RHIZOPHORACEAE ALKALOIDS

Preliminary Studies in the synthesis of Gerrardine.

by

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SUMMARY

The synthesis envisaged the building of the dithiolane ring on to homoproline, the synthesis of which was effected from tetrahydrofurfuryl alcohol and from proline itself. The reactions involved in these syntheses are discussed with particular reference to the protection of the secondary nitrogen, the difficulties encountered in the application of the Arndt-Eistert reaction, and the possible application of the Prins reaction.

I N T R O D U C T I O N

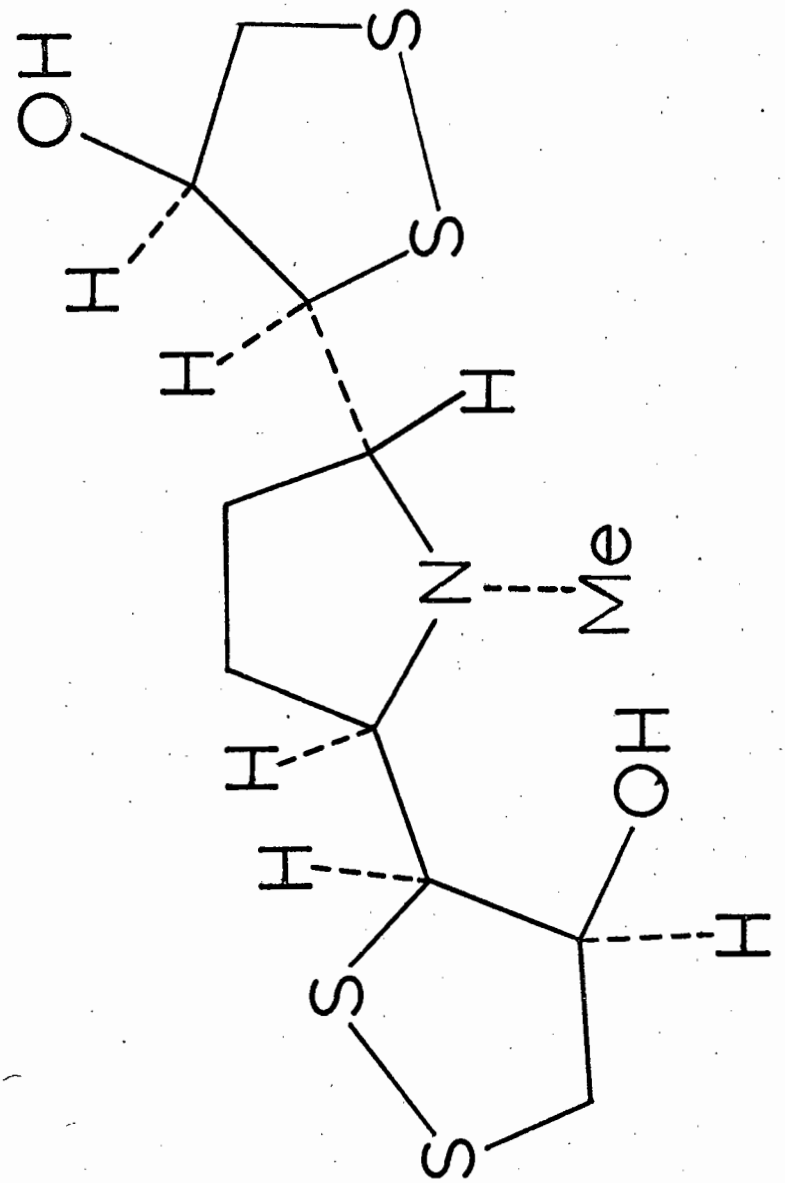
INTRODUCTION

1. THE STRUCTURE OF GERRARDINE

Gerrardine, $C_{11}H_{19}NO_2S_4$, from Cassipourea gerrardii,[1] contained an NCH_3 group, and was assigned structure (1) on evidence from a study of the products from desulphurisation and the mass-spectrum of the alkaloid.

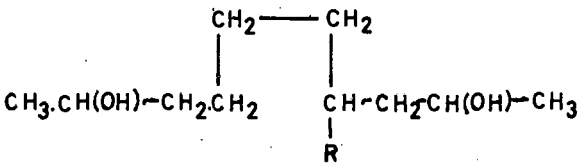
The mass spectrum of the alkaloid showed no molecular ion at m/e 325 but a peak at 100% abundance at m/e 204 which corresponded to the molecular ion $(C_8H_{14}NOS_2)^+$. The other cleavage product was thus $C_3H_5OS_2$ so that both fission products contained two sulphur atoms and one oxygen atom. It was concluded that the nitrogen atom was the seat of the removal of an electron, and the occurrence of only one such fragment suggested that the molecule was symmetrical. Since the infra red spectrum of the alkaloid showed no double bonds the fragments in the mass spectrometer must have had ring structures so that a 2,5-substituted N-methylpyrrolidine was indicated. The stability of the alkaloid suggested that $C_3H_5OS_2$ was a 1,2-dithiolan-4-ol since an acetal or semiacetal would be much more unstable.

Desulphurisation of gerrardine with Raney nickel gave $C_{10}H_{22}O_2$ which according to the melting



GERRARDINE (1)

point was probably decane-2,9-diol (2a), and indicated that the ten carbon atoms formed a normal chain, and revealed the position of the hydroxyl groups and the positions of attachment of the dithiolan rings. The structure for gerrardine as 1-methyl-2,5-bis-(4'-hydroxy-1',2'-dithiolan-3'-yl)pyrrolidine (1) accommodated these findings.



a) R = H

b) R = $N(CH_3)_2$

(2)

The U.V. absorption of the alkaloid was in agreement with that expected from comparison with 7-hydroxylipoic acid [36] and other compounds containing the 1,2-dithiolan ring. On desulphurisation with Raney nickel in methanol the basic fraction $C_{12}H_{27}NO_2$ was obtained, the formation of which was explained by the fission of one of the C-N bonds of the pyrrolidine ring accompanied by methylation to give 4-dimethylaminodecane-2,9-diol (2b).

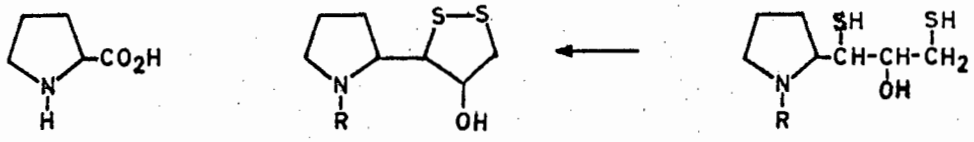
X-ray studies of a single crystal confirm structure (1) and place the two dithiolanyl groups trans to one another and the two hydroxy groups having the same symmetry[1]. The structure may thus be represented as in fig. (1)

2. DISCUSSION ON THE SYNTHESIS OF GERRARDINE

Gerrardine contains six asymmetric centres, and any attempted synthesis must thus start with or build asymmetric centres.

Gerrardine consists of two dithiolan rings which are symmetrically attached to the 2,5-positions of pyrrolidine. Difficulties experienced in the synthesis of gerrardine would thus in all likelihood also emerge in the synthesis of 1-methylpyrrolidin-2-(1',2'-dithiolan-3'-yl-4'-ol) (3). Several syntheses were envisaged on this line. All except the one starting with (-)-proline (4) would introduce the maximum of three asymmetric centres and it would be necessary to adjust any synthetic reaction to permit resolution.

Since the pyrrolidine ring is readily available the problem of the synthesis resolves itself to the synthesis of 1,2-dithiolan-4-ol. This ring is easily synthesised from the 3-substituted 1,3-dimercaptopropan-2-ol (5) and accordingly it was necessary to consider methods of 1,3-dithiol synthesis.



(4) (3) (5)

3. METHODS OF PREPARATION OF DITHIOLS[2].

The majority of aliphatic dithiols have been prepared from the corresponding dihalides by the direct reaction of the dihalide with an alkali-metal hydrogen sulphide or by way of the bisthiocyanate, bisdithiourethane, bisthiouronium salt or bisthiolacetate. Dihalides have been converted into the cyclic disulphide followed by reduction with sodium in liquid ammonia[3]. Hydroxy-α-dithiols have been synthesised by reaction of the appropriate acetylated dibromide with potassium thiolacetate, followed by deacetylation.

The following summarises the several methods:-

a) The direct conversion of 2,3-dibromopropanol to 2,3-dimercaptopropanol with sodium sulphide[4],

$$CH_2Br.CHBr.CH_2OH \xrightarrow{Na_2S} CH_2SH.CHSH.CH_2OH$$

which occurs readily if both groups are primary; but when one of the groups is secondary the yields are usually poor.

b) The conversion of the dihalide via the thiol-acetate [5] to the dithiol:-

$$CH_2Br.CHBr.CH_2OH \xrightarrow[+\ \text{pyridine}]{AcSH} CH_2(SAc).CH(SAc).CH_2OH \longrightarrow CH_2SH.CHSH.CH_2OH$$

The reagents employed have been both thiolacetic acid in pyridine and potassium thiolacetate. The reaction in which the thiolacetate is formed is often more convenient and has been used for members of the polyhydric series of alcohols. The reactions indicated may be modified using a p-toluene-sulphonate in place of halogens. This sequence is useful when the corresponding halide is not easily available.

Primary groups react readily, but the toluenesulphonates of secondary alcohols show differences in behaviour.

c) The reaction of alkyl halides with thiourea to yield the diisothiouronium salts [6] which on alkaline hydrolysis yield thiols [7].

$$CH_2Br.CH_2Br + 2NH_2.CS.NH_2 \longrightarrow \begin{matrix} S\text{-}CH_2\text{-}CH_2\text{-}S \\ \uparrow \qquad\qquad \uparrow \\ NH_2.C{=}\overset{+}{N}H_2 \quad NH_2.C{=}\overset{+}{N}H_2 \end{matrix} \; 2Br^-$$

d) The opening of episulphides with hydrogen sulphide [8] to yield vicinal dithiols; but this method gives poor yields due to polymerisation.

$$\begin{matrix} CH_2\text{-}CH_2 \\ \diagdown S \diagup \end{matrix} + H_2S \longrightarrow CH_2SH.CH_2SH$$

e) The reaction of thiolacetic acid on suitably activated alkynes yield addition products, as for example hex-1-yne which gives 1,2-dithiolacetates [9].

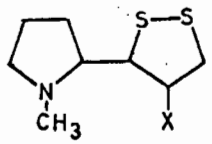
$$C_4H_9.C{\equiv}CH \xrightarrow{AcSH} C_4H_9.CH{=}CHSAc + C_4H_9.CHSAc.CH_2SAc$$

f) The addition of an alkylthiol or hydrogen sulphide to an activated double bond

$$R.CH{=}CH.COOH + R'SH \longrightarrow R.CH(SR).CH_2.COOH$$

4. GENERAL METHODS FOR SYNTHESIS OF 3-(N-METHYL-PYRROLIDIN-2'-YL)-1,2-DITHIOLANE AND ITS 4-HYDROXY DERIVATIVE

Several syntheses suggested themselves for the synthesis of the dithiolane ring attached to a pyrrolidine ring. It was thought desirable to study in the first instance the synthesis with one such ring only, as in (6a) or (6b).



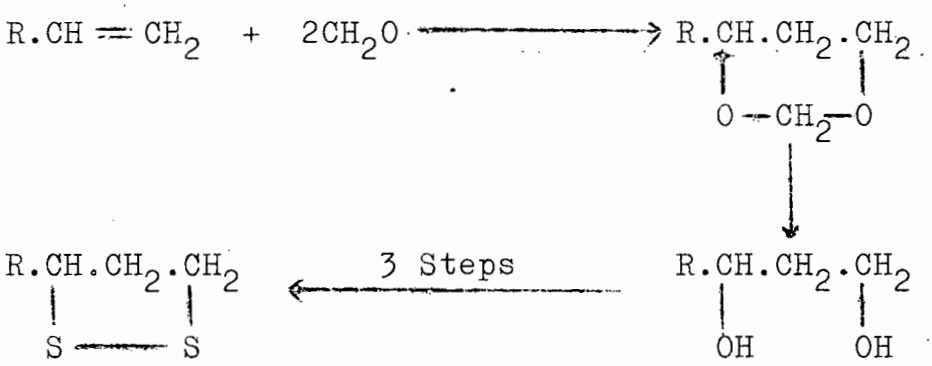
(6)

a) X = OH

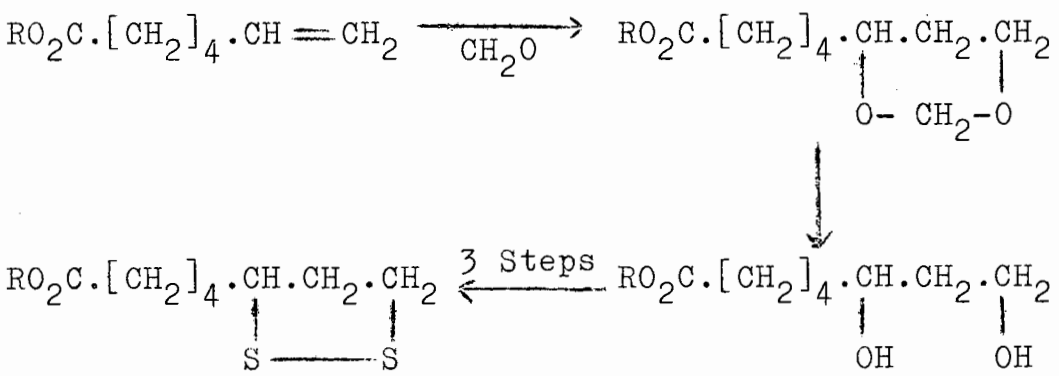
b) X = H

The study of such compounds would also be of interest in view of the known physiological properties of gerrardine. With this in view the following reactions were considered.

(i) The Prins Reaction



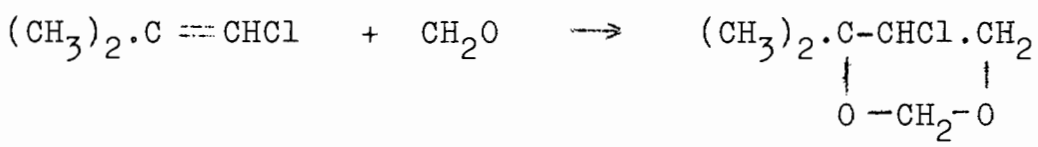
The Prins reaction has been applied by Braude, Linstead and Wooldridge [10] for the synthesis of lipoic acid (7); but for the synthesis of the



(7)

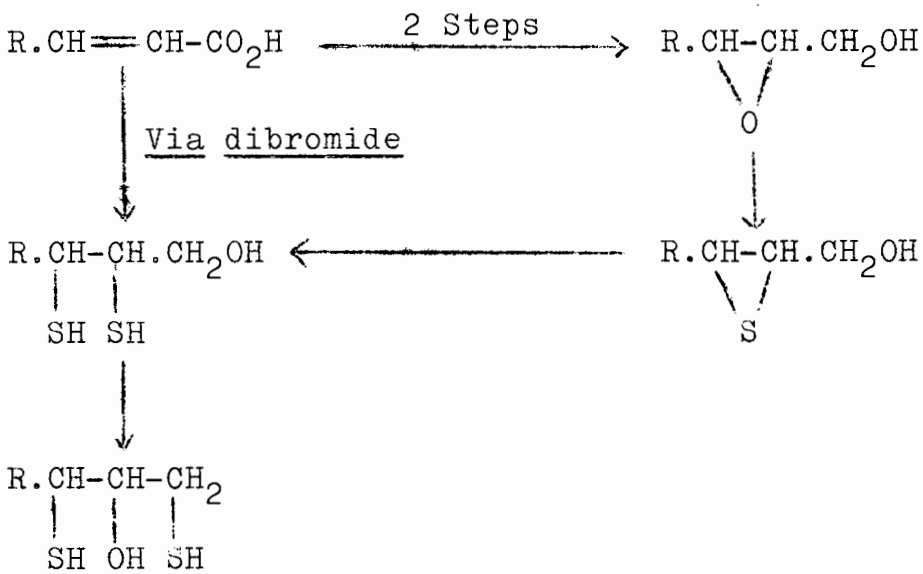
4-hydroxy-1,2-dithiolane a disubstituted ethylene would be the required starting material and then the mode of addition would be important. Arundale and Mikeska [11] claim to have formed compounds

containing chlorine in the 5-position, e.g. 4,4-dimethyl-5-chloro-m-dioxane from 1-chloro-2-methyl-prop-1-ene; but the procedure was recorded in a

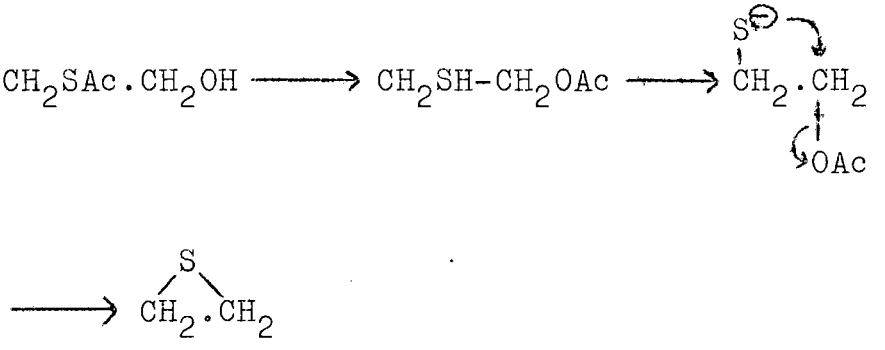


U.S. patent and the actual conditions for this reaction were not immediately available. Attempts were made to effect the condensation with enol-acetates from acetone, namely isopropenyl acetate, and from butyraldehyde, namely but-1-en-1-ol acetate; but no isolable m-dioxane could be obtained.

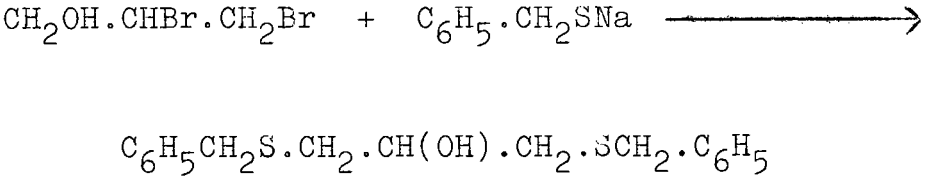
(ii)



The synthesis of dithiols can be influenced by neighbouring group effects [2], as for example the formation of an episulphide from S-acetylmonothioglycol and O-acetylmonothioglycol [12]:-

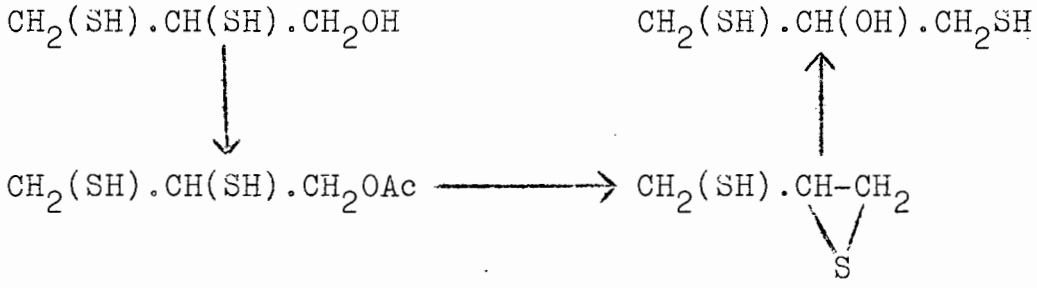


The effect of the formation of such sulphides as intermediates has been observed when hydroxythiols are prepared from bromhydrins when there is always the possibility of rearrangement, as for example when 2,3-dibromopropan-1-ol reacts with the sodium salt of benzyl mercaptan to yield 1,3-dimercapto-propan-2-ol [13,14]. Furthermore British



Anti-Lewisite (BAL) or 2,3-dimercaptopropanol has

been converted to the 1,3-dimercaptopropan-2-ol by this sequence of changes

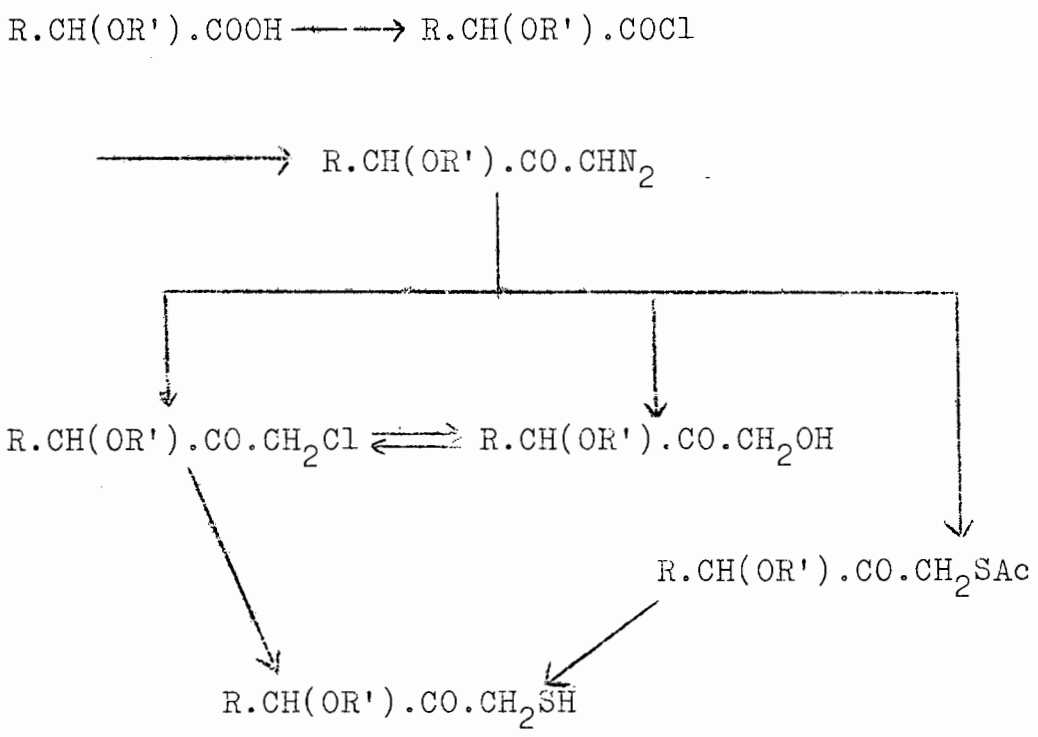


Because of the close similarity of BAL to the compound required, these possible changes would have to be considered.

(iii) The reduction of a 2-keto-ester

$$R.CO.CH_2.COOR' \longrightarrow RCHOH.CH_2.CH_2OH$$

(iv) The addition of a terminal hydroxyl group by the decomposition of a diazoketone or by way of the halogen compound,



The terminal thiol grouping itself could be obtained *via* the thiolacetate.

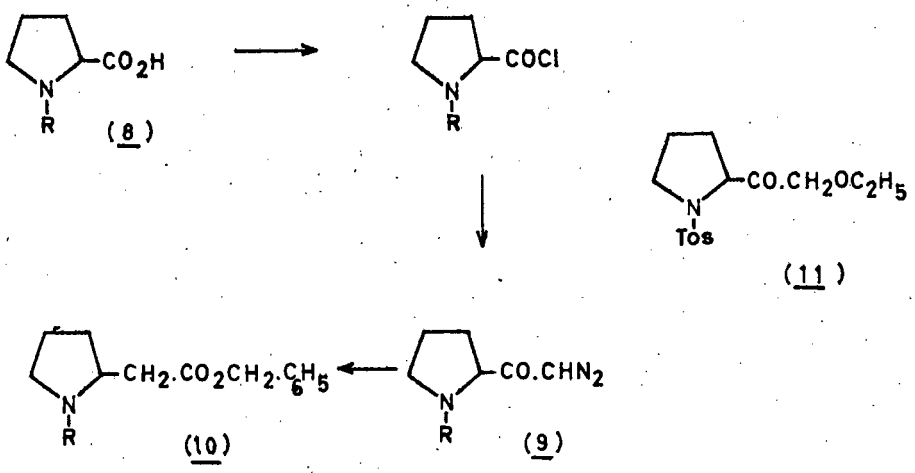
D E T A I L S O F

S Y N T H E S I S

DETAILS OF SYNTHESIS

1. SYNTHESIS USING (-)-PROLINE

The use of proline (8a) as starting material introduces the required asymmetric carbon atom and the Arndt-Eistert rearrangement was envisaged as the route for the synthesis of homoproline. (See appendix 1 for the Baker, Schaub and Williams synthesis of homoproline).



