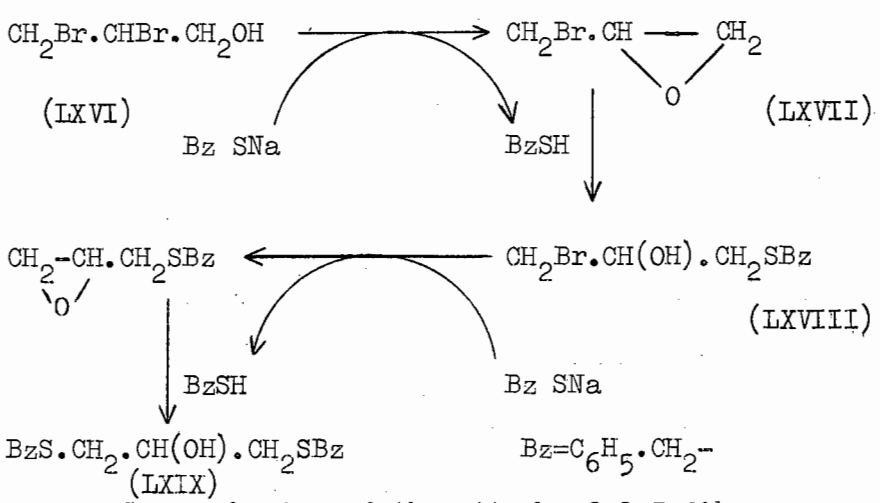
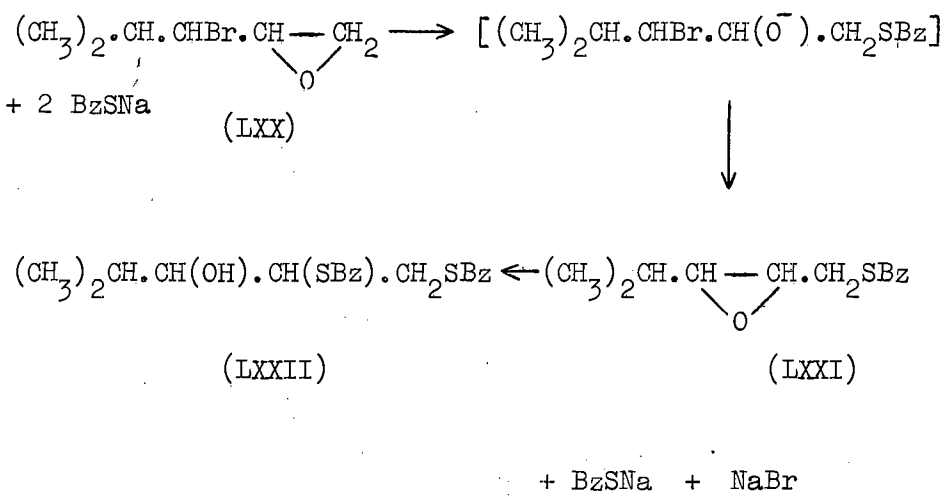


Figure 5. Mechanism of the attack of 2,3-dibromo-propanol by the sodium salt of toluene-ω-thiol.

The significance of the presence or otherwise of toluene-ω-thiol itself in this reaction sequence was tested by experiment :-

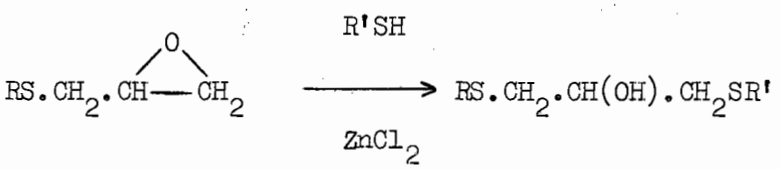
First, an ethanolic solution of 4-methyl-3-bromo-1,2-epoxypentane (LXX), prepared from the vicinal dibromo-alcohol, was heated for several hours under reflux with the sodium salt of toluene-ω-thiol in an atmosphere of nitrogen in the dark. The products obtained were identified to be the mono-(LXXI) and disubstituted (LXXII) products by their infra-red spectra and sulphur analyses. The disubstituted product was identified by debenzylation, desulphurisation, oxidation to the ketone and formation of the 2,4-dinitrophenylhydrazone (m.p. 107.5^{0}) to consist only of 4-methyl-1,2-dibenzylthiopentan-3-ol (LXXII). (See section 3.4.5).



The slow rate of the above reaction was established by analysis for sodium bromide which showed that only 77% of the bromo-epoxide (LXX) had reacted after one and a half hours in refluxing ethanol. The slow reaction rate was attributed to the presence of only the sodium salt of toluene-ω-thiol without any toluene-ω-thiol (see above).

Secondly, the reaction was repeated as before but with an excess of toluene-ω-thiol. Mainly the disubstituted product (LXXII) was formed in accordance with the concept of protonation outlined above.

The opening of the epoxide ring of compounds of the nature of (LXXIII) has been studied by Todes and Andrianova[33] employing zinc chloride as catalyst.

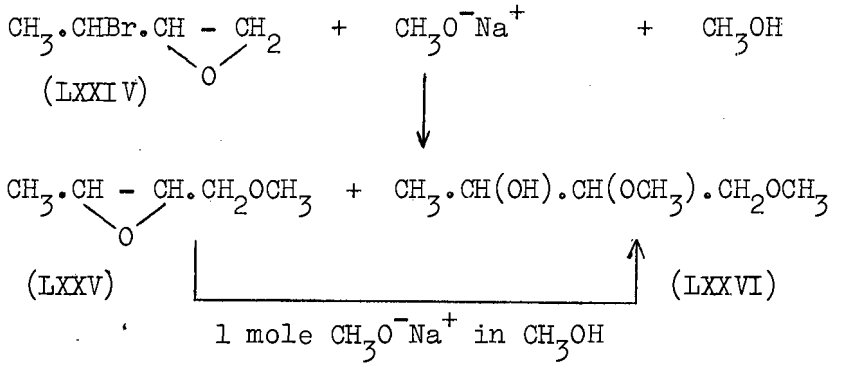


(LXXIII)

It was hoped that the addition of a catalyst might drive the reaction to completion by accelerating the rate of epoxide fission. The reaction was repeated on the bromo-epoxide (LXX) in the presence of zinc chloride yielding once again a mixture of mono- and disubstituted products as shown by thin-layer chromatography.

Since the reaction of the bromo-epoxide (LXX) with an excess of base yielded a mixture of the mono- and di-substituted products , an attempt was made to proceed as far as the mono-substituted epoxide by reacting the starting material with only one mole of the sodium salt of toluene-ω-thiol. A large quantity of unreacted material together with the mono- and disubstituted products were isolated from the mixture.

An analogous reaction by Waters and VanderWerf [36] of sodium methoxide on 3-bromo-1,2-epoxybutane (LXXIV) has been carried out leading to a mixture of 1-methoxy-2,3-epoxybutane (LXXV) and the disubstituted 1,2-dimethoxy-butan-3-ol (LXXVI). A quantity of monosubstituted epoxide (LXXV) was allowed to react further with one mole of sodium methoxide giving an 80% yield of the disubstituted product (LXXVI) after several hours in refluxing methanol .

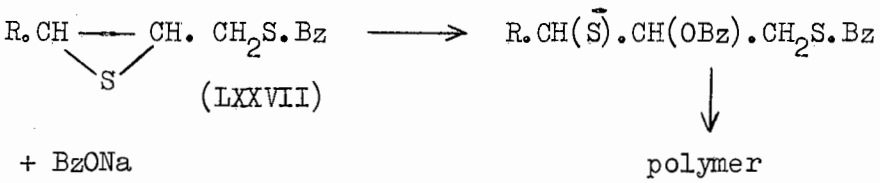


2.5 Further methods for the preparation of 3-substituted 1,3-dithiolpropan-2-ol

As outlined in previous sections, no difficulty was experienced in the substitution of a sulphur containing group on the terminal atoms of a butyl-, pentyl- and 4-methylpentyl systems. Substitution of a second sulphur containing group took place only on carbon 2 of the 4-methylpentyl system as shown by the formation of a derivative and perhaps on analogous carbon atoms in the pentyl- and butyl systems as described in section 2.3 since the alcohols could be identified only as primary or secondary alcohols by g.l.c. The synthesis thus resolved itself into the utilisation of a reaction by which a sulphur containing group attached to carbon 3 of a 3-substituted propyl chain would be the product isolated, while both carbon 1 and 2 remained available for further reaction.

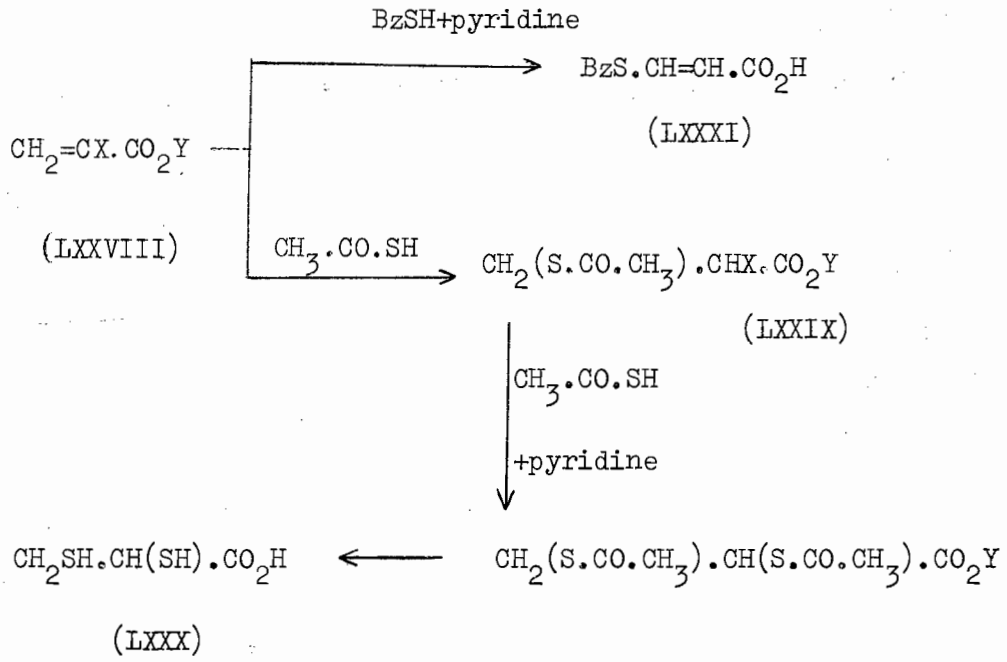
According to Reynolds and Fields [28], under basic conditions especially in the presence of polarising solvents, ring opening of epoxides and episulphides is similar. In an analogous reaction to the epoxide opening of 4-methyl-2,3-epoxy-1-benzylthiopentane (LXXI) with the sodium salt of toluene-ω-thiol yielding the disubstituted alcohol (LXXII) it could be expected that the opening of the episulphide (LXXVII) by the sodium salt

of benzyl alcohol would yield a sulphide ion attached to carbon 3. The sulphide ion, being a stronger nucleophile than the benzyloxy anion, would attack a further episulphide with the formation of a polymer by the repetition of this process.



An alternative solution to the problem would be the addition of a sulphur containing group at carbon 3 of the propyl chain (which is attached to pyrrolidine) by a reaction other than halogen replacement. Owen and Babatunde Somade [24] found that thiolacetic acid added to 2-bromoacrylic acid (LXXVIII, X=Br, Y=H) to give 2-bromo-3-acetylthiopropionic acid (LXXIX, X=Br, Y=H).

The compound (LXXIX, X=Cl, Y=CH_3) was found by Lazier, Pavlic and Peppel [20] to undergo further substitution yielding 2,3-dithiolpropionic acid (LXXX) after hydrolysis.



Owen and Babtunde Somade discovered that the reaction of toluene-ω-thiol in pyridine on 2-bromoacrylic acid (LXXVIII, X=Br, Y=H) yielded 3-benzylthioacrylic acid (LXXXI). 1-Bromocrotonic acid failed to undergo addition of the reagent, indicating that diminution of ethenoid activity is brought about not only by the methyl group in the 3-position, but also by the halogen atom since crotonic acid underwent the reaction. We attempted the reaction on 4-methyl-2-bromopent-2-enoic acid. The only materials isolated were thiolacetic acid together with the starting material.

Halogen substitution, in a compound containing a

vicinal hydroxy group, by a nucleophilic sulphide ion often leads to a rearranged product by way of the epoxide as was shown previously. The formation of the epoxide could be prevented by the use of an alcohol protective group or by oxidation to the ketone before the substitution reaction is undertaken. The choice of oxidation to the ketone would remove an asymmetric carbon atom and convert the alcohol into a group which would remain unaffected during the substitution.

2.6 Steps proposed for the completion of the synthesis

As was outlined in section 2.2 and is shown in figure 7, the dibromo-alcohol (XCVI) was synthesised from (-)-proline by way of the Knoevenagel reaction. On treatment with base the dibromo-alcohol yielded the epoxide which on reaction with hydrobromic acid gave the crystalline secondary alcohol (XCVII). Oxidation yielded the ketone, the halogen atoms of which were substituted by thiolacetate groups giving XCIX. The synthesis was completed this far and the steps proposed for the completion of the synthesis must be chosen such that the configuration of the molecule is preserved during all the stages, the

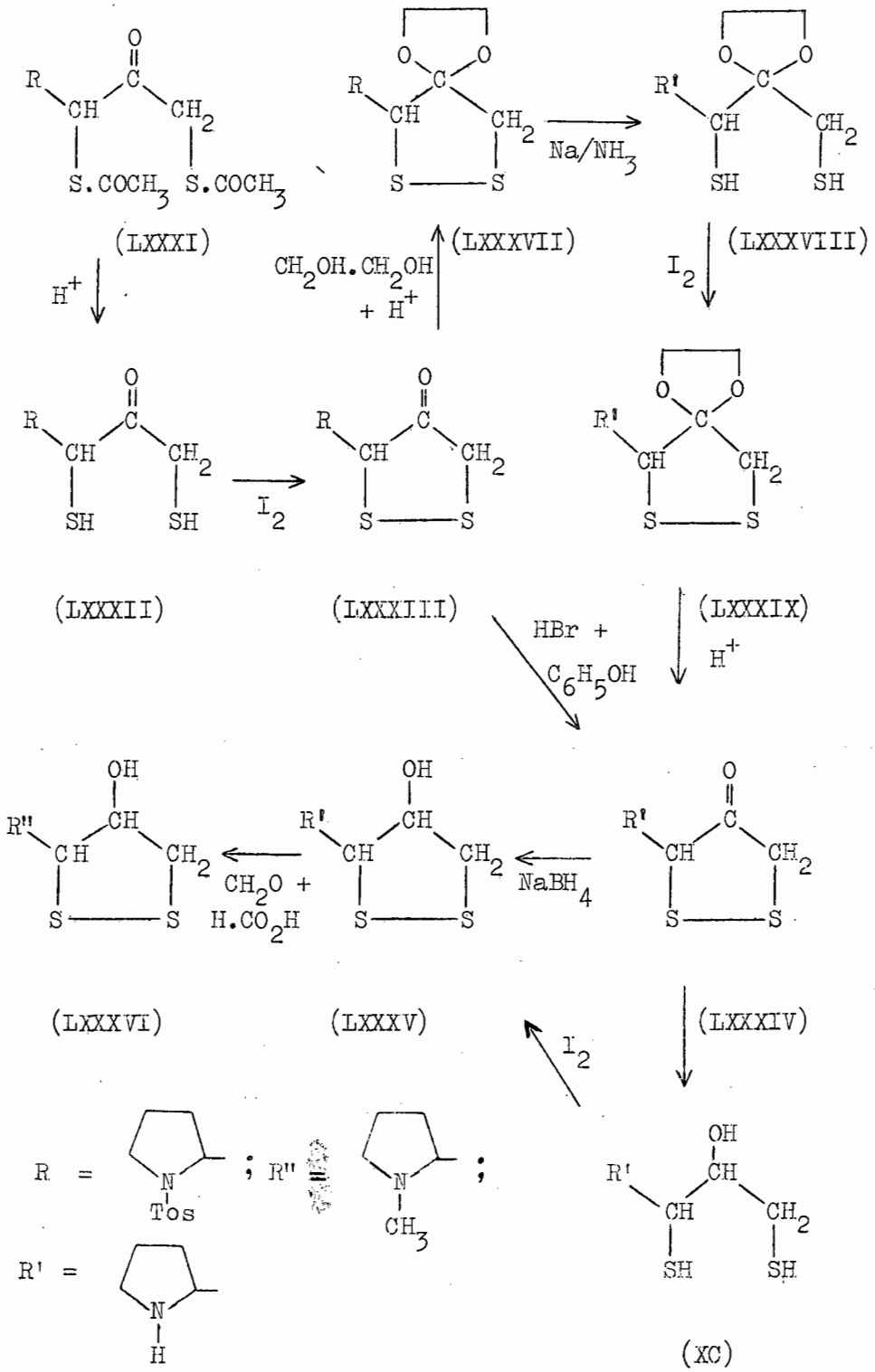


Figure 6. Reaction sequence proposed for the completion of the synthesis.

stereochemical factors of which will be discussed in section 2.7. All stages in the proposed reaction sequence will contain either the ketonic or alcoholic grouping. Since both will give rise to a racemised product in basic solution a reaction sequence should be chosen such that reactions will be carried out only in neutral or in acidic solution. If no sequence conforming to the above requirements can be found the use of the dioxolane derivative, formed by reaction of the ketone with ethylene glycol in acidic solution will provide a stable form of protection for the carbonyl function in basic solution. The introduction and removal of this protective group will add a further two steps to the synthesis.

The proposed reaction sequence from LXXXI to LXXXVI is depicted in figure 6 where no basic reagents are employed. Hydrolysis of the dithiolacetate (LXXXI) to yield the dithiol (LXXXII) can be achieved by employing a solution of aqueous hydrochloric acid in methanol. Tests indicate that hydrolysis in acidic solution, unlike basic solution, proceeds at a low reaction rate. The dithiol produced, being sensitive to oxidation and further unwanted reactions, could be made inert to many reactions by conversion into the

dithiolane (LXXXIII) by mild oxidation with iodine dissolved in aqueous potassium iodide. Under basic conditions, aliphatic disulphides rapidly decompose yielding the sulphide together with hydrogen sulphide [4].

Since the p-toluenesulphonyl nitrogen protecting group is so large and being three atoms removed from the keto group (relatively close with respect to the size of the protecting group), we might expect steric hinderance to the approach of the borohydride ion during the proposed stereospecific reduction of the ketone to yield the alcohol. It will thus be advisable to remove the tosyl group before reduction is attempted. Removal of the N-tosyl group has been effected by allowing a solution of the compound in acetic acid to stand for several hours in the presence of hydrobromic acid and phenol to yield the amine (LXXXIV). This method has given high yields of detosylated product [26].

If this method gives only low yields, the efficient sodium in liquid ammonia reductive detosylation can be employed after having first protected the ketone from possible racemisation in basic solution by formation of the dioxolane derivative (LXXXVII). This form of reduction will cleave also the disulphide

yielding the dithiol (LXXXVIII) as was shown by du Vigneaud in the cleavage of cystinyl-peptides to cysteine derivatives [8]. Hydrolysis of the dioxolane dithiol derivative in acid solution after mild oxidation would yield the dithiolane (LXXXIV).

The borohydride ion, being a mild reducing agent, "seems to have considerable difficulty in reducing disulphides if it can do so at all"[11].

Metal hydride reduction of a group in conjugation with an alkene usually leads to a product where both the group and the alkene have been reduced. The attempted reduction of crotonaldehyde with sodium borohydride, (being alkaline due to the presence of sodium hydroxide as impurity), yielded no product with a boiling point corresponding to crotyl alcohol. The reaction was repeated maintaining the neutrality of the solution by the addition of dilute hydrochloric acid during the slow addition of the reducing agent to the aqueous solution of crotonaldehyde. This mild form of reduction gave a moderate yield of the pure product. Reduction of the ketone (LXXXIV) in neutral solution should not lead to decomposition of the disulphide which occurs in alkaline solution. Were reduction of the dithiolane to take place yielding the dithiol,

the product (XC) would be reoxidised to the dithiolane by titration with a solution of iodine.

The Eschweiler-Clarke method of methylation provides a route by which only the nitrogen atom will be methylated leaving the alcohol group unreacted as was shown in the methylation of prolinol giving a moderate yield of N-methylprolinol (see 3.6.1.2). It is proposed that methylation in the series depicted should be postponed until reduction of the ketone to the alcohol is complete since "under the influence of bases present, the carbonyl components of the reaction mixture may undergo condensations of the aldol type. It is likely that they are concerned in the formation of the resinous by-products sometimes obtained [22]".

2.7 Stereochemical factors

In spite of the success of the reaction referred to in 1.3.4. which would permit extensions to include the chloro derivative as adopted by Schmidt, Grafen and Goedde[30], the stereochemical concepts had to be considered.

2.7.1 Synthesis by way of the acrylic acid

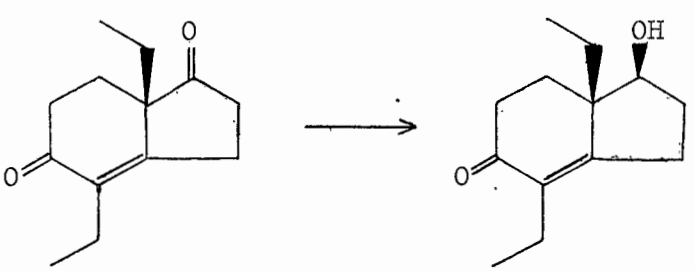
The synthesis outlined in figure 7 has the advantage that resolution of the asymmetric atoms can be carried out separately for each carbon atom working systematically from the pyrrolidine ring towards the terminal end of the propyl chain.

Although the asymmetry of carbon 2 of (-)-proline was preserved during the formation of the alcohol (XCI) and aldehyde (XCII), the Knoevenagel reaction yielded the acrylic acid where much racemisation had taken place. Resolution would be effected at this stage thereby resolving the carbon atom at position 2 of the pyrrolidine ring. The configuration of this carbon atom could be obtained by oxidation since XCIII would yield (-)-proline. The addition of bromine yielded presumably XCIV and XCV which would be separated to give an optically active centre at position 3 of the propyl chain. The product after bromination we may expect to contain one form which will predominate (say XCV). The resolved acid (say XCV) would then be subjected to reduction, epoxidation, treatment with hydrobromic acid to yield the secondary alcohol (XCVII) and oxidation by sodium dichromate in acetic acid to yield the ketone XCVIII. Since the described reactions of the ketone and

secondary alcohol were performed in acidic solutions it is hoped that the asymmetry of the optically active carbon atoms would be left undisturbed.

A solution of sodium thiolacetate on reaction with the dibromide (XCVIII) yielded the dithiolacetate (XCIX) where it is assumed that inversion has taken place at carbon 3 of the propyl chain. The envisaged hydrolysis of this product in acidic solution should yield the dithiol (C) leaving the asymmetric carbon atoms unaffected. Mild oxidation of this product could be effected by the addition of iodine dissolved in aqueous potassium iodide yielding the dithiolane (CI) and hydrogen iodide as products. Removal of the p-toluenesulphonyl nitrogen protecting group in acidic solution is not expected to cause racemisation.

Stereospecific reduction with sodium borohydride at 5^{o} dissolved in ethanol has been successfully achieved by Zurflüh, Wall, Siddall and Edwards [40] in the reduction of an asymmetric cyclopentanone.



Sodium borohydride in neutral solution, as explained in 2.6, is a mild reducing agent insensitive to sulphides and it is hoped that reduction of a disulphide in the form of the 3-substituted 4-keto dithiolane (CII) to yield the alcohol (CIII) will be easily effected without reduction of the dithiolane to yield the dithiol. Methylation of the pyrrolidine nitrogen atom would be effected by the Eschweiler-Clarke method which is carried out by heating for several hours in acidic solution.

The synthesis set out above contains several reactions carried out under strongly acidic conditions. They are:-

a) oxidation of the secondary alcohol (XCVII) to yield the ketone (XCVIII) which was carried out with sodium dichromate dissolved in acetic acid for a long period of time.

b) hydrolysis of the dithiolacetate (XCIX) with methanolic hydrochloric acid to yield the dithiol(C)

c) the removal of the tosyl group with hydrobromic acid and phenol in acetic acid as solvent.

Under these conditions racemisation of the carbon atom vicinal to the pyrrolidine ring could take place since it is in the α-position with respect

to an alcoholic or ketonic function. Were racemisation to take place the stereospecific reduction with sodium borohydride would give the pyrrolidine function and hydroxyl group cis with respect to each other on the dithiolane ring to yield CIII and its racemate. The configuration of the carbon atom at position 2 of the pyrrolidine ring should remain defined during the proposed synthesis since it would be resolved immediately after the synthesis of the acrylic acid. Two isomers would be expected and resolution could be achieved by formation of the phthalate mono-ester of the alcoholic product, followed by resolution and hydrolysis.

Proline was converted to (-)-N-(p-toluenesulphonyl)-proline, m. p. 86°, by the method of Pravda and Rudinger [27], which gave the methyl (-)-1-(p-toluenesulphonyl pyrrolidine-2-carboxylate, m. p. 75.5°, $[\alpha]_D$ -93.5°. Reduction with lithium alumir hydride gave in 95% yield N-(p-toluenesulphonyl)-prolinol, m. p. 87.5°, $[\alpha]_D$ -91.3° characterised further as its 3,5-dinitrobenzoate, m. p. 171.5°. Oxidation using dimethyl sulphoxide and dicyclohexylcarbodiimide gave an oil which with methanol gave the acetal of N-(p-toluenesulphonyl)-prolinal (XCII), m. p. 86°, which failed to analyse consistently and which was decomposed with acid to give the aldehyde itself, m. p. 119°, $[\alpha]_D$ -177.6°, further characterised as its 2,4-dinitrophenyl-hydrazone, m. p. 178.5°. The Knoevenagel reaction of XCII with malonic acid gave an oily acid which was esterified to give methyl trans-3-[1'-(p-toluene-sulphonyl)-pyrrolidin-2'-yl]-propionate (XCIII), m. p. 104.5°, $[\alpha]_D$ -6.9°, showing $\nu_{max.}$ 980 cm.$^{-1}$ and τ 4.01 (d, J16) indicative of the trans configuration. Bromination of the sodium salt of XCIII in the presence of sodium bromide gave 2,3-dibromo-3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]—propionic acid, (XCIV) and (XCV), m. p. 88°. Reduction of the dibromo compound with diborane resulted in a quantitative yield of 2,3-dibromo-3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propanol (XCVI), m. p. 169 - 170°, $[\alpha]_D$ -10.6°, and showing no carbonyl frequency in the i.r.

Treatment of this dibromo compound with ethanolic sodium hydroxide gave 1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-1-bromo-2,3-epoxypropane, m. p. 154 - 156°, $\nu_{max.}$ 860 and 820 cm.$^{-1}$ (epoxide), which with hydrobromic acid gave 1,3-dibromo-1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propan-2-ol (XCVII), m. p. 150 - 151°. Oxidation with chromic acid gave the corresponding ketone (XCVIII), m. p. 101 - 105°, showing $\nu_{max.}$ 1745 cm.$^{-1}$ characteristic of an $\alpha\alpha'$-dihalogenoketone. Reaction with potassium thiolacetate yielded a dithiolacetate which failed to crystallise and could not be obtained pure.

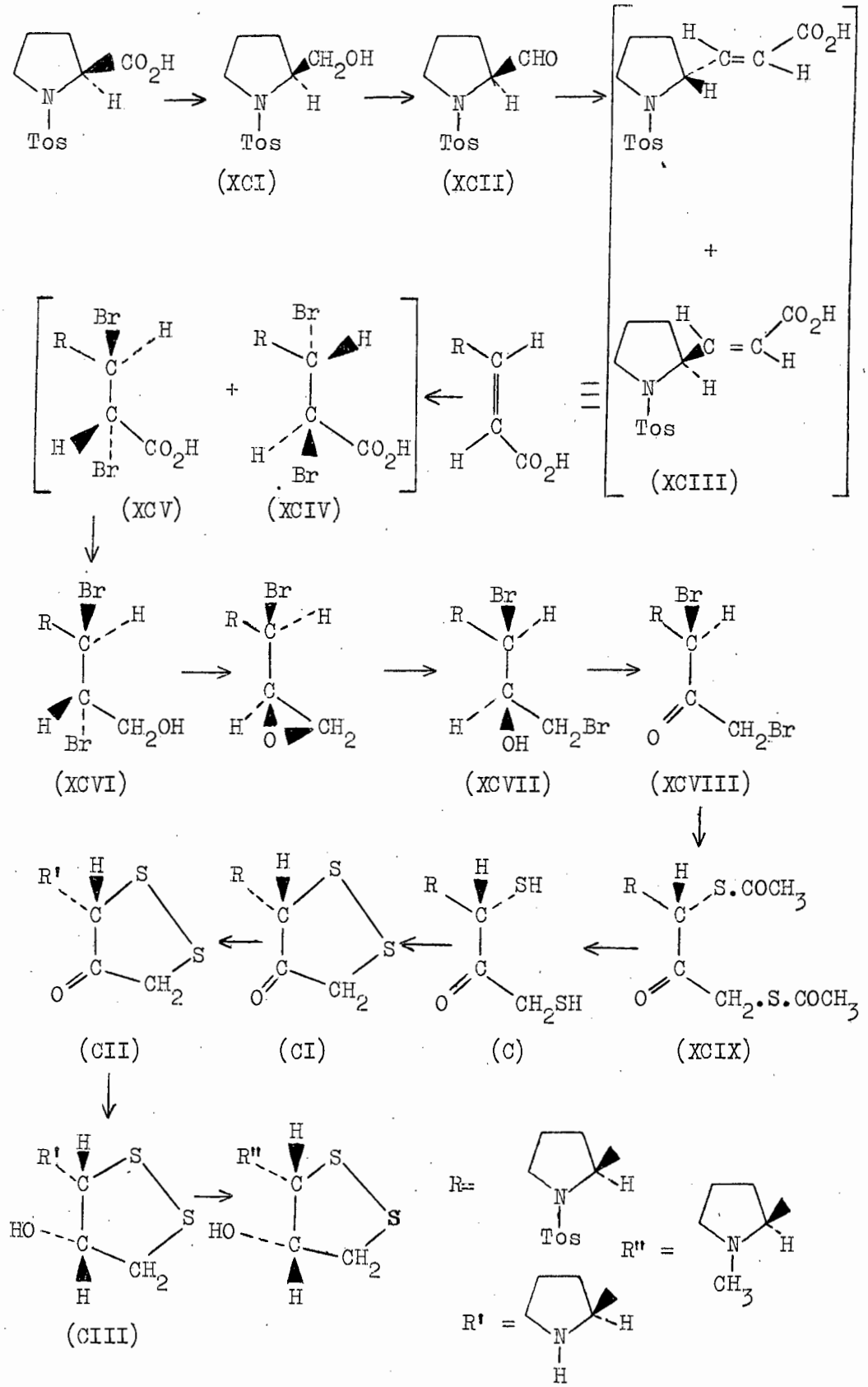
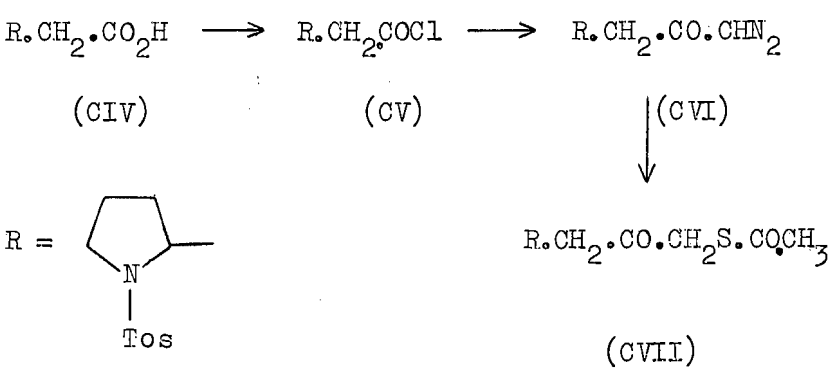


Figure 7. A possible synthesis of gerrardine by way of the acrylic acid.

2.7.2 Synthesis by way of the homoproline derivative

The synthetic pathway employed by Schmidt, Grafen and Goedde[30] has been previously explored by the candidate [18].

N-(p-Toluenesulphonyl)-proline was converted into the homoproline derivative (CVIII) and (CIX) by employing the Arndt-Eistert reaction (Wilds-Meader modification) on the diazoketone (fig. 8). The reaction carried out at 190° gave only a small yield of product (CVIII and CIX) exhibiting good optical activity. A sequence similar to the one employed by the above authors in the lengthening of the chain was employed in the remaining steps (see 1.3.4). The 2-substituted acetic acid (CIV) was converted into the diazoketone (CVI) by addition of diazomethane to the acetyl chloride (CV).



Addition of thiolacetic acid to the diazoketone yielded the thiolacetate (CVII).

It was the intention to convert the acetic acid into the α-bromo acid bromide (CX) by way of the Hell-Volhard-Zelinsky reaction followed by a reaction sequence similar to the one outlined above to yield the 3-substituted 1,3-dibromopropan-2-one (CXI). To confirm that no halogen substitution would take place on the pyrrolidine ring, a solution of N-(p-toluenesulphonyl)-pyrrolidine in chloroform was heated with bromine for several hours under reflux yielding only the original product. It was the intention to follow the reaction sequence outlined in 1.3.4 starting with CXI.

The synthesis showed promise since the Arndt-Eistert reaction yielded a crude product CVIII and CIX exhibiting strong optical activity. Resolution of this mixture will define the configuration of the carbon atom at position 2 of the pyrrolidine ring.

No further resolution of the two remaining asymmetric carbon atoms would be carried out during the reaction sequence. It was the intention to form the phthalate mono-ester of the 3-substituted 4-hydroxy dithiolane and resolve this product containing two asymmetric carbon atoms.

The outlined sequence, although showing promise since similar syntheses had followed the same lines as those intended by us, was rejected since the Arndt-Eistert reaction gave only small yields of product.

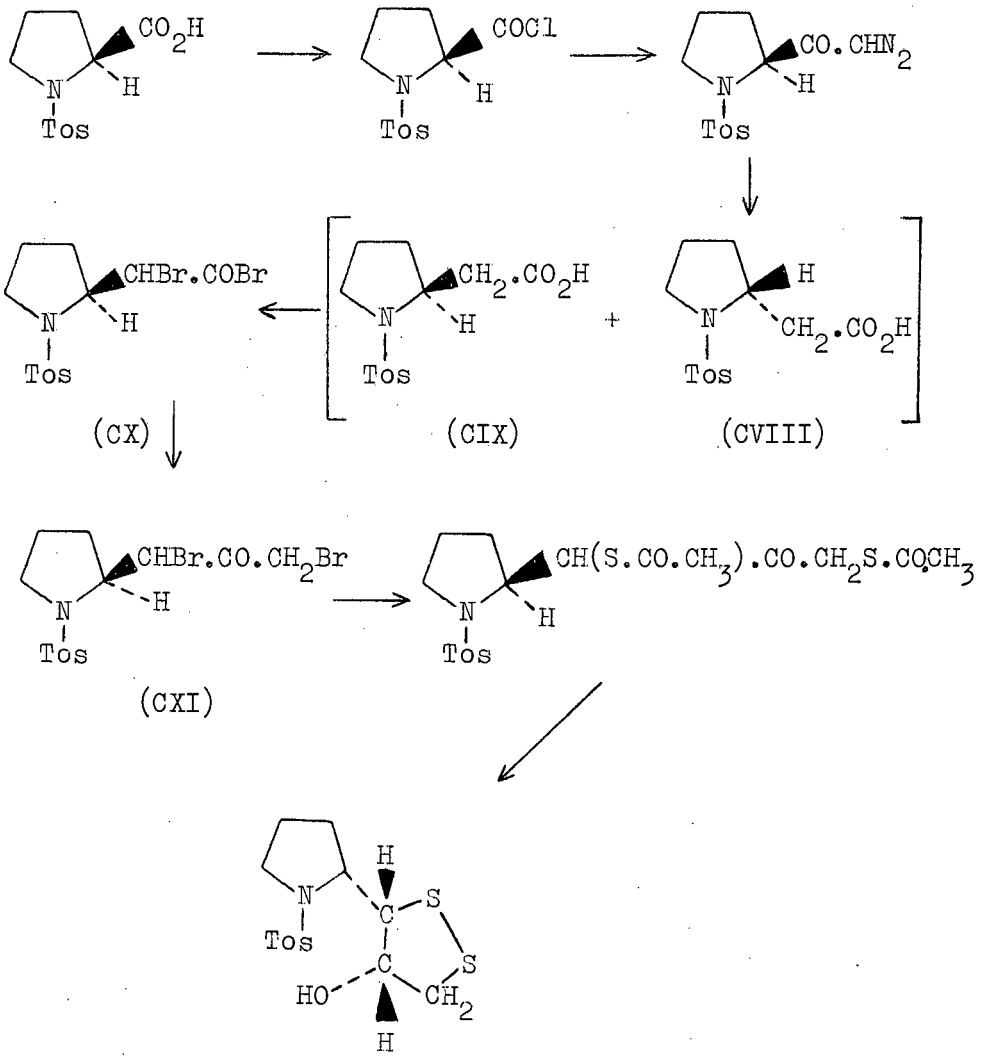


Figure 8. A possible synthesis of gerrardine by way of the Arndt-Eistert reaction.

2.7.3 Synthesis by way of the acetylenic compound

A further reaction route briefly explored envisaged proceeding by way of the substituted allyl alcohol (CXIII) from CXII. The reaction of sodium acetylide on N-(p-toluenesulphonyl)-prolinal (XCII) yielded CXII as was shown by subsequent reduction yielding 1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propan-1-ol (CXV). It was the intention to reduce the product with the Lindlar catalyst yielding CXIII followed by bromination yielding the dibromo-alcohol (CXIV). It was assumed that the analagous rearrangement described by Johary and Owen[14] to yield the 3-substituted 1,3-bisbenzylthiopropanol (see 1.4) could be successfully executed. This assumption was subsequently disproved by us by the reactions carried out on 2,3-dibromobutanol, 2,3-dibromopentanol and 4-methyl-2,3-dibromopentanol. The reaction sequence seemed attractive since the carbon atom at position 2 of the pyrrolidine ring was expected to retain its asymmetry during the Grignard reaction. It was the intention to carry out the resolution of the two remaining carbon atoms when the reaction sequence had been completed as was described in 2.7.2. The reaction sequence was abandoned when it was found that only low yields of product (CXII) were obtained

by the reaction of sodium acetylide on the aldehyde (XCII). In the reaction of ethynylmagnesium bromide on the aldehyde, no product could be recovered.

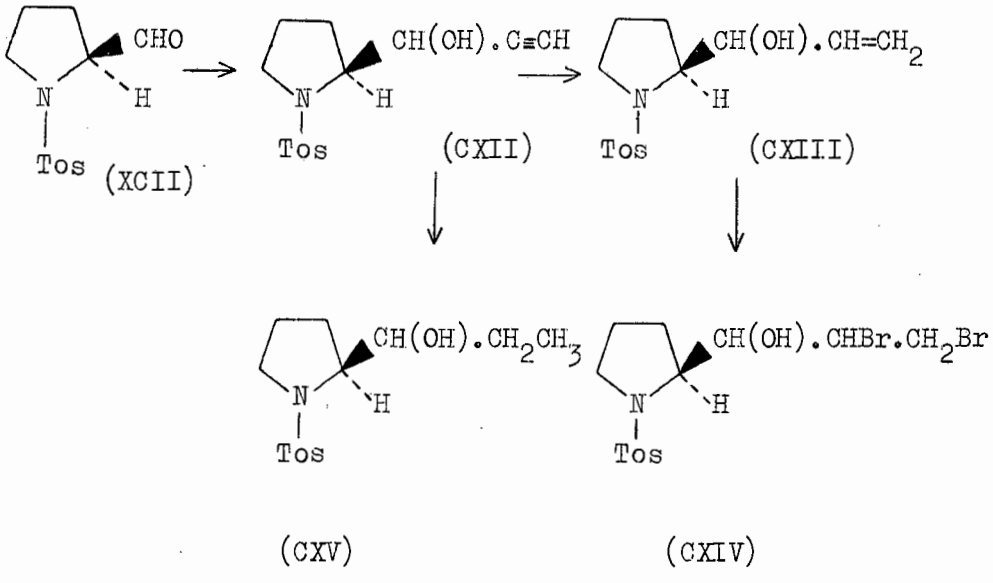


Figure 9. A proposed route for the synthesis of gerrardine by way of the acetylenic compound.

EXPERIMENTAL

3.1.3 continued

N-(p-Toluenesulphonyl)-prolinol previously recrystallised from petroleum ether/ether gave $\nu_{max.}$ (KBr) 3600 (OH), 2950 (C-H), 1600 (aromatic C=C), 1345 and 1160 (N-SO_2), 1040 (CH_2OH), 835 $cm.^{-1}$. (p-disubstituted aromatic). τ ($CDCl_3$) 2.44 (q, $C_6\underline{H}_4$), 6.32 (s, $C\underline{H}_2OH$) 6.6 (m, $C\underline{H}_2$-N-C$\underline{H}$), 7.00 (s, O$\underline{H}$, disappeared on D_2O exchange), 7.57 (s, $C\underline{H}_3$), 8.3 (m, N-CH_2-$C\underline{H}_2$-$C\underline{H}_2$).

(D. L. Morgan, Ph.D. thesis, University of Cape Town, 1970 gives m. p. 87 - 87.5°).

addition of wet ether (250 ml.) followed by water (20 ml.). The mixture was filtered and the residue washed with ether (4 X 50 ml.). After drying the solution over anhydrous sodium sulphate (2 X 5 g.) and removal of ether the colourless oil crystallised to give N-(p-toluenesulphonyl)-prolinol as crystals, m.p. 87.5 (Yield 23.2 g. ; 95%). $[\alpha]_D^{19}$ -91.3° (c, 10% in ethanol) after recrystallisation from pet. ether/ether.

N-(p-toluenesulphonyl)-prolinyl 3,5-dinitrobenzoate crystallised from benzene in pink crystals m.p. 171.5° .

Found : C, 51.0 ; H, 4.22; N, 9.24

$C_{19}H_{19}N_3O_8S$ requires : C, 50.8 ; H, 4.26; N, 9.35%

3.1.4 N-(p-Toluenesulphonyl)-prolinal

N-(p-Toluenesulphonyl)-prolinol (10.0 g.; 1 mol.) was dissolved in dry dimethylsulphoxide (40 ml.), absolute phosphoric acid (1.06 ml.; 0.5 mol.) and dicyclohexylcarbodiimide (22.8 g.; 3 mol.) was added. The solution was shaken and cooled in an ice bath for the first 15 minutes. After five hours ether (100 ml.) followed by oxalic acid (16.5 g.) dissolved in methanol (40 ml.) was added and set aside for one hour until gas evolution had ceased. The solution was filtered and the residue washed with benzene (5 X 50 ml.). The combined filtrate and benzene washings were shaken out with saturated sodium bicarbonate solution (2 X 100 ml.) and water (2 X 100 ml.). The combined aqueous washings were extracted with benzene (3 X 50 ml.) which were washed as before with saturated sodium bicarbonate (2 X 30 ml.) and water (2 X 30 ml.). The benzene

3.1.4 continued

N-(p-Toluenesulphonyl)-prolinal, m.p. 119°, was recrystallised from benzene/ether.

	Found :	C, 56.7; H, 5.8; N, 5.5
$C_{12}H_{15}NO_3S$	requires :	C, 56.9; H, 6.0; N, 5.5%.

The infra-red spectrum (KBr) showed $\nu_{max.}$ 2950 (C-H), 1730 (C=O), 1595 (aromatic C=C), 1340 and 1160 ($N-SO_2$), 825 $cm.^{-1}$ (p-disubstituted aromatic).

washings were evaporated under reduced pressure, the residue dissolved in warm methanol (30 ml.) and stored at 0° for 12 hours to induce crystallisation of the acetal. The crystals were filtered off and washed with cold methanol. The filtrate and washings were concentrated to give a further quantity of acetal. The acetal was decomposed by shaking with 30% hydrochloric acid (300 ml.) and ether (4 X 50 ml.). The combined extracts were extracted with water (30 ml.), dried over anhydrous sodium sulphate (2 X 5 g.) and evaporated yielding aldehyde (6.54 g.; 66%), m.p. 119°, $[\alpha]_D^{19}$ -177.6° (c, 10% in benzene).

N-(p-toluenesulphonyl)-prolinal 2,4-dinitrophenylhydrazone recrystallised from ethyl acetate, m.p. 178.5°.

Found : C, 50.1 ; H, 4.6 ; N, 16.2 ; S, 7.5

$C_{18}H_{19}O_6N_5S$ requires : C, 49.9 ; H, 4.4 ; N, 16.2 ; S, 7.4%

3.1.5 Methyl 3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propenate.

N-(p-Toluenesulphonyl)-prolinal (6.97 g.; 1 mol.) was dissolved in dry pyridine (130 ml.) and pipiridine (2 ml.) after which vacuum dried malonic acid (8.59 g.; 3 mol.) was added and warmed to 80° over three hours. The temperature was maintained at 90 - 95° for a further three hours until no more bubbling was observed. The solution was allowed to cool. After the addition of concentrated hydrochloric acid (200 ml.) the solution was extracted with benzene (8 X 100 ml.). This extract was shaken out with 10% sodium hydroxide solution (3 X 100 ml.) which was acidified with concentrated hydrochloric acid (100 ml.) and re-extracted with benzene (6 X 60 ml.).

3.1.5 continued

Methyl 3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propenate showed $\nu_{max.}$ (KBr) 2950 (C-H), 1720 (C=O), 1660 (aliphatic C=C, 1600 and 1500 (aromatic C=C), 1315 (-CH=CH- trans), 1340 and 1160 ($N-SO_2$), 980 (-CH=CH- trans), 820 $cm.^{-1}$ (p-disubstituted aromatic). τ ($CDCl_3$) 2.52 (q, $C_6\underline{H}_4$), 3.19 (dd, J16 and 6 Hz., CH-C$\underline{H}$=CH), 4.01 (d, J16, CH=C$\underline{H}$-CO_2), 5.60 (m, N-C$\underline{H}$-CH=), 6.29 (s, O-$C\underline{H}_3$), 6.65 (m, $CH_2-C\underline{H}_2-N$), 7.58 (s, $C_6H_4-C\underline{H}_3$), 8.3 (m, $N-CH_2-C\underline{H}_2-C\underline{H}_2$).

The benzene extracts from acidified sodium hydroxide solution were evaporated under reduced pressure and the residue esterified by refluxing with absolute methanol (120 ml.) and concentrated sulphuric acid (1.5 ml.) for 18 hours. The methanolic solution was added to a saturated sodium bicarbonate solution (500 ml.) and extracted with dichloromethane (5 X 50 ml.). After drying the solution over anhydrous sodium sulphate (2 X 5 g.) and the solvent removed under reduced pressure, the residue was dissolved in benzene (15 ml.) and run through a neutral alumina column collecting the benzene and ether fractions. After evaporation under reduced pressure methyl 3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propenate, m.p. 104.5°, was obtained. $[\alpha]_D^{28}$ - 6.9° (c, 7% in ethyl acetate) (Yield 7.33 g.; 86%).

Found : C, 58.0 ; H, 6.0 ; N, 4.6

$C_{15}H_{19}O_4NS$ requires : C, 58.2 ; H, 6.2 ; N, 4.5%

3.1.6 3-[1'-(p-Toluenesulphonyl)-pyrrolidin-2'-yl]-prop-2-enol

Methyl 3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propenate (6.81 g.; 1 mol.) previously dried under vacuum was dissolved in dry ether (300 ml.). A solution of lithium aluminium hydride (1.262 g.; 1.5 mol.) in dry ether (100 ml.) previously deactivated by the addition of absolute ethanol (1.456 g. ; 1.5 mol.) was added to the stirred solution in four equal portions at one hour intervals. After stirring for seven hours the solution was deactivated by the addition of wet ether (200 ml.) followed by the cautious

3.1.6 continued

3-[1'-(p-Toluenesulphonyl)-pyrrolidin-2'-yl]-prop-2-enol showed $\nu_{max.}$ (KBr) 3600 (broad OH), 2950 (C-H), 1595 (aromatic C=C), 1350 and 1160 ($N-SO_2$), 980 (-CH=CH- trans), 820 $cm.^{-1}$ (p-disubstituted aromatic). τ ($CDCl_3$) 2.56 (q, $C_6\underline{H}_4$), 4.27 (m, $CH_2-C\underline{H}=CH-$), 5.30 (m, $CH=C\underline{H}-CH$), 5.75 (m, $N-C\underline{H}-CH=$), 6.20 (m, $CH=CH-C\underline{H}_2$), 6.72 (m, $CH_2-C\underline{H}_2-N$), 7.35 (s, O$\underline{H}$), 7.60 (s, $C\underline{H}_3$), 8.37 (m, $N-CH_2-C\underline{H}_2-C\underline{H}_2$).

addition of water (10 ml.). When bubbling had ceased, the white precipitate was removed by filtration and washed with ether (5 X 30 ml.). The ethereal solution was dried over anhydrous sodium sulphate (2 X 5 g.) and evaporated giving crude product (4.3 g.) which showed four components on thin-layer and which was purified by passing through a neutral alumina column (80 g.; 1.6 X 40 cm.) yielding 3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-prop-2-enol (2.16 g.; yield 29%) as a yellow, glassy solid. $[\alpha]_D^{25}$ -53.2° (c, 7% in ethanol). The centre portion which showed no band in the 1700 - 1800 cm^{-1} region, analysed as follows :-

Found : C, 59.5 ; H, 6.9 ; N, 4.8

$C_{14}H_{19}O_3NS$ requires : C, 59.8 ; H, 6.8 ; N, 5.0%

3.1.7 2,3-Dibromo-3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propanoic acid

A solution of previously recrystallised 3-[1'-(p-toluene-sulphonyl)-pyrrolidin-2'-yl]-propenoic acid (1.90 g. ; 1 mol.) in methanol (50 ml.) was titrated with methanolic potassium hydroxide using phenolphthalein as indicator. After removal of methanol under reduced pressure, the residue was dissolved in water (10 ml.) and titrated slowly with a solution of bromine (1.03 g. ; 1 mol.) in saturated aqueous sodium bromide. The mixture was set aside for twelve hours, acidified with hydrochloric acid, followed by extraction with chloroform (4 X 20 ml.). The extract was washed with water (20 ml.), dried over

3.1.7 continued

2,3-Dibromo-3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]- propanoic acid showed $\nu_{max.}$ (KBr) 3450 (broad OH), 2950 (C-H), 2650 (intra-molecular H-bonded OH), 1720 (C=O), 1595 (aromatic C=C), 1345 and 1155 (N-SO_2), 825 $cm.^{-1}$ (p-disubstituted aromatic). The n.m.r. spectrum determined by D. L. Morgan showed τ [$(CD_3)_2CO$] 2.36 (q, $C_6\underline{H}_4$), 3.95 (broad singlet, $CO_2\underline{H}$, disappeared on D_2O exchange), 4.79 (dd, J12 and 3 Hz., N-CH-$C\underline{H}$Br-CHBr), 5.57 (d, J12 Hz., $C\underline{H}$Br-CO_2H), 5.85 (sextet t, J6 Hz. split J3 Hz., N-$C\underline{H}$-CHBr), 6.6 (m, $C\underline{H}_2N$), 7.55 (s, $C\underline{H}_3$), 8.2 (m, N-CH_2-$C\underline{H}_2$-$C\underline{H}_2$).

anhydrous sodium sulphate (3 g.)and evaporated to dryness yielding a semi-crystalline oil which was dissolved in a little warm, wet dichloromethane and allowed to crystallise. After removal of the crystals by filtration, the liquor was concentrated and the crystallisation procedure repeated two more times yielding a total of 1.70 g.; 56% of crystalline material which on recrystallisation from wet dichloromethane yielded colourless, cubic crystals of 2,3-dibromo-3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propanoic acid, m.p. 88°.

Found : C, 35.6 ; H, 4.0 ; S, 6.9; Br, 33.8

$C_{14}H_{17}O_4NSBr_2.H_2O$ requires : C, 35.5 ; H, 4.0 ; S, 6.8; Br, 33.8%

3.1.8 2,3-Dibromo-3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propanol

To vacuum dried 2,3-dibromo-3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propanoic acid (0.50 g.; 1 mol.) dissolved in previously dried tetrahydrofuran (15 ml.), was added a solution of diborane in tetrahydrofuran (2.94 ml. of 0.37 M B_2H_6; 2.0 mol.) and set aside for seventy hours. After carefully pouring the solution into ice cold water (50 ml.) with slight evolution of hydrogen, the solution was extracted with benzene (4 X 25 ml.). The extract was washed with water (25 ml.), dried over anhydrous sodium sulphate (5 g.) and evaporated yielding crystals(0.47 g. ; 99%) which were recrystallised from a mixture of benzene and ethanol giving white crystals of 2,3-dibromo-3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propanol, m.p. 169 - 170°, $[\alpha]_D^{20}$ 10.6°

3.1.8 continued

2,3-Dibromo-3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propanol showed $\nu_{max.}$ (KBr)3550 (OH), 2950 (C-H), 1595 (aromatic C=C), 1345 and 1155 (N-SO_2), 828 $cm.^{-1}$ (p-disubstituted aromatic).

(c, 3% in dimethyl sulphoxide).

Found : C, 38.7; H, 4.2; S, 7.3; Br, 35.9

$C_{14}H_{19}NO_3SBr_2$ requires : C, 38.1; H, 4.3; S, 7.3; Br, 36.2%

3.1.9 Reaction of 2,3-dibromo-3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propanol with the sodium salt of toluene-ω-thiol.

Freshly cleaned sodium (0.053 g.; 2.05 mol.) was dissolved in absolute ethanol (15 ml.) followed by the addition of freshly distilled toluene-ω-thiol (0.289 g.; 2.05 mol.). The solution was warmed at 60° for ten minutes, solvent removed by evaporation under reduced pressure and the crystalline residue evacuated for thirty minutes. The residue was dissolved in previously dried dimethyl formamide (40 ml.) and added to a solution of 2,3-dibromo-3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propanol (0.50 g.; 1.0 mol.) in dry dimethylformamide (20 ml.) under nitrogen in the dark. The flask was set aside at room temperature for fifteen hours, the contents poured into water (300 ml.) previously saturated with sodium sulphate and extracted with benzene (4 X 60 ml.). The benzene extracts were washed with saturated sodium sulphate solution (6 X 50 ml.) and the benzene then removed by distillation under reduced pressure yielding a white, crystalline residue. Separation by elution from an alumina column yielded dibenzyl disulphide (0.14 g.) accounting for 50% of the toluene-ω-thiol employed together with a colourless, viscous oil which crystallised after being set aside for several months.

3.1.9 continued

3-[1'-(p-Toluenesulphonyl)-pyrrolidin-2'-yl]-prop-2-enol exhibited $\nu_{max.}$ (KBr) 3500 (broad OH), 2950 (C-H), 1595 (aromatic C=C), 1345 and 1155 ($N-SO_2$), 980 (C=C), 825 $cm.^{-1}$ (p-disubstituted aromatic).

3.1.10 continued

1-[1'-(p-Toluenesulphonyl)-pyrrolidin-2'-yl]-1-bromo-2,3-epoxypropane showed $\nu_{max.}$ (KBr) 2950 (C-H), 1600 (aromatic C=C), 1350 and 1165 ($N-SO_2$), 1255, 860 and 820 (epoxide), 825 $cm.^{-1}$ (p-disubstituted aromatic).

The oil exhibited a strong infra-red absorption band at 980 cm^{-1} corresponding to an alkene. Ensuing experiments with 2,3-dibromopentanol confirmed that dehalogenation had occurred yielding 3-[1'-(p-toluene-sulphonyl)-pyrrolidin-2'-yl]-prop-2-enol.

Found : S, 11.1

$C_{14}H_{19}O_3NS$ requires : S, 11.4%

3.1.10 1-[1'-(p-Toluenesulphonyl)-pyrrolidin-2'-yl]-1-bromo-2,3-epoxypropane

A solution of ethanolic sodium hydroxide (0.286 g. in 11.2 ml. of ethanol; 1.3 mol.) was added to a suspension of crystalline 2,3-dibromo-3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propanol (2.42 g.; 1.0 mol.) in benzene (50 ml.). The suspension was warmed at 70° for ten minutes, during which time all solids dissolved, and the solution poured into cold water (250 ml.). The aqueous solution was then salted out with sodium sulphate and extracted with benzene (4 X 50 ml.). After drying over anhydrous sodium sulphate (2 X 5 g.), the volume was reduced by evaporation under reduced pressure and set aside to crystallise. The procedure was repeated several times on the filtrate yielding colourless crystals (1.38 g.; 70%), m.p. 154.5 - 156° of 1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'yl]-1-bromo-2,3-epoxypropane.

Found : C, 47.3 ; H, 5.1 ; S, 8.9

$C_{14}H_{18}NO_3SBr$ requires : C, 46.7 ; H, 5.0 ; S, 8.9%

3.1.11 1,3-Dibromo-1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'yl]-propan-2-ol

To the above epoxide (0.96 g.; 1.0 mol.) dissolved in dry

3.1.11 continued

1,3-Dibromo-1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propan-2-ol showed $\nu_{max.}$ (KBr) 3500 (OH), 2950 (C-H), 1600 (aromatic C=C), 1340 and 1160 ($N-SO_2$), 822 $cm.^{-1}$. (p-disubstituted aromatic).

dioxane (30 ml.) was added 15% hydrobromic acid (5.2 ml.; 3.0 mol.) and the solution warmed at 50° for thirty minutes with constant swirling. The mixture was poured into water (100 ml.), salted out with sodium sulphate and extracted with benzene (4 X 40 ml.). The benzene was removed by evaporation under reduced pressure yielding a mass of white crystals (1.16 g.; 98.5%) which was recrystallised from a benzene/ethanol/water mixture and gave crystals of 1,3-dibromo-1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propan-2-ol, m.p. 150-1°

Found : C, 38.1; H, 4.4; S, 7.3

$C_{14}H_{19}NO_3SBr_2$ requires : C, 38.1; H, 4.3; S, 7.3%

3.1.12 1,3-Dibromo-1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propan-2-one

The dibromoalcohol (1.54 g.; 1.0 eq.) described in the previous section, suspended in dry acetic acid was treated with a solution of sodium dichromate (0.57 g.; 1.5 eq.) in acetic acid (10 ml.) under nitrogen and the mixture stirred for seventy hours while the temperature of the flask was maintained at 30°. The contents were poured into water (250 ml.) and extracted with benzene (4 X 50 ml.), the extracts of which were washed with water (40 ml.) and dried over anhydrous sodium sulphate (5 g.). On evaporation a mass of oily crystals was obtained which, on solution in a small volume of benzene was applied to two 10 X 10 cm. plates of silica gel of 2 mm. thickness. Separation of

3.1.12 continued

1,3-Dibromo-1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propan-2-one showed $\nu_{max.}$ (NaCl) 2950 (C-H), 1745 (α,α'-dihalo ketone), 1700 (aromatic C=C), 1350 and 1160 (N-SO_2), 822 $cm.^{-1}$ (p-disubstituted aromatic).

the alcohol and ketone was achieved using benzene-ether (9 : 1) as solvent and then removing the layer of silica gel containing the ketone. Repeated washing with benzene followed by evaporation of the solvent under reduced pressure yielded the product (0.70 g.; 46%). Recrystallisation from ethanol yielded fine, white crystals of 1,3-dibromo-1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propan-2-one, m.p. 101 - 105°.

Found : C, 38.5 ; H, 3.8; Br, 36.1

$C_{14}H_{17}NO_3SBr_2$ requires : C, 38.3 ; H, 3.9 ; Br, 36.4%

3.1.13 1,3-Dithiolacetyl-1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propan-2-one

To a solution of 1,3-dibromo-1-[1'-(p-toluenesulphony)-pyrrolidin-2'-yl]-propan-2-one (0.70 g.; 1.0 mol.) in methanol (10 ml.) was added a solution of potassium thiolacetate in methanol (10 ml.). This was prepared by the addition of a solution of potassium hydroxide (0.34 g.; 3.8 mol.) to thiolacetic acid (0.46 g.; 3.8 mol.). The reaction was set aside for three hours and warmed at 50° for a further hour. The methanol was removed by evaporation under reduced pressure and after the addition of water (15 ml.), the residue extracted with benzene (4 X 15 ml.). The benzene extract was washed with saturated sodium bicarbonate solution (15 ml.) and water (15 ml.). After drying over anhydrous sodium

sulphate (2 g.), the solvent was removed by evaporation under reduced pressure yielding an orange coloured oil. A sample was placed under vacuum for several days before being sent for analysis.

Found : S, 25.3 $\pm$ 5

$C_{18}H_{23}NO_5S_3$ requires : S, 22.4%

The oil failed to crystallise. Unsuccessful attempts were made to purify the sample by passing through a column of neutral alumina.

3.1.14 continued

The colourless oily acid, not further purified, exhibited $\nu_{max.}$ (KBr) 3300 - 2500 (broad OH and C-H), 1670 (C=O), 1595 (aromatic C=C), 1555 and 1400 (CO_2^-), 1330 and 1155 (N-SO_2), 815 $cm.^{-1}$ (p-disubstituted aromatic). τ ($CDCl_3$) 2.55 (q, $C_6\underline{H}_4$), 6.24 (m, N-C$\underline{H}$-CH_2), 6.71 (m, N-$C\underline{H}_2$), 7.10 (s, O$\underline{H}$), 7.60 (s, $C\underline{H}_3$), 7.71 (m, $C\underline{H}_2$-CO), 8.41 (m, N-CH_2-$\underline{CH}_2$-$\underline{CH}_2$) 8.69 (m, $C\underline{H}_2CH_2CO$).

3.1.14 3-[1'-(p-Toluenesulphonyl)-pyrrolidin-2'-yl]-propanoic acid

3-[1'-(p-Toluenesulphonyl)-pyrrolidin-2'-yl]-propenoic acid (0.58 g.), dissolved in 0.3N ethanolic potassium hydroxide (60 ml.), was shaken with platinum oxide (0.1 g.) in an atmosphere of hydrogen for fifty hours. After filtration and evaporation of the ethanol under reduced pressure, the residue was dissolved in water (50 ml.) and purified by extraction with benzene (3 X 15 ml.). The solution was acidified with concentrated hydrochloric acid and extracted with benzene (3 X 20 ml.) which on evaporation under reduced pressure yielded a colourless oil (0.54 g.; 94%). The S-benzyl iso-thiuronium salt of 3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propanoic acid was formed, m.p. 151.5°.

Found : C, 57.3 ; H, 6.4; N, 9.3; S, 13.6

$C_{22}H_{29}O_4N_3S_2$ requires : C, 57.0 ; H, 6.3; N, 9.1; S, 13.8%

3.1.15 Methyl 3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propanoate

The propanoic acid (0.8 g.) produced in the previous section was dissolved in methanol (30 ml.), concentrated sulphuric acid (0.1 ml.) added and allowed to reflux for twelve hours. The solution was poured into a saturated solution of sodium bicarbonate (150 ml.) and extracted with ether (8 X 30 ml.) which, after drying over anhydrous sodium sulphate (10 g.), evaporation under reduced pressure and evacuation yielded methyl 3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'yl]-

3.1.15 continued

Methyl 3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propanoate was purified by passing through a neutral alumina column using benzene as elutant; the first fraction contained the bulk of material and showed one spot on t.l.c. The sample exhibited $\nu_{max.}$ (KBr) 2950 (C-H), 1750 (C=O), 1600 (aromatic C=C), 1345 and 1160 ($N-SO_2$), 820 $cm.^{-1}$ (p-disubstituted aromatic).

3.1.16 continued

The 3,5-dinitrobenzoate of 3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propanol showed $\nu_{max.}$ (NaCl) 3950 (C-H), 1740 (C=O), 1600 (aromatic C=C), 1550 ($C-NO_2$), 1345 and 1155 ($N-SO_2$), 820 $cm.^{-1}$ (p-disubstituted aromatic).

propanoate as a colourless oil.

Found : C, 57.8; H, 6.7; S, 10.2

$C_{15}H_{21}O_4NS$ requires : C, 58.9; H, 6.8; S, 10.3%

3.1.16 3-[1'-(p-Toluenesulphonyl)-pyrrolidin-2'-yl]-propanol

The methyl ester (0.59 g.; 1.0 mol.), prepared in the previous section, dissolved in dry ether (5 ml.) was added slowly from a dropping funnel to a solution of lithium aluminium hydride (0.20 g.; 3.5 mol.) in dry ether (25 ml.). The mixture was refluxed for four hours, water (2 ml.) added dropwise, insoluble material removed from the ethereal solution by filtration, which, after drying over anhydrous sodium sulphate (3 g.) and evaporation yielded 3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propanol as a colourless oil (0.36g.; 67%), $[\alpha]_D^{21}$ -51.3° (c, 8.5% in ethanol). Formation of the 3,5-dinitrobenzoate in benzene yielded a viscous, yellow oil which was sent for analysis after being placed under vacuum for several days after elution from a neutral alumina column.

Found : C, 54.4; H, 5.0; N, 8.8

$C_{21}H_{23}N_3O_8S.\frac{1}{3}C_6H_6$ requires : C, 54.9; H, 5.0; N, 8.4%

3.1.17 Oxidation of N-(p-toluenesulphonyl)-prolinal

Finely ground potassium permanganate (0.30 g.; 1.1 eq.) was slowly added to a solution of N-(p-toluenesulphonyl)-prolinal (0.66 g. ; 1.0 eq.) in acetone (50 ml.). The flask was set aside for four hours, the acetone removed by distillation

under reduced pressure and the residue dissolved in 5% sodium hydroxide (40 ml.). Manganese dioxide was removed by filtration, the aqueous solution extracted with ether (2 X 10 ml.) followed by acidification with hydrochloric acid and extraction with benzene (3 X 15 ml.). Evaporation of the benzene yielded colourless crystals of N-(p-toluenesulphonyl)-proline (0.44 g.; 63%) showing an infra-red spectrum identical to the genuine sample. Recrystallisation from benzene gave colourless crystals, m.p. 78°, $[\alpha]_D^{20}$ - 83.4° (c, 10% in ethanol).

3.1.18.1 The reaction of N-(p-toluenesulphonyl)-prolinal with sodium acetylide and reduction of the product

Pure acetylene was passed into liquid ammonia (250 ml.) whilst sodium metal (0.48 g.; 1.05 mol.) was added slowly so that the blue colour persisted for a few moments only. Acetylene was purified by first passing through a trap cooled by a mixture of acetone and dry ice, mercury suckback bubbler, concentrated sulphuric acid and finally through a soda lime drying tube.

Vacuum dried N-(p-toluenesulphonyl)-prolinal (5.0 g.; 1.0 mol.) dissolved in diglyme (150 ml.), which had previously been dried by standing over lithium aluminium hydride and subsequent distillation, was dripped into sodium acetylide dissolved in liquid ammonia during three quarters of an hour with stirring, while acetylene was bubbled into the solution. The flow of acetylene was continued for a further eight hours. Ammonium chloride (2.0 g.) was added until

3.1.18.1 continued

The unstable product (unpurified 1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-prop-2-yn-1-ol) showed peaks at 3300 and 2120 $cm.^{-1}$ attributed to alkyne absorption.

vigorous effervescence ceased, ammonia was boiled off on a water bath and the residue was filtered from the remaining diglyme solution and washed with benzene in the dark. The solution was dried over anhydrous sodium sulphate (5 g.) and the solvents removed by distillation under reduced pressure. The residue was dissolved in absolute ethanol (200 ml.), palladium oxide (0.3 g.) added and shaken with hydrogen for forty eight hours in the absence of light. After filtration and evaporation of the solvent a tar was obtained which was thoroughly washed with benzene. Evaporation of the benzene yielded oily crystals (0.45 g.; 8.5%) the infra-red spectrum of which was identical with 1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propan-1-ol. Crystals purified by recrystallisation from benzene showed m.p. 99.5°.

Found : S, 11.1

$C_{14}H_{21}NO_3S$ requires : S, 11.3%.

3.1.18.2 The reaction of N-(p-toluenesulphonyl)-prolinal with ethylmagnesium bromide

Magnesium (0.142 g.; 1.5 mol.) was added to a solution of ethyl bromide (1.29 g.; 3.0 mol.) (previously dried over calcium chloride) and dry tetrahydrofuran (20 ml.). A small crystal iodine was added and the solution warmed

3.1.18.2 continued

1-[1'-(p-Toluenesulphonyl)-pyrrolidin-2'-yl]-propan-1-ol showed $\nu_{max.}$ (KBr) 3550 (OH), 2950 (C-H), 1600 (aromatic C=C), 1340 and 1155 ($N-SO_2$), 820 $cm.^{-1}$ (p-disubstituted aromatic).

for thirty minutes before all the magnesium had dissolved.

Dry N-(p-toluenesulphonyl)-prolinal (1.0 g.; 1.0 mol.), dissolved in dry tetrahydrofuran (15 ml.), was dripped into the stirred solution of the Grignard reagent at room temperature for five minutes. After refluxing for fifteen minutes, the solution was set aside for seven hours, poured into a saturated ammonium chloride solution (50 ml.) and after separation, the aqueous layer extracted with ether (2 X 30 ml.). The solution, consisting of the combined ether extracts and tetrahydrofuran, was dried over anhydrous sodium sulphate (3 g.) and evaporated yielding an oil which was purified by passing through a neutral alumina column and eluting with a mixture of benzene and ether. After evaporation of the solvent 1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propan-1-ol (0.11 g.; 10%) was obtained, m.p. 80°, $[\alpha]_D^{22}$ - 84.2° (c, 5% in ethanol).

Found : C, 59.0; H, 7.4; S, 11.4

$C_{14}H_{21}NO_3S$ requires : C, 59.4; H, 7.5; S, 11.3%

3.1.19 Attempted bromination of N-(p-toluenesulphonyl)-pyrrolidine

N-(p-Toluenesulphonyl)-pyrrolidine (0.50 g.; 1.0 mol.), kindly supplied by D. L. Morgan, was dissolved in chloroform (20 ml.), treated with bromine (0.277 g.; 0.77 mol.) and gently refluxed for one hour with the

3.1.19 continued

The bulk of material was recovered unchanged and the by-products were not further studied.

evolution of hydrogen bromide gas. After the addition of a further quantity of bromine (0.079 g.; 0.33 mol.) followed by heating under reflux for one hour longer, the chloroform was removed by evaporation under reduced pressure yielding colourless crystals. On recrystallisation from ethanol they showed m.p. 119.5 - 121° and with N-(p-toluenesulphonyl)-pyrrolidine mixed m.p. 119.5° showing that no bromination had taken place.

Found : C, 58.0; H, 6.6

$C_{11}H_{15}O_2NS$ requires : C, 58.6; H, 6.7%

3.2 Rearrangement by reaction of the sodium salt of toluene-ω-thiol on 2,3-dibromobutan-1-ol

3.2.1 Synthesis of crotyl alcohol

3.2.1.1 From methyl crotonate (Davidson, Günther, Waddington - Feather and Lythgoe[5])

Methyl crotonate b.p. 118 - 126°/755 mm. (10.0 g.; 100 m.mol.) was dissolved in dry ether (150 ml.) lithium aluminium hydride (8.36 g.; 220 m.mol.), which had been deactivated with absolute ethanol (10.14 g.; 220 m.mol.), was added in four equal portions at hour intervals at room temperature with constant stirring. After stirring for five hours wet ether (250 ml.) followed by water (15 ml.) was added with stirring, the solution filtered, the residue washed with ether (3 X 50 ml.) and dried over anhydrous sodium sulphate (2 X 5 g.). On distillation the fraction

3.2.1.1 continued

Crotyl alcohol showed τ ($CDCl_3$) 4.3 (m, C<u>H</u>=C<u>H</u>), 5.95 (m, C<u>H</u>$_2$OH), 6.24 (s, O<u>H</u>), 8.30 (m, C<u>H</u>$_3$).

3.2.1.2. continued

Crotyl alcohol showed $\nu_{max.}$ (NaCl) 3400 (OH), 2950 (C-H), 1460 (C-H), 1070 (CH_2OH), 965 cm^{-1} (C=C).

3.2.2 continued

2,3-Dibromobutan-1-ol had previously been prepared employing this method by Charon, <u>Ann. Chim. Phys.</u> 1899, <u>17</u>, 226.

b.p. 115 - 130°, was collected. The i.r. spectrum showed bands at 1670 and 965 cm^{-1}. Yield 0.98 g.; 14%.

3.2.1.2 From crotonaldehyde (Wolfrom and Wood[37])

Crotonaldehyde (45 g.; 1 eq.) was dissolved in water (400 ml.). The pH was adjusted to 7 with 2N sulphuric acid, and a solution of sodium borohydride (24 g.; 2.5 eq.) dissolved in water (100 ml.) was added with stirring while the temperature was kept at 10 - 20° in an ice bath and the pH was maintained at 6.5 - 7.5. The flask was set aside at room temperature for 15 hours and then distilled through a Vigreux column collecting the fraction with b.p. 92 - 98°. The aqueous distillate was saturated with sodium sulphate (10 g.) and extracted with ether (4 X 60 ml.). The ether extract, dried over anhydrous sodium sulphate gave after the removal of the ether, an oil which distilled, b.p. 121°/765 mm. Yield 29.9 g.; 65%. The n.m.r. spectrum showed bands at τ 8.30 (one CH_3), 4.3($CH_3 \cdot CH{=}CH$), 5.95 (CH_2OH) and 6.2 (CH_2OH).

3.2.2 2,3-Dibromobutan-1-ol

Bromine (11.7 g.; 1 mol.) in chloroform (80 ml.) was added slowly to crotyl alcohol (5.0 g.; 1 mol.) in chloroform so as to keep the temperature below 20° and keep the solution a straw colour and set aside for one hour. The solvent was removed under reduced pressure, chloroform added, the solvent removed, which process was repeated, to give 2,3-dibromobutan-1-ol as an orange liquid.

3.2.3 continued

The mixture of butanols showed $\nu_{max.}$ (NaCl) 3450 (OH), 3020 and 2950 (C-H), 1600 and 1490 (aromatic), 1450 (aromatic and $C-CH_3$), 700 $cm.^{-1}$ (monosubstituted aromatic).

3.2.3 Reaction of 2,3-dibromobutan-1-ol with toluene-ω-thiol

Freshly cleaned sodium metal (3.20 g.; 2.05 mol.) was reacted with absolute alcohol (50 ml.), freshly distilled toluene-ω-thiol (17.22 g.; 2.05 mol.) added, and the mixture warmed to 70° for ten minutes. The ethanol was removed under reduced pressure and the crystalline residue evacuated for 30 minutes. 2,3-Dibromobutan-1-ol was added slowly with cooling in an atmosphere of nitrogen in the dark. After 11 hours at room temperature in the dark the precipitate of sodium bromide (13.8 g.; 2.0 mol.) was filtered off and the remaining oil distilled on an oil bath to remove liquids (b.p.$<90^{\circ}$) to leave a semi-crystalline residue. The semi-solid product was washed with ether and filtered to leave a solid (5.6 g.) which charred on ignition. The portion soluble in ether, run through an alumina column yielded an oil which distilled at $135^{\circ}/1.85$ cm. to give an oil (12.77 g.; 58%) which proved to be 1,3-dibenzylthiobutan-2-ol and/or 1,2-dibenzylthiobutan-3-ol containing a small quantity of 2,3-dibenzylthiobutan-1-ol. A small portion was redistilled for analysis.

Found : C, 68.6; H, 6.8; S, 19.4

$C_{18}H_{22}OS_2$ requires : C, 67.9; H, 7.0; S, 20.1%

3.2.4 Debenzylation of dibenzylthiobutanol mixture

The above crude dibenzylthiobutanol (9.13 g.) mixture in liquid ammonia (250 ml.) containing ethanol (10 ml.) was treated with sodium (6.5 g.), added in small pieces with stirring, until a permanent blue colour was obtained.

The ammonia was evaporated on a water bath and ice (100 g.) added, followed by 10% sodium hydroxide (20 ml.). The solution was extracted with ether (6 X 25 ml.) to remove non-thiol material, acidified with 50% hydrochloric acid (100 ml.) in an ice bath and continuously extracted with ether for 12 hours. After drying over anhydrous sodium sulphate ether was removed under reduced pressure to yield an oil (1.54 g.; 39%) which was distilled in a nitrogen atmosphere to give 1,3-dithiobutan-2-ol and/or 1,2-dithiobutan-3-ol containing some 2,3-dithio - butan-1-ol as a colourless oil b.p. 100°/1 mm. (The purity by iodine titration was 93%).

3.2.5 Desulphurisation of the dithiobutanol

The dithiobutanol (0.71 g.) in water was heated with grade W2 Raney nickel for four hours on a boiling water bath. The aqueous solution was distilled and the first distillate (5 ml.) which contained some oily drops was collected, ether (40 ml.) and anhydrous sodium sulphate (2 X 5 g.) was added, and the ether removed by distillation through a Vigreux column yielding a small quantity of high boiling material. G.l.c. separation on a diethylene glycol succinate column at 125° using argon as carrier gas showed that it was a mixture of sec-butanol : n-butanol : : 7 : 1.

3.2.6 Oxidation of butanol mixture

Oxidation of the alcohol was carried out by the addition of a small quantity of the alcohol mixture (0.1 g.) to a hot solution of potassium dichromate (0.15 g.) in 4N sulphuric acid (5 ml.). The distillate gave a 2,4-dinitrophenylhydrazone. T.l.c. showed that it was a mixture of two components. The mixture was purified by passing through two alumina columns and several recrystallisations showed m.p. 111°, 2,4-dinitrophenylhydrazone of methyl ethyl ketone (m.p. 115°) and mixed which showed m.p. 114°.

3.3 Rearrangement by reaction of the sodium salt of toluene-ω-thiol on 2,3-dibromopentan-1-ol

3.3.1 Pentenoic acid and 2,3-dibromopentanoic acid (K.v.Auwers[34])

The Knoevenagel reaction (Döbner modification) of malonic acid on propionaldehyde proceeded spontaneously at room temperature giving after 19 hours a 58% yield of pent-2-enoic acid, b.p. 60°/7 mm. The potassium salt of pent-2-enoic acid dissolved in water was titrated with an aqueous solution of bromine in saturated sodium bromide, set aside for ten hours and extracted from the acidified aqueous solution with ether. Distillation gave 2,3-dibromopentanoic acid, b.p. 120 - 130°/4 mm. as an orange coloured oil.

Found : Br, 55.3 ± 1.0

$C_5H_8O_2Br$ requires : Br, 61.5%

3.3.2 continued

The distilled, but still impure, 2,3-dibromopentanol showed $\nu_{max.}$ (NaCl) 3400 (broad OH), 2920 (C-H), 1450 (CH_3C), 1070 (CH_2OH), 800 $cm.^{-1}$ (CH_3C).

3.3.2 2,3-Dibromopentanol

A solution of diborane in tetrahydrofuran (1.8 mol.) was added to a dry ethereal solution of 2,3-dibromopentanoic acid (1 mol.) and allowed to stand at room temperature for sixty hours. The product, worked up as described above, gave 2,3-dibromopentanol, b.p. 96 - 110°/10 mm. as a yellow oil (77% yield).

Found : Br, 61.1 ± 2

$C_5H_{10}OBr_2$ requires : Br, 65.0%

3.3.3 S-Benzylation of 2,3-dibromopentanol

Freshly distilled toluene-ω-thiol (5.2 g.; 2.05 mol.) was added to an ethanolic solution of freshly cleaned sodium (0.96 g.). After treatment as before, evaporation yielded white crystals to which 2,3-dibromopentanol (5.0 g.; 1.0 mol.), dissolved in absolute ethanol, under nitrogen in the dark was slowly added with cooling. The flask was set aside for ten hours in the dark, the crystals removed by filtration and lixiviated with benzene to separate the dibenzyl disulphide from the sodium bromide crystals.

The filtered liquor was fractionally distilled through a Vigreux column to remove the solvents. The cooled residue was filtered from the crystalline dibenzyl disulphide which was washed with ethanol. The filtrate after removal of the ethanol by distillation, was chromatographed through alumina to give more dibenzyl disulphide (accounting in all for 84% of the toluene-ω-thiol employed) and a mixture of 1,3-dibenzylthiopentan-2-ol and/or 1,2-dibenzylthiopentan-

3.3.3 continued

The distilled mixture of the dibenzylthiopentanol showed $\nu_{max.}$ (NaCl) 3450 (OH), 2900 (C-H), 1600 and 1490 (aromatic), 1450 (aromatic and C-CH_3), 700 $cm.^{-1}$ (monosubstituted aromatic).

3-ol and 2,3-dibenzylthiopentan-1-ol as an oil, b.p. 135°/6 mm. (0.4 g.; 6%).

Found : C, 68.5; H, 7.0; S, 18.8

$C_{19}H_{24}OS_2$ requires : C, 68.7; H, 7.3; S, 19.3%.

3.3.4 Debenzylation and desulphurisation of the dibenzylthiopentanol

The dibenzylthiopentanol (0.3 g.) in liquid ammonia (100 ml.) containing ethanol (5 ml.) was treated with sodium (1.5 g.) until a permanent blue colour was obtained. After evaporation of the ammonia, acidification with hydrochloric acid and extraction with ether, the mixture was fractionally distilled on an oil bath where the temperature of the bath did not rise above 140°.

A methanolic solution of the oil was heated with an excess of grade W2 Raney nickel for three hours, filtered and methanol removed by distillation through a fractionating column. Water was added to the remaining product and the mixture azeotropically distilled. The distillate was saturated with sodium sulphate and extracted with ether. After drying over anhydrous sodium sulphate and careful evaporation of the ether a small quantity of oil was obtained. This was shown to be mainly pentan-2-ol and/or pentan-3-ol together with a small quantity of

3.3.5 continued

The 2,4-dinitrophenylhydrazone was recrystallised from a benzene/ether mixture.

Pent-2-enol showed $\nu_{max.}$ (NaCl) 3500 (OH), 2950 (C-H), 1640 (C=C), 1050 (CH_2OH), 970 $cm.^{-1}$ (C=C).

pentan-1-ol by gas-liquid chromatography using a column impregnated with diethylene glycol succinate.

3.3.5 Debromination of 2,3-dibromopentanol with toluene-ω-thiol

Freshly distilled toluene-ω-thiol (2.99 g.) was added to an ethanolic solution of freshly cleaned sodium (0.555 g.) and after warming and evaporation under reduced pressure, the crystalline sodium salt of toluene-ω-thiol was evacuated for ten hours. The flask was flushed with nitrogen followed by addition of 2,3-dibromopentanol (2.90 g.) while cooling the flask by immersion in an ice bath. After the exothomic reaction had subsided the molten mixture was set aside for two hours, the crystalline product washed several times with dry ether. Evaporation of the ether gave a semi-solid

tion from an oil bath left dibenzyl disulphide and gave pent-2-enol as a colourless liquid, b.p. 135-145° (0.55 g.; 54%) which after oxidation with active manganese dioxide gave a 2,4-dinitrophenylhydrazone, m.p. 154 - 155.5°. The product made by debromination of 2,3-dibromopentanol with chromous sulphate yielded mixed m.p. 154.5 - 155°.

The samples were recrystallised from a benzene/ether mixture.

Found : C, 50.1; H, 4.8; N, 20.7

$C_{11}H_{12}O_4N_4$ requires : C, 50.0; H, 4.6; N, 21.2%

3.3.6 Debromination of 2,3-dibromopentanol with chromous sulphate

A solution of chromic sulphate (20 g.; 3.95 mol.) in

distilled water (150 ml.) was stirred with zinc dust (4 g.) under nitrogen atmosphere for twelve hours during which time a change of colour was observed. After filtration 2,3-dibromopentanol (2 g.; 1 mol.) dissolved in acetone (30 ml.) (previously flushed with nitrogen during distillation) was added to the aqueous chromous sulphate solution. The flask was set aside for 24 hours, the aqueous solution saturated with sodium sulphate and continuously extracted with ether for twelve hours. After drying over anhydrous sodium sulphate, distillation yielded a colourless oil, b.p. 135 - 141°/754 mm.(0.40 g.; 57%). Oxidation with active manganese dioxide yielded the aldehyde of which the 2,4-dinitrophenylhydrazone, m.p. 157°, was formed.

Found : C, 49.7; H, 4.6; N, 20.1

$C_{11}H_{12}O_4N_4$ requires : C, 50.0; H, 4.6; N, 21.2%

3.4 Reaction of the sodium salt of toluene-ω-thiol with 2,3-dibromo-4-methylpentan-1-ol

3.4.1 4-Methylpent-2-enoic acid (Goldberg and Linstead[12])

A solution of dry malonic acid (130 g.; 3 mol.) in dry pyridine (500 ml.), pipiridine (41.2 ml.; 1 mol.) and isobutyraldehyde (30.0 g.; 1 mol.) was set aside at room temperature for eight hours, warmed for one and a half hours and the temperature maintained at 60° for nine hours. After cooling and acidification with concentrated hydrochloric acid (400 ml.), the solution

was extracted with ether (4 X 300 ml.) followed by extraction of the extract with 10% sodium hydroxide solution (3 X 100 ml.). The aqueous extract was acidified with concentrated hydrochloric acid and extracted with ether (4 X 100 ml.), dried over anhydrous sodium sulphate (6 g.) and after decantation, the ether removed under reduced pressure. The remaining colourless liquid was distilled b.p. 116-120°/ 22 mm. yielding (33.2 g.; 70%) of 4-methylpent-2-enoic acid.

3.4.2 2,3-Dibromo-4-methylpentanoic acid (Goldberg and Linstead[12])

4-Methylpent -2-enoic acid (33.2 g.; 1 mol.) dissolved in methanol (50 ml.) was titrated with methanolic potassium hydroxide using phenolphthalein as indicator. Methanol was removed under reduced pressure, the crystalline residue dissolved in distilled water (100 ml.) and titrated slowly with bromine (47.0 g.; 1.01 mol.) dissolved in saturated sodium bromide solution. During the titration the colour was rapidly discharged with the subsequent formation of a white precipitate. The solution was set aside for two hours, acidified with concentrated hydrochloric acid (30 ml.) and extracted with ether (4 X 200 ml.), dried over anhydrous sodium sulphate (8 g.) and evaporated yielding white crystals of 2,3-dibromo-4-methylpentanoic acid, (73.9 g.; 93%). A portion was recrystallised from benzene and petroleum ether (m.p. 124.5°). Goldberg and Linstead give m.p. 124°.

3.4.3 continued

2,3-Dibromo-4-methylpentan-1-ol showed $\nu_{max.}$ (NaCl) 3350 (OH), 2950 (C-H), 1385 and 1370 [$(CH_3)_2C$-], 1060 $cm.^{-1}$ (CH_2OH).

Found : Br, 59.0

$C_6H_{10}O_2Br_2$ requires : Br, 58.4%

3.4.3 2,3-Dibromo-4-methylpentan-1-ol

A solution of diborane in tetrahydrofuran (428 ml. of 0.62 M B_2H_6; 2.0 mol.) was added to a solution of 2,3-dibromo-4-methylpentanoic acid (72.1 g.; 1.0 mol.) in dry ether (50 ml.). After standing at room temperature for seventy hours, the solution was poured slowly into ice cold water (400 ml.) and extracted with ether (5 X 150 ml.), the extract washed with water (200 ml.), dried over anhydrous sodium sulphate (15 g.) and the solution distilled under reduced pressure collecting 2,3-dibromo-4-methylpentan-1-ol (48.1 g.; 70%), b.p. 100°/3 mm.

Found : Br, 58.7

$C_6H_{12}OBr_2$ requires : Br, 61.5%

3.4.4 Reaction of 2,3-dibromo-4-methylpentan-1-ol with the sodium salt of toluene-ω-thiol

Freshly cleaned sodium (0.746 g.; 2.05 mol.) was allowed to dissolve in absolute ethanol (25 ml.) followed by the addition of freshly distilled toluene-ω-thiol (4.02 g.; 2.05 mol.) and the solution warmed at 60° for ten minutes. After flushing out the flask with nitrogen, 2,3-dibromo-4-methylpentan-1-ol (4.11 g.; 1.0 mol.) in absolute ethanol (10 ml.) was then dripped into the

3.4.4 continued

The crude unsaturated alcohol (4-methylpent-2-enol) showed $\nu_{max.}$ (NaCl) 3350 (broad OH), 2950 (C-H), 1670 (aliphatic C=C), 1380 and 1365 [$(CH_3)_2C$-], 1080 (CH_2OH), 970 $cm.^{-1}$ (*trans* CH=CH).

Beilsteins Handbuch der Organischen Chemie, Zweites ergänzungswerk, Julius Springer, Berlin, 1941, *1*, 487, gives b.p. 150°.

flask in the presence of light while cooling by immersion in an ice bath. The remaining dibromo-alcohol was rinsed into the reaction flask with dry ether and the mixture set aside for eighteen hours. The crystals which had formed were removed by filtration and solvent removed from the filtrate by distillation under reduced pressure until the volume was 10 ml. The above procedure of concentration and filtration was repeated several times yielding an oil which had b.p. 150°/ 760 mm. (0.67 g.; 43%) and the i.r. spectrum of which showed it to be an unsaturated alcohol. The crystals obtained were washed with benzene and refiltered yielding sodium bromide (2.91 g.; 90%). Evaporation of the benzene washings yielded dibenzyl disulphide (3.42 g.), m.p. 68°, mixed m.p. 68°, accounting for 86% of the toluene-ω-thiol employed. A small quantity of the alcohol was oxidised over active manganese dioxide and the 2,4-dinitrophenyl-hydrazone formed (m.p. 181°) thus proving the alcohol to be 4-methylpent-2-en-1-ol.

Found : C, 52.1; H, 5.3; N, 20.6

$C_{12}H_{14}O_4N_4$ requires : C, 51.8; H, 5.1; N, 20.1%

3.4.5.1 4-Methyl-3-bromo-1,2-epoxypentane

4-Methyl-2,3-dibromopentanol (10.0 g.; 1 mol.) was added to a solution of sodium hydroxide (1.85 g.; 1.2 mol.) in ethanol (130 ml.) and then warmed at 60° with swirling

3.4.5.1 continued

4-Methyl-3-bromo-1,2-epoxypentane showed $\nu_{max.}$ (NaCl) 2950 (C-H), 1385 and 1370 [$(CH_3)_2C$-], 1255 and 865 $cm.^{-1}$ (epoxide).

for ten minutes. Ethanol was removed by evaporation under reduced pressure until the remaining volume was 20 ml., the remaining solution poured into water (300 ml.) and the aqueous solution saturated with sodium sulphate followed by extraction with ether (4 X 80 ml.). After drying over anhydrous sodium sulphate (2 X 5 g.) distillation at 50°/1 mm. yielded 4-methyl-3-bromo-1,2-epoxypentane as a colourless oil (4.37 g.; 64%).

Found : Br, 44.0

$C_6H_{11}OBr$ requires : Br, 44.6%

3.4.5.2 Reaction of 4-methyl-3-bromo-1,2-epoxypentane with toluene-ω-thiol

Freshly cleaned sodium (1.97 g.; 2 mol.) was dissolved in absolute ethanol (150 ml.) followed by the addition of freshly distilled toluene-ω-thiol (15.90 g.; 3.0 mol.) and the solution warmed to 60° for ten minutes. 4-Methyl-3-bromo-1,2-epoxypentane (7.67 g.; 1.0 mol.) in absolute ethanol (30 ml.) was added and the mixture refluxed under nitrogen for eleven and a half hours in the dark. The ethanolic solution was decanted from crystalline sodium bromide and the volume of the solution reduced to 50 ml. by evaporation under reduced pressure. After the addition of 20% sulphuric acid (50 ml.) the solution was heated at 70° for two hours with occasional swirling. The solution was basified by the addition of sodium bicarbonate, extracted with

3.4.5.2 continued

4-Methyl-1,2-dibenzylthiopentan-3-ol exhibited $\nu_{max.}$ (NaCl) 3500 (OH), 3050 and 2950 (C-H), 1610 and 1510 (aromatic), 1455 (aromatic and C-CH_3), 700 $cm.^{-1}$ (monosubstituted aromatic).

benzene (3 X 20 ml.) and the extract dried over anhydrous sodium sulphate (4 g.). Distillation at 190 - 210°/ 0.2 mm. yielded 13.9 g. of a light coloured viscous oil. On redistillation of the condensate the fraction b.p. 197 - 200°/0.2 mm. (5.08 g.; 34%) was collected which proved to be 4-methyl-1,2-dibenzylthiopentan-3-ol.

Found : C, 69.3; H, 7.3; S, 18.5

$C_{20}H_{26}OS_2$ requires : C, 69.3; H, 7.6; S, 18.5%

3.4.5.3 Debenzylation of 4-methyl-1,2-dibenzylthiopentan-3-ol

Liquid ammonia (250 ml.) was added to a solution of the above alcohol (4.0 g.) in ethanol (10 ml.) and sodium (4.8 g.) added in small pieces until a permanent blue colour was obtained. The ammonia was evaporated on a water bath followed by the slow addition of ice cold water (30 ml.) followed by extraction with ether (4 X 10 ml.). The aqueous solution was acidified with 50% hydrochloric acid and continuously extracted with ether (150 ml.) for twelve hours. The ethereal solution was dried over anhydrous sodium sulphate (2 X 3 g.) and the ether removed by distillation through a fractionating column yielding a yellow, oily residue. After evacuation for 15 minutes 1.43 g.; 75% of 4-methyl-1,2-dithiolpentan-3-ol was obtained.

3.4.5.4 Desulphurisation of the 4-methyl-dithiopentanol

The dithiopentanol (1.10 g.) in ethanol (50 ml.) was refluxed with grade W2 Raney nickel (15 g.) for four hours.

The Raney nickel was removed by filtration and washed with ethanol (3 X 5 ml.). The ethanolic solution was fractionally distilled yielding a colourless oil which was distilled on an oil bath at 160°. A small sample separated by gas-liquid chromatography using a 4 foot, 30% DGS on chromosorb W column, nitrogen at 60° as carrier gas, showed the unknown to consist of 4-methylpentan-2-ol and/or 4-methylpentan-3-ol. Resolution of the isomers on g.l.c. was attempted by forming the trimethylsilanyl derivatives without success.

3.4.5.5 Oxidation of 4-methylpentan-3-ol

To potassium dichromate (0.025 g.) dissolved in warm 4N sulphuric acid (3 ml.) was added the alcohol (0.2 g.) and the mixture heated, with occasional swirling, collecting the azetropic distillate. A solution of 2,4-dinitrophenylhydrazine in aqueous sulphuric acid (30 ml.) was added and set aside for twelve hours to crystallise. The crystals were removed by filtration, washed with a little 1N sulphuric acid, and recrystallised from an ethanol/water mixture. The crystals proved to be a mixture of the required hydrazone together with the hydrazone of acetaldehyde. Separation was effected on a silica gel G plate eluting with a mixture of benzene and petroleum ether (b.p. 60 - 80°) in the ratio 4 : 1.

The required band was scraped off the plate and washed off the silica gel with ethanol. Excess ethanol was removed by blowing the warm solution with a stream of nitrogen. Careful addition of water caused crystals to form and after drying under reduced pressure showed m.p. 107.5 and with the 2,4-dinitrophenylhydrazone of 4-methylpentan-3-one, mixed m.p. 107.5 - 109°.

3.4.6 Synthesis of 4-methylpentanol

3.4.6.1 2-Methylbromopropane (Kamm and Marvel[16])

An aqueous solution of sodium bromide (123.6 g.) and 2-methylpropanol (71.2 g.; 1.0 mol.) was treated with concentrated sulphuric acid (88 ml.). After refluxing the mixture for three and a half hours, the product was azeotropically distilled, treated with water, 10% sulphuric acid, sodium carbonate and after drying over calcium chloride was distilled at 91 - 94°/748 mm. yielding 45.5 g.; 34% of 2-methylbromopropane.

3.4.6.2 4-Methylpentanol from 2-methylbromopropane and oxirane (Dreger[7])

Magnesium (3.0 g.; 1.03 mol.) and 2-methylbromopropane (16.44 g.; 1.0 mol.) in dry ether were allowed to react followed by dry oxirane (6.0 g.; 1.1 mol.) which was

3.4.6.2 continued

Beilsteins Handbuch der Organischen Chemie, Erstes ergänzungswerk, Julius Springer, Berlin, 1918, 1, 411 gives for 4-methylpentanol b.p. 147-148°/753mm.

3.4.7.1 continued

Beilstein, (loc. cit.) p.410 gives for 4-methylpentan-2-ol b.p. 130 - 131°.

added dropwise to the cooled solution. The solution was allowed to reflux for one hour, a portion of the ether removed by distillation followed by decomposition with water. Extraction with ether followed by distillation yielded 4-methylpentanol, b.p. 143 - 154°/751 mm. (2.40 g.; 20%).

3.4.7 Synthesis of 4-methylpentan-2-ol

3.4.7.1 4-Methylpentan-2-ol from 2-methylbromopropane and acetaldehyde (Drake and Cooke [6])

An ethereal solution of 2-methylbromopropane (13.4 g.; 1.09 mol.) was allowed to react with magnesium (1.92 g.; 0.86 mol.) followed by the addition of acetaldehyde (4.0 g.; 1.0 mol.) to the ice cold solution. The product was decomposed with ice and the aqueous solution extracted with ether. After drying over anhydrous sodium sulphate, distillation yielded 4-methylpentan-2-ol, b.p. 130°/763 mm. (3.52 g.; 35%).

3.4.7.2 Oxidation yielding 4-methylpentan-2-one and formation of the 2,4-dinitrophenylhydrazone.

This was done as described in section 3.4.5.5. The 2,4-dinitrophenylhydrazone of 4-methylpentan-2-one exhibited m.p. 86 - 87°.

3.4.8.1 continued

Beilstein, (loc. cit.) p.410 gives for 4-methylpentan-3-ol b.p. 127-127.5°/721 mm.

Found : C, 51.2; H, 5.9; N, 19.9

$C_{12}H_{16}O_4N_4$ requires : C, 51.4; H, 5.8; N, 20.0%

3.4.8 Synthesis of 4-methylpentan-3-ol

3.4.8.1 4-Methypentan-3-ol

Freshly cleaned magnesium (1.20 g.; 1.2 mol.) and dry ether (50 ml.) were placed in a 100 ml. flask fitted with a dropping funnel and a reflux condenser the upper ends of which were fitted with calcium chloride drying tubes. Bromoethane (9.1 g.; 2.0 mol.) was added together with a small crystal of iodine and set aside for sixteen hours before the magnesium had dissolved. Dry 2-methylpropanal (3.0 g.; 1.0 mol.) in dry ether (10 ml.) was dripped into the solution for twenty minutes and set aside for eight hours. The ether solution was poured into saturated ammonium chloride (100 ml.) and after separation, the aqueous solution extracted with ether (2 X 30 ml.). The combined ethereal solutions were dried over anhydrous sodium sulphate (3 g.) followed by distillation collecting the fraction b.p. 125 - 130°/744 mm. (2.10 g.; 37%).

3.4.8.2 Oxidation yielding 4-methylpentan-3-one and formation of the 2,4-dinitrophenylhydrazone

This was done as described in section 3.4.5.5. The 2,4-dinitrophenylhydrazone of 4-methylpentan-3-one exhibited m.p. 108.5° - 109.5°.

Found : C, 51.1; H, 5.9; N, 19.9

$C_{12}H_{16}O_4N_4$ requires : C, 51.4; H, 5.8; N, 20.0%

3.5 The preparation of benzyl thiolcrotonate

Freshly distilled toluene-ω-thiol (11.80 g.; 0.095 mol.) was added to sodium ethoxide prepared from sodium (2.18 g.; 0.095 mol.) and absolute ethanol (100 ml.). The solution was warmed at 70° for ten minutes, ethanol removed under reduced pressure and the crystals of the sodium salt of toluene-ω-thiol evacuated for one hour.

Crotonyl chloride (10.43 g.; 0.1 mol.) was dripped slowly into an ice cold, stirred solution of the sodium salt of toluene-ω-thiol in dry dimethyl sulphoxide (80 ml.). The solution was set aside at room temperature for twelve hours, benzene (100 ml.) added and the solution extracted with saturated sodium bicarbonate solution (6 X 200 ml.). The aqueous extracts were re-extracted with benzene (100 ml.) which was washed with sodium bicarbonate solution (6 X 50 ml.). The combined benzene extracts were dried over anhydrous sodium sulphate (5 g.), filtered and evaporated under reduced pressure yielding oily crystals (14.60 g.; 80%) which, after removal by filtration, were recrystallised from petroleum ether giving benzyl thiolcrotonate, m.p. 65 - 68°.

Found : C, 68.3; H, 5.8; S, 16.7

$C_{11}H_{12}OS$ requires : C, 68.7; H, 6.3; S, 16.7%

3.6 Nitrogen substituents

3.6.1.1 continued

Prolinol showed $\nu_{max.}$ (NaCl) 3400 (OH), 3950 (C-H), 1610 (NH), 1045 $cm.^{-1}$ (CH_2OH).

3.6.1 Methyl

3.6.1.1 Prolinol

Finely powdered, vacuum dried, proline (10.0 g.; 1.0 mol.) was added to a solution of lithium aluminium hydride (5.0 g.; 1.5 mol.) in dry tetrahydrofuran over thirty minutes. The solution was heated under reflux for two and a half hours and the solution decomposed first by the addition of dry ether (100 ml.), followed by wet ether (20 ml.) and the dropwise addition of water until no more effervescence occurred. The white precipitate was removed by filtration and washed with methanol (5 X 50 ml.). The solutions were combined and the solvents removed by distillation through a fractionating column warming the flask on a water bath. The remaining oil was mixed with 50% sodium hydroxide (15 ml.) and continuously extracted with ether for twelve hours. The ethereal solution was dried over anhydrous sodium sulphate followed by distillation collecting the fraction b.p. $105^{\circ}/4$ cm. as a colourless oil (6.70 g.; 76%). The picrate (m.p. 107°) was formed by evaporation of ethanol from a solution of prolinol in alcoholic picric acid until crystallisation took place.

Found : C, 40.5; H, 4.2; N, 17.1

$C_{11}H_{14}O_8N_4$ requires : C, 40.0; H, 4.3; N, 17.0%

3.6.1.2 continued

1-Methylprolinol exhibited $\nu_{max.}$ (NaCl) 3400 (OH), 2950 (C-H), 1450 ($N-CH_3$), 1020 $cm.^{-1}$ (CH_2OH).

3.6.1.2 1-Methylprolinol by methylation of prolinol

To a solution of prolinol (5.40 g.) in 6 N hydrochloric acid (8.9 ml.) was added 40% formaldehyde solution (15 ml.) and the mixture heated under reflux for three hours. After the addition of 90% formic acid solution (15 ml.), the mixture was heated on a boiling water bath for ten hours longer. The unreacted formic acid and formaldehyde was removed by evaporation under reduced pressure. The residue was dissolved in water (5 ml.) and 2 N hydrochloric acid (2 ml.) and extracted with ether (4 X 10 ml.). The aqueous solution was basified by the solution of potassium hydroxide (8 g.) followed by continuous extraction with ether for twenty hours. After drying over anhydrous sodium sulphate (3 X 3 g.), distillation collecting the fraction b.p. 80 - 140°/3 cm. yielded 1-methylprolinol (4.55 g.; 74%). Addition of a small quantity of 1-methylprolinol to ethanolic picric acid yielded yellow crystals, m.p. 172.5°.

Found : C, 41.9; H, 4.6

$C_{12}H_{16}O_8N_4$ requires : C, 41.9; H, 4.7%

3.6.2 Acetyl

3.6.2.1 1-Acetylprolinol

A solution of prolinol (3.0 g.; 1.0 mol.) and acetamide

3.6.2.1 continued

1-Acetylprolinol showed $\nu_{max.}$ (NaCl) 3300 (OH), 2980 (C-H), 1620 (C=O), 1040 $cm.^{-1}$ (CH_2OH).

(3.6 g.; 2.0 mol.) was heated by immersion in an oil bath at 170° for three hours while blowing a slow stream of nitrogen over the refluxing liquid to remove ammonia as it was formed. The apparatus was then set up for distillation under reduced pressure catching the fraction b.p. 230 - 260°/5 cm. (3.09 g.; 73%). A small sample was redistilled at 150°/4 mm. collecting the middle fraction for analysis which proved to be 1-acetylprolinol.

Found : N, 9.76

$C_7H_{13}O_2N$ requires : N, 9.78%

3.6.2.2 1-Acetylprolinal

A mixture of 1-acetylprolinol (1.58 g.; 1.0 mol.), acetic anhydride (25 ml.) and previously dried dimethyl sulphoxide (48 ml.) was set aside at room temperature for twenty hours. After the addition of water (20 ml.), the solution was evaporated under reduced pressure for one hour, a further quantity of water (30 ml.) added and the solution continuously extracted with ether for eight hours. The extract was evaporated free of ether followed by extraction with saturated sodium bicarbonate solution (3 X 50 ml.) and washed with water (3 X 40 ml.). The combined aqueous solutions were extracted with ether (50 ml.) and this, on addition to the treated extract, was dried over anhydrous sodium sulphate

(2 X 5 g.). After evaporation of the ether, the colourless oil was evacuated for ten hours yielding 1.07 g. ; 68% of 1-acetylprolinal which exhibited the required absorption bands in the infra-red.

The infra-red spectrum of impure 1-acetylprolinal, after being placed under vacuum for several hours, exhibited $\nu_{max.}$ (NaCl) 1740 (-CHO), 1640 $cm.^{-1}$ ($N-CO-CH_3$).

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