RHIZOPHORACEAE ALKALOIDS

An approach to the synthesis of
Cassipourine

by

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C.S.I.R. Natural Products Research Unit.
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3. EXPERIMENTAL

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SUMMARY

The chemistry and structure of cassipourine are outlined, and a number of various possible synthetic approaches are discussed in the light of the chemistry of 1,2-dithiols and of the pyrrolizidine ring system.

A route commencing with L-proline having been chosen, this was converted into 1-(p-toluenesulphonyl)-pyrrolizidine-2-aldehyde by protecting the amine with the p-toluenesulphonyl group, esterifying, reducing to the alcohol and then oxidising to the aldehyde. The reduction of the corresponding acid chloride directly to the aldehyde proved less successful.

The next step envisaged being the preparation of cis -1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-1,2-epoxy-3-benzyloxy-propane, a number of routes leading to this compound were attempted. The yield of 1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-3-benzyloxy-prop-1-ene, prepared by a Wittig reaction was too low for practical purposes. A novel reaction, the fissioning of the sulphonamide bond by the ylid to give 2-benzyloxyethyl-p-tolylsulphone was noted in this preparation. Attempts to prepare trans-1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-3-benzyloxy-prop-1-ene by reduction of ethyl-3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propenoate followed by benzylation were unsuccessful, as were attempts to prepare the same compound by the allylic rearrangement of 1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-1-hydroxyprop-2-ene.

The cis-epoxide was finally successfully prepared by converting the 1-(p-toluenesulphonyl)-pyrrolidine-2-aldehyde

into 3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propenoic acid by a Knoevenagel-Doebner reaction. Bromination of the double bond was followed by reduction of the acid to an alcohol, which on treatment with base gave a bromo-epoxide. This was treated with benzyl alcohol to form a benzyloxy-bromo-hydrin which gave the required cis-1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-1,2-epoxy-3-benzyloxypropane. This sequence of reactions was studied first in a series of model compounds, as were the proposed later stages of the synthesis.

INTRODUCTION

1. INTRODUCTION

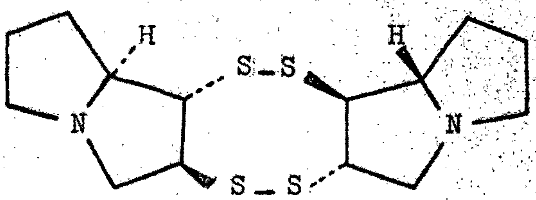
1.1 Sulphur containing alkaloids

The number of alkaloids that have been isolated and characterised is legion, but very few have been found to contain sulphur as part of the molecule. Cassipourine (I), the synthesis of which was the subject of the present work, is one of this small group, being a tetrathiocane derivative. Two Rhizophoraceae species have yielded the alkaloid; Cassipourea gummiflua Tvl. var verticellata from Natal and C. barteri from the Ivory Coast (1, 2, 3, 4).

Rhizophoraceae species have also yielded dithiolane alkaloids. Cassipourea gerrardii was found to contain a number of sulphur-containing bases, one of which, gerrardine, has the bisdithiolane structure (III). The closely related mangrove, Bruguiere sexangular gave rise to brugine (IV) (6).

A few other examples of alkaloids where the sulphur atom is present as a sulphide group are known. A number of the Nuphar, or waterlily alkaloids, for instance thiobinupharidine (VI) are thiolane derivatives (7), whilst some pyrrolizidine alkaloids have a sulphur-containing acid moeity, for example Planchonelline, (VII) from Planchonella thyrsoida is the ester of trans-3-thiomethoxyacrylic acid with laburnine (8).

An interesting dithiolane base of animal origin, the very poisonous nereistoxin has been isolated from the worm lumbriconereis heteropoda and has been shown to be 2-methylamino-1,3-dithiolane (V) (9).



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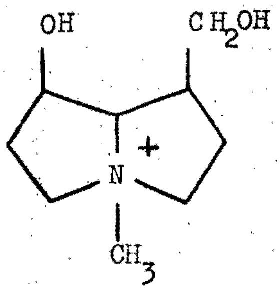

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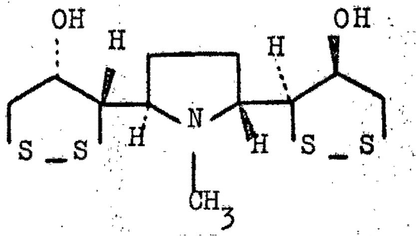
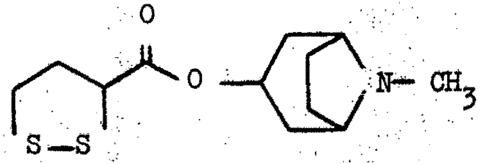


III



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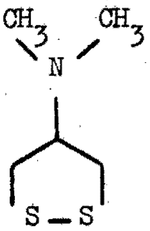


V

1.2 The structure and chemistry of cassipourine

The chemistry of cassipourine was investigated by Cooks *et al* (1, 3), who found the molecular formula to be $C_{14}H_{22}N_2S_4$. The only product on Raney nickel desulphurisation was pyrrolizidine, whilst a zinc dust distillation gave pyrrolo-[1, 2a]-pyrrolidine in almost quantitative yield. The alkaloid gave only one product, envisaged as 1-methyl-2-allylpyrrole, on undergoing the Hofmann degradation.

The alkaloid was very stable towards oxidising agents, and hot concentrated nitric acid was necessary to oxidise it to a single disulphonic acid.

The isolation of single products from all these reactions suggested that cassipourine is a symmetrical bis-disulphide arising from two molecules of a dimercapto-pyrrolizidine, but it required the use of X-ray crystallography to establish the structure as $1\alpha,1'\beta$: $2\beta,2'\alpha$-bis-dithio-8α-pyrrolizidine (I, or its enantiomorph.)

Cassipourine is an interesting compound in a number of respects. It is one of the few known alkaloids derived from the pyrrolizidine, as distinct from the 1-methylpyrrolizidine skeleton. Most pyrrolizidine alkaloids are esters of a hydroxylated 1-methyl pyrrolizidine with mono- or dibasic acids. A few non-ester pyrrolizidine bases are known, but most incorporate the 1-methyl pyrrolizidine system. The occurrence of the quaternary base verticellatine together with cassipourine in *C. gummiflua* is thus noteworthy as it is probably the 1-methyl pyrrolizidine derivative (II) (10).

The most striking chemical property of cassipourine is its extreme inertness to oxidation, reduction and nucleophilic fission of the disulphide linkages, which, in simpler compounds, are generally noted for their ease of reaction. Attempts at reduction, using a wide variety of reagents failed to give recognisable products and generally resulted in unreacted starting material being recovered in high yield. Fission of the disulphide bonds by cyanide and hydroxyl ions was investigated, but no reaction was observed to take place. Mild oxidising agents such as dilute nitric acid and hydrogen peroxide, which usually gave sulphoxides, were without effect on cassipourine. As mentioned above, very much more vigorous conditions were needed to give the disulphonic acid.

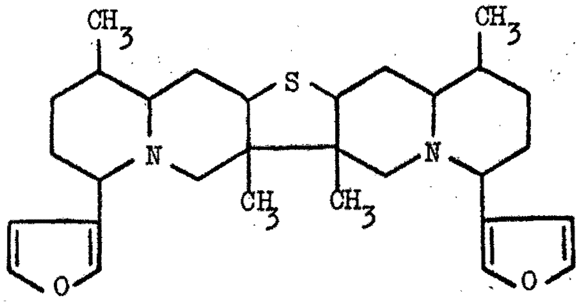
This uncharacteristic behaviour of the disulphide groups in cassipourine must be due to steric protection by the rest of the molecule. The hindrance must be extreme as di-t-butyl disulphide, which is very resistant to reduction, may be reduced by sodium in ethanol, whereas cassipourine is inert to this reagent.

1.3 The 1,2,5,6-tetrathiocane and tetrathiocin ring systems

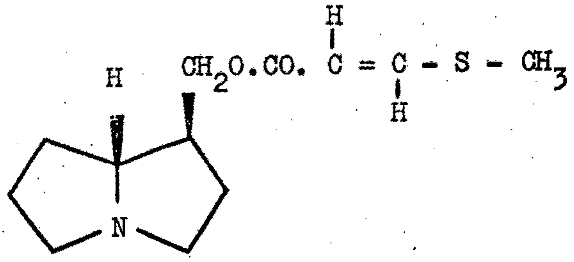
The 1,2,5,6-tetrathiocane ring in cassipourine represents the first known occurrence of this system in a natural product. The preparations of a number of derivatives of this ring system, and of the unsaturated 1,2,5,6-tetrathiocin system have been accomplished in recent years (11, 12). Oxidation of 1,2-dithiols has given the tetrathiocanes, generally together with polymer. The early report of the preparation of the parent ring compound by oxidation of ethane-1,2-dithiol is suspect in that the high melting-point of the compound isolated probably corresponds to polymeric material (13). The problem of polymerisation has been overcome by carrying the reaction out under conditions of high dilution (14).

The tetrathiocins have been prepared by methods other than oxidation. Two examples are 3,4,7,8-tetra-(trifluoromethyl)-1,2,5,6-tetrathiocin (VIII), which arose by dimerisation of the dithietin (IX) (15), and the compound (X) which was prepared by heating the alkaloid nicotyrine (XI) with sulphur (16).

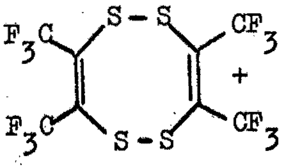
In carbocyclic eight-membered rings three conformations are regarded as having the lowest energy, namely the puckered crown, boat and chair forms. Other forms without any distortion of bond angles are also possible (fig. 1). The tetrathiocane ring may also assume these various conformations, but in cassipourine constraints are introduced by the pyrrolizidine rings having the sulphur atoms rigidly *trans*-fused. By inspection of models it can be seen that there are only four conformations possible without having prohibitive bond-angle distortion. These conformations are illustrated in fig. 2, and correspond to a distorted boat form (1), two half boat - half crown forms (2 and 3) and a distorted crown form (4). The amount of interaction between the *trans*-annular hydrogen atoms would appear to be in the order 1 2 3 4, and the total distortion of the two C-S-S-C dihedral angles from the "normal" value of about 104° probably follows the same order. The form of



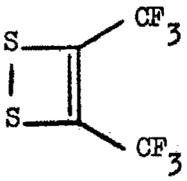
VI



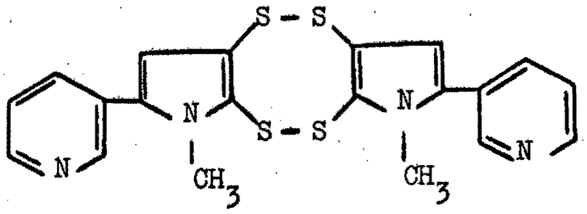
VII



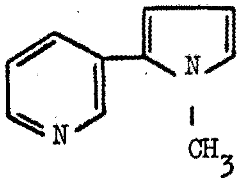
VIII



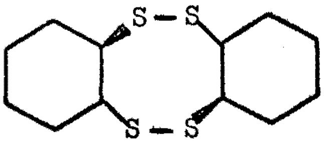
IX



X



XI



XII

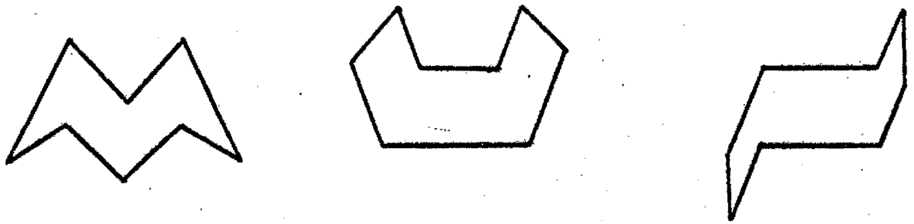
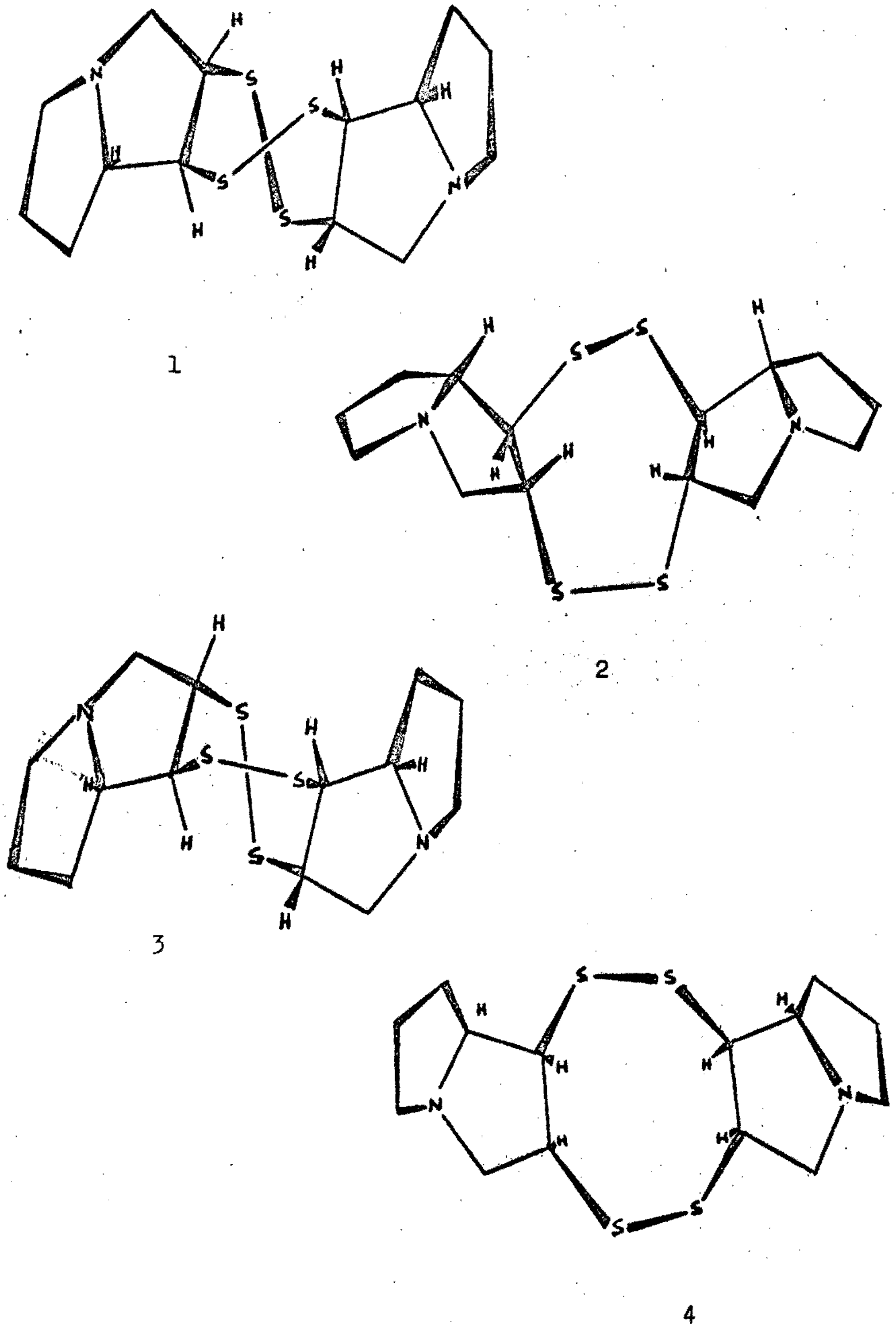


Fig. 1



1

2

3

4

Fig. 2.

least energy would then appear to have structure 4, but the model of the cassipourine molecule prepared by the X-ray analyst gives structure 2 as the conformation adopted in the crystal, with the crystal-packing forces favouring the conformation found.

1.4 Approaches to the synthesis of cassipourine

1.4.1 Closure of the tetrathiocane ring

As cassipourine is a symmetrical bisdisulphide an obvious last step in the synthesis would be the oxidation of two molecules of pyrrolizidine-1,2-dithiol. Intramolecular disulphide formation is sterically not possible, but there would be competition between dimerisation and polymerisation. The latter may be minimised by working at high dilution, as was done by preparing the cyclohexyl derivative (XI) in 52% yield (14). The trans-substitution of the sulphur atoms on the pyrrolizidine ring would probably facilitate dimer formation; once one disulphide bond has formed the other sulphur atoms are very suitably placed to form the second disulphide link.

The sulphur atom on C-2 appears more sterically accessible than that on C-1, and so the first disulphide link would probably be between C-2 and C-2', leading ultimately to cassipourine. If the first disulphide link was between C-2 and C-1' an isomer would result. If the dithiol is a racemic mixture two distereoisomeric bisdisulphides are sterically equally possible for each of the two positional isomers, so that four racemic products would result. Oxidation of optically pure dithiol would give twice the yield of optically pure cassipourine than the oxidation of racemic dithiol would give of racemic cassipourine.

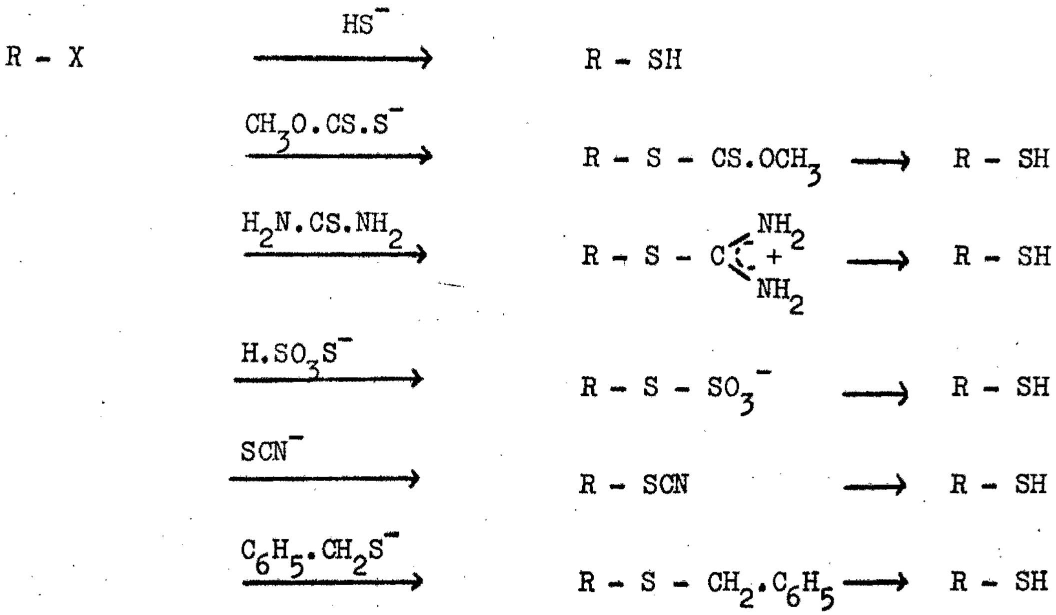
The choice of oxidising reagent is very wide, as almost any mild oxidising agent will oxidise thiols to disulphides. Commonly used reagents are oxygen (or air), particularly in the presence of ferric ions which catalyse the reaction, iodine and hydrogen peroxide (17). The nitrogen atoms in cassipourine would very likely be oxidised to N-oxides under these conditions, and whilst these could easily be reduced without affecting the disulphide bonds, the use of dimethyl sulphoxide as the oxidising agent has been reported to give very high yields of disulphide without oxidising amine groups (18).

1.4.2 The preparation of 1,2-dithiols

Monothiols may be readily prepared in a number of ways. The most frequently used method is by the displacement of a halide or sulphonate ester with hydrosulphide ion to give the thiol directly (19), or by a variety of nucleophiles which then give the thiol indirectly. The use of thiolacetate as the attacking group followed by hydrolysis to the thiol is widely used (20). Treatment of alkyl halides with thiourea and thiosulphate gives isothiouronium and S-sulphonates (Bunté salts) respectively (21, 22), both of which may be hydrolysed to thiols. Thiocyanates, prepared by reaction of a halide with thiocyanate ions, give thiols on metal-acid reduction (23), whilst benzyl thioethers give thiols by catalytic hydrogenolysis or metal-ammonia reduction (24). These reactions are summarised in fig. 3. In all these reactions there is inversion at the carbon atom involved in the reaction.

Grave problems due to neighbouring group participation arise when these methods are used to prepare *vic*-dithiols. The required product is generally obtained in good yield when both the halide groups being replaced are at primary carbon atoms, in fair yield when one of the halide groups is at a secondary carbon atom, but generally in very poor yield if both are secondary (25). The use of thiolacetic acid in pyridine has succeeded in some, but not all cases (26, 27), where both halogen atoms are at secondary carbon atoms. The reaction which does generally occur is the dehalogenation of the molecule to give an olefin. The mechanism, probably similar to the dehalogenations induced by zinc, iodide ions and phosphines, is given in fig. 4; the reaction occurs by the soft-base attack of the sulphur nucleophile on a halogen atom, which is a soft acid centre, together with simultaneous formation of olefin and elimination of the other halogen atom. The sulphur compound is converted into disulphide (28).