a) R = $-CO.C_6H_5$

b) R = $-SO_2.C_6H_4.CH_3$

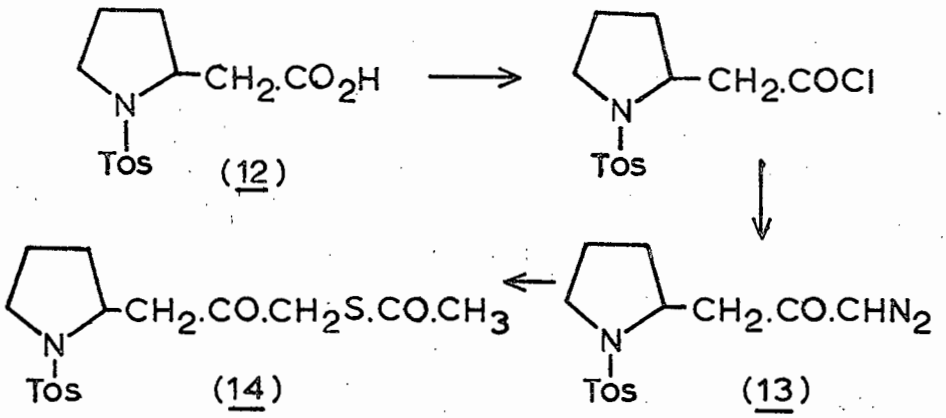
c) R = $-H$

The synthesis as far as the diazoketone (9a) using benzoyl protection was carried out by Baker, Querry, Kadish and Williams (15). We employed

p-toluenesulphonyl protection since purification of products was simplified by easy crystallisation. When the Wilds and Meader modification [16] of the Arndt-Eistert reaction using dimethylaniline as catalyst was attempted, benzyl N-(p-toluenesulphonyl)-homoproline (10b) was isolated. When silver oxide [17] which is the most common catalyst for the Arndt-Eistert reaction was employed, 1-(p-toluene-sulphonyl)-2-(1'-keto-2'-hydroxy-ethyl)-pyrrolidine (11) was isolated, showing that rearrangement had not been effected.

An attempt was made to lengthen the acid chain of 1-(p-toluenesulphonyl)-pyrrolidin-2-yl-acetic acid (12) via its acid chloride to the diazo-ketone (13) which was converted to the thiolacetate (14). (See Appendix 2). Since insufficient material was available no evidence could be drawn from carbon-hydrogen analysis, but sulphur analysis yielded encouraging results. The feasibility of the method was confirmed by the synthesis of 1-phenyl-1-oxo-2-thiolacetyl ethane (15) from benzoyl chloride employing the same method. The 2,4-dinitro-phenylhydrazone characterised this compound

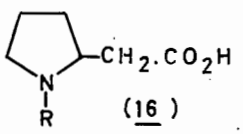
but could not be isolated in the case of 1-[N-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-3-thiol-acetylpropan-2-one (14)



$C_6H_5.CO.CH_2S.CO.CH_3$ (15)

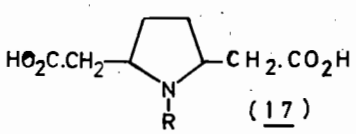
2. HOMOPROLINE AS STARTING MATERIAL

The possible use of homoproline (16a) as the starting material for the synthesis seemed attractive since the synthesis could be extended later for the incorporation of the two dithiolane rings using compound (17).



a) R = H

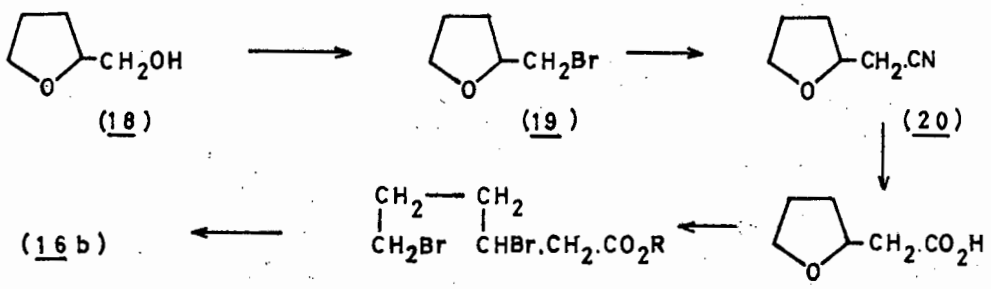
b) R = CH_3



c) R = $SO_2.C_6H_4.CH_3$

d) R = $CH_2.C_6H_5$

The synthesis of N-methyl-homoproline (16b), also known as homohygric acid, has been effected from tetrahydrofurfuryl alcohol (18) by way of its bromide (19) and cyanide (20) which was hydrolysed to the carboxylic acid [30] (21), the furan ring opened to 3,6-dibromohexanoic acid which was condensed with methylamine [18] to give (16b).



a) R = -H

b) R = $-C_2H_5$

Although in the final product the N-methyl derivative was required it was desirable that the nitrogen should be protected as an amide group during the synthesis. The reaction of ammonia on the dibromo acid would be expected to yield the quaternary spiran [19] compound. Nevertheless it was thought that the p-toluenesulphonyl derivative

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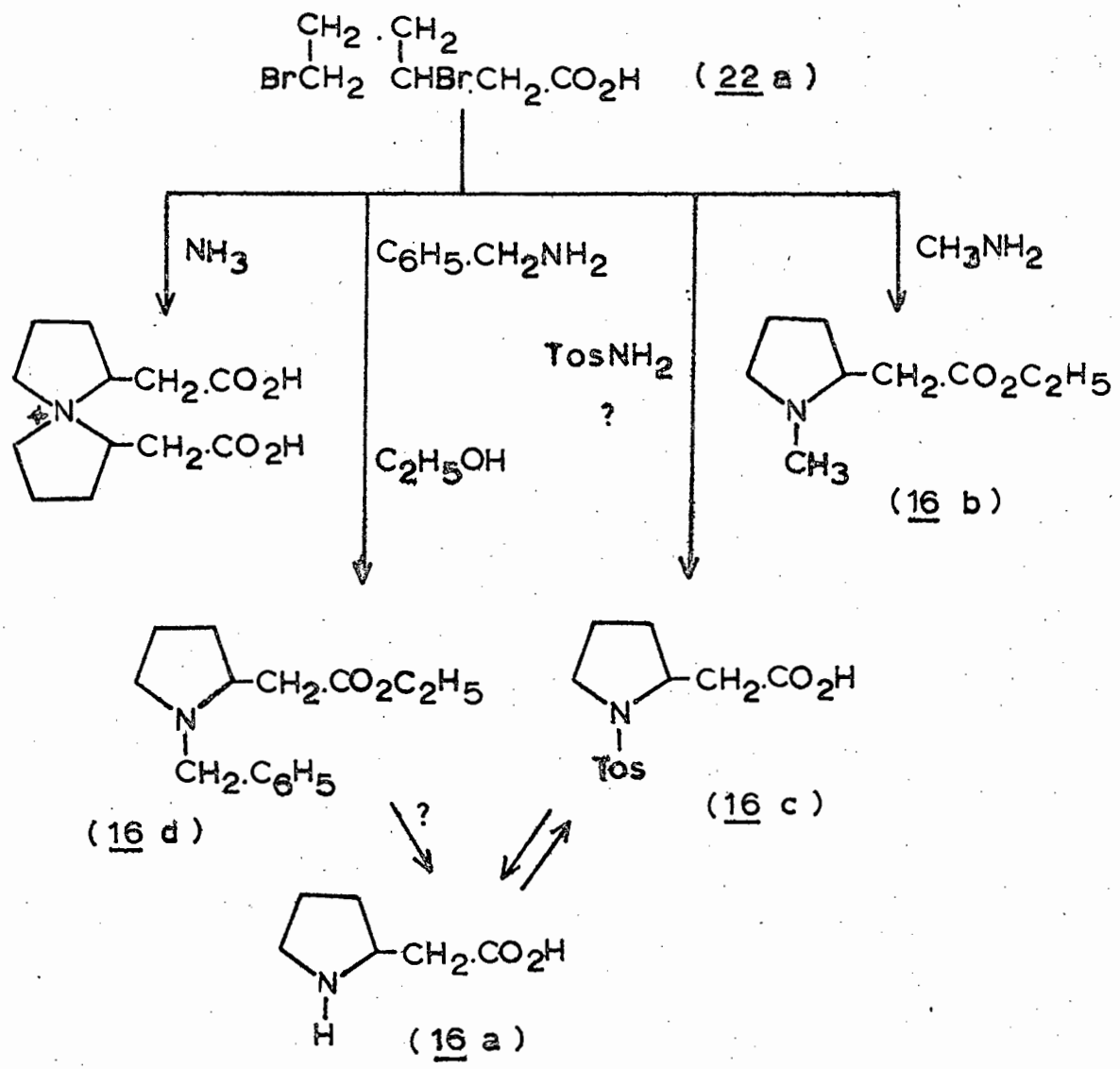
THE REACTION OF 3,6-DIBROMOHEXANOIC ACID TO FORM DERIVATIVES OF HOMOPROLINE

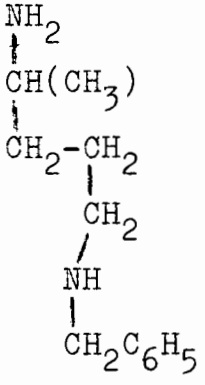


Tos = $-SO_2.C_6H_4.CH_3$

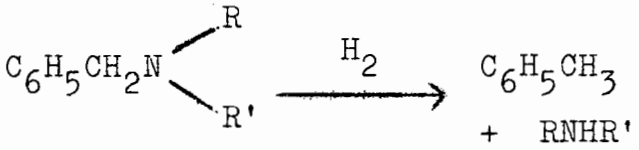
(16c) might be formed by the action of toluene-sulphonamide with the dibromo-acid, because aryl sulphonamides can be N-alkylated and N-arylated with alkyl or aryl halides in alkaline medium, if necessary in the presence of cuprous salts or copper as catalysts (Houben-Weyl) [20]. Furthermore N-p-toluene-sulphonylpyrrolidine has been synthesised by the reaction of 1,4-dibromobutane with p-toluenesulphonamide [21]. In addition 3-bromo-N-benzenesulphonyl-mesidine with methyl bromoacetate and sodium methoxide in methanol yielded 3-bromo-N-benzenesulphonyl-N-carbomethoxymethylmesidine [22], and in this reaction the ester group is preserved, a condition which would be necessary for the condensation of ethyl 3,6-dibromohexanoate (22b) with p-toluenesulphonamide. Attempts to effect this condensation failed to give the desired N-p-toluenesulphonylhomoproline.

The condensation of benzylamine with the dibromo-acid gave the desired N-benzylhomoproline (16d) which was isolated as its ethyl ester, and characterised as the picrate of the ethyl ester. The desired hydrogenolysis of the benzyl group was not effected under the normal hydrogenation conditions.

This finding is contrary to that expected since secondary amines containing one benzyl and one alkyl group appear not to undergo hydrogenolysis (e.g. 23) but tertiary amines containing one benzyl group readily undergo the reaction [23] as was shown for compound (24).

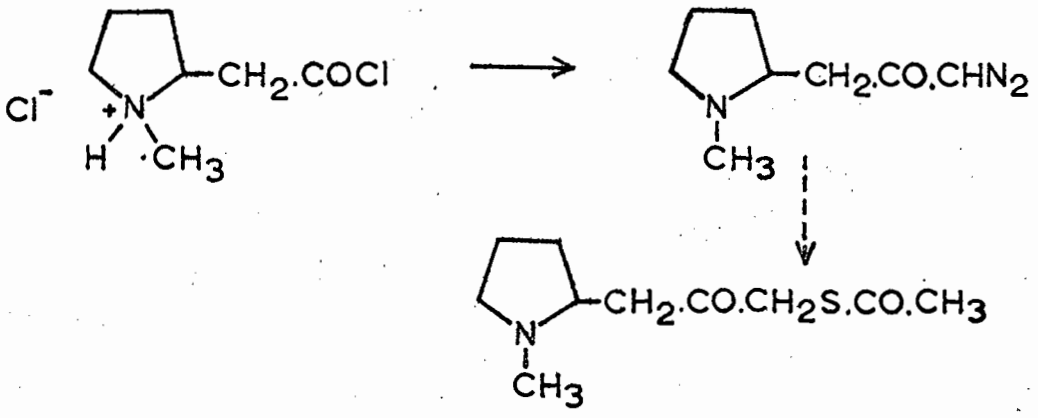


(23)



(24)

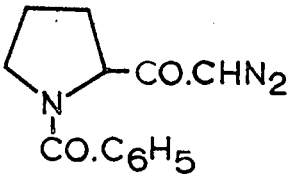
In view of these difficulties a study was made of the possibility of using N-methylhomoproline itself which was readily synthesised as indicated above.



N-Methylhomoproline with thionyl chloride gave the hydrochloride of the acid chloride which with diazomethane gave in small yield the corresponding diazomethyl ketone. The yield and conversion however, did not permit further study by way of this route. The diazomethyl ketone was characterised by its distinctive absorption band in the i.r. [24]. The yellow crystals which were obtained decomposed rapidly yielding a brown, ether insoluble oil, which failed to give any tractable material on treatment with hydrochloric acid and was not further investigated.

3. CHOICE OF AN AMINOPROTECTION GROUP FOR PROLINE

Since the use of the Arndt-Eistert reaction involved the formation of an acid chloride it was necessary to protect the amino group during this process. The benzoyl group had been used previously in a similar synthesis by Baker, Querry, Kadish and Williams [15] up to the diazoketone (9a); but the yield and difficulties in purification of benzoyl-proline precluded its use. Attempts to prepare



(9a)

acetyl proline either by the action of acetic anhydride [25] or of ketene [26] gave only oils whilst the acetyl group was susceptable to hydrolysis under acid conditions likely to result in the later stages of the syntheses. It was finally decided to use the tosyl derivative which could be prepared readily in good yield in crystalline form and which was stable to hydrolysis in both acid and basic solutions, whilst its easy removal by hydrogenolysis by solution of sodium in liquid ammonia was assured.

E X P E R I M E N T A L

EXPERIMENTAL

1. THE SYNTHESIS FROM (-)-PROLINE

N-(p-Toluenesulphonyl)-(-)-proline [27]

A solution of sodium bicarbonate (21 g.; 4.0 mol.) and proline (10.0 g.; 1 mol.) in water (500 ml.) was treated with p-toluenesulphonyl chloride (9.5 g. + 2 x 5 g.; 1.75 mol.) in acetone (200 ml.) while stirring rapidly with a mechanical stirrer. The first 100 ml. of the p-toluenesulphonyl chloride was added straight away and the remainder in two portions after the first half hour and hour respectively. The stirring was continued for three hours, the acetone removed under reduced pressure, and the residue extracted with ether (3 x 40 ml.). The solution was acidified with 2N hydrochloric acid (100 ml.) and the solution immediately extracted with benzene (3 x 50 ml.). Crystallization started taking place in the aqueous solution and to overcome this the solution was warmed to 50° and extracted again with warm benzene (30 ml.). The combined benzene extracts were evaporated on a warm bath to a volume of 50 ml. and set aside to crystallise. More crystals were obtained from the benzene liquors. After drying in a vacuum desiccator

the yield 25.5 g.; 95.5% of solvated N-(p-toluene-sulphonyl)-(-)-proline, $(CH_3.C_6H_4.SO_2.C_4H_7N.COOH)_2.C_6H_6$, m. p. 86°, was obtained.

1-(p-Toluenesulphonyl)-pyrrolidin-2-yl diazomethyl ketone

N-(p-toluenesulphonyl)-(-)-proline (10 g.; 1 mol.) was added to a mixture of sodium dry benzene (20 ml.) and thionyl chloride (14 ml.; 1.6 mol.) in a system protected from moisture. The mixture was refluxed for 45 minutes during which time hydrogen chloride gas was evolved. More thionyl chloride (5 ml.) was added and refluxed for another 30 minutes towards the end of which time gas evolution ceased. The orange brown solution which remained was evaporated under reduced pressure. The oily residue which remained was dissolved in dry ether and the solvent again removed under reduced pressure to wash out any remaining thionyl chloride and hydrogen chloride. This procedure was repeated two more times. The acid chloride thus formed was dissolved in ether (120 ml.) and added dropwise with shaking to a dry ethereal solution of diazomethane, prepared from nitrosomethylurea (23 g.) by Arndt's method [42] and cooled

in a freezing mixture. The whole was kept at room temperature overnight and after filtration the ether was removed under reduced pressure. The orange coloured oil which remained yielded a crop of yellow crystals on standing. The oil which could not be induced to crystallise was passed through a column of neutral alumina yielding a further quantity of diazoketone. Total yield 6.15 g.; 56%. Crystallization of a portion from ethanol gave p-toluenesulphonyl diazomethyl ketone as yellow, needle-like crystals, m. p. 107°.

Found : C. 53.2; H, 5.10%

$C_{13}H_{15}N_3O_3S$ requires: C. 53.2; H, 5.11%

Benzyl 1-(p-toluenesulphonyl)-pyrrolidin-2-yl-acetate.

1-(p-Toluenesulphonyl)-pyrrolidin-2-yl diazomethyl ketone (3.0 g.) was dissolved in a mixture of benzyl alcohol (15 ml.) and dimethyl aniline (15 ml.) contained in a 100 ml. round bottomed flask. The benzyl alcohol having been purified according to Wilds and Meader [16] and the dimethyl aniline by distillation. The flask was plunged into an oil bath at 190°. After an induction period of

two minutes nitrogen was evolved and the solution became dark in colour. After 9 minutes no more nitrogen was evolved, the flask was removed and allowed to cool. Ether (30 ml.) was added and the solution extracted with 2N hydrochloric acid (4 x 40 ml.) after which time the extract was colourless. The ether was removed and the remaining oil distilled under reduced pressure (115°/ 0.5 mm.) for 2 hours to remove benzyl alcohol. The residue was dissolved in ether (30 ml.) leaving a brown insoluble gum. The concentrated ether extract was passed through a column of neutral alumina (10 g.; 0.8 x 18 cm.) and total fraction which came through in ether (200 ml. was collected. On removal of the ether a slightly brown, very viscous oil was obtained. Yield 1.34 g.; 35%. For analysis 0.3 g. of the oil was again passed through a column of neutral alumina (69 g.; 11 x 0.8 cm) and the middle ether fractions taken for analysis.

Found : C, 65.5; H, 6.4%

$C_{20}H_{23}NO_4S$ requires : C, 64.4; H, 6.2%

1-(p-Toluenesulphonyl)-2-(1'-keto-2'-hydroxyethyl)-pyrrolidine

To a solution of diazoketone (1.25 g.; 1 mol.) in ethanol (13 ml.) at 55 - 60° was added a small amount of slurry of silver oxide, prepared from 10% silver nitrate solution (0.8 ml.; 1.07 mol.) and 2N sodium hydroxide, and stirred with 96% ethanol (2.5 ml.). As soon as the evolution of nitrogen had subsided more silver oxide was added and this process continued until all the slurry had been added. The mixture was refluxed for 15 minutes, filtered, and evaporated to dryness under reduced pressure. The viscous brown gum which remained was shaken with ether. On evaporation of the ether extract an oil remained which slowly yielded a crop of crystals (0.30 g.) which crystallised from ethanol/water gave solvated 1-(p-toluenesulphonyl)-2-(1'-keto-2'-hydroxy-ethyl)-pyrrolidine, m. p. 98°.

Found : C, 51.9; H, 5.6%

$C_{13}H_{17}NO_4S.H_2O$ requires : C, 51.8; H, 6.3%

1-(p-Toluenesulphonyl)-pyrrolidin-2-yl-acetic acid

Benzyl 1-(p-toluenesulphonyl)-pyrrolidin-2-yl-acetate (7.0 g.) was mixed with a solution of

33% aqueous hydrobromic acid and glacial acetic acid. It was allowed to stand at room temperature for 26 hours and the volatiles then removed on warm water under reduced pressure. The remaining oil was basified with 2N sodium hydroxide and extracted with ether (3 x 15 ml.) to purify. The aqueous solution was acidified with 2N sulphuric acid and re-extracted with ether (6 x 15 ml.). On removal of the ether under reduced pressure, crystals of 1-(p-toluenesulphonyl)-pyrrolidin-2-yl-acetic acid were obtained. Crystallisation of the S-benzyl-iso-thiuronium salt yielded white crystals (m. p. 189°).

Found : C, 56.0; H, 6.0%

$C_{21}H_{27}O_4N_3S_2$ requires : C, 56.1; H, 6.1%

Phenyl diazomethyl ketone

Freshly distilled benzoyl chloride (1.0 g.) in dry ether (2 ml.) was added dropwise with shaking to a dry ethereal solution of diazomethane (28 ml.) at -5° prepared from nitrosomethylurea [28]. The solution was allowed to warm to room temperature. After 5 hours the ether was removed under reduced pressure yielding yellow crystals (m. p. 42°).

1-Phenyl-1-oxo-2-thioacetyl ethane

Phenyl diazomethyl ketone (0.5 g.; 1 mole) was added to anhydrous thioacetic acid (0.43 ml.; 1.5 moles). The solution was warmed to 60°, left overnight and basified with 20% sodium hydroxide solution. The solution was extracted with ether (3 x 10 ml.). An oil was obtained on evaporation of the ether. The 2,4-dinitrophenylhydrazone was formed.

Found : C, 51.3; H, 3.8%

$C_{16}H_{14}N_4O_5S$ requires : C, 51.3; H, 3.8%

2. SYNTHESIS FROM TETRAHYDROFURFURYL ALCOHOL

Tetrahydrofurfuryl bromide

The apparatus used by Smith [29] consisted of a 500 ml. three necked flask fitted with a mercury-sealed stirred, thermometer, dropping funnel and calcium chloride tube. In the flask was placed re-distilled (b. p. 174-6°/ 760 mm.) phosphorous tri-bromide (96 g.; 56.5 ml.; 0.36 mol.) and azeotropic-ally dried benzene (50 ml.). Dry pyridine (15 g.; 15 ml.) was added from the dropping funnel with stirring over a period of 15 minutes. The flask

was then surrounded by an ice-salt mixture and the contents cooled to -5°. A mixture of re-distilled ($174 - 177^{\circ}$/ 760 mm.) tetrahydrofurfuryl alcohol (102 g.; 1 mol.) and dry pyridine (5 g.) (total pyridine 20 g.; 0.25 mol.) was added dropwise from the funnel with stirring over a period of four hours. During this time the internal temperature was not allowed to rise above -3°. Stirring was continued for one hour longer and the cooling bath was then allowed to warm up to room temperature.

The mixture was allowed to stand for 24 - 48 hours and then transferred to a 500 ml. Claisen flask. Two small portions of benzene (2 x 10 ml.) were used to rinse the flask. The benzene was distilled by reducing the pressure gradually to about 60 mm. and heating the flask gently in an oil bath (not above 90°). After the benzene had been removed, the solution was heated slowly to 160° / 12 mm. until no more material distilled. At this temperature a white substance sublimed. The crude distillate, washed with saturated sodium bicarbonate solution (3 x 20 ml.) and dried over anhydrous sodium sulphate, distilled to give tetrahydrofurfuryl bromide, b. p. $64 - 76^{\circ}$/ 25 mm. The yield was 68 - 73 g. (40 - 43%).

Tetrahydrofurylacetonitrile (30)

A mixture of tetrahydrofurfuryl bromide (70 g.; 1.0 mol.), potassium cyanide (29 g.; 1.0 mol.), water (50 ml.) and ethanol (80 ml.) was refluxed for 17 hours. A further quantity of potassium cyanide (29 g.; 1 mol.) was added and refluxed a further 28 hours (total 45 hours). Ethanol was removed by distillation until the boiling point reached 90°. Water (50 ml.) was added and the solution extracted with ether (6 x 20 ml.). After drying the etheral extract over sodium sulphate the oil remaining after evaporation of the ether was distilled under reduced pressure. Unconverted tetrahydrofurfuryl bromide was recovered at 65 - 95°/ 25 mm. and tetrahydrofurfurylacetonitrile collected at 100 - 120°/ 25 mm. Yield 16.2 g.; 35%

Tetrahydrofurfurylacetonitrile (30)

A mixture of tetrahydrofurfuryl bromide (20 g.; 1 mol.), ethanol (200 ml.) potassium hydroxide (24 g.; 2.6 mol.) and water (50 ml.) was refluxed (10 hours) until ammonia was no longer evolved. The ethanol was removed by distillation, the residue was carefully acidified with concentrated hydrochloric

acid (25 ml.) and continuously extracted with ether. The ether extract was dried over sodium sulphate, gave tetrahydrofurfurylacetic acid as a colourless, extremely viscous oil, b. p. 148 - 160°/ 25 mm. Yield 19.4 g.; 83%.

3,6-Dibromo-n-hexanoic acid

Ring opening of the tetrahydrofurfuryl-acetic acid to yield 3,6-dibromohexanoic acid was performed according to the method of Šorm (18).

Forty seven per cent hydrobromic acid (90 ml.; 0.77 mol.) was added dropwise to ice cooled acetic anhydride (450 ml.; 4.76 mol.). Tetrahydro-furfurylacetic acid (11.5 g.; 0.09 mol.) added to this solution and the mixture heated for six hours at 100° in six sealed tubes. Volatile matter was distilled off under reduced pressure, the residue taken up in ether (30 ml.), shaken with water (3 x 20 ml.) and dried over sodium sulphate. The ether, removed under reduced pressure, left 3,6-dibromo-hexanoic acid as a brown oil. Yield 21.4 g.; 95%.

Ethyl 1-methylpyrrolidin-2-yl-acetate (31)

A solution of dibromohexanoic acid (13.0 g.;

1.0 mol.) and anhydrous methylamine (12.0 g.; 3.77 mol.) in methyl alcohol (19.0 ml.) was heated in three sealed tubes at 100° for four hours and at 108° for half an hour. The semi-solid product remaining after evaporation of the golden-yellow liquid under diminished pressure at 40° was dried over night in a vacuum desiccator and refluxed for eight hours with ethyl alcoholic hydrogen chloride (57 g. of 15%). The ethanol was removed under reduced pressure, cold water (20 ml.) added and the solution basified with cold, aqueous 2N sodium hydroxide. The solution was quickly extracted with ether (4 x 20 ml.), the combined ether extracts shaken out with water (10 ml.) and dried over sodium sulphate. After removal of the ether, the remaining oil was distilled under reduced pressure (100°/ 2 cm.). Yield 3.57 g.; 44%. Cold, alcoholic picric acid gave a bright yellow picrate, m. p. 112.5°.

Found : C, 45.7; H, 5.1 ; N, 13.8 ± 0.4%

$C_{15}H_{20}N_4O_9$ requires : C, 45.4; H, 5.1; N, 14.0%

1-Methylpyrrolidin-2-yl-acetic acid

Hydrolysis was carried out according to the method described by Šorm [18]. The ethyl ester

(3.57 g.; 1 mol.), water (240 ml.) and finely powdered barium hydroxide (14.3 g.; 2.2 mol.) were set aside for three days at 30°, the flask being shaken from time to time. Carbon dioxide was then passed through the warmed solution until the solution had pH 6 and filtered. The filtrate was titrated with 2N sulphuric acid until no more barium sulphate was formed, two further drops added and the solution shaken with barium carbonate (0.3 g.). After filtration and evaporation under reduced pressure the remaining oil was allowed to crystallise in a vacuum desiccator. Yield 2.94 g.; 99% from the ester to the acid.

Ethyl 1-benzylpyrrolidin-2-yl-acetate

A solution of dibromohexanoic acid (4.0 g.; 1 mole) and benzylamine (10.8 ml.; 7 moles) was heated at 132° for five hours. The solution was dissolved in 10% sodium hydroxide (40 ml.), extracted with ether (6 x 15 ml.), just acidified with 30% hydrochloric acid, and evaporated to dryness under reduced pressure. The residue was refluxed for eight hours with a 10% solution of hydrogen chloride in absolute ethanol to esterify the acid. The solvent was

removed under reduced pressure and 10 ml. cold water added. The solution was basified with 2N sodium hydroxide (20 ml.) and extracted with ether (4 x 10 ml.). The ether extract washed with water (5 ml.) and dried over anhydrous sodium sulphate, gave an oil b. p. 180 - 200°/ 3 cm. Yield 0.55 g.; 16%. Alcoholic picric acid yielded ethyl 1-benzylpyrrolidin-2-yl-acetate picrate, m. p. 98°.

Found : C, 53.0; H, 5.2; N, 11.7%

$C_{21}H_{24}N_4O_9$ requires : C, 53.0; H, 5.0; N, 11.8%

Attempted hydrogenolysis of ethyl 1-benzylpyrrolidin-2-yl-acetate

Ethyl 1-benzylpyrrolidin-2-yl-acetate (0.3 g.; 1 mole) was dissolved in anhydrous acetic acid (10 ml.) and 5% Pd/C catalyst (0.1 g.) added. The mixture was shaken with hydrogen (30 lb/ sq. in.) for six hours. After the addition of concentrated hydrochloric acid (0.5 ml.) the solution was evaporated under reduced pressure. The remaining oil was shaken with water (5.ml.) and sodium carbonate added until it was basic. The solution was extracted with ether (3 x 5 ml.). After drying the ether solution over anhydrous sodium sulphate and evaporation of ether an i. r. spectrum showed the presence of the

benzyl group.

Attempted ring closure of ethyl 3,6-dibromohexanoate with p-toluenesulphonamide

Crushed sodamide (80 - 90%; 0.7 g.; 2 moles), suspended in dry toluene (30 ml.), and p-toluenesulphonamide (2.26 g.; 2 moles) were stirred and heated at 80° for one hour. Ammonia was evolved vigorously with the formation of a white sludge. After cooling, ethyl 3,6-dibromohexanoate (2.0 g.; 1 mole) was added dropwise and the mixture then refluxed for five hours. The solution was allowed to cool, 4N hydrochloric acid added dropwise until no more bubbling took place and then water (20 ml.). The basic aqueous solution was extracted with ether (5 x 10 ml.). The aqueous solution was acidified with 4N hydrochloric acid and re-extracted with ether (4 x 10 ml.). The acidic and basic ether extracts yielded p-toluenesulphonamide (1.61 g.). The toluene solution was concentrated and then run through a neutral alumina column. The fractions separated in this manner were either p-toluenesulphonamide or contained bromine.

In unsuccessful attempts to induce ring

closure the following procedures were also employed:-

(a) Sodium metal (0.25 g.; 4 moles) was dissolved in absolute ethanol (4 ml.) and a solution of p-toluenesulphonamide (0.51 g.; 1 mole) in absolute ethanol (2 ml.) was added. Benzyl 3,6-dibromohexanoate (1.08 g.; 1 mole) in absolute ethanol (4 ml.) was added and the solution refluxed for three hours.

(b) Part (a) was repeated except ethyl 3,6-dibromohexanoate was used instead of benzyl 3,6-dibromohexanoate. The solution was refluxed for thirty six hours.

3. THE PRINS REACTION

The Preparation of Ketene

(a) Ketene was first prepared according to the method of Hurd [32]. Acetone was pyrolysed in a quartz tube filled with porcelain chips yielding ketene in the exit gas. Since the yield of ketene was low an improved apparatus was used in its production.

(b) The apparatus of Williams and Hurd [33] shown in appendix 3 was used in our experiments since a large quantity of ketene could be prepared without

much attention having to be given to the apparatus. Air was driven from the pyrolysis chamber by first refluxing acetone for five minutes before passing current through the coils. After absorption of ketene from the gas stream the rate of flow of the residual gas was measured. The rate of ketene production was calculated roughly employing the equation:-

$$CH_3COCH_3 \longrightarrow CH_2=C=O + CH_4$$

The preparation of isopropenyl acetate (34)

Ketene was bubbled through boiling acetone containing from 1 - 1.4% acetylsulphoacetic acid. The acetylsulphoacetic acid was prepared by the reaction of acetic anhydride with concentrated sulphuric acid and the acetic acid distilled off under reduced pressure.

Acetone (7 g.; 1 mol.) in which was dissolved acetylsulphoacetic acid (0.9 g.) was heated to boiling and ketene passed into the solution. The rate of ketene production was estimated by measuring the volume of gas which emerged from the appartus after bubbling through the boiling acetone. The gas was assumed to be pure methane. After eight

hours it was estimated that 88 litres of ketene (4 mol.) had been produced. The solution was distilled from the catalyst and then fractionated through a Vigreux column to give isopropenyl acetate, b. p. 96 - 104°/ 760 mm. (Yield 92 g.: 68%).

The preparation of but-1-en-1-ol acetate (34)

n-Butyraldehyde (7.2 g.; 1 mol.) and isopropenyl acetate (15 g.; 1.5 mol.) and p-toluenesulphonic acid (0.2 g.) were heated to reflux on a Vigreux column 40 cm. long. Acetone was fractionated off slowly as it was formed. The reaction mixture was cooled and then neutralised with saturated sodium bicarbonate solution. After drying the organic layer by azeotroping out the water with unchanged butyraldehyde and excess isopropenyl acetate, but-1-en-1-ol acetate was obtained (b. pl 128 - 132°/ 760 mm.). Yield 2.0 g.; 18%.

The Prins reaction on but-1-en-1-ol acetate

To a mixture of but-1-en-1-ol acetate (2.0 g.; 1 mol.) and 40% aqueous formaldehyde solution (1.8 ml.; 1 mol.) was added 25% sulphuric acid (5 ml.) and shaken for four hours. The solution was

extracted with ether (3 x 5 ml.) and the ether extract dried over anhydrous sodium sulphate. On distillation no products were obtained which boiled above 130°. Since the experiment on this enol acetate was unsuccessful in our hands, we attempted to form the m-dioxane of isopropenyl acetate.

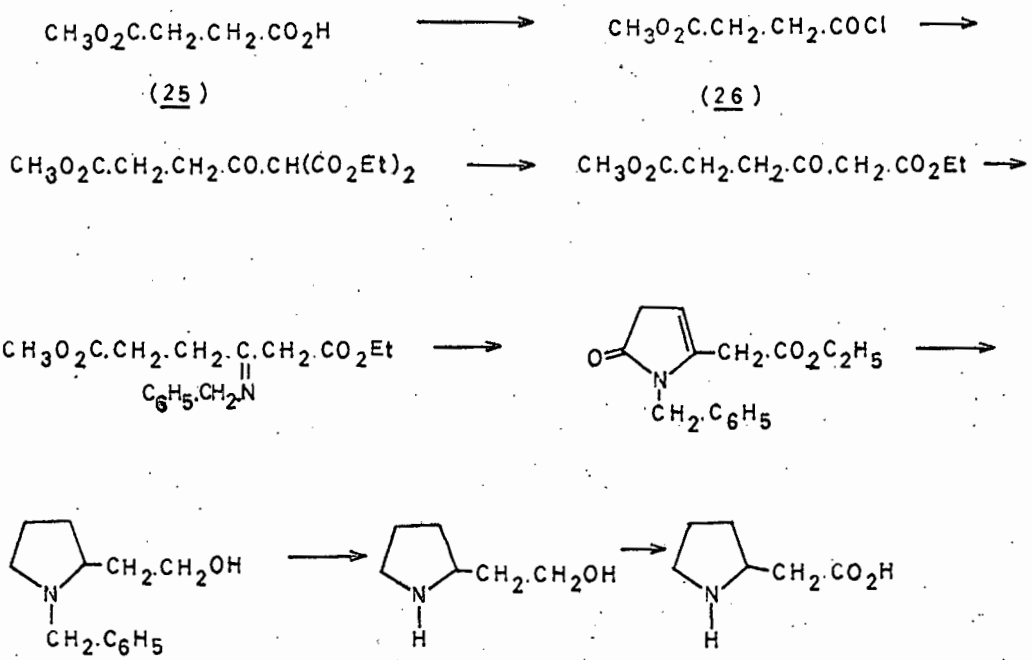
The Prins reaction on isopropenyl acetate

Isopropenyl acetate (15 g.; 1 mol.), 40% aqueous formaldehyde solution (14 ml.; 1 mol.) and 50% sulphuric acid (30 ml.) was shaken for eight hours. After extraction with ether (3 x 15 ml.) and distillation no high boiling products were obtained. The experiment was repeated using 25% and 71% sulphuric acid solutions. All the experiments were unsuccessful in our hands.

APPENDIX

1. THE SYNTHESIS OF HOMOPROLINE

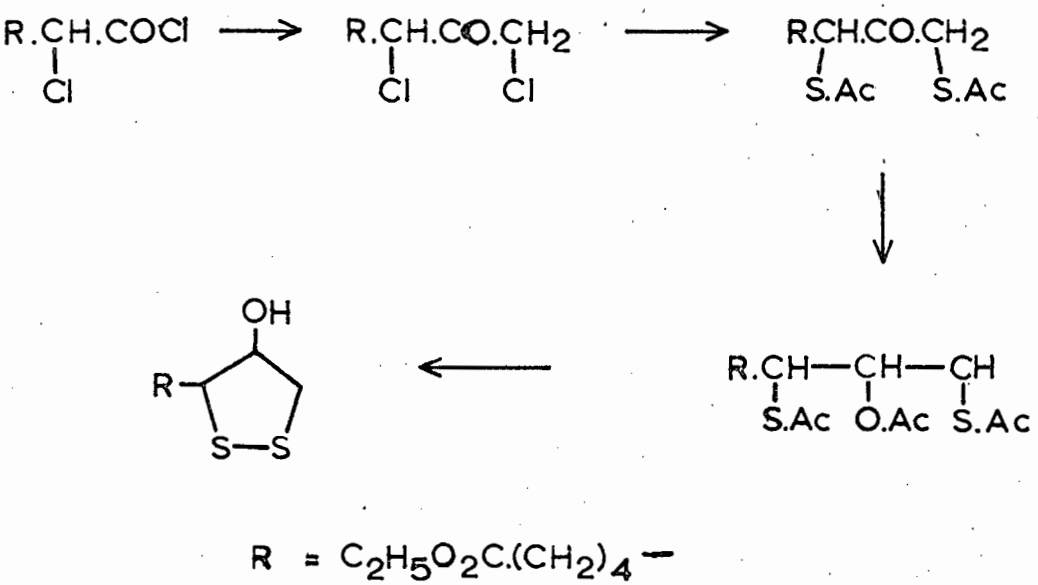
Baker, Schaub and Williams[35] have synthesised homoproline from monomethyl succinate (25) in eight stages as follows:-



The yield of homoproline from methyl succinyl chloride (26) was 8% obtained in six steps. Two syntheses were worked out which it was hoped, would give homoproline in a greater yield and in less steps.

2. HOMOPROLINE AS A SYNTHETIC INTERMEDIATE

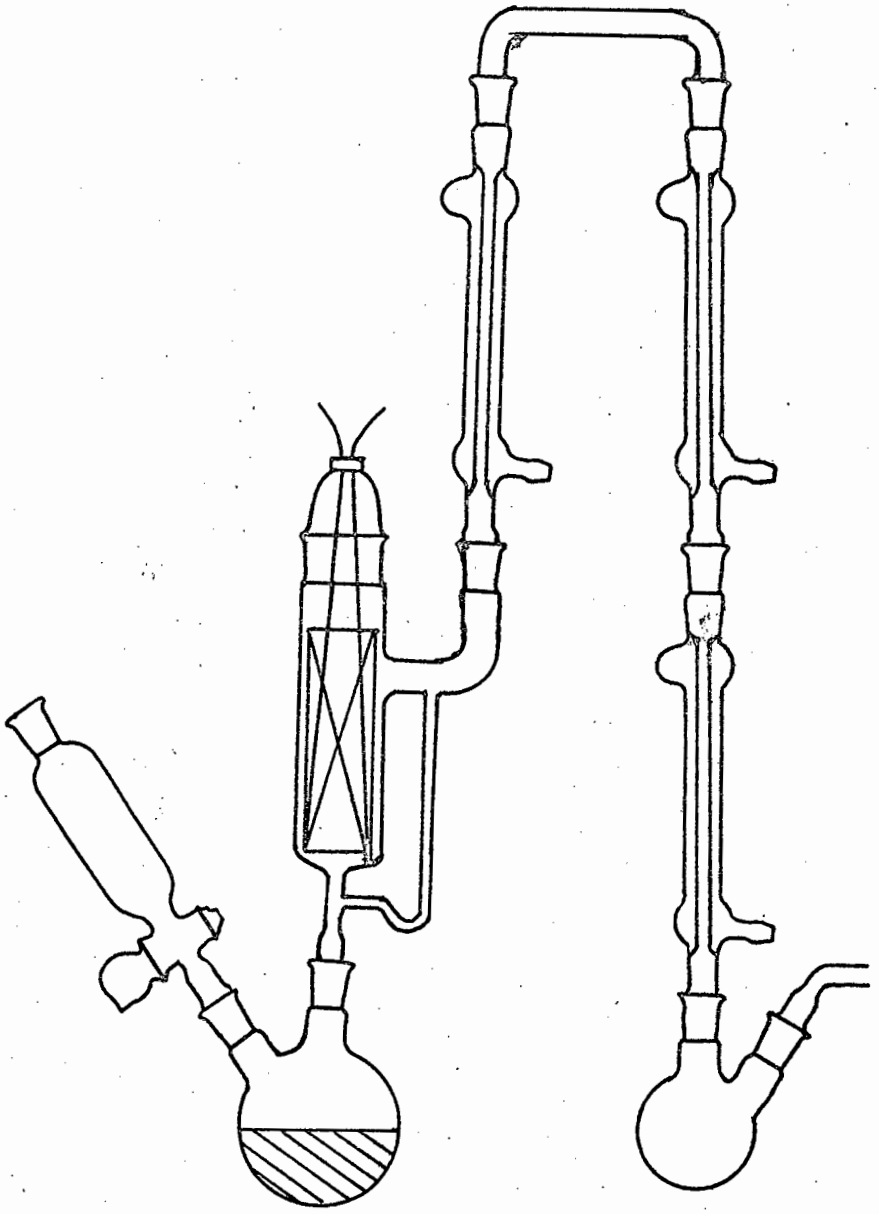
7-Hydroxy-α-lipoic acid was synthesised from the ethyl ester of pimelic acid chloride by Schmidt, Grafen and Goedde [36] i.e.



$R = C_2H_5O_2C.(CH_2)_4-$

In an analagous way it was proposed to synthesise 1-methyl-pyrrolidin-2-(1',2'-dithiolan-3'-yl-4'-ol) from N-substituted homoproline. Since homoproline was a key intermediate it was necessary to obtain this product in bulk.

APPENDIX 3



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