Dithiocyanates are readily prepared in good yield by the *trans* addition of thiocyanogen to double bonds (29, 30). The stereochemistry of the addition has been well substantiated and the method could be a very attractive means of introducing sulphur into the molecule. However metal-acid reduction of 1,2-dithiocyanates gives 2-imino-1,3-dithiolane salts (31),



$$R - X \xrightarrow{HS^-} R - SH$$

$$\xrightarrow{CH_3O.CS.S^-} R - S - CS.OCH_3 \longrightarrow R - SH$$

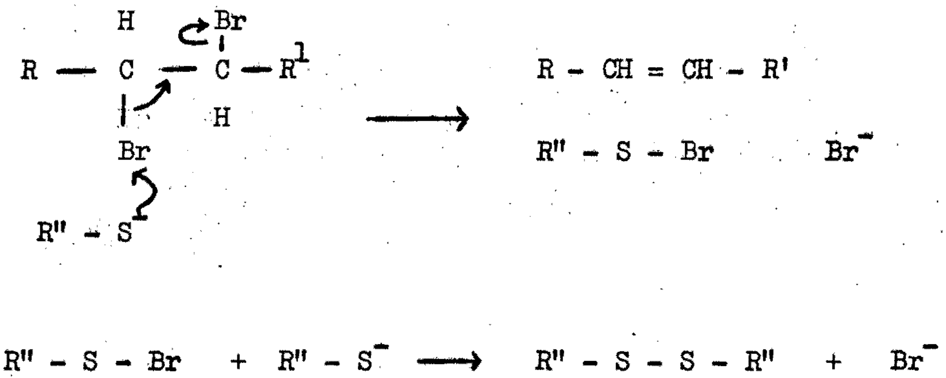
$$\xrightarrow{H_2N.CS.NH_2} R - S - C(NH_2)_2^+ \longrightarrow R - SH$$

$$\xrightarrow{H.SO_3S^-} R - S - SO_3^- \longrightarrow R - SH$$

$$\xrightarrow{SCN^-} R - SCN \longrightarrow R - SH$$

$$\xrightarrow{C_6H_5.CH_2S^-} R - S - CH_2.C_6H_5 \longrightarrow R - SH$$

Fig. 3



$$R'' - S - Br + R'' - S^- \longrightarrow R'' - S - S - R'' + Br^-$$

Fig. 4

and basic conditions give episulphides (fig. 5) (32). The formation of episulphides is not necessarily a disadvantage as they can be converted to dithiols. Opening of the ring with sulphur nucleophiles leads to the required product, but yields are poor (33). Formation of a cyclic trithiocarbonate or 1,3-dithiolane-2-thione by treatment of the episulphide with xanthate, followed by reduction with lithium aluminium hydride offers a very attractive route to dithiols. Better still, the reaction is not limited to episulphides, as epoxides and halohydrins are converted to episulphides, and hence to trithiocarbonates under the reaction conditions used (34, 35, 36).

The mechanism which has been proposed to account for these reactions is shown in fig.6 (37). The stereochemistry implied by this mechanism has been confirmed by N.M.R. (38). The formation of the episulphide from the epoxide occurs with inversion at both carbon atoms, and a further inversion at one of the carbon atoms takes place during the formation of the trithiocarbonate. The episulphide may be attacked at either carbon atom, so that if an optically active epoxide were used, it would first be converted into the enantiomeric episulphide, which would then give a mixture of two stereo-isomeric trithiocarbonates, and depending on the relative ease of attack on each carbon atom, so one form or another would predominate. An optically pure *cis*-epoxide is converted into an optically pure *cis*-episulphide which then becomes a mixture of two stereo-isomeric dithiolanethiones.

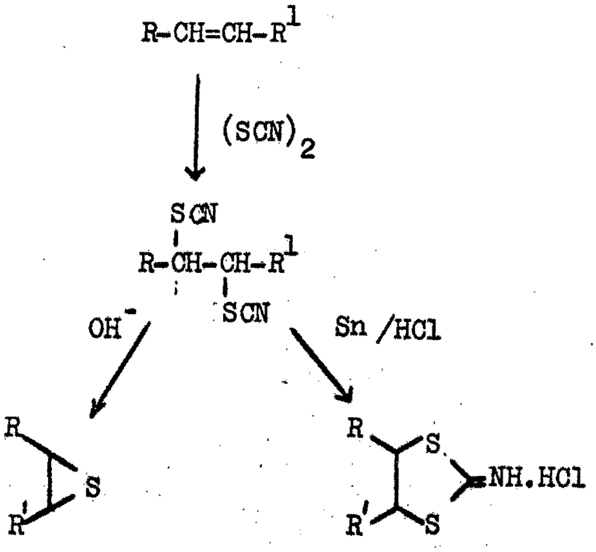
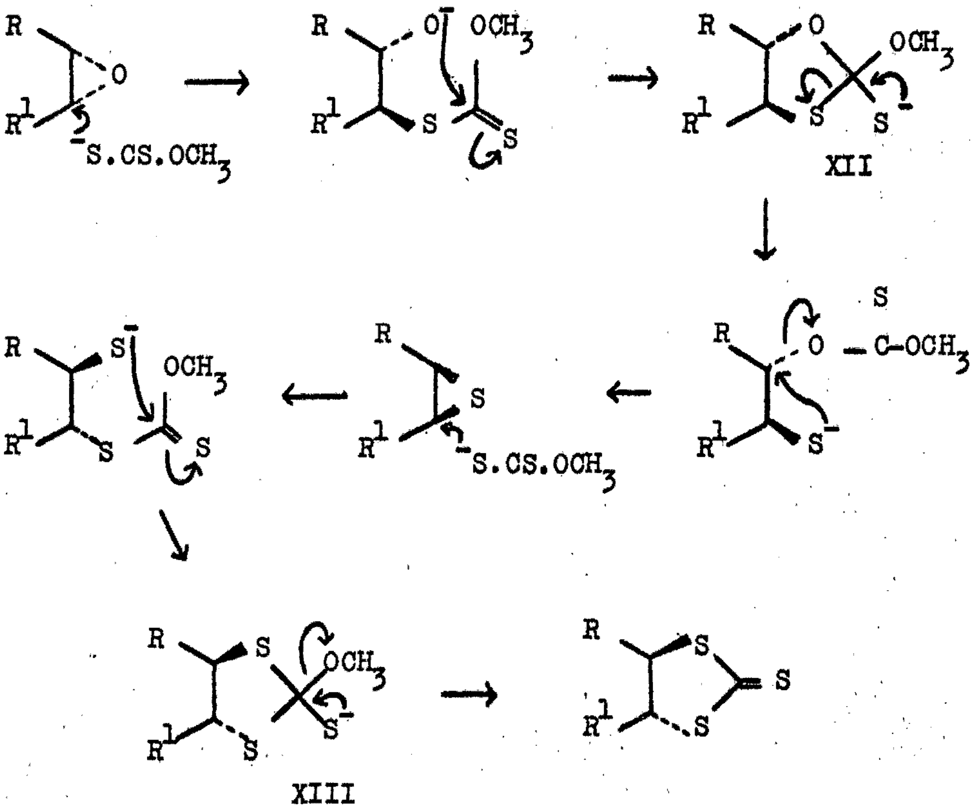


Fig. 5



X
XI} $R,R^1 = -C_3H_6-$

Fig. 6

This preparation of cyclic trithiocarbonates from epoxides has been widely used to give vic-dithiols, particularly in the sugar series (25). The reaction is straight forward in the case of open-chain epoxides, or of epoxides on six-membered rings. Owen et al showed however, that it was not possible to prepare a trithiocarbonate from cyclopentene oxide, or from other five-membered ring epoxides, but that cyclopentene sulphide reacted to give the expected product (36). The block must be in the conversion of epoxide into episulphide and is probably due to the difficulty of forming the intermediary (**XII**) which would have two trans-fused five-membered rings. The similar intermediary (**XIII**) in the reaction with episulphide, where sulphur replaces oxygen does ring-close to give the trithiocarbonate with the two five-membered rings trans-fused, which may be explained by the greater nucleophilic reactivity of the thiol **anion**, and is probably facilitated by the greater ease of deformation of the sulphur bond angles.

1.4.3 The synthesis of pyrrolizidine-1,2-dithiol

The synthesis of pyrrolizidine-1,2-dithiol may be approached in a number of different ways. Some of these were examined in greater detail to enable a final choice of the general route to be made, with particular attention being paid to the ease of introduction of the sulphur atoms, the overall stereochemistry, whether the method lent itself to the determination of the absolute configuration of the final product and to the availability of suitable starting materials.

The pyrrolizidine ring system consists of two *cis* - fused five-membered rings, the configuration of which is controlled by the configuration of the bridgehead carbon atom. The required pyrrolizidine-1,2-dithiol has the *arabino*-configuration, the two sulphur atoms being trans-substituted on the ring (XX). The synthesis could be approached by introducing the sulphur atoms directly on to a pyrrolizidine system, or one of the rings could be open, with the sulphur atoms being attached either to the remaining ring or to the open chain, followed by closing the second ring.

For the first approach the starting material envisaged was $\Delta^{1,2}$-pyrrolizidine (XV), which might be prepared by the method outlined in fig. 7. This appears feasible as it has been reported that pyrrolizidone (XIV) has been prepared in this way (39), and that the other steps have been carried out on various methyl derivatives (40). The $\Delta^{1,2}$-pyrrolizidine prepared in this way would be a racemate, but if resolution were effected oxidation would give a derivative of proline, which has a known absolute configuration. A reasonably accessible model compound was heliotridene, 1-methyl- $\Delta^{6,7}$-pyrrolizidne, a degradation product of the alkaloid retrorsine, which was available (41, 42).

The introduction of the sulphur atoms could present difficulties (fig. 8). Naturally occuring derivatives of

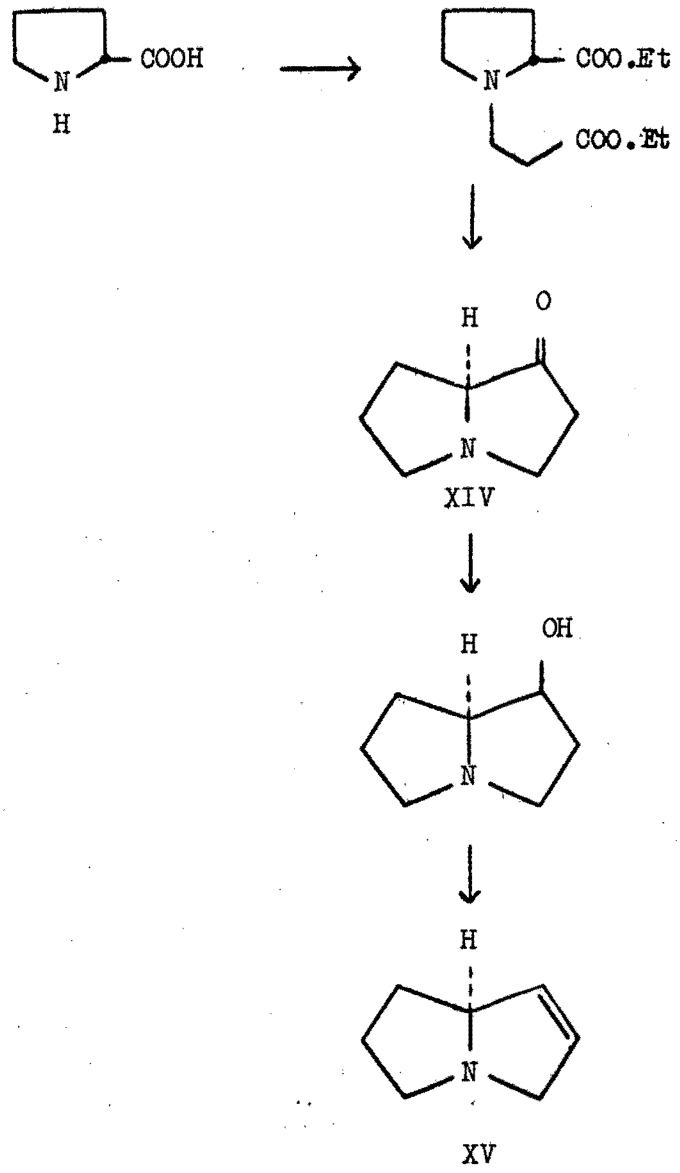
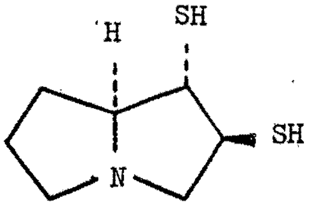
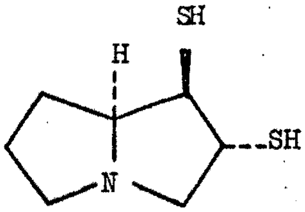


Fig. 7



XX



XXI

pyrrolizidine-1,2-oxide are known and have been synthesised (43, 44) but the conversion of the epoxide (XVI) to the episulphide (XVII) might not prove feasible. Even if the episulphide could be prepared the reaction to form the *trans*-fused trithiocarbonate (XVIII) could be hindered by the extra rigidity of the pyrrolizidine system. If this were the case then the direct reduction of the pyrrolizidine-1,2-dithiocyanate to the dithiol should not be complicated by the similarly *trans*-fused dithiolane-iminium salt (XIX).

In all of these approaches the possibility of two forms of the *trans*-substituted dithiol exist, i.e. the wanted *arabino*-form (XX), and the unwanted *xylo*-form (XXI). As the pyrrolizidine system is assymmetric one form might be expected to predominate, but it would be difficult to predict which that would be.

The problem posed by the rigidity of the pyrrolizidine system would be overcome by opening ring A, that is by having a Δ^3-pyrroline as the starting compound (fig. 9). Any complications arising from the basic nature of the pyrrolizidine nitrogen atom could also be surmounted by converting the nitrogen of the pyrroline into a non-basic form. The need for preparing the trithiocarbonate from the episulphide and not directly from the episulphide would remain, as would the formation of two *trans*-substituted isomers.

The racemic Δ^3-pyrroline (XXII) might be prepared by reduction of the corresponding pyrrole (45, 46), and if resolution could be accomplished oxidative fission of the double bond would give a derivative of glutamic acid to

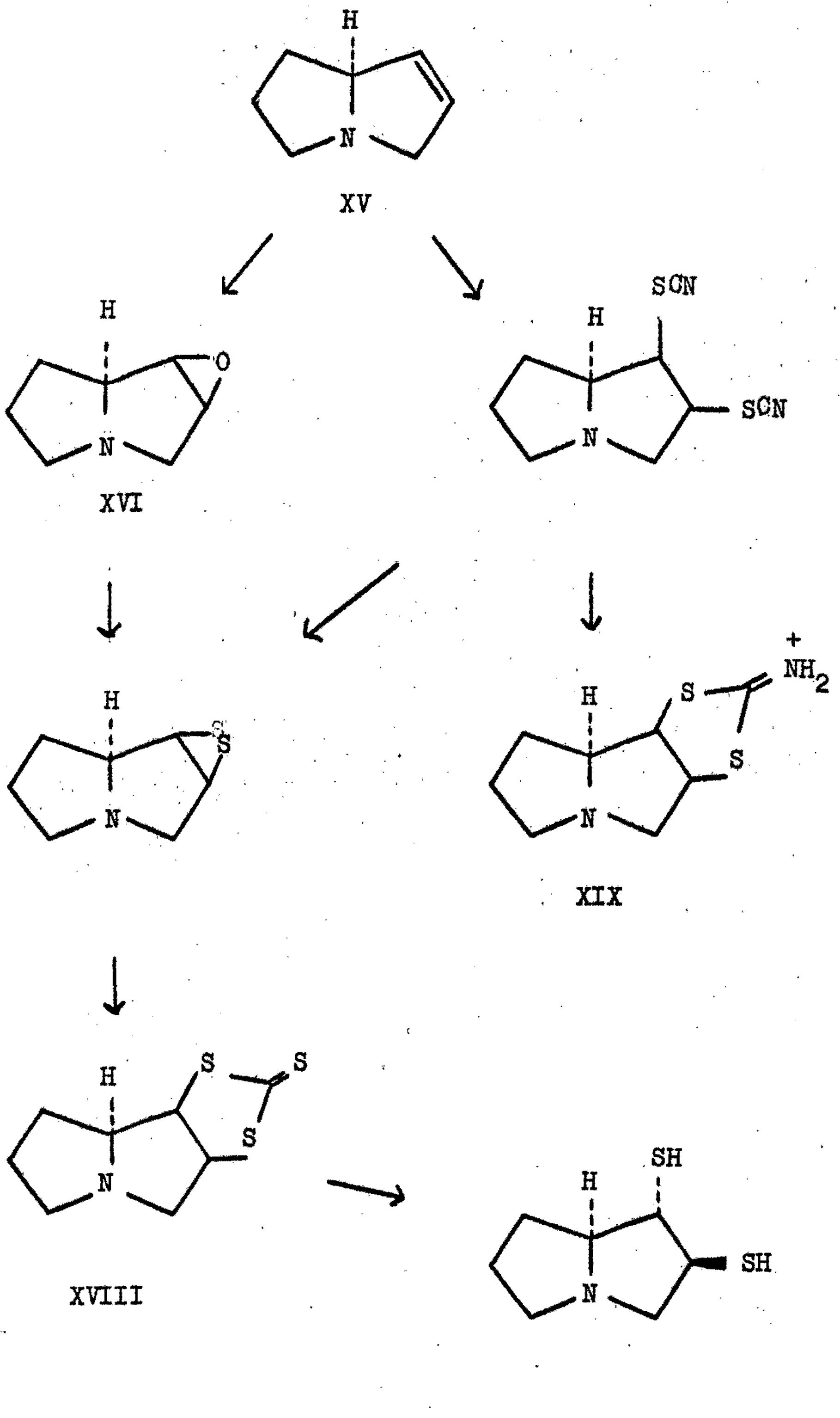


Fig. 8.

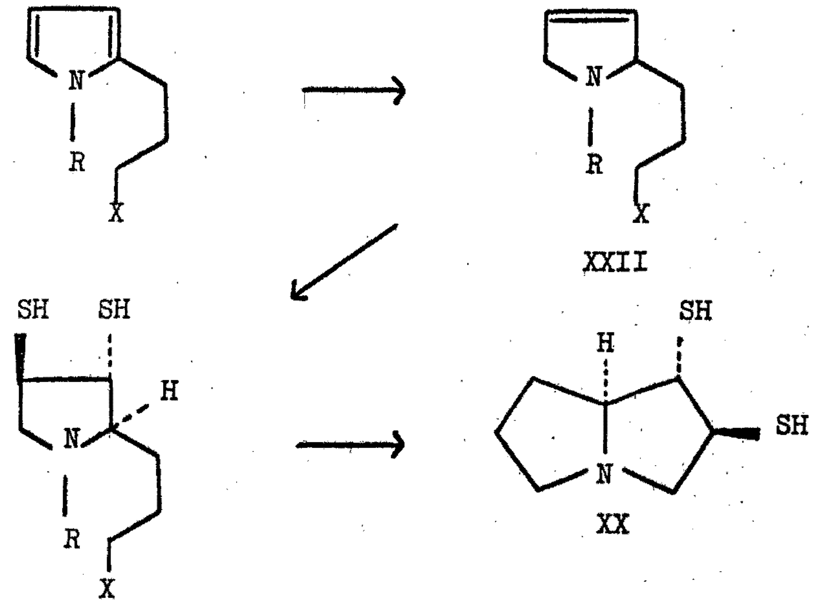

N
R
X
N
R
X
XXII
SH
SH
H
N
R
X
SH
H
SH
N
XX

Fig. 9

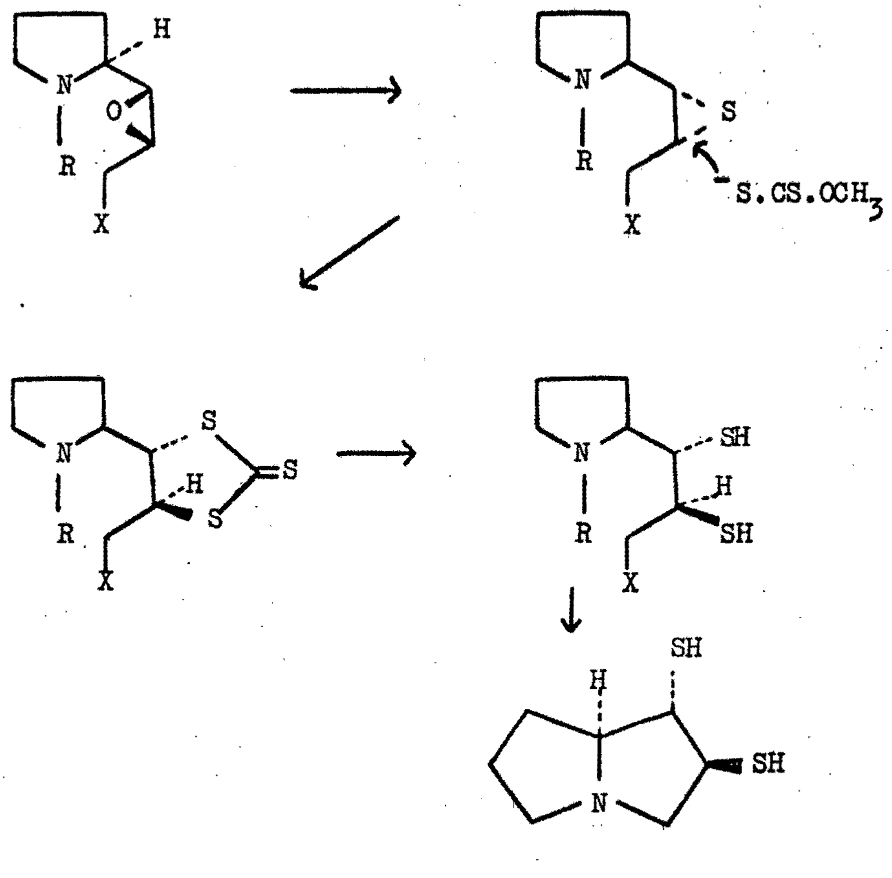

H
N
O
R
X
N
S
R
X
S.CS.OCH$_3$
S
N
S
R
H
S
X
N
SH
H
R
SH
X
SH
H
SH
N
XX

Fig. 10

establish the absolute configuration. The second ring would be closed after introduction of the sulphur atoms.

The final general approach considered was that of placing the sulphur atoms onto an open chain and following this with ring-closure to form the pyrrolizidine. This method would avoid the problems and uncertainties associated with placing the sulphur atoms onto a five-membered ring.

A suitable choice of starting material of known absolute configuration would define the absolute configuration of the pyrrolizidine, and as the open-chain dithiol must have the *arabino*-configuration the relative configuration of the two sulphur atoms must be *threo*-.

This approach was the one chosen, particularly as a very suitable starting material, *L*-proline was readily available; with one ring of the pyrrolizidine closed from the start the synthesis would continue by extending the chain length of the substitution on the ring by two carbon atoms, then introducing the sulphur atoms and finally closing the second ring. This approach had the advantage of flexibility, so that should one route prove impractical a wide variety of possible variations were available.

The absolute configuration of the pyrrolizidine bridgehead carbon atom would, provided that racemisation had not occurred during the synthesis, be defined by the known absolute configuration of *L*-proline i.e. (S)-pyrrolidine-2-carboxylic acid.

The epoxide to trithiocarbonate method of introducing the sulphur atoms appeared to be the best choice. As the required configuration of the pyrrolizidine-1,2-dithiol (XX) and hence of the trithiocarbonate is arabino-, and assuming that the formation of the trithiocarbonate from the intermediate episulphide would occur preferentially by attack of the xanthate ion on the least sterically hindered side of the episulphide ring, that is the carbon atom furthest from the pyrrolidine ring, then the required episulphide must have the ribo- configuration and the epoxide the lyxo- configuration (fig. 10).

Once the sulphur atoms had been introduced the ring-closure to the pyrrolizidine would require the removal of any protective groups and the presence of some suitable leaving group on the last carbon atom of the chain, for instance a bromine atom, to be displaced by the deblocked amine group of the pyrrolidine ring. Pyrrolizidine itself has been prepared in this way from 1-(pyrrolidine-2'-yl)-3-bromopropane hydrobromide on basification (47). Better yields were obtained by the reductive closure of 1-(pyrrolidin-2'-yl)-3-hydroxypropane in the presence of Raney nickel, but this procedure is inapplicable in the present case as the catalyst would desulphurise the dithiol.

The closure of 1-(pyrrolidin-2'-yl)-1,2-dithio-3-bromopropane would be expected to occur readily, but a possible competing reaction would be the displacement of the bromine atom by one or other of the thiol groups to give an episulphide or a thietane (48). The former would be expected to predominate as three-rings generally from much more rapidly than similar four-rings (49). The episulphide could then be attacked by the amine group to give the required product with no change in the stereochemistry (50), but the thietane would not be attacked by the amine group (51) and so would be undesirable. If the sulphur atoms interfered seriously with the ring-closure it would be necessary to protect them.

DISCUSSION

2. DISCUSSION

2.1 General

The initial attempt to synthesise the lyxo-epoxide (XXIII) is outlined in fig. 11. The starting material was L-proline, but the presence of a free amine group would cause difficulties at a number of stages of the proposed synthesis so that conversion to a non-basic form was necessary. Blocking up of the group by forming an amide would not be satisfactory, as a number of reduction steps using lithium aluminium hydride were anticipated, and this reagent will reduce amides. Primary sulphonamides are not reduced by lithium aluminium hydride, and although secondary sulphonamides are reduced, to sulphinic acids and thiols, the rate is very slow in relation to the reduction of other functional groups (52). In particular it has been reported that the sulphonamide group of 1-(p-toluenesulphonyl)-2-hydroxymethylpyrrolidine-p-toluene-sulphonate was quite stable towards lithium aluminium hydride (53).

The p-toluenesulphonyl derivative appeared to be very suitable for blocking the amine function of proline. The compound may be readily prepared without racemisation, whilst the presence of the toluene group would be expected to increase the crystallinity of the various intermediates in the chain of synthesis. The p-toluenesulphonamide

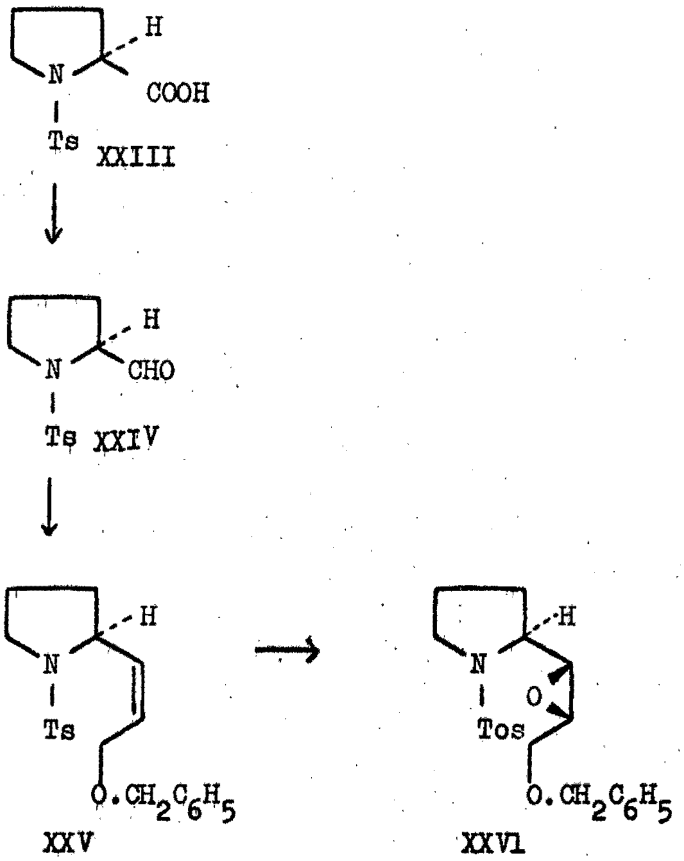

H
N
COOH
Ts
XXIII
H
N
CHO
Ts
XXIV
H
N
Ts
O.CH₂C₆H₅
XXV
H
N
O
Tos
O.CH₂C₆H₅
XXVl

Fig. 11

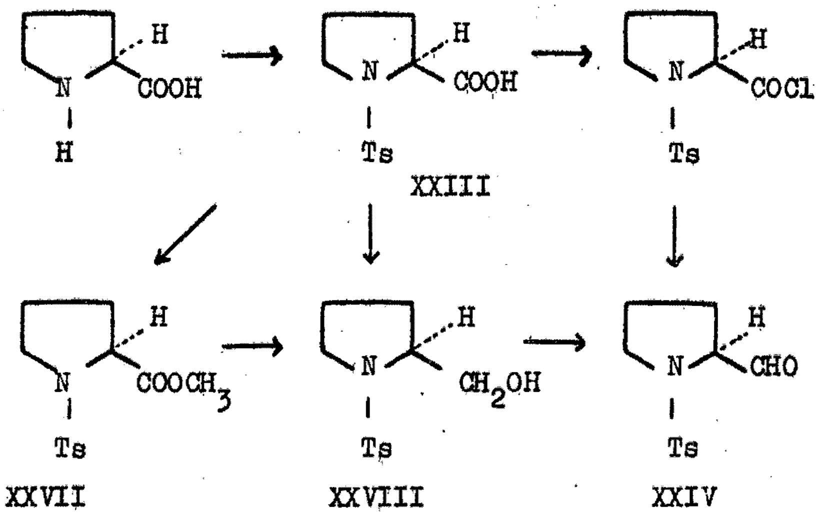

H
N
COOH
H
H
N
COOH
Ts
XXIII
H
N
COCl
Ts
H
N
COOCH₃
Ts
XXVII
H
N
CH₂OH
Ts
XXVIII
H
N
CHO
Ts
XXIV

Fig. 12

group may be removed, when necessary either by reduction with sodium in liquid ammonia or by treatment with a hydrobromic acid/phenol mixture (54, 55).

At this stage it was necessary to consider the final stage of the synthesis of the pyrrolizidine-1,2-dithiol, that is the ring closure to give the pyrrolizidine system. To achieve this some suitable leaving group such as a bromo-group would be needed at the end of the chain, to be displaced by the deblocked amine group of the pyrrolidine ring.

As the leaving group would undergo unwanted displacement during the formation of the trithiocarbonate and its reduction to dithiol it may only be introduced into the molecule after these reactions have been performed, and the position must be protected during the course of these reactions. The benzyloxy group appeared to be a fit choice, as it is stable under basic conditions and towards hydride reducing agents (56), and may be removed by the same reagents which cleave the sulphonamide (57, 58).

Sodium in liquid ammonia would give the free alcohol which would then have to be converted into some group suitable for displacement. A sulphonate ester would be convenient, but impractical as sulphonamides form faster than sulphonates, so blocking the amine function. The bromo-compound could be formed, but then it would be easier to fission the protective groups with hydrobromic acid, which would give the bromo-amine in one step.

2.2 The synthesis of L-1-(p-toluenesulphonyl)-pyrrolidine-2-aldehyde

The preparation of L-1-(p-toluenesulphonyl)-pyrrolidine-2-carboxylic acid was effected in high (91 - 96%) yield from L-proline by a method similar to that of Pravda and Rudinger (59), the product being isolated as crystals m.p. 95 - 97°, containing half a molecule of benzene of crystallisation.

The first objective of the synthesis as outlined in fig. 11 was the preparation in good yield of 1-(p-toluenesulphonyl)-pyrrolidine-2-aldehyde.

A wide variety of methods exist for the preparation of aliphatic aldehydes, generally either by the reduction of acyl derivatives or by the oxidation of primary alcohols or alcohol derivatives. Either of these approaches could be used on proline as reduction to the alcohol would be possible. The most commonly employed methods are the reduction of the acid chloride, using either hydrogen over a partially poisoned catalyst, the Rosenmund reaction (60), or partially substituted lithium aluminium hydrides such as tri-t-butoxy lithium aluminium hydride (61). Amides may be reduced to aldehydes by lithium aluminium hydride as also can nitriles (62, 63). Nitriles may be reduced to aldehydes by stannous chloride (64).

A number of inorganic oxides will convert alcohols to aldehydes, but over-oxidation to the acid is a serious side reaction which may be overcome by the more specific action of dimethylsulphoxide together with a variety of "activating" agents (65). Primary alkyl halides and sulphonates may also be oxidised by dimethylsulphoxide (66), whilst alkyl iodides are converted to aldehydes by the action of tert-amine-N-oxides (67).

The reduction of the acid chloride would provide the most direct approach to the preparation of the pyrrolidine aldehyde from N-p-toluenesulphonyl proline. The Rosenmund reaction was tried in these laboratories but failed to give any of the required product. The reduction using lithium tri-t-butoxyaluminium hydride appeared attractive as published yields (50 - 60%) for this reaction were reasonable, and the reagent was simple to prepare. The best conditions, as found by Brown and Subba Rao (61) were to use diglyme as the solvent and to carry out the reaction at dry ice temperature.

The acid chloride was prepared from the N-p-toluenesulphonyl proline using thionyl chloride, and the crude crystalline material was reduced without purification, other than removal of excess reagent, at - 78° in diglyme. To minimise over-reduction the reductant was added to the solution of acid chloride. The work-up proved puzzling. Diglyme is infinitely miscible with water, and the aldehyde was expected to have a very low solubility in water, so the reaction mixture was added to a large excess of water and the precipitate of aluminium salts and hopefully, aldehyde, collected by centrifugation. The precipitate was extracted with ether to give a small quantity of an oil which showed an absorption at 1730 cm^{-1} corresponding to the aldehydic carboxyl group, and which gave a 2,4-dinitrophenyl hydrazone. The centrifugate was then concentrated, when crystals, of the 1-(p-toluenesulphonyl)-pyrrolidine-2-aldehyde separated, in 40% yield. The infra-red spectrum, particularly the aldehydic absorption at 1730 cm^{-1}, and the analysis of the 2,4-dinitrophenylhydrazone served to identify the compound.

The behaviour of the aldehyde in being found in the aqueous centrifugate was totally inexplicable as it is insoluble in aqueous diglyme of the same concentration. The aldehyde was contaminated with about 8.5% of a substance, probably aluminium oxide, that was insoluble in pyridine. This figure is of the same order as that required by the aluminium salt of the aldehyde hydrate (11.8%), but there is no reason to believe that this compound would be soluble, let alone stable in the aqueous solution.

The low yield of aldehyde that was obtained by this method suggested that an alternative should be sought, and so the various oxidative routes to aldehydes were considered. It seemed preferable to oxidise the alcohol, which could be prepared from the acid by reduction, rather than a derivative, whilst dimethylsulphoxide was the reagent of choice because of the specificity of the oxidation. Of the several "activating" agents that have been studied in this reaction dicyclohexylcarbodiimide has been reported to give the most satisfactory yields of aldehyde. Pfitzner and Moffatt, who originated the method, claim yields of up to 90% in favourable cases (70, 71).

This method required the production of the alcohol, 1-(p-toluenesulphonyl)-2-hydroxymethylpyrrolidine (XXVIII).

This was accomplished by the direct lithium aluminium hydride reduction of the acid XXIII, but a substantially better overall yield (82% against 68%) was obtained by reducing the methyl ester (XXVII), which could be prepared in high yield (94 - 97%) by refluxing N-p-toluenesulphonylproline in methanol with an acid catalyst. Witkop and collaborators (72) had prepared the alcohol in a similar fashion but had used diazomethane to prepare the ester and lithium boro - hydride for the reduction. The product that was obtained by the lithium hydride reduction of the methyl ester had very similar properties to the alcohol obtained by Witkop, and was further characterised by the formation of a crystalline acetate $C_{14}H_{19}NO_4S$, m.p. 59.5 - 60°.

The oxidation of the alcohol, as described by Pfitzner and Moffat (70), was effected by a mixture of dimethylsulphoxide, which may also be present as the solvent, and a large excess of dicyclohexylcarbodiimide together with half - a-mol. of a moderately strong acid catalyst. They found that pyridinium trifluoro-acetate gave the best results as catalyst, closely followed by o-phosphoric acid. The solvent did not necessarily need to be pure dimethylsulphoxide, as the use of up to 90% of benzene was found to give satisfactory results. The reaction took place at room-temperature and required a few hours to go essentially to completion, using o-phosphoric acid, and several hours using pyridinium trifluoro-acetate. The by-products of the reaction were dimethylsulphide and dicyclohexylurea, and at the end of the reaction the excess dicyclohexylcarbodiimide was converted into the urea by reaction with oxalic acid. The aldehyde was then isolated.

When this reaction was first carried out on 1-(p-toluenesulphonyl)-2-hydroxymethylpyrrolidine, pyridinium trifluoro-acetate was used as the catalyst, but the aldehyde obtained was very impure. A better, though still impure product was obtained when o-phosphoric acid was substituted.

The reaction did not appear to commence immediately on mixing all the necessary compounds together, but after a few minutes a copious precipitate of dicyclohexylurea began to form as a thick gel, with the evolution of a considerable amount of heat. The high viscosity of the gel made cooling, which was imperative at this stage to prevent decomposition, very difficult, particularly when more than a few grams of alcohol were being oxidised. This problem was overcome by adding 50% benzene as a diluent. The mixture was left overnight at room-temperature and the excess dicyclohexylcarbodiimide destroyed by the addition of oxalic acid. After filtration of the urea the aldehyde was extracted into benzene, the dimethylsulphoxide removed by washing with water and the solvent removed to give the crude aldehyde.

Purification was effected by dissolving the crude aldehyde in dry methanol, when on cooling crystals of the methyl hemi - acetal separated in yields of about 70% on the alcohol. No catalyst was necessary, but quicker deposition occurred if the solution was seeded. This compound was essentially stable, although samples which had been pumped out for some time showed the presence of free aldehyde. Analysis gave the formula as $C_{13}H_{19}NO_4S$ and the infra-red and proton magnetic resonance spectra clearly showed that the compound was the hemi-acetal and not the acetal, particularly the hydroxyl absorption at 3450 cm^{-1}.

The aldehyde was regenerated by shaking an ethereal solution of the hemi-acetal with dilute hydrochloric acid. Concentration of the solvent gave crystalline 1-(p-toluene-sulphonyl)-pyrrolidine-2-aldehyde in yields of about 90 - 95% on the hemi-acetal, that is 62 - 65% on the alcohol.

The aldehyde, $C_{12}H_{15}NO_3S$, showed the characteristic carboxyl bond at 1730 cm^{-1}, and was characterised as its 2,4-dinitrophenylhydrazone m.p. 181 - 182°, which was identical by mixed melting point to that given by the aldehyde prepared by reduction of the acid chloride.

The aldehyde was optically active, with $[\alpha]_D$ 160° in chloroform.

An interesting impurity was noted in one batch of aldehyde prepared by this method, when the products of reaction with vinyl magnesium bromide were separated chromatographically. A quantity of a white crystalline substance, $C_{15}H_{22}N_2O_3$, which was shown to have been present originally in the aldehyde, was isolated and identified as dicyclohexylparabanic acid (XXVII).

The infra-red spectrum showed a strong carboxyl absorption at 1730 cm^{-1}, whilst two absorptions at 1255 cm^{-1} and 896 cm^{-1} suggested the presence of a substituted cyclohexyl ring system. The proton magnetic resonance spectrum supported this, two multiplets being found at τ6.05 and τ8.2, integrating in the ratio 1 : 11.8. The mass spectrum showed the molecular ion at m/e 278, the base peak at m/e 197, with other strong peaks at m/e 115, 83, 67 and 55.

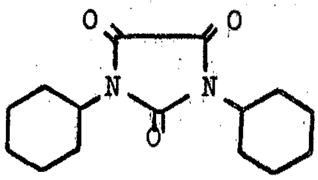
This evidence suggested strongly that the compound was a cyclohexylamide, the mass spectra of which show a very pronounced M - 81 due to the loss of the ring (68·), in this case giving rise to the base peak, and that it was in fact dicyclohexylparabanic acid. This has been prepared by Ulrich and Sayigh (73), who reported a melting point of 174 - 175° (found 173 - 174°), and an infra-red absorption peak at 1730 cm^{-1}.

The dicyclohexylparabanic acid must have arisen by reaction of one molecule of oxalic acid with two molecules of dicyclohexylcarbodiimide, one of which acted as a dehydrating agent, notwithstanding the claim in the literature (74) that oxalic acid is converted quantitatively to a mixture of carbon monoxide and carbon dioxide by carbodiimides. A very similar reaction, in which malonic acids were treated with two mols. of various carbodiimides to synthesise a series of substituted barbituric acids has been reported (75).

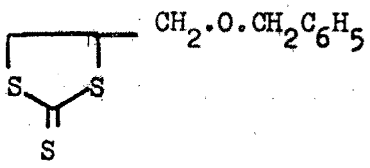
The formation of this impurity was simply overcome by decomposing the excess carbodiimide with aqueous oxalic acid, although this took a little longer as the reaction mixture was no longer homogeneous.

2.3 The synthesis of cis-1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-1,2-epoxy-3-benzyloxypropane.

The first method proposed for the preparation of the lyxo-1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-1,2-epoxy-3-



XXVII



XXVIII

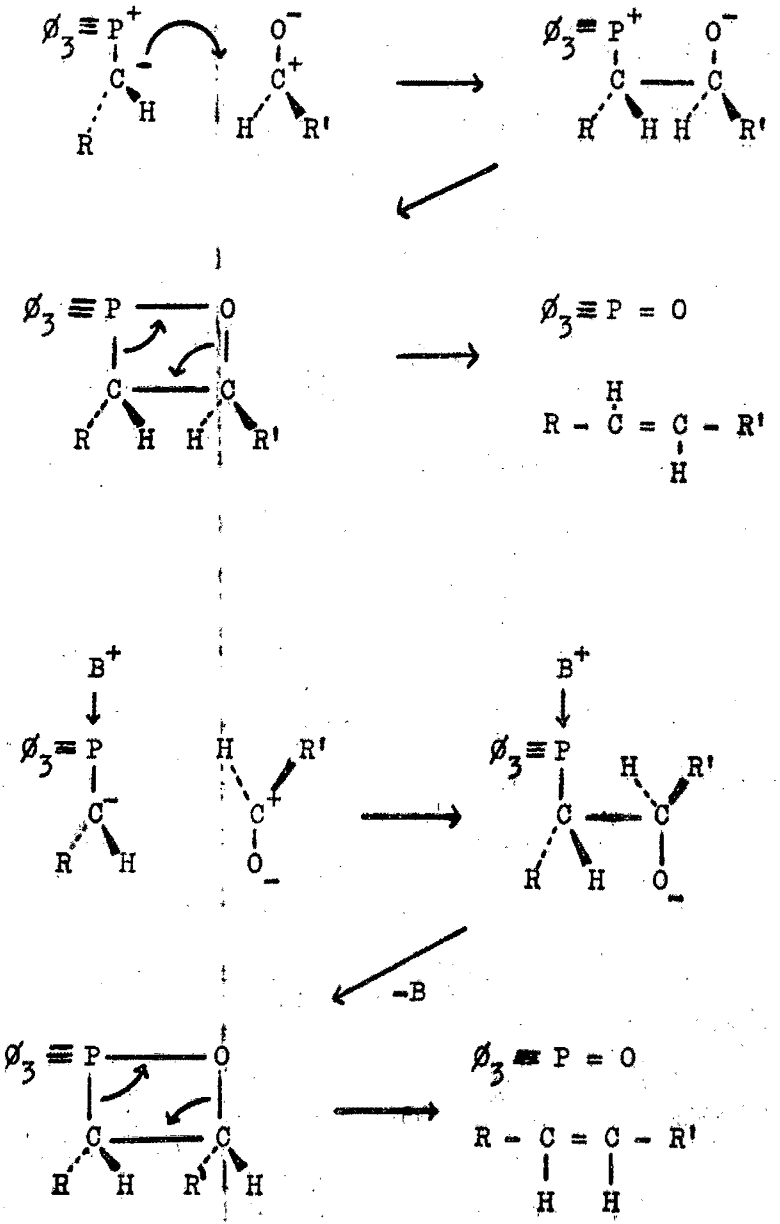


Fig. 13

epoxides by per-acids is increased by electron donating and decreased by electron withdrawing substituents (77).

Terminal olefins react slowly, and as the benzyloxy-group has a -I effect the oxidation of allyl benzyl ether was expected to be slow. The reaction was allowed to proceed at room-temperature for twenty-one days, when the crude epoxide was isolated, and found to be 55% pure (by reaction with hydrochloric acid in dioxane).

The epoxide was reacted without further purification with potassium methyl xanthate to give the 4-benzyloxymethyl-1,3-dithiolane-2-thione, which was isolated as an intensely yellow oil by chromatography on alumina in 56% yield. All attempts to crystallise the product were in vain.

The structure of the compound, $C_{11}H_{12}OS_3$ was confirmed by its spectra which showed the presence of a benzyl ether, whilst the ultra-violet spectrum showed an absorption at 316 m , ε 14,600. Further proof of the structure was provided by conversion of the dithiolanethione into 2-hydroxymethyl-1,4-dithiaspiro [4, 5] decane m.p. 59 - 60° by reduction to the dithiol with lithium aluminium hydride, debenzylation with sodium in liquid ammonia to give 2,3-dimereaptopropanol and reaction of this with cyclohexanone; this compound proved identical with a sample of the mercaptole m. p. 59.5 - 60.5° prepared from genuine 2,3-dimercaptopropanol.

Immediately subsequent to the completion of this section of the work the results of Anisuzzaman and Owen became available (78). These workers prepared the 4-benzyloxy -

methyl-1,3-dithiolane-2-thione, in crystalline form, by reacting 1-benzyloxy-2,3-epoxypropane with potassium methyl xanthate, and similarly converted it into 2-hydroxymethyl-1,4-dithiaspiro[4, 5] decane. The ultra-violet absorption spectrum found by them for 4-hydroxymethyl-1,3-dithiolane-2-thione, λ_{max} 317nm , ε 14700, agreed very closely with that found for the 4-benzyloxymethyl derivative.

2.3.2 The synthesis of 1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-3-benzyloxyprop-1-ene.

The olefin, 1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-3-benzyloxyprop-1-ene, (XXV) was required in the cis - configuration. The most frequently used methods for the preparation of cis-olefins have been the cis-hydrogenation of the corresponding acetylenic compound (79), isomerisation of the corresponding trans-olefin (80), and by way of the Wittig reaction (81). The preparation of the necessary acetylene appeared to be difficult, so this approach was not pursued, whilst the isomerisation of the trans-olefin on irradiation with ultra-violet light would not be feasible in the present case because of the sensitivity of the sulphonamide to U.V. irradiation, with fissioning occurring to give the free amine (82). The Wittig reaction, however, appeared to offer an attractive method of preparing the olefin.

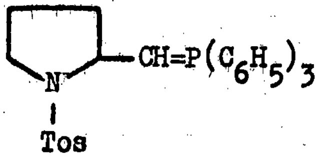
The Wittig reaction involves the condensation of an aldehyde or ketone with an alkylidenephosphorane, or ylid,

$C_6H_5.CH_2.O.CH = P(C_6H_5)_3$

XXIX

$C_6H_5.CH_2.O.CH_2-\overset{+}{P}(C_6H_5)_3\ \ I^-$

XXX



XXXI

$C_6H_5.CH_2.O.CH_2CHO$

XXXII

Fig. 14

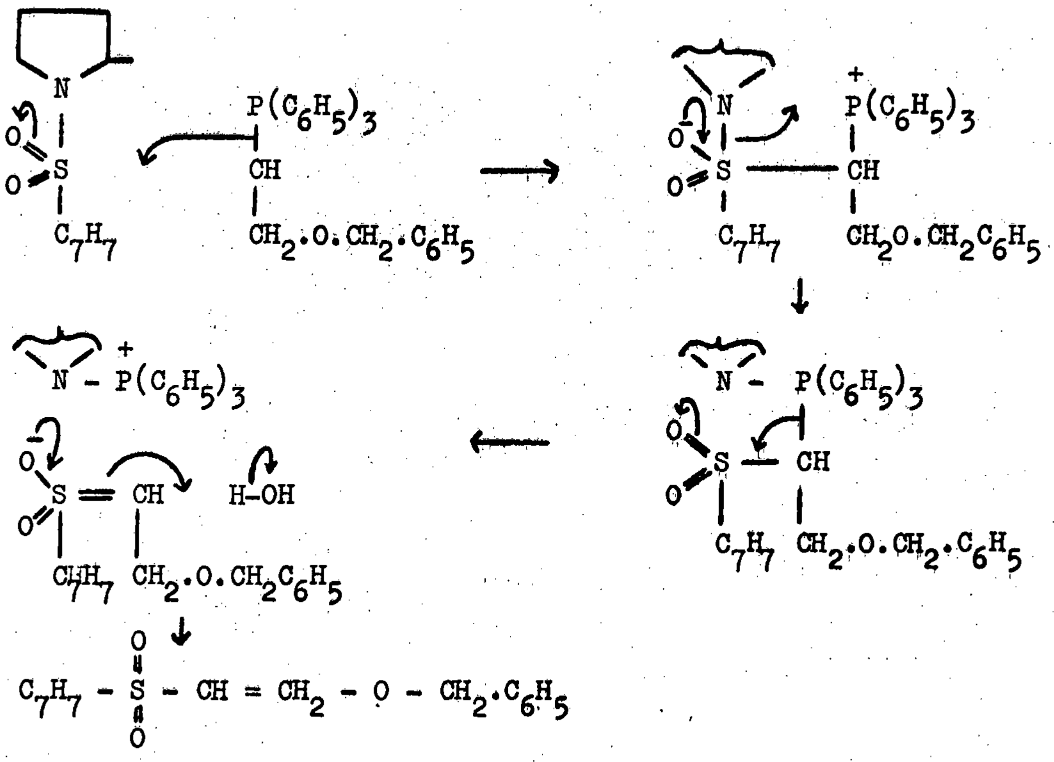


Fig. 15

to give the olefin and phosphine oxide. By suitable choice of conditions the formation of either the cis- or the trans- isomer may be favoured to the almost complete exclusion of the other. These conditions have been studied and listed by Bergelson and Shemyakin (81), who found that the formation of the cis-isomer relative to the trans- was promoted by performing the reaction in a polar aprotic solvent and by the presence of Lewis bases, for example iodide ions or amines, although the addition of Lewis bases retarded the overall rate of reaction.

The mechanism of the reaction is shown in fig. 13. The initial step is the reaction of the phosphorane and the aldehyde to give a betaine. In a non-polar solvent and in the absence of Lewis base the relative orientation of the reacting groups is controlled by their dipole-dipole interaction and by the mutual repulsion of the substituents, leading to the threo-betaine. Elimination of the phosphine oxide via the four-membered cyclic intermediate gives the trans-olefin.

When a Lewis base is added it interacts with the phosphorous atom of the phosphorane, making it less electrophilic and sterically less accessible. The dipole-dipole interaction as the groups react then has less effect on the orientation of the groups; the erythro-betaine forms preferentially, giving the cis-olefin. If the reaction is carried out in a polar aprotic solvent the dipole-dipole interaction is shielded by the solvation of the phosphorous and carbonyl oxygen atoms, again leading to the preferential formation of the erythro-betaine, and cis-olefin.

Bergelson and Shemyakin found that almost complete formation of the cis-olefin could be attained by performing the reaction in the presence of iodide ions, and using dimethylformamide as the solvent.

The preparation of 1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-3-benzyloxyprop-1-ene (XXV), might be accomplished in two ways by the Wittig reaction; by reacting 1-(p-toluenesulphonyl)-pyrrolidine-2-aldehyde (XXIV) with 2-benzyloxyethylidene-triphenylphosphorane (XXIX), or by reacting triphenyl-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]methylenephosphorane (XXXI) with 2-benzyloxy-ethanal (XXXII). The reaction conditions are usually chosen so that there is an excess of the ylid (83), so for greatest economy the less accessible portion of the molecule is reacted as the aldehyde. In the present case the pyrrolidinesulphonamide was the less accessible part, and so the first pair of reactants were required. The aldehyde had been synthesised from L-proline, and the ylid would be prepared by the action of base on 2-benzyloxyethyltriphenylphosphonium iodide (XXX), which would also provide the iodide ions needed to function as the Lewis base.

2.3.2.1 The preparation of 2-benzyloxyethyltriphenylphosphonium iodide.

The starting material for the preparation of 2-benzyloxyethyltriphenyl phosphonium iodide (XXX) was ethylene glycol, which was converted into its monobenzyl ether by a method similar to that of Bennet (84). Benzyl chloride was reacted with a solution of the mono-sodium salt of ethylene glycol in a large excess of the glycol (to minimise di-ether formation). The 2-benzyloxyethanol was isolated in 80% yield, and converted to 1-benzyloxy-2-iodo-ethane by two routes. The first was to prepare 1-benzyloxy-2-chloroethane b.p. $127^{\circ}/20$ m.m. by reaction with thionyl chloride and dimethylaniline in 67% yield; (this method also being due to Bennet). Reaction of the chloro-compound with sodium iodide in acetone gave the iodo-compound, b.p. 100 - $110^{\circ}/5$ m.m. in 49% yield, but this was contaminated with unreacted chloro-compound, as shown by gas-liquid chromatography and the analysis, which was consistent with a mixture of 94% iodo-compound and 6% chloro-compound. Complete conversion was not attained even with extended reaction times, and the two compounds did not separate cleanly on distillation.

A simpler method, giving the iodo-compound in much higher yield was to prepare the 2-benzyloxyethyl-p-toluenesulphonate, m.p. 43 - 43.5° by reacting the alcohol with p-toluenesulphonyl chloride in pyridine. This ester, $C_{16}H_{18}O_4S$, obtained in 80% yield, was allowed to react with sodium iodide in acetone, to give the 1-benzyloxy-2-iodoethane in almost quantitative yield.

Refluxing the iodo-compound with triphenylphosphine in benzene gave 2-benzyloxy-ethyl triphenyl phosphonium iodide as an oil which crystallised on shaking with diethyl ether.

The yield was 90.3%.

The salt, $C_{27}H_{26}OPI$, showed absorptions in the infra-red corresponding to benzene rings (1605 cm^{-1}, 735 cm^{-1} and 690 cm^{-1}) and to an ether linkage (1110 cm^{-1}).

2.3.2.2. The preparation of 1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-3-benzyloxyprop-1-ene.

The usual approach adopted when performing a Wittig reaction is to mix the aldehyde with a solution of the **ylid,** prepared, generally without isolation, by the action of some suitable base on the phosphonium salt. In the present case, however, this approach was totally unsuccessful.

Sodium methoxide was chosen as the base. When this was added to a solution of 2-benzyloxyethyl-triphenyl phosphonium iodide in dimethylformamide an intensely yellow colouration appeared immediately, but this changed to a dark red within a few seconds. The yellow colour was probable due to the ylid, this being typical for an unconjugated ylid. No discharge of the red colouration occurred when the aldehyde was added, as would have been expected if reaction had taken place, and the only products isolated were traces of triphenylphosphine and triphenylphosphine oxide.

The lack of any useful product, and the colour-change suggested that decomposition of the ylid had occurred, probably by the β-elimination of the benzyloxy-group to give the vinyl phosphonium salt (fig. 14). Similar eliminations have been observed when 2-bromo and 2-methoxy-ethyl triphenyl phosphonium salts have been treated with base (85, 86).

To overcome this difficulty the base was added to a mixture of the aldehyde and the phosphonium salt, so that the aldehyde could react with the ylid as it was formed. Chromatography of the crude products on neutral alumina yielded crystals of the required product, 1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-3-benzyloxyprop-1-ene (XXV) in 10% yield. The compound, $C_{21}H_{25}NO_3S$, exhibited absorptions in the infra-red corresponding to the sulphonamide group (at 1325 cm^{-1} and 1145 cm^{-1}), an ether linkage (at 1090 cm^{-1}) and both mono- and di- substituted benzene rings (746 cm^{-1} and 815 cm^{-1} respectively). The proton magnetic resonance spectrum confirmed the presence of the above groups, and showed an absorption at τ 4.40 arising from the olefinic protons. This signal was a broad multiplet, however, and it was not possible to extract the value for the spin-spin coupling constant between the two olefinic protons, and hence it was not possible to specify the stereo-chemistry about the double bond; (the value of the coupling constant, J, is 11 to 19 for <u>trans</u>-olefins, and 5 to 14 for <u>cis</u>-olefins (87)).

Further elution of the column led to the isolation of an oil, identified as 2-benzyloxyethyl-p-toluenesulphone (XXXIII), in 6% yield. The compound, $C_{16}H_{18}O_3S$, having an infra-red spectrum indicative of the presence of a sulphone group (1315 cm^{-1} and 1145 cm^{-1}), an ether group (1080 cm^{-1})

and both mono- and p-disubstituted benzene rings (815 cm^{-1} and 735 cm^{-1} respectively). The proton magnetic resonance spectrum showed nine aromatic protons (τ 2.5 and 2.8), aromatic methyl group at τ 7.61, a singlet at τ 5.62 due to the benzyl methylene protons and an AA'BB' pattern centred at τ 6.38 arising from the ethylene protons. The spectrum was very similar to that of 2-benzyloxyethyl-p-toluenesulphonate, with a shift of 0.3 τ in the signal due to the ethylene protons.

A possible mechanism for this unexpected reaction is given in Fig. 15. The ylid is envisaged as interacting with the polarised S – N bond of the sulphonamide, to give the sulphone and an amino-phosphonium salt via a four-membered intermediate. The amino-phosphonium salt would then be hydrolysed during the aqueous workup to triphenylphosphine oxide and the amine salt (88).

The yield of the required product is reduced in two ways by this side-reaction; by consuming ylid, and by fissioning the sulphonyl group from olefin that has been formed to give an amino-olefin that would be water soluble, and hence lost. A further important side reaction encountered in applying the Wittig reaction to an aliphatic aldehyde is the aldol condensation catalysed by the strongly basic ylid, and in the present case by the base needed to generate the ylid. This was probably the most significant side-reaction, and its importance was underlined by the behaviour of the aldehyde on reaction with other basic reagents, where yields were poor on reaction with the strongly basic Grignard reagents, but much higher on reaction with the far less basic anion from triethylphosphonoacetate.

The alternative approach to the olefin of reacting the ylid (XXXl) with 2-benzyloxy-ethanal would still suffer from the problems of aldehyde self-condensation and reaction of the ylid with the sulphonamide, and was therefore not attempted.

2.3.3 Attempts at the preparation of *trans*-1-[1'-(*p*-toluenesulphonyl)-pyrrolidin-2'-yl]-3-benzyloxyprop-1-ene

The very low yield given by the Wittig reaction, and the uncertainty about the configuration of the olefin obtained suggested that an alternative route to the *cis*-epoxide (XXVl) should be sought.

A number of methods of preparing the corresponding *trans*-olefin (XXXIV) appeared feasible; this could be converted into the *cis*-epoxide by *cis*-hydroxylation using potassium permanganate or osmium tetroxide as the oxidising agent (89) to give the *threo*-glycol (Fig. 16). Formation of the mono-tosylate followed by basification would give the *cis*-epoxide by intramolecular elimination of the sulphonate group, with inversion occurring during the elimination (90).

2.3.3.1 The attempted preparation of 1-[1'-(*p*)-toluenesulphonyl)-pyrrolidin-2'-yl]-3-chloro-prop-1-ene.

The first approach to *trans*-1-[1'-(*p*-toluenesulphonyl)-pyrrolidin-2'-yl]-3-benzyloxy-prop-1-ene that was envisaged

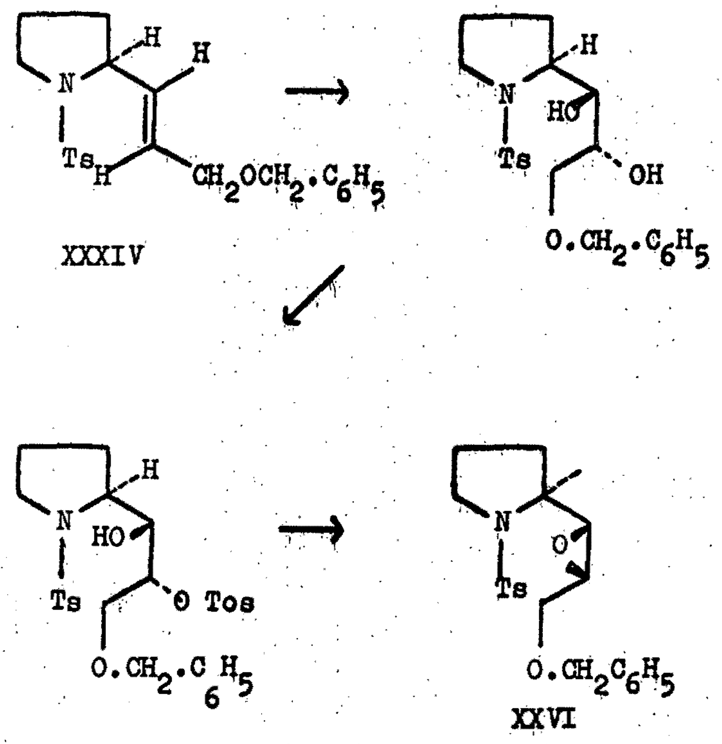

H
H
N
Ts
H
CH2OCH2.C6H5
XXXIV
H
N
HO
Ts
OH
O.CH2.C6H5
H
N
HO
Ts
O Tos
O.CH2.C6H5
N
O
Ts
O.CH2C6H5
XXVI

Fig. 16

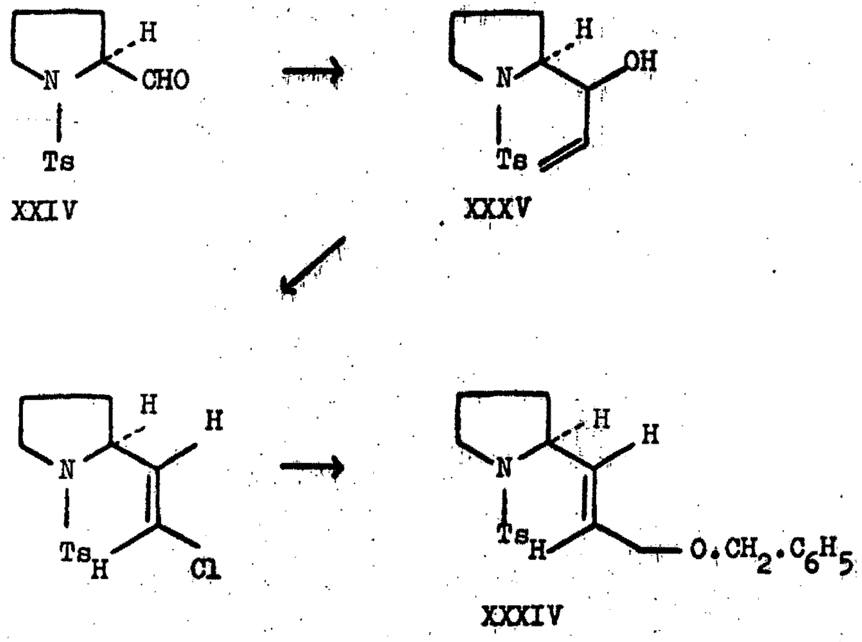

H
N
CHO
Ts
XXIV
H
OH
N
Ts
XXXV
H
H
N
Ts
H
Cl
H
H
N
Ts
H
O.CH2.C6H5
XXXIV

Fig. 17

was to prepare the allylic carbinol (XXXV), by reaction of the aldehyde (XXIV) with vinyl magnesium bromide. This would be subjected to an allylic rearrangement and then benzylated to give the required product.

The Grignard reaction has been used very widely for the preparation of carbinols, but it is only comparatively recently that allylic alcohols have been successfully prepared by this method. The difficulty lay with the instability displayed by most of the vinyl magnesium halides in diethyl ether solution. It has been found however, chiefly as a result of the work of Normant (91) that these reagents may be prepared in high yield in certain other solvents, particularly tetrahydrofuran, and that they give reasonably good yields of carbinols on reaction with aldehydes and ketones, provided that the reagent is taken in excess, and that the reaction temperature is kept low (69).

Vinyl magnesium bromide was prepared from vinyl bromide (92) and allowed to react with the aldehyde (XXIV). The carbinol was liberated from the magnesium salts by addition of aqueous ammonium chloride (the use of mineral acid would bring about partial rearrangement), extracted into ether and isolated by chromatography on a neutral alumina column. Elution of the column with ether gave the 1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-prop-2-en-1-ol, m.p. 45°, in 20% yield. The compound $C_{14}H_{19}NO_3S$, crystallised on removal of the eluting solvent, but could not be induced to recrystallise from a solvent.

Confirmation that the compound was the secondary allylic alcohol, and that rearrangement had not occurred during the workup was provided by the proton magnetic resonance spectrum, which showed a complex multiplet at τ 4.6, arising from three olefinic protons. Furthermore hydrogenation of the allylic carbinol over Adams catalyst gave a compound $C_{14}H_{21}NO_3S$, m.p. 103 - 104°, which showed the presence of an ethyl group in its P.M.R. spectrum.

The yield of product from the Grignard reaction was disappointingly low, probably as a result of self-condensation of the aldehyde catalysed by the basic Grignard reagent.

Forming the allylic carbinol creates a second assymmetric centre in the molecule. While one stereoisomer might be expected to predominate this is of little significance, however, as in the allylic rearrangement this extra assymmetry would be destroyed.

The allylic rearrangement may be effected in a number of ways. Simple treatment of the secondary allylic carbinol with acid would give an equilibrium mixture of the two isomers, the primary alcohol predominating (88). The isomers would have to be separated, and the yield after isolation would probably not be good. The trans-isomer of the primary alcohol would be formed exclusively, as it would be the thermodynamically most stable form. A better method appeared to be one based on the studies of

W. G. Young and co-workers (93), who treated the isomeric methyl allyl alcohols with a dilute solution of thionyl chloride in diethyl-ether and found that they were converted almost completely into the corresponding rearranged methyl allyl chlorides. They proposed a mechanism based on rigidly oriented undissociated ion-pairs, with the hydrogen chloride liberated during the reaction being complexed by the ether acting as a Lewis base, preventing any acid catalysed rearrangement of the allylic alcohol. The *trans*-isomer would be expected from this reaction.

The primary allyl chloride could be converted into the primary benzyl ether by reaction with sodium benzylate. A further allylic rearrangement could occur during this reaction, but it has been found that provided the conditions favour SN_2 rather than SN_1 reaction then very little rearrangement is observed (94).

When ethereal thionyl chloride was reacted with 1-[1'-(*p*-toluenesulphonyl)-pyrrolidin-2'-yl]-prop-2-ene-1-ol a mixture of products resulted. Two substances were isolated by fractional crystallisation, one m.p. 70 - 72° in small quantity, and the other, $C_{14}H_{18}NO_2SCl$ m. p. 122 - 123° which was identified as 1-[1'-(*p*-toluenesulphonyl)-pyrrolidin-2'-yl]-1-chloroprop-2-ene, that is the unrearranged chloro-compound, on the basis of its proton magnetic resonance spectrum, which showed a multiplet at τ 4.7 arising from three olefinic protons.

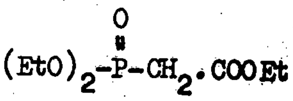
In view of this non-specificity of rearrangement, and of the poor yield of allylic carbinol this approach to the trans-olefin was abandoned.

2.3.3.2 The preparation and reduction of ethyl 3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-prop-2-enoate.

The next approach to the synthesis of the trans-olefin (XXXIV) that was considered was the reduction of the α, β-unsaturated ester (XXXVII) to the unsaturated alcohol (XXXVIII), which could then be benzylated (Fig. 18).

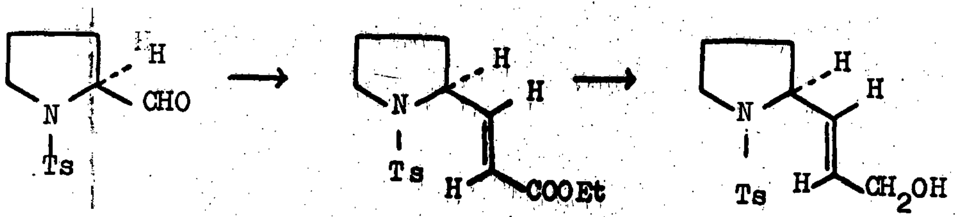
The preparation of allylic alcohols by reduction is complicated by the simultaneous reduction of the double bond. An isolated double bond is stable to lithium aluminium hydride, but when conjugated with a carbonyl group it is polarised and may be attacked, to give ultimately the saturated alcohol. While the yields of unsaturated alcohol in certain cases have been satisfactory using lithium aluminium hydride, particularly if the temperature had been kept low (95), better yields have been claimed when partially deactivated lithium aluminium hydrides were used. The deactivation was effected by reacting, for example, one mol. of ethanol with each mol. of hydride, to give an ethoxy-lithium aluminium hydride (96). Other alcohols have been employed for this purpose but ethanol was chosen in the present case.

The trans-α, β-unsaturated ester (XXXVII) was prepared by reacting 1-(p-toluenesulphonyl)-pyrrolidine-2-aldehyde with the anion derived from triethylphosphono-acetate (XXXVI).



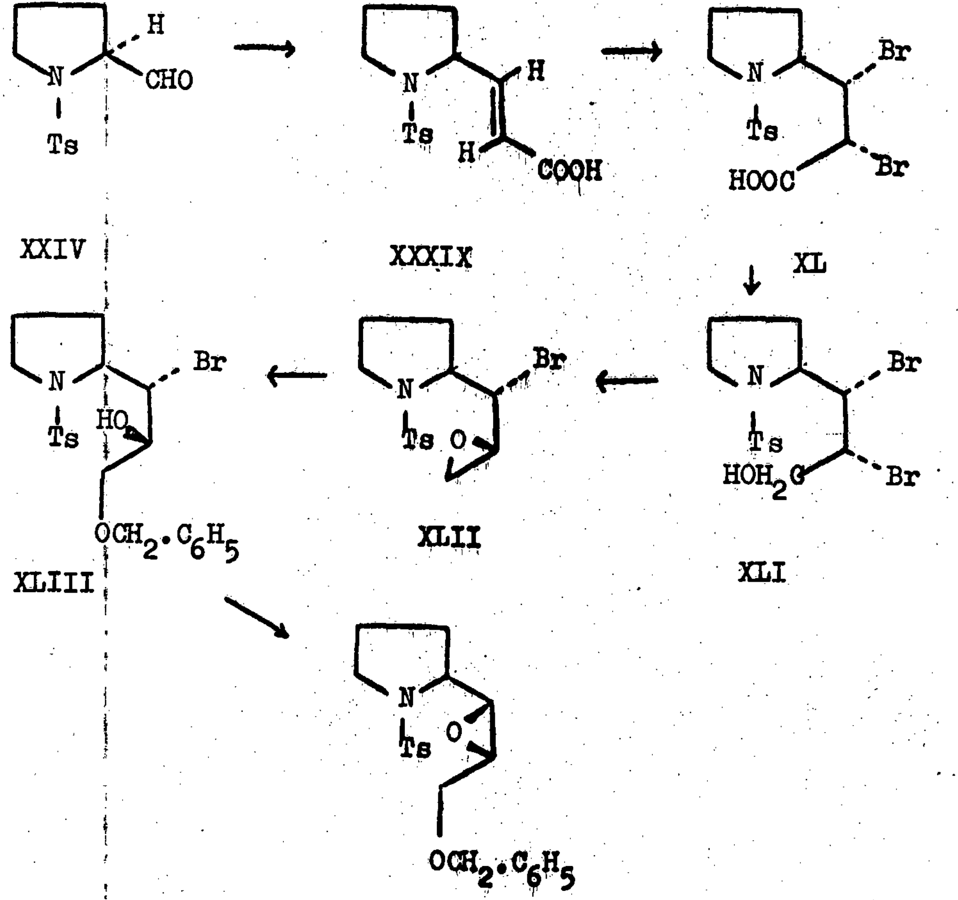
$(EtO)_2-\overset{O}{\overset{\|}{P}}-CH_2.COOEt$

XXXVI



XXIV

Fig. 18



XXIV

XXXIX

XL

XLI

XLII

XLIII

XLIV

Fig. 19

This reaction, extensively studied by Wadsworth and Emmons (97), is very similar to the Wittig reaction, which could also have been used to prepare the ester, but has the advantages that the anion is much more reactive than the required ylid, and that the work-up is simpler. As **the anion** is less basic than compounds reacted previously with the aldehyde less self-condensation and enolisation would be expected, giving a better yield of optically purer product.

The stereochemistry of the product of this reaction has been reported to be invariably trans, irrespective of the reaction conditions (98).

Triethylphosphono-acetate was prepared from triethylphosphite by the Arbuzov reaction (99), converted into the anion with sodium hydride and reacted with (L-1-(p-toluenesulphonyl)-pyrrolidine-2-aldehyde to give the L-ethyl 3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-prop-2-enoate in 65% yield. The compound, $C_{16}H_{21}NO_4S$, m.p. 62 - 64° had $[\alpha]_D$-132° in chloroform and showed a strong absorption at 1720 cm^{-1} in the infra-red spectrum, arising from the ester group. The proton magnetic resonance spectrum showed the presence of two olefinic protons, at τ 5.99 and 6.82, J = 15 c/s, indicating that the compound was the trans - isomer. Hydrogenation over Adams catalyst gave a dihydro-derivative, $C_{16}H_{23}NO_4S$, m.p. 52 - 53°.

A less satisfactory method of preparing the α, β-unsaturated ester was by converting the aldehyde into the α, β-unsaturated acid using the Knoevenagel-Doebner reaction (see section 2.3.4.2) which could be readily esterified. Racemisation occurred, however, during preparation of the acid and the Wadsworth-Emmons procedure was preferred.

The reduction of the α, β-unsaturated ester was not, however, a successful method of preparing the unsaturated alcohol.

When ethoxy lithium aluminium hydride was used as the reductant, under mild conditions a number of products were noted on thin-layer chromatography. Chromatography on neutral alumina gave four fractions.

The first was a crystalline compound, $C_{14}H_{17}NO_3S$, m.p. 127 - 128°, isolated in 2% yield and identified as trans-3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propenal. The infra-red spectrum showed a strong absorption at 1690 cm^{-1}, typical for an α,β'-unsaturated aldehyde while the proton magnetic resonance spectrum showed absorptions, in addition to those arising from the N-tosyl-pyrrolidinyl group, corresponding to two olefinic protons, at τ 3.20 and τ 3.79, J = 16 c/s and to an aldehydic proton, τ 0.44, coupled to the olefinic proton at τ 3.79 with J = 7 c/s. This structure was confirmed by the formation of a red 2,4-dinitrophenylhydrazone m.p. 103°.

The second fraction, an oil which could not be crystallised was identified as the required product, 3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-prop-2-en-1-ol. The yield was generally only a trace, but in one instance 20% was realised. The oil, which could not be induced to crystallise, analysed to $C_{14}H_{19}NO_3S$ and showed a strong hydroxyl absorption at 3500 cm^{-1} in the infra-red spectrum, whilst the proton magnetic resonance spectrum showed a complex absorption at τ 4.25 corresponding to two olefinic protons. The compound was reacted with acetic anhydride in pyridine to give an acetate, isolated as an oil analysing to $C_{16}H_{21}NO_4S$, and which showed absorptions in the infra-red spectrum corresponding to a ester group (at 1750 cm^{-1}) and an acetate group (at 1240 cm^{-1}). The complex multiplet in the proton magnetic resonance spectrum was found at τ 4.21, and the acetate methyl group gave a singlet at τ 7.95.

The third and fourth fractions were gums, with the bulk of the reaction product being found in the fourth fraction. Judging by their proton magnetic resonance spectra both were mixtures of similar compounds. They were not examined further and probably arose by 1,4-addition of the alcohol across the unsaturated aldehyde and ester, or by any one of a number of condensation reactions possible under the basic conditions.

2.3.4 The preparation of cis-1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-1,2-epoxy-3-benzyloxypropane

The synthesis of cis-1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-1,2-epoxy-3-benzyloxypropane that finally proved successful is outlined in Fig. 19.

The **starting** material was the trans-α, β-unsaturated acid (XXXIX), accessible as the racemate by performing the Knoevenagel-Doebner reaction on 1-(p-toluenesulphonyl)-pyrrolidine-2-aldehyde (XXIV). Bromination would give a mixture of two racemic erythro-dibromo-acids, that is the ribo- and lyxo- forms. After separation of the required ribo-isomer (XL) and reduction of the acid group to an alcohol (XLI) reaction with base would give the arabino-bromo-epoxide (XLII), with inversion occurring at C-2. The use of a basic reducing agent, for example lithium aluminium hydride, would give the epoxide directly, the alkoxide ion formed on reduction immediately replacing the bromine atom. This approach has been widely employed to prepare epoxides from α-halogeno-aldehydes and ketones, (100) and in a few cases from α-halogeno-acids and esters (101) but as the reduction of an acid by lithium aluminium hydride is slower than the reduction of an aldehyde or ketone so the possible side reactions, such as reduction of epoxide as it is formed, or hydrogenolysis of the halogen groups, would assume greater importance. For this reason the formation of the bromo-epoxide (XLII) was carried out in two steps by reducing the dibromo-acid with the acidic reagent diborane, followed by treatment with base.

Diborane reduces carboxylic acids rapidly and in high yield to the corresponding alcohols and is inert towards carbon-halogen bonds (102). No report has appeared, however, on the reduction of α,β-dihalogeno-acids by this reagent.

The first step in the reduction is the formation of a boronic ester with the evolution of hydrogen. The acidic diborane then attacks the basic or electron-rich carboxyl oxygen atom, and any reduction in the electron density on the oxygen atom by, for example, substitution of an α-halogen atom would be expected to reduce the rate of reduction. This is borne out by the inertness displayed by chloral towards reduction by diborane (103), where there are three chlorine atoms substituted α- to the carbonyl group. Thus the reduction of an α,β - dibromo-acid would be expected, and was found to be, a slow reaction.

The overall stoichiometry of the reaction is that one mole of acid is reduced by one mole of BH_3.

The next step, after treating the dibromo-alcohol (XLI) with base to form the bromo-epoxide (XLII) is the opening of the epoxide ring to introduce the terminal benzyloxy-group, to give the ether (XLIII).

The opening of 3-halogeno-1,2-epoxides with alcohols has been studied under conditions of both acid and base catalysis. Acid catalysis leads generally to attack by the alcohol on the epoxide ring carbon atom furthest from the halogen atom, i.e. the terminal carbon atom, to give the threo-1-alkoxy-2-hydroxy-3-halogeno-compound (104). This is contrary to the usual predominant attack on the secondary carbon atom of an un-halogenated terminal epoxide that is observed under the same conditions (105). Other electron-withdrawing groups such as trifluoromethyl show the same effect (106), and it has been suggested that attack on the carbon atom furthest from the substituent is favoured because the electron movement occuring when the terminal carbon-oxygen bond of the epoxide breaks is in the same direction as the pull exerted by the electron-withdrawing group.

Base catalysis under mild conditions yields the same bromohydrin-ether, although more slowly. With molar quantities of base the bromohydrin gives the epoxy-ether together with substantial quantities of products resulting from attack by the alcohol on the epoxy-ether (108).

In the present case acid catalysis was chosen for the opening of the 3-bromo-1,2-epoxide (XLII) with benzyl alcohol to give the bromo-hydrin (XLIII). This would then, on treatment with base, give the epoxy-ether (XLIV). Inversion would occur at C-3 on elimination of the bromine atoms, so the epoxide would have the _erythro_-configuration i.e. it would be the required _cis_-compound.

This series of reactions was carried out, initially using crotonic acid as a model (Fig.20) and then on _trans_-3-[1'-(_p_-toluenesulphonyl)-pyrrolidin-2'-yl]-prop-2- enoic acid (XXXIX), to give ultimately the required _cis_-1-[1'-(_p_-toluenesulphonyl)-pyrrolidin-2'-yl]-1,2-epoxy-3-benzyloxy-propane.

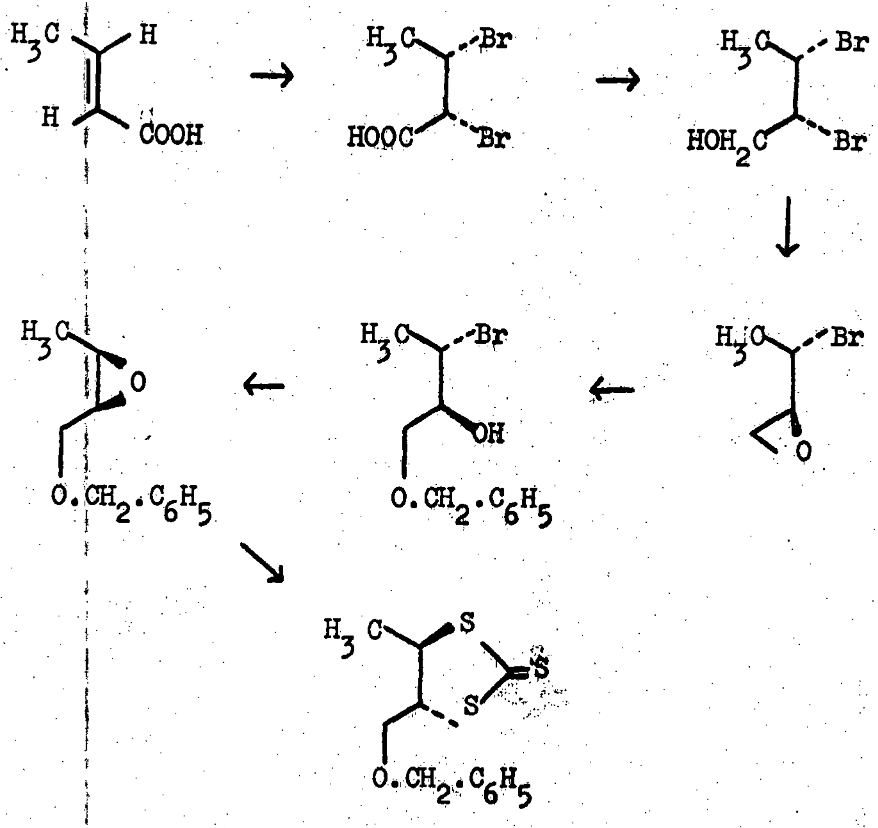
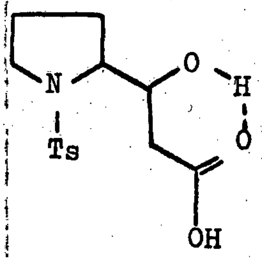
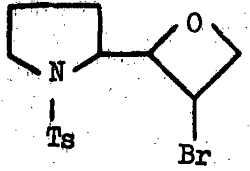


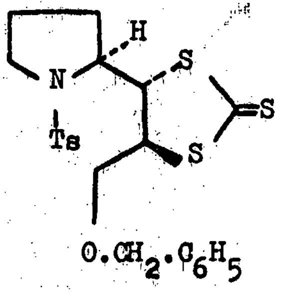
Fig. 20



XLV



XLVI



XLVII

2.3.4.1 The conversion of crotonic acid to *trans*-1-benzyloxymethyl-2-methyl-3,5-dithiolan-4-thione, *via* 1-benzyloxy-2,3-epoxybutane.

Crotonic acid was brominated to give *erythro*-2,3-dibromobutanoic acid, which was then reduced with diborane in tetrahydrofuran solution.

This reagent has been prepared in a great number of ways (109); the method chosen was that of reacting sodium borohydride with boron trifluoride etherate in diglyme solution, and sweeping the diborane formed into dry tetrahydrofuran. The concentration of the complex BH_3. T.H.F. formed was determined by measuring the volume of hydrogen liberated by reaction with water, and was typically of the order of 1M in BH_3. The yield was generally about 80%.

The reduction was effected with a fifty percent excess of diborane, at room-temperature, and was followed by observing the disappearance of the carbonyl band at 1720 cm^{-1} in the infra-red spectrum. Unreduced acid remained after 24 hours, but had reacted completely after 42 hours. The 2,3-dibromobutan-1-ol, $C_4H_8OBr_2$, m.p. 29 - 30^o (lit. value 31^o (110)), was isolated in 83% yield after recrystallisation from light petroleum at -78^o.

The slow reduction of the 2,3-dibromo-acid was checked by reacting 2,3-dibromo-3-phenylpropionic acid with diborane, when a similar slow rate was observed. The yield of recrystallised 1,2-dibromo-1-phenyl-propan-3-ol, $C_9H_{10}OBr_2$, m.p. 68 - 70^o (lit. value 74^o (111)), was 72%.

The formation of 1,2-epoxy-3-bromobutane was effected by refluxing the dibromo-alcohol with a 1.3 mols. of potassium hydroxide in methanol. The epoxide was isolated by vacuum distillation from a little unreacted alcohol in 76% yield. The use of an equimolar quantity of base gave an inferior yield of epoxide.

It was hoped to isolate the threo-1-benzyloxy-2-hydroxy-3-bromobutane obtained by opening the epoxide ring with benzyl alcohol using boron trifluoride as catalyst, but extensive decomposition occurred on attempted high vacuum distillation of the reaction products.

The benzyl alcohol was present in large excess, but would probably not interfere at later stages so the sequence of reactions was carried through to the preparation of the trithiocarbonate without isolation of the intermediate products.

The epoxide was treated with benzyl alcohol and a small amount of boron trifluoride, then reacted with methanolic potassium hydroxide to give the 1-benzyloxy-2,3-epoxybutane which on refluxing with an excess of potassium methyl xanthate gave an intensely yellow solution that yielded crystalline trans-1-benzyloxymethyl-2-methyl-3,5-dithiolan-4-thione in 54% yield from the 1,2-epoxy-3-bromobutane.

The compound, $C_{12}H_{14}OS_3$, m.p. 65 - 66° showed absorptions in the proton magnetic resonance spectrum arising from a methyl (at τ 8.40) and benzyloxy-(at τ 5.44 and

2.69) groups, in addition to a very complex multiplet (τ 5.5 to 6.4), from four protons. The structure was confirmed most convincingly by comparison of the ultraviolet spectrum with that of 1-benzyloxymethyl-2,4-dithiolan-3-thione (section 2.3.1.). The methyl derivative gave a band at 316nm, ε 15,300 with a shoulder at 298nm ε 12,000 and a weak band at 253nm, ε 1000. The spectrum of 1-benzyloxymethyl-2,4-dithiolan-3-thione had a band at 3.6nm, ε 14,600 with a shoulder at 298 m ε 11,700, together with the weak band at 250nm ε 700. Both showed bands at 212nm, due to the benzyl group.

The *trans* configuration of the substituents on the ring expected from a consideration of the stereochemical course of each reaction could not be confirmed. Overberger and Drucker (112) have assigned I.R. bands in the thione region (1000 - 1100 cm^{-1}) to *cis* and *trans*-1,2-dimethyl-2,5-dithiolan-4-thione, but in the present case the ether bands also fall in the same region so that no correlation could be made. The value of the spin-spin coupling constants between the two ring protons in the proton magnetic resonance spectrum, which might suggest which isomer was present, could not be extracted from the very complicated series of bands arising from the A_2BCX_3 nature of the system.

This series of reactions was then carried out on *trans*-3-[1'-(*p*-toluenesulphonyl)-pyrrolidin-2'-yl]-propenoic acid (XXXIX) to give the *cis*-epoxide (XLIV).

2.3.4.2 The preparation of trans-3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propenoic acid.

The preparation of the trans-3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propenoic acid was accomplished by the Knoevenagel-Doebner reaction on 1-(p-toluenesulphonyl)-pyrrolidine-2-aldehyde (113). Initial experiments gave poor results, but the yield could be greatly increased, as shown by Kleynhans in these laboratories, by the careful control of the reaction conditions, particularly temperature. Using his procedure yields of 70 - 75% were obtained, but the product was probably racemic, the measured optical activity of the acid being very close to zero ($[\alpha]_D$ - 0.6°). This may be fortuitous, but the dibromo-acid formed on bromination also has no optical activity and it seems unlikely that both compounds, if optically active, would have zero rotation at the same wavelength. This racemisation probably resulted from the basic conditions of the Knoevenagel-Doebner reaction fostering the reversible formation of the symmetric enolate anion from the aldehyde.

The Knoevenagel-Doebner reaction gives trans - unsaturated acids, which was confirmed in the present case by the P.M.R. spectrum. The spin-spin coupling constant between the two olefinic protons was 15 c/s, typical for trans-disubstitution.

The ethyl ester of the unsaturated acid was available, and was optically active (section 2.3.3.2), but gave, on basic hydrolysis, not the unsaturated acid but an acidic compound identified as 3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-3-hydroxypropanoic acid (XLV), which would have been formed by the 1,4-addition of water across the unsaturated system. The compound $C_{14}H_{19}NO_5S$, showed a strongly hydrogen-bonded hydroxyl absorption at 3220 cm^{-1} in the infra-red spectrum, arising from the hydroxyl hydrogen atom bonding intermolecularly with the carboxyl group to give a six-membered ring.

2.3.4.3 Preparation of (±)-2,3-erythro-3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-2,3-dibromopropionic acid.

Some difficulty was experienced in brominating the acid. In the dark no detectable reaction took place with bromine in carbon tetrachloride, nor with pyridinium perbromide hydrobromide in the acetic acid. There are two positions (the allylic, and benzylic carbon atoms) which may undergo light-induced bromination (114), so that light had to be excluded.

The initial step of the bromination is electrophilic attack of the double bond by the bromine to give an intermediate π -complex or bromonium ion. This may then be attacked by the nucleophilic bromide ion to give overall trans-dibromination (115). Any reduction of the elctron density on the double bond will reduce the rate of attack by the bromine; this is accomplished by the carboxyl group.

The problem was overcome quite simply by preparing the salt of the acid by titration with methanolic potassium hydroxide. The methanol was removed under reduced pressure at a low temperature to minimise its possible 1,4-addition to the salt. Reaction with bromine was carried out in aqueous solution for solubility purposes. To minimise the competitive attack of the intermediate bromonium ion by water molecules, to give a bromohydrin, the solution was saturated with sodium bromide. The reaction occurred almost instantaneously, with a drop in PH of the solution from about 8 to 6 as the more strongly acidic dibromo-acid was formed. Acidification and extraction gave the crude dibromo-acid as an oil that resisted attempts to induce it to crystallise. Fortunately it was found that crystals with one molecule of water of crystallisation formed from dichloromethane solution, in 60 - 65% yield. The crystals, on heating melted partially at about 95°, with evolution of gas, resolidified at about 135° and remelted at 179°. Analysis gave the formula $C_{14}H_{17}NO_4SBr_2.H_2O$ that is the dibromo-acid monohydrate which was confirmed by the proton magnetic-resonance spectrum which showed a broad single absorption at τ 3.95, integrating for three protons, arising from the carboxyl proton and two hydrate protons giving one signal by rapid exchange. This signal disappeared on the addition of D_2O. The I.R. spectrum (K Br disk) showed an absorption at 3450 cm^{-1}, indicating bonded hydroxyl groups, and absorptions at 1720 cm^{-1}

indicating an α-halogen substituted acid, 1335 cm^{-1} and 1155 cm^{-1} indicating the sulphonamide group, and 823 cm^{-1}, from the p-disubstituted benzene ring.

Prolonged heating under reduced pressure gave the anhydrous dibromo-acid, $C_{14}H_{17}NO_4SBr_2$, m.p. 175 - 178°.

The trans-bromination of the trans-unsaturated acid would give two stereo-isomeric dibromo-acids. As there was an assymmetric carbon atom in the unsaturated acid these would be distereoisomers, the ribo- and lyxo-forms. The crystallinity of the dibromo-acid isolated, and its sharp magnetic resonance spectrum indicated that it was only one of these forms, but it was not possible to say which one. The measured optical rotation was vanishingly small, which taken with the similar value for the rotation of the unsaturated acid would indicate that both compounds were racemates.

The first opportunity for making an assignment of the relative stereochemistry would be on the trithiocarbonate (XLVII), when the optical rotatory dispersion spectrum could possibly be employed to give the absolute configuration of the trithiocarbonate ring (116). The configuration of a number of trithiocarbonates have been assigned by this method, but it requires an optically active compound, so the dibromo-acid would need to be resolved and the absolute configuration of the pyrrolidine-ring substitution determined, (possibly by dibromination and oxidation to N-tosylproline).

The synthesis was continued, however, on the racemic dibromo-acid.

2.3.4.4 The preparation of (±)-1,2-erythro-1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-1,2-dibromo-3-hydroxypropane.

The reduction of the 3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-2,3-dibromopropionic acid hydrate was effected smoothly by diborane, a suitable excess of which was added to react with the water. The isolation of the product was complicated by its relative insolubility in the common organic solvents, and was best carried out by destroying the excess of diborane, removing all the solvent under reduced pressure and then lixiviating the residue with acetone. Addition of light petroleum to the extract gave crystals of (±)-1,2-erythro-1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-1,2-dibromo-3-hydroxypropane (XLI) in 84% yield.

The compound, $C_{14}H_{19}NO_3SBr_2$, m.p. 190 - 191° showed a sharp absorption at 3500 cm^{-1} in the infra-red spectrum, typical for a hydroxyl group hydrogen bonded to an adjacent halogen atom. On reaction with acetic anhydride (without the addition of base, which might give rise to the epoxide), the alcohol yielded an acetate, $C_{16}H_{21}NO_4SBr_2$ m.p. 133-135°.

2.3.4.5. The preparation of (±)-1,2-threo-1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-1-bromo-2,3-epoxypropane.

Heating 1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-1,2-dibromo-3-hydroxypropane with 1.3 mols of methanolic potassium hydroxide gave the ($\pm$)-1,2-threo-1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-1-bromo-2,3-epoxypropane (XLII) in 62% yield after recrystallisation.

The compound, $C_{14}H_{18}NO_3Br$, m.p. 109 - 110° showed no hydroxyl absorption in the infra-red whilst there was a peak of moderate intensity at 1250 cm^{-1}, characteristic of the epoxy group.

The reaction of epoxides with an excess of hydrochloric acid in dioxane solution may be used for their determination, by back titration of the unsaturated acid (117). When this assay was applied to the compound obtained acid was consumed, but the reaction was slow, requiring seven hours to go to 80% completion (assuming that pure 1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-1-bromo-2,3-epoxypropane was being analysed). This is due probably to the high dilution of acid necessary because of the very small molar quantity of the epoxide that **could** be spared for the analysis.

An attempt was made to hydrolyse the epoxide, using dilute hydrochloric acid, to the diol, but the crystalline product isolated, m.p. 144-145°, analysed as $C_{14}H_{19}NO_3S$ BrCl, and was most probably 1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-1-bromo-2-hydroxy-3-chloropropane arising by nucleophilic attack by a chloride ion on the epoxide carbon atom furthest from the bromine substituent, as has been found for a number of 3-halo-1,2-epoxides (118). The presence of a hydroxyl group was confirmed by an absorption at 3500 cm^{-1} in the infra-red spectrum.

All the above evidence is consitent with the product obtained from the dibromo-alcohol being the 3-bromo-1,2-epoxide, but it does not exclude the possibility of the isomeric structure of 2-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-3-bromo-oxetane (XLVI). This structure is most unlikely, however, as simple 2,3-dibromopropanols, such as the parent compound, give the epoxide and not the oxetane on reaction with base, and it has been shown that β-halohydrins cyclise to epoxides at a much higher rate than similar γ-halohydrins cyclise to oxetanes, in accordance with the general rule that three-rings form more quickly than similar four-rings (79).

2.3.4.6 Preparation of (±)-1,2-threo-1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-1-bromo-2-hydroxy-3-benzyloxypropane.

The epoxide ring of 1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-1-bromo-2,3-epoxypropane (XLII) was opened by reaction with a large excess of benzyl alcohol, using borom trifluoride as the catalyst. After reaction the excess of benzyl alcohol was best removed by steam distillation; (the benzyl alcohol/water azeotrope contains 9% of the alcohol). The 1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-1-bromo-2-hydroxy-3-benzyloxypropane (XLIII) was extracted into dichloromethane and crystals m.p. 75-76° precipitated in 86% yield on the addition of light petroleum.

The structure of the compound, $C_{21}H_{26}NO_4SBr$, was confirmed by its spectra, which showed, in addition to the tosyl-pyrrolidinyl-group, the presence of a hydroxy-group (at 3500 cm^{-1} in the infra-red spectrum) and a benzyl group (743 cm^{-1} in the infra-red, and singlets at τ 5.46 and 2.70 in the proton magnetic resonance spectrum).

2.3.4.7. The preparation of (+)-cis-1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-1,2-epoxy-3-benzyloxypropane

The reaction of 1,2-threo-1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-1-bromo-2-hydroxy-3-benzyloxypropane (XLIII) with methanolic potassium hydroxide gave cis-1-[-1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-1,2-epoxy-3-benzyloxy-propane (XLIV), in 72.4% yield after recrystallisation from dioxane/light petroleum.

The compound, $C_{21}H_{25}NO_4S$, m. p. 78 - 80°, showed no hydroxyl absorption in the infra-red. The presence of the p-methylphenyl-group was indicated by the presence of a strong absorption at 825 cm^{-1} in the infra-red, and a singlet and quartet at τ 7.60 and 2.50 arising from the methyl- and aromatic-protons respectively.

The absorption at 742 cm^{-1} in the infra-red, and two singlets at τ 5.41 and 2.69 in the proton magnetic resonance spectrum confirmed the presence of the benzyloxy-group. The absorption at 1250 cm^{-1} in the infra-red suggested an epoxide, but the signals in the proton magnetic resonance spectrum arising from the protons along the chain were too complex to permit analysis, although a doublet at τ 6.31 was assigned to the terminal methylene group.

The assignment of the substitution on the epoxide ring as <u>cis</u>- could not be supported by physical evidence, as the coupling constant between the two epoxide ring protons could not be extracted from the very complex signal in the proton magnetic resonance spectrum, and while absorptions near 890 cm^{-1} and 830 cm^{-1} in the infra-red have been tentatively ascribed to ring vibrations of the epoxy ring in <u>trans</u>- and <u>cis</u>- compounds respectively (107), in the present case the compound exhibits several bonds near both of these wavenumbers. The assignment is thus based only on the generally accepted stereochemical paths followed by each of the reactions that were employed in the synthesis.

The various approaches to the synthesis of cassipourine which had been attempted all had as a common important intermediate <u>cis</u>-1-[1'-(<u>p</u>-toluenesulphonyl)-pyrrolidin-2'-yl]-1,2-epoxy-3-benzyloxypropane (XLIV). The successful synthesis of this compound that was finally achieved may be considered as being practical as the overall yield of nearly 8% on the starting material, <u>L</u>-proline, was achieved, implying an average yield per step of 79%.

The continuation of the synthesis, which had to be halted at this stage for lack of time and material, showed promise, however, as the model experiments had shown that the introduction of the sulphur atoms and removal of the protective groups might be expected to proceed readily. The chief problems that would remain are the two ring closures - to form first the pyrrolizidine system and then the tetrathiocane system of cassipourine.

EXPERIMENTAL

3.1 Preparation of *L*-1-(*p*-toluenesulphonyl)-pyrrolidine-2-carboxylic acid.

L-Proline (11.5 g.) and sodium bicarbonate (24.2 g.) were dissolved in water (550 ml.). The solution was cooled in an ice bath and stirred while a solution of *p*-toluenesulphonyl chloride (22.5 g.) in acetone (440 ml.) was added in several portions over thirty minutes. After stirring for three hours the solution was filtered and the acetone distilled off under reduced pressure. The residue was extracted with benzene (50 ml.), acidified, warmed to 60° and quickly extracted with warm benzene (4 x 200 ml.). The benzene extract was washed with water (100 ml.), concentrated to 30 ml. and cooled, when crystals of *L*-1-(*p*-toluenesulphonyl)-pyrrolidine-2-carboxylic acid, with half a molecule of benzene of crystallisation (28.5 g., 92.6%) were deposited. Recrystallisation from benzene gave crystals m.p. 95 - 97°.

Found : C, 58.1 ; H, 6.0 ; N, 4.8 ; S, 10.4%.
Calculated for $C_{15}H_{18}NO_4S$: C, 58.4 ; H, 5.9 ; N, 4.5 ; S, 10.4%.

The I.R. spectrum (K Br disk) showed absorptions at :- 3000 cm^{-1} s (O-H), 1730 cm^{-1} s (C=O), 1445 cm^{-1} s and 1160 cm^{-1} s ($N-SO_2$), 820 cm^{-1} m (p-disubstituted ring), 692 cm^{-1} m (benzene ring).

An S-benzyl-*iso*-thiouronium salt was prepared. Recrystallisation from ether gave plates m.p. 170°.

Found : C, 55.2 ; H, 6.0 ; N, 9.5 ; S, 14.6%.
$C_{20}H_{25}N_3O_4S_2$ requires : C, 55.2 ; H, 5.8 ; N, 9.7 ; S, 14.7%.

3.2 The preparation of L-1-(p-toluenesulphonyl)-pyrrolidine-2-carbonyl chloride.

A solution of 1-(p-toluenesulphonyl)-pyrrolidine-2-carboxylic acid (5 g.) in dry benzene (25 ml.) was gently refluxed under anhydrous conditions with purified thionyl chloride (1.4 ml.) for twenty minutes. Thionyl chloride (0.2 ml.) was added and the mixture refluxed for a further five minutes. The benzene was distilled off under reduced pressure and the residual oil pumped out on an aspirator pump (fitted with a calcium chloride-containing guard tube) for two hours. The crude acid chloride was then dissolved in dry ether (10 ml.), the latter distilled off under reduced pressure and the residue pumped out as before. The last step was repeated twice, when the oil partially crystallised. The crude product was used as such for the next experiment.

3.3 Preparation of lithium aluminium tri-tert-butyloxy hydride, and reduction of L-1-(p-toluenesulphonyl)-pyrrolidine-2-carbonyl chloride to L-1-(p-toluenesulphonyl)-pyrrolidine-2-aldehyde.

t-Butyl alcohol (4.5 ml.), dried by distillation from sodium, was slowly added over a period of thirty minutes to a suspension of lithium aluminium hydride (0.62 g.) in dry diglyme (15 ml.), the mixture being kept cool during the addition.

This solution of lithium aluminium tri-tert-butoxy hydride was then added dropwise over thirty minutes to a vigorously stirred, cold (-78°) solution of L-1-(p-toluenesulphonyl)-pyrrolidine-

2-carbonyl chloride (prepared as above from 5 g. of L-1-(p-toluenesulphonyl)-pyrrolidine-2-carboxylic acid) in diglyme (30 ml.). The reaction mixture was allowed to warm to room-temperature overnight, poured into water (500 ml.), with stirring and the resulting suspension centrifuged. The precipitate was washed with water (500 ml.), centrifuged and then made acid with 2N hydrochloric acid to give a suspension which was extracted with ether (3 x 20 ml.). The ether extract was washed with saturated sodium bicarbonate solution (2 x 50 ml.), water (50 ml.) and then dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave the L-1-(p-toluenesulphonyl)-pyrrolidine-2-aldehyde as an oil (0.73 g.). This gave a 2,4-dinitrophenyl-hydrazone, m.p. 181-183° after recrystallisation from methanol/water.

Found : C, 49.9 ; H, 4.6 ; N, 15.6 ; S, 7.4%.
$C_{18}H_{19}N_5O_6S$ requires : C, 49.9 ; H, 4.4 ; N, 16.2 ; S, 7.4%.

The centrifugate was concentrated under reduced pressure to a very small volume when crystals (1.4 g.) of the L-1-(p-toluenesulphonyl)-pyrrolidine-2-aldehyde precipitated. These gave a 2,4-dinitrophenylhydrazone identical with that obtained from the oil. The total yield of crude material was 51%.

3.4 Preparation of L-1-(p-toluenesulphonyl)-2-hydroxymethyl pyrrolidine.

The apparatus used consisted of a 250 ml. round bottomed flask fitted with a pressure-equalising funnel surmounted by a condenser. L-1-(p-toluenesulphonyl)-pyrrolidine-1-carboxylic acid (10.0 g.), previously dried *in vacuo* was placed in the funnel over a little dry cotton-wool. Lithium aluminium hydride (1.6 g.), suspended in dry ether (180 ml.), was placed in the flask which was warmed to distil a little ether into the funnel. The solution of acid formed was then run back into the flask at such a rate as to maintain a steady distillation of ether into the funnel. The 1-(p-toluenesulphonyl)-pyrrolidine-2-carboxylic acid had all been added after about thirty minutes, after which the suspension was gently refluxed for four hours. Excess lithium aluminium hydride was destroyed with wet ether, the solution filtered and the precipitate well washed with ether. The combined ether solutions were washed with 2N hydrochloric acid (50 ml.), which removed a little colour, saturated sodium bicarbonate solution (50 ml.) and water (50 ml.), dried over anhydrous sodium sulphate and then taken to dryness under reduced pressure, to give crystals of L-1-(p-toluenesulphonyl)-2-hydroxymethyl-pyrrolidine (5.7 g. 68%). Recrystallisation from ether gave prisms m.p. 87 - 87.5°. (Y. Fujita, A. Gottlieb, B. Peterkofsky, S. Udenfriend and B. Witkop J. Am. Chem. Soc. 1964 86 4709 found m.p. 87 - 88°).

Found : C, 56.6 ; H, 6.6 ; N, 5.7%.

Calculated for $C_{12}H_{17}NO_3S$: C, 56.5 ; H, 6.7 ; N, 5.5%.

The I.R.spectrum (K Br disk) showed absorptions at : 3600 cm^{-1} s (-OH), 2950 cm^{-1} m (C-H), 1600 cm^{-1} m (C=C), 1445 cm^{-1} s and 1160 cm^{-1} s ($-N-SO_2$), 1040 cm^{-1} s (C-OH), 820 cm^{-1} s (p-disubstituted ring).

The P.M.R. spectrum (deuterochloroform solution) showed absorptions at (τ) :-

8.3 m ($-\underline{CH_2}-\underline{CH_2}-$)-, 7.66 s (Ø-$\underline{CH_3}$), 7.00 s (-O$\underline{H}$, disappeared on D_2O exchange), 6.6 m ($\underline{CH_2}-N-\underline{CH}-CH_2-$), 6.32 s ($-\underline{CH_2}-OH$), 2.48 q ($-SO_2-\underline{C_6H_4}\ CH_3$).

Reaction of the 1-(p-toluenesulphonyl)-2-hydroxymethyl-pyrrolidine with acetic anhydride in pyridine followed by dilution with water afforded crystals of 1-(p-toluenesulphonyl)-2-acetoxymethyl-pyrrolidine, which when recrystallised from ethanol had m.p. 59.5 - 60°.

Found : C, 56.6 ; H, 6.3 ; N, 4.9%.

$C_{14}H_{19}NO_4S$ requires : C, 56.6 ; H, 6.4 ; N, 4.7%.

The I.R. spectrum (K Br disk) showed absorptions at :- 2950 cm^{-1} m (C-H), 1740 cm^{-1} s (C=O), 1600 cm^{-1} m (C=C), 1445 cm^{-1} s ($N-SO_2$), 1240 cm^{-1} s ($O-COCH_3$), 1160 cm^{-1} s ($N-SO_2$), 820 cm^{-1} s (p-disubstituted ring).

3.5 Preparation of L-methyl-1-(p-toluenesulphonyl)-pyrrolidine-2-carboxylate.

L-1-(p-Toluenesulphonyl)-pyrrolidine-2-carboxylic acid (5.0 g.) was dissolved in dry methanol (50 ml.), concentrated sulphuric acid (0.5 ml.) was added and the solution gently refluxed overnight. The reaction mixture was added to 10% sodium carbonate solution (100 ml.) and the whole extracted with dichloromethane (3 x 50 ml.). The extracts were washed with water (50 ml.), dried over anhydrous sodium sulphate and the solvent removed under reduced pressure to give an oil, which crystallised to give the L-methyl-1-(p-toluenesulphonyl)-pyrrolidine-2-carboxylate (4.54 g., 94%). On recrystallisation from ether the ester had m.p. 75.5 - 76.5°. (Y. Fujita, A. Gottlieb, B. Peterkofsky, S. Udenfriend and B. Witkop, J. Am. Chem. Soc. 1964 86 4709 found m.p. 75 - 76°).

Found :	C, 55.4; H, 6.0; N, 5.0; S, 11.2%.
Calculated for $C_{13}H_{17}NO_4S$:	C, 55.1; H, 6.1; N, 5.0; S, 11.3%.

The I.R. spectrum (K Br disk) showed absorptions at :- 2950 cm^{-1} m (C-H), 1750 cm^{-1} s (C=O), 1600 cm^{-1} m (C=C), 1345 cm^{-1} s and 1160 cm^{-1} s (N-SO_2), 830 cm^{-1} s (p-substituted ring), 715 cm^{-1} s.

3.6 Reduction of L-methyl-1-(p-toluenesulphonyl)-pyrrolidine-2-carboxylate.

L-Methyl-1-(p-toluenesulphonyl)-pyrrolidine-2-carboxylate (4.01 g.), dissolved in dry ether (50 ml.), was treated with lithium aluminium hydride (0.75 g.) in small portions and then heated under reflux for one hour. Excess lithium aluminium hydride was destroyed with wet ether, the solution filtered, and the precipitate well washed with ether. The ether solution was washed with 2N hydrochloric acid (5 ml.), saturated sodium bicarbonate solution (10 ml.), water (10 ml.) and then dried over anhydrous sodium sulphate. The ether was removed under reduced pressure to give crystals of L-1-(p-toluenesulphonyl)-2- hydroxymethyl -pyrrolidine (3.27 g. 90.6% yield).

3.7 Preparation of L-1-(p-toluenesulphonyl)-pyrrolidine-2-aldehyde and its purification via L-1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-1-methoxymethanol.

L-1-(p-toluenesulphonyl)-2-hydroxymethyl-pyrrolidine (15.3 g.) was dissolved in a mixture of dry dimethylsulphoxide (60 ml.) and dry benzene (30 ml.). ortho-Phosphoric acid (1.62 ml.) and dicyclohexylcarbodiimide (37 g.) were added. After a few minutes a gelatinous precipitate of dicyclohexyl urea began to form and the temperature of the reaction mixture rose. To prevent decomposition the reaction was moderated by cooling the contents of the flask. Once the initial reaction had subsided the mixture was left at room-temperature overnight. Benzene (250 ml.) and a solution of oxalic acid dihydrate (25 g.) in water (100 ml.) were then added. The mixture was stirred until the evolution of gas had ceased (about 45 minutes) and then filtered. The crystals of dicyclohexyl urea were well washed with benzene. The benzene layer of the filtrate was separated and washed with 5% sodium bicarbonate solution (3 X 60 ml.), water (60 ml.) and dried over anhydrous sodium sulphate. Removal of the benzene gave the crude aldehyde, which was dissolved in hot dry methanol (30 ml.). A seed crystal of the methyl hemi-acetal was added and crystallisation allowed to proceed overnight in a refrigerator. The L-1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-1-methoxymethanol (11.9 g., 69.6%) was collected and washed with a little methanol. A sample recrystallised from methanol had m.p. 128 - 130°.

Found :	C, 54.6 ; H, 6.2 ; N, 4.5 ; S, 11.3%.
$C_{13}H_{19}NO_4S$ requires :	C, 54.7 ; H, 6.7 ; N, 4.9 ; S, 11.2%.

The I.R. spectrum (K Br disk) showed absorptions at :- 3450 cm^{-1} s (-OH), 2950 cm^{-1} m (C-H), 1730 cm^{-1} w (aldehyde impurity), 1600 cm^{-1} m (C=C), 1440 cm^{-1} s and 1160 cm^{-1} s (N-SO$_2$-), 1080 cm^{-1} s (C-O-C), 825 cm^{-1} s (p-disubstituted ring).

The L-1-(p-toluenesulphonyl)-pyrrolidine-2-aldehyde was regenerated by shaking the hemi-acetal (11.9 g.) in a separatory funnel with benzene (100 ml.) and 25% hydrochloric acid (100 ml.) for ten minutes. The benzene layer was separated, washed with water (30 ml.), dried over anhydrous sodium sulphate and concentrated to a small volume to give crystals of L-1-(p-toluenesulphonyl)-pyrrolidine-2-aldehyde (10.0 g., 94.6% from hemi-acetal, 65.8% from the alcohol).

A sample of the aldehyde recrystallised from ether as rods, m.p. 137 - 138° (dec). $[\alpha]_D$ + 160° in chloroform.

Found :	C, 56.6 ; H, 6.3 ; N, 4.9%.
$C_{12}H_{15}NO_3S$ requires :	C, 56.6 ; H, 6.4 ; N, 4.7%.

The I.R. spectrum (K Br disk) showed absorptions at :- 2950 cm^{-1} w (C-H), 1730 cm^{-1} s (C=O), 1595 cm^{-1} m (C=C), 1440 cm^{-1} s and 1160 cm^{-1} s ($N-SO_2$), 825 cm^{-1} s (p-disubstituted ring).

3.8 Preparation of 2-hydroxymethyl-1,4-dithiaspiro[4,5] decane.

A solution of 2,3-dimercaptopropanol (1.0 ml.) and cyclohexanone (1.0 ml.) in dry ether (3 ml.) was treated with concentrated hydrochloric acid (2 drops), refluxed gently for two minutes and then allowed to stand at room temperature for four hours. The ether solution was washed with a little aqueous sodium carbonate solution and then dried over anhydrous sodium sulphate. On concentration the solution yielded 2-hydroxymethyl-1,4-dithiaspiro[4,5] decane as oily crystals, which after two recrystallisations from light petroleum (b.p. 40-60°) had m.p. 60 - 60.5°.

Found:	C, 52.7; H, 7.9; S, 31.6%.
Calculated for $C_9H_{16}OS_2$:	C, 52.9; H, 7.9; S, 31.3%.

The I.R. spectrum (liquid film) showed absorptions at :-
3450 cm^{-1} s (-OH), 2950 cm^{-1} s (C-H), 1450 cm^{-1} s ($-CH_2-$),
1260 cm^{-1} m (cyclohexyl-), 1040 cm^{-1} s (C-OH).

The P.M.R. spectrum (deuterochloroform solution) showed absorptions at (τ):-
8.50 m ($-CH_2-\underline{CH_2}-\underline{CH_2}-\underline{CH_2}-CH_2-$), 8.04 m ($S-C(S-)-(\underline{CH_2}-)_2$),
7.46 s ($-O\underline{H}$, disappeared on D_2O exchange), 6.70 m ($-\underline{CH_2}-OH$),
6.25 m ($S-\underline{CH_2}-\underline{CH}-(CH_2OH)S-$).

3.9 Preparation of allyl benzyl ether.

Sodium (12.0 g.) was dissolved in dry allyl alcohol (80 ml.) to give a gel that was suspended in dry benzene (200 ml.). Redistilled benzyl chloride (60 g.) was added and the mixture refluxed for 7 hours. Water (100 ml.) was added, the organic layer separated, dried over anhydrous sodium sulphate and distilled. The fraction b.p. 204 – 210° /760 mm. weighing 54 g. was collected, but the allyl benzyl ether was found to be contaminated with benzyl alcohol.

Purification was accomplished by preparative gas-liquid chromatography on a twenty foot long column packed with 30% SE 30 silicone gum rubber on chromasorb-P , using nitrogen as the carrier gas. At 150° and 200 ml/minute nitrogen the retention times of the benzyl alcohol and allyl benzyl ether were 28.5 minutes and 60.0 minutes respectively. Pure (single peak on G.L.C.) allyl benzyl ether (16 ml) was collected; b.p.203 – 205°/760 mm. (v. Braun, Ber. 43 1352 gives b.p. 204 – 205°).

3.10 Preparation of 3-benzyloxy-1,2-epoxypropane.

Monoperphthalic acid (230 ml., 0.235 M in ether) was prepared as in Organic Syntheses Coll. vol. III 619. To this was added benzyl allyl ether (7.5 g.), and the mixture left at room-temperature for twenty-five days, when the solution was washed with 10% sodium bicarbonate solution (3X60 ml.) and dried over anhydrous sodium sulphate. The ether was distilled off under reduced pressure to give the crude 3-benzyloxy-1,2-epoxypropane (6.87 g.) as an oil.

A sample of the oil was assayed for epoxide content and found to be 55.3% pure.

3.11 Preparation of 4-benzyloxymethyl-1,3-dithiolan-2-thione.

A solution of potassium hydroxide (3.5 g.) and carbon disulphide

(5.7 g.) in absolute methanol was added to 3-benzyloxy-1,2-epoxy propane (6.6 g. of 55% purity i.e. 3.6 g.) and left at room-temperature for five days. Ether (300 ml.) was added, the solution filtered, concentrated to 20 ml. and partitioned between ether (250 ml.) and water (50 ml.). The ether layer was dried over anhydrous sodium sulphate and the solvent removed to give an intensely yellow oil (4.6 g.), which was chromatographed on an alumina column. Elution with ether/5% ethanol gave the 4-benzyloxymethyl-1,3-dithiolan-2-thione as an oil (2.6 g. 56.2%) that could not be crystallised.

Found: C, 52.4 ; H, 4.3%.

Calculated for $C_{11}H_{12}OS_3$: C, 51.6 ; H, 4.7%.

The I.R. spectrum (liquid film) showed absorptions at:- 2950 cm^{-1} w (CH), 1500 cm^{-1} w and 1445 cm^{-1} w (C = C), 1100 cm^{-1} m, 1070 cm^{-1} s 1035 cm^{-1} m (C-O-C and -S-C(S)-S-), 960 cm^{-1} m, 735 cm^{-1} m and 697 cm^{-1} m (benzene ring).

The P.M.R. spectrum (deuterochloroform solution) showed absorptions at (τ):

6.36 m (-S-$\underline{CH_2}$-CH-S), 6.12 q (-S-CH-$\underline{CH_2}$-O-), 5.75 m (S-$\underline{CH_2}$-CH-S), 5.50 s (-O-$\underline{CH_2}$-Ø), 2.80 s (CH_2-$\underline{C_6H_5}$).

The U.V. spectrum (ethanol solution) showed absorptions at : λ 212 mμ , ε 10,900 ; λ 316 mμ, ε 14,600 shoulder at 298 mμ, ε 11,700.

3.12 Reduction and debenzylation of 4-benzyloxymethyl-1,3-dithiolan-2-thione, and characterisation of the 2,3-dimercaptopropanol formed.

Lithium aluminium hydride (0.4 ml.) was suspended in dry ether (10 ml.). A solution of 4-benzyloxymethyl-1,3-dithiolan-2-thione (1.03 g.) in dry ether (5 ml.) was added over ten minutes, with stirring. The solution was stirred for a further four hours and the excess lithium aluminium hydride then destroyed with wet ether. The resulting suspension was made acid with 2N hydrochloric acid, the ether layer separated and dried over anhydrous sodium sulphate. Evaporation of the ether under reduced pressure gave an oil (0.9 g.).

This oil (0.85 g.) was added to liquid ammonia (20 ml.) and whilst being vigorously stirred small pieces of clean sodium were added until the blue colour persisted for fifteen minutes. A little ammonium chloride was added to discharge the blue colour and the ammonia allowed to evaporate. The residue was made acid with 2N hydrochloric acid and extracted with chloroform (8 x 10 ml.). The chloroform extracts were dried over anhydrous sodium sulphate and concentrated to give an evil-smelling oil (0.49 g.).

The I.R. spectrum (liquid film) showed absorptions at : 3500 cm^{-1} vs (-OH), 2950 cm^{-1} s (C-H), 2560 cm^{-1} m (S-H), 1040 cm^{-1} s (C-O-H).

Cyclohexanone (0.5 ml.) was mixed with a solution of the oil in ether (1 ml.) and concentrated hydrochloric acid (1 drop) was then added. The solution was refluxed gently for two minutes and then allowed to stand at room temperature for four hours, after which it was washed with a little sodium carbonate solution, dried over anhydrous sodium sulphate and then taken to dryness. The residue was crystallised from light petroleum and after recrystallisation from the same solvent the crystals had m.p. 59 - 60°. A mixed melting point with authentic crystals of 2-hydroxymethyl-1,4-dithiaspiro[4,5]decane, m.p. 59.5 - 60.5°, had m.p. 59 - 60°.

3.13 Preparation of 2-benzyloxy-ethanol.

Dry ethylene glycol (100 ml.) was placed in a flask fitted with a Liebig condenser, and heated to approx. 100°C. Clean sodium (4.8 g.) in very small pieces was added cautiously down the condenser. A very vigorous reaction resulted. When all the sodium had reacted the flask and contents were cooled, benzyl chloride (23.1 ml.) and finely ground potassium iodide (1 g.) were added. The mixture was stirred and heated at 130° for three hours. After cooling the contents of the flask were added to water (200 ml.) together with a few drops of sodium thiosulphate solution to remove a little colour. The organic layer was separated. The aqueous layer was extracted with benzene (3 x 50 ml.), the extracts dried over anhydrous sodium sulphate and the solvent removed under reduced pressure to give an oil. The lower organic layer was added to benzene (60 ml.) to give a solution which separated into an upper organic phase and a lower aqueous phase. The upper phase was separated from the aqueous phase, which was extracted with benzene (20 ml.). The upper phase and the benzene extract were dried over anhydrous sodium sulphate, the solvent removed under reduced pressure and the residue combined with the oil obtained above. The crude product was distilled through a well-lagged 10 cm. column, the fraction boiling in the range 254 - 260°/760 mm. being collected. (Bennet , J. Chem. Soc. 1925 127 1279 found b.p. 138°/15 mm.). The yield was 20.0 g., 72%.

Found : C, 70.8 ; H, 7.9%.

Calculated for $C_9H_{12}O_2$: C, 71.0 ; H, 8.0%.

3.14 Preparation of 1-benzyloxy-2-chloro-ethane.

A mixture of 1-benzyloxy-2-hydroxy-ethane (20 ml., 22 g.) and N,N-dimethylaniline (18.6 ml.) were treated at 0°C with thionyl chloride (12.0 ml.) in chloroform (20 ml.). The mixture was then heated on a water bath for thirty minutes to give a ruby-red solution which was poured into sufficient 2N hydrochloric acid to acidify the mixture. The solution was extracted with chloroform (2 x 20 ml.), the extracts washed with water (40 ml.), dried over anhydrous sodium sulphate and the solvent removed under reduced pressure. The turquoise residue was distilled under reduced pressure through a 10 cm. Vigreaux column, the fraction b.p. 124 - 128°/20 mm. being collected. (Bennet, J. Chem. Soc. 1925 127 1279 found b.p. 124°/20 mm.). A fraction b.p. 127°/20 mm. was collected for analysis. Total yield 16.9 g.

Found : C, 63.7 ; H, 6.7%.

Calculated for $C_9H_{11}OCl$:C, 63.3 ; H, 6.5%.

3.15 Preparation of 2-benzyloxyethyl-p-toluenesulphonate.

A solution of 2-benzyloxy-ethanol (18.3 g.) in dry pyridine (180 ml.) was cooled in ice and solid p-toluenesulphonyl chloride (40 g.) added. The solution was left in the refrigerator for 60 hours, when crystals of pyridinium hydrochloride precipitated. The reaction mixture was poured over ice and the crystals of 2-benzyloxyethyl-p-toluenesulphonate (29.4 g., 80.3%) filtered and dried.

A sample was recrystallised from light petroleum, at -70° as fine needles m.p. 43 - 43.5°.

Found : C, 62.5 ; H, 5.7 ; S, 10.5%.

$C_{16}H_{18}O_4S$ requires : C, 62.7 ; H, 5.9 ; S, 10.5%.

The I.R. spectrum (K Br disk) showed absorptions at :- 2850 cm^{-1} 4 (C-H), 1600 cm^{-1} m and 1500 cm^{-1} m (C=C), 1350 cm^{-1} s and 1190 cm^{-1} s ($-SO_2-O-$), 1130 cm^{-1} s ($-CH_2-O-CH_2-$), 920 cm^{-1} s, 810 cm^{-1} s (p-di-substituted ring), 785 cm^{-1} s and 735 cm^{-1} s (benzyl ring).

The P.M.R. spectrum (deuterochloroform solution) showed absorptions at (τ) :-
7.59 s ($Ø-\underline{CH_3}$), 6.06 AA'BB' system ($-\underline{CH_2}-\underline{CH_2}-$), 5.51 s ($Ø-\underline{CH_2}-O-$), 2.70 s ($O-CH_2-\underline{C_6H_5}$), 2.43 q ($CH_3-\underline{C_6H_4}-SO_2-$).

3.16 Preparation of 1-benzyloxy-2-iodo-ethane.

Procedure (i).

Sodium iodide (45 g.) dissolved in methanol (250 ml.) was refluxed with 1-benzyloxy-2-chloro-ethane (22 g.) for five hours, the solution filtered from the precipitate of sodium chloride and taken to dryness under reduced pressure. The residue was suspended in water (100 ml.) and extracted with chloroform (2 x 50 ml.). The extract was dried over anhydrous sodium sulphate, ane the chloroform removed under reduced pressure to give an oil which was vacuum distilled, the fraction boiling 100 - 110°/5 mm. being collected (16 g.). Gas chromatographic analysis on a 30% SE 30 column showed two peaks, that corresponding to the chloro-compound being estimated at about 5% of the whole.

Found : C, 42.6 ; H, 4.3 ; I, 46.8%.

$C_9H_{11}OI$ requires : C, 41.2 ; H, 4.2 ; I, 48.5%.

i.e. the analysis corresponding to 94% iodo-compound and 6% chloro-compound.

The P.M.R. spectrum (deuterochloroform solution) showed absorptions at (τ) :-

6.50 AA'BB' multiplet $(O\text{-}\underline{CH_2}\text{-}\underline{CH_2}\text{-}I)$, 5.43 s $(\phi\text{-}\underline{CH_2}\text{-})$, 2.66 s $(CH_2\text{-}\underline{C_6H_5})$.

Procedure (ii)

Sodium iodide (31 g.) and 2-benzyloxyethyl-p-toluenesulphonate (30.6 g.) were dissolved in acetone (300 ml.). The solution was left at room-temperature for 48 hours, during which time sodium p-toluenesulphonate precipitated. This was filtered off, and the filtrate concentrated under reduced pressure. Water (250 ml.) was added and the solution extracted with chloroform (2 x 150 ml.). The combined chloroform extracts were washed with water (100 ml.) containing a little sodium thiosulphate to remove a trace of free iodine, dried over anhydrous sodium sulphate and the chloroform removed to give the 1-benzyloxy-2-iodo-ethane, 25.8 g., 98% yield. This was used to prepare 2-benxyloxyethyl-triphenyl phosphonium iodide without further purification.

3.17 Preparation of 2-benzyloxyethyl-triphenyl phosphonium iodide.

Triphenyl phosphine (9.8 g.) was dissolved in benzene (50 ml.) and the solution refluxed for eight hours with 1-benzyloxy-2-iodo-ethane (9.8 g.). The benzene was removed under reduced pressure to give an oil. Dry ether (20 ml.) was added to the flask, which was vigorously shaken, to give white crystals of 2-benzyloxyethyl-triphenyl phosphonium iodide. The crystals were filtered, washed with a little ether and dried. Yield 18 g.

Found :	I 24.3%
$C_{27}H_{26}OPI$ requires :	I 24.2%

The I.R. spectrum (K Br disk) showed absorptions at :- 3010 cm^{-1} w and 2950 cm^{-1} w (C-H), 1605 cm^{-1} w, 1500 cm^{-1} w and 1450 cm^{-1} m (C=C), 1110 cm^{-1} s (C-O-C), 735 cm^{-1} s and 690 cm^{-1} s (aromatic rings).

3.18 Preparation pf L-1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-3-benzyloxy-prop-1-ene.

Sodium hydride (0.57 g. of a 50% suspension in mineral oil) was reacted with dry methanol (2.0 ml.). The excess methanol was removed under reduced pressure and the residue of sodium methoxide dissolved in dry dimethylformamide. This solution was added dropwise over 15 minutes to an ice-cold solution of L-1-(p-toluenesulphonyl)-pyrrolidine-2-aldehyde (2.5 g.) and 2-benzyloxyethyl triphenylphosphonium iodide (6.2 g.) in dry dimethylformamide.

The mixture was left at room-temperature for twenty hours, diluted with water (100 ml.) and extracted with light petroleum (8 x 40 ml.). The extract was washed with water (100 ml.), dried over anhydrous sodium sulphate and the solvent removed to give an oil (2.2 g.).

This was chromatographed on an alumina column, eluting with light petroleum (5 x 10 ml.), petroleum/50% ether (20 x 10 ml.) and then ether (30 x 10 ml.).

Fractions 3-8 contained mineral oil (from the sodium hydride) and a trace of triphenylphosphine.

Fractions 21-35 contained oils, identified as *L*-1-[*p*-toluenesulphonyl)-pyrrolidin-2'-yl]-3-benzyloxy-prop-1-ene. (Combined weight 0.85 g.). On recrystallisation from ether/light petroleum 0.64 g. of flaky crystals m.p. 57 - 57.5° were obtained. Further recrystallisation raised the m.p. to 59-60.5° $[\alpha]_D$ -49.7° in chloroform.

Found :	C, 68.0; H, 6.7; N, 3.9; S, 8.6%.
$C_{21}H_{25}NO_3S$ requires :	C, 67.9; H, 6.8; N, 3.8; S, 8.6%.

The I.R. spectrum (K Br disk) showed absorptions at :- 3020 cm^{-1} w and 2950 cm^{-1} m (C-H), 1605 cm^{-1} w and 1500 cm^{-1} m (C=C), 1325 cm^{-1} s and 1145 cm^{-1} s ($-N-SO_2-$), 1090 cm^{-1} s (C-O-C), 815 cm^{-1} m (*p*-di-substituted ring), 746 cm^{-1} m (benzyl ring).

The P.M.R. spectrum (deuterochloroform solution) showed absorptions at (τ) :-
8.3 m ($-\underline{CH_2}-\underline{CH_2}-$), 7.61 s ($Ø-\underline{CH_3}$), 6.67 m ($CH_2-\underline{CH_2}-N-$), 5.81 d, J = 4.5 c/s ($=CH-\underline{CH_2}-O$), 5.6 m ($N-\underline{CH}-(CH_2)-CH=$), 5.45 s ($Ø-\underline{CH_2}-O$), 4.40 m ($-\underline{CH}=\underline{CH}-$) 2.69 s ($-CH_2-\underline{C_6H_5}$), 2.54 q ($CH_3-C_6\underline{H_4}-SO_2-$).

Further elution (fractions 37-44) contained oils, combined weight 0.15 g., identified as 2-benzyloxyethyl-*p*-toluenesulphone. This was distilled at 200°/1 mm.

Found : C, 66.1 ; H, 6.5% ; S, 10.3%.

$C_{16}H_{18}O_3S$ requires : C, 66.2%; H, 6.3% ; S, 11.0%.

The I.R. spectrum (liquid film) showed absorptions at :- 2900 cm^{-1} m (C-H), 1600, 1490, 1450 cm^{-1} m (C=C), 1315, 1145 cm^{-1} both s ($C-SO_2-C$), 1080 cm^{-1} s (C-O-C), 815 cm^{-1} s (*p*-di-substituted ring), 735, 690 cm^{-1} both s (benzyl ring).

The P.M.R. spectrum (deuterochloroform solution) showed absorptions at (τ)-

7.61 s ($\phi-\underline{CH}_3$), 6.38 AA'BB' pattern ($-SO_2-\underline{CH}_2-\underline{CH}_2-O$), 5.62 s ($\phi-\underline{CH}_2-O$), 2.80 s ($-CH_2-C_6\underline{H}_5$), 2.50 q ($SO_2-\underline{C_6H}_4-CH_3$).

3.19 The preparation of vinyl magnesium bromide, and its reaction with 1-(p-toluenesulphonyl)-pyrrolidine-2-aldehyde to prepare 1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'yl]-prop-2-en-1-ol.

Pure magnesium turnings (0.30 g.) and dry tetrahydrofuran (5 ml.) were placed in a conical flask, together with a magnetic stirring bar. A cold finger containing dry ice/acetone was fitted to the flask, and vinyl bromide (1.4 ml.) and a small crystal of iodine were added. The solution was stirred rapidly and warmed slightly. After a few minutes a very vigorous reaction began, which was moderated by cooling the flask. The magnesium dissolved after twenty minutes. The solution was then cooled in an ice-bath, the stirring being continued. The vinyl magnesium bromide precipitated to form a thick slurry.

A solution of 1-(p-toluenesulphonyl)-pyrrolidine-2-aldehyde (2.53 g.) dissolved in dry tetrahydrofuran (15 ml.) was added over forty minutes to the stirred ice-cold suspension of Grignard reagent, and the clear green reaction mixture allowed to warm to room-temperature overnight. A solution of ammonium chloride (1.1 g.) in water (20 ml.) was added, and the mixture extracted with ether (2 x 50 ml.). The ether extract was washed with water (20 ml.) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure. Prolonged pumping was required to remove the last traces of tetrahydrofuran from the residual oil (2.55 g.).

This oil was chromatographed on a neutral alumina column. Ether was passed through the column and collected in twenty ml. fractions. Fractions 11, 12 and 13 were combined and the ether removed to give crystals of 1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-prop-2-ene-1-ol. (0.57 g. 20.3%) m.p. 45°. All attempts to recrystallise the waxy crystals failed.

Found : C, 59.6 ; H, 6.6 ; S, 11.2%.

$C_{14}H_{19}NO_3S$ requires: C, 59.8 ; H, 6.8 ; S, 11.4%.

The infra-red spectrum (K Br disk) showed absorptions at:- 3520 cm^{-1} m (-OH), 1600 cm^{-1} m (C=C), 1335 cm^{-1}s and 1145 cm^{-1} s (both $>$N-SO$_2$-), 1090 cm^{-1} s (C-OH), 990 cm^{-1} m (CH=CH$_2$), 922 cm^{-1} m $(-\underset{\text{OH}}{\text{CH}}-\underline{\text{CH=CH}_2})$, 820 cm^{-1} m (p-subst. benzene ring).

The P.M.R. spectrum (deuterochloroform solution) showed absorptions at (τ) :-

8.3 m $(-\underline{\text{CH}_2}-\underline{\text{CH}_2}-)$, 7.57 s (Ø-$\underline{\text{CH}_3}$), 6.7 m $(-\underline{\text{CH}_2}-\text{N}-)$, 6.5 s (-O$\underline{\text{H}}$, disappeared on D_2O exchange), 5.6 m $(=\underline{\text{CH}}-\text{N}-$ and $-\underline{\text{CH}}(\text{OH})-)$, 4.6 m $(-\underline{\text{CH}}=\underline{\text{CH}_2})$, 2.50 q (aromatic ring).

A portion was hydrogenated over Adams catalyst for six hours at atmospheric pressure. Removal of the catalyst and solvent left an oil which was chromatographed on an alumina column. Elution with ether gave crystalline 1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propan-1-ol. Recrystallisation from ether/light petroleum gave needles m.p. 103.5 - 104°.

Found : C, 59.4 ; H, 7.5 ; S, 11.3%.

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

The infra-red spectrum (K Br disk) showed absorptions at:- 3550 cm^{-1} s (-OH), 1605 cm^{-1} m (C=C), 1330 cm^{-1} s, 1155 cm^{-1} s ($>$N-SO$_2$-), 1090 cm^{-1} s (C-OH), 835 cm^{-1} m (p-subst. ring).

The P.M.R. spectrum (deuterochloroform solution) showed absorptions at (τ) :-

9.0 t, J = 7 c/s $(-\text{CH}_2-\underline{\text{CH}_3})$, 8.65m., J = 7 c/s $(-\underline{\text{CH}_2}-\text{CH}_3)$, 8.4 m $(-\underline{\text{CH}_2}-\underline{\text{CH}_2}-)$, 7.64 s (-OH, disappeared on D_2O exchange), 7.60 s

(Ø-$\underline{CH_3}$), 6.65 m (-$\underline{CH_2}$-N), 6.10 m (-N-$\underline{CH}$-(CH_2-)$\underline{CH}$(OH-.CH_2-)
2.54 q (aromatic protons).

3.20 Reaction of 1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-prop-2-en-1-ol with ethereal thionyl chloride.

An ethereal solution of thionyl chloride (4.6 ml. of a 0.5M solution) was added to 1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-prop-2-en-1-ol (0.64 g.) in dry ether (2 ml.). The mixture was left at room-temperature for four days. The volatile matter was then removed on a rotary evaporator, leaving a crystalline residue. This was recrystallised three times from ether/light petroleum to give crystals (45 mg.) m.p. 69.5 - 72°.

The mother liquors were filtered through a short alumina column to give 0.56 g. crystalline material that was further purified by chormatography on alumina. Elution with light petroleum/50% benzene gave crystals of 1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl)-1-chloro-prop-2-ene (165 mg.), m.p. 122-123° after recrystallisation from ether/light petroleum.

Found :	C, 56.2; H, 6.0; N, 4.7; S, 10.7; Cl, 12.0%.
$C_{14}H_{18}NO_2SCl$ requires :	C, 56.0; H, 6.0; N, 4.7; S, 10.7; Cl, 11.8%.

The infra-red spectrum (K Br disk) showed absorptions at :-
2950 cm^{-1} m (C-H), 1600 cm^{-1} m (C=C), 1340 cm^{-1} s and 1155 cm^{-1} s (>N-SO_2-), 820 cm^{-1} s (p-substituted ring) 692 m (C-Cl ?).

The P.M.R. spectrum (deuterochloroform solution) showed absorptions at (τ) :-
8.4 m (-$\underline{CH_2}$-$\underline{CH_2}$-), 7.60 s (Ø-$\underline{CH_3}$), 6.80 m (CH_2-$\underline{CH_2}$-N-), 6.15 m
(CH_2-$\underline{CH}$-(N)-$\underline{CH}$-Cl), 4.7 m (-$\underline{CH}$=$\underline{CH_2}$), 2.54 q (aromatic protons).

3.21 Identification of N,N-dicyclohexylparabanic acid as an impurity in a batch of 1-(p-toluenesulphonyl)-pyrrolidine-2-aldehyde.

In a preparation of 1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-prop-2-en-1-ol, starting with 1-(p-toluenesulphonyl)-pyrrolidine-2-aldehyde (2.3 g.) a white crystalline substance (0.55 g.) was eluted from the alimina column before the required product. This was recrystallised as rods m.p. 172.5 - 173.5° from ether and identified as N,N-dicyclohexylparabanic acid.

Found : C, 64.7 ; H, 8.0 ; N, 10.1%.
Calculated for $C_{15}H_{22}N_2O_3$: C, 65.0 ; H, 8.0 ; N, 10.2%.

The I.R. spectrum (K Br disk) showed absorptions at :- 2950 cm^{-1} m and 2850 cm^{-1} m (C-H), 1730 cm^{-1} s (C=O), 1410 cm^{-1} s ($-CH_2-$), 1255 cm^{-1} w and 896 cm^{-1} w (cyclohexyl ring), 760 cm^{-1} m ($-CH_2-$).

The P.M.R. spectrum (deuterochloroform solution) showed absorptions at (τ) :-
8.7 m ($-CH_2.CH_2.\underline{CH_2}.CH_2.CH_2-$), 8.2 m ($-\underline{CH_2}-\underline{CH_2}CH_2\underline{CH_2}\underline{CH_2}$), 6.05 m ($N-\underline{CH}=(CH_2-)_2$).

There was an absorption in the ultra-violet(ethanol solution); λ_{max} 224 nm., ε_{max} 10,300.

The mass spectrum of the compound was determined. The mass peak was at m/e 278.163998; ($C_{15}H_{22}N_2O_3$ sums to 278.163032 a.m.u.). (H. Ulrich and A. A. R. Sayigh, J. Org. Chem. 1965 30 2781 found the m.p. of dicyclohexylparabanic acid to be 174 - 175°, and the carboxyl absorption in the infra-red occurred at 1730 cm^{-1} in chloroform solution).

3.22 Preparation of triethylphosphono-acetate.

Triethyl phosphite was prepared by the method given in organic syntheses coll. vol. IV, p 955. $[\alpha]_D^{18}$ 1.413 (reported $[\alpha]_D^{20}$ 1.4131).

Triethyl phosphite (60 g.) and ethyl bromacetate (45 g.) were placed in a flask fitted with a thermometer, a nitrogen inlet tube and an air-condenser. Gases issuing from the top of the condenser were passed into a liquid nitrogen-cooled trap.

The apparatus was flushed with a gentle stream of nitrogen and the contents of the flask were heated to 190°, when a vigorous reaction commenced. This was moderated by cooling the flask. A quantity of material collected in the trap. Heating was continued at 190 - 200° for four hours, when very little additional material was being collected in the trap. (A total of 28 g. was collected - the theoretical quantity of ethyl bromide is 22 g.).

The product was distilled under reduced pressure, the fraction b.p. 105 - 110°/ 0.8 mm being collected. The weight was 43.4 g., i.e. 72% yield, based on the ethyl bromacetate.

3.23 Preparation of L-ethyl 3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-prop-2-enoate.

Sodium hydride (2.0 g. of a 50% dispersion in oil) was washed free of the oil with dry petrol (2x5 ml.) and suspended in dry dioxane (35 ml.) in a flask fitted with an efficient stirrer, a nitrogen inlet tube and a pressure-equalising dropping funnel closed with a calcium chloride tube.

The apparatus was flushed with nitrogen and the flask was cooled in cold water. Triethylphosphono-acetate (8.8 g.) was added dropwise to the stirred suspension. A moderate evolution of hydrogen occured. When the addition was complete the mixture was stirred for 60 minutes at room-temperature to give a clear pale yellow solution. This was cooled in cold water and a solution of L-1-(p-toluenesulphonyl)-pyrrolidine-2-aldehyde (10.0 g.) in dry dioxane (50 ml.) was added dropwise over 45 minutes. A gelatinous precipitate formed. The mixture was stirred at room-temperature for 60 minutes and then at 80° for thirty minutes.

The bulk of the dioxane was removed on a rotary evaporator and the residue partitioned between water (100 ml.) and dichloromethane (100 ml.). The water layer was washed with dichloromethane (30 ml.), and the combined dichloromethane layers washed with water (2x30 ml.), and dried over anhydrous sodium sulphate. The solvent was removed on a rotary evaporator to give an oil (12.8 g.), which was crystallised from ether/petrol to give L-ethyl 3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propenoate (6.6 g.). Crystallisation of the mother liquors gave a further 3.1 g. product (total yield 65%).

The ester, recrystallised from ether, had m.p. 62 - 64°. $[\alpha]_D$ -132° in chloroform.

Found :	C, 59.5 ;	H, 6.2 ;	N, 4.4 ;	S 10.0%.
$C_{16}H_{21}NO_4S$ requires :	C, 59.4 ;	H, 6.5 ;	N, 4.3 ;	S 9.9%.

The I.R. spectrum (B Br disk) had absorptions at :- 2950 cm^{-1} s (C-H), 1720 cm^{-1} vs (C = O), 1660 cm^{-1} s (alaphatic C = C), 1600 cm^{-1} m and 1500 cm^{-1} m (aromatic C = C), 1340 cm^{-1} s and

1160 cm^{-1} s ($N - SO_2$), 820 cm^{-1} s (p-disubstituted ring).

The P.M.R. spectrum (deuterochloroform solution) showed absorptions at (τ) :-

8.72 t, J = 7 c/s, ($CH_2-\underline{CH_3}$), 1.7 m ($-\underline{CH_2}-\underline{CH_2}-$), 2.42 s ($\phi-\underline{CH_3}$), 3.3 m ($CH_2-\underline{CH_2}-N$), 4.17 q, J = 7 c/s superimposed on a complex multiplet, ($-O-\underline{CH_2}-CH_3$ and $N-\underline{CH}-CH=$), 5.99 d, J = 15 c/s ($-CH=\underline{CH}-COO$), 6.82 q, J = 15 and 6 c/s ($-CH-\underline{CH}=CH-$) 7.50 q (aromatic protons).

A portion of the ethyl 3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-prop-2-enoate dissolved in ethanol was hydrogenated over Adams catalyst, for six hours at room-temperature and pressure. Crystallisation of the product afforded ethyl 3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propanoate, m.p. 52 - 53°.

Found:	C, 59.2 ; H, 7.0 ; N, 4.2 ; S, 9.9%.
$C_{16}H_{23}NO_4S$ requires :	C, 59.1 ; H, 7.1 ; N, 4.3 ; S, 9.8%.

3.24 Reduction of L-ethyl 3-[1'-(p-toluenesulphonyl)-pyrrolidin -2'-yl]-propenoate.

A solution of L-ethyl 3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propenoate (5.1 g.) in dry ether (100 ml.) was cooled to 0°, and a fourth part of a suspension of lithium aluminium hydride (0.6 g.) and ethanol (0.73 g.) in dry ether (10 ml.) was added. The mixture was stirred and allowed to warm to room-temperature. After an hour the solution was cooled to 0° and a further portion of the hydride added. This procedure was repeated until all the hydride had been added. The stirring was continued for a total of six hours.

The excess hydride was destroyed with wet ether, the solution filtered and dried over anhydrous sodium sulphate. Removal of the solvent gave a pale yellow gum (4.3 g.).

This was chromatographed on neutral alumina ; elution with light petroleum/50% ether gave 3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-propenal (0.039 g.), which when recrystallised from ether had m.p.. . 127 - 128°.

Found : C, 60.2 ; H, 6.1 ; S, 11.5%.

$C_{19}H_{17}NO_3S$ requires : C, 60.2 ; H, 6.3 ; S, 11.5%.

The I.R. spectrum (K Br disk) showed absorptions at :- 2950 cm^{-1} m (C-H), 1690 cm^{-1} s (C = O), 1640 cm^{-1} m (aliphatic C = C), 1605 cm^{-1} m and 1500 cm^{-1} w (aromatic C = C), 1350 cm^{-1} s and 1160 cm^{-1} s (N-SO_2), 1000 cm^{-1}s (*trans*-C = C ?), 820 cm^{-1} s (p-disubstituted ring).

The P.M.R. spectrum (deuterochloroform solution) showed absorptions at (τ):-

8.2 m (-$\underline{CH_2}$-$\underline{CH_2}$-), 7.57 s (Ø -$\underline{CH_3}$), 6.65 m (-CH_2-$\underline{CH_2}$-N-), 5.6 m (N-C$\underline{H}$-CH=), 3.79 q, J = 7 and 16 c/s (-CH=$\underline{CH}$-CHO), 3.20 q, J = 5 and 16 c/s (-C'H-$\underline{CH}$=CH-), 2.51 q (SO_2-$C_6\underline{H_4}$-CH_3), 0.44 d, J = 7 c/s (CH=CH-C$\underline{H}$O).

Further elution of the column with light petroleum/50% ether gave a trace of a substance, probably 3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl)-prop-2 en-1-ol.

In a similar experiment the reduction of the ester (4.6 g.) gave 0.8 g. of this compound as an oil that could not be crystallised.

Found : C, 59.2 ; H, 7.0 ; N, 4.9 ; S, 11.2%.

$C_{14}H_{19}NO_3S$ requires : C, 59.8 ; H, 6.8 ; N, 5.0 ; S, 11.4%.

The I.R. spectrum showed absorptions at :-
3500 cm^{-1} s (-OH), 2950 cm^{-1} s (C-H), 1605 cm^{-1} m (C = C), 1445 cm^{-1} s and 1160 cm^{-1} s ($N-SO_2$), 820 cm^{-1} s (p-distributed ring).

The P.M.R. spectrum (deuterochloroform solution) showed absorptions at (τ) :-
8.35 m ($-\underline{CH_2}-\underline{CH_2}-$), 7.60 s ($\phi-\underline{CH_3}$), 6.83 s ($-O\underline{H}$, disappeared on D_2O exchange), 6.7 m ($-N-\underline{CH_2}-CH_2-$), 6.2 m ($N-\underline{CH}-CH=$), 5.90 d, J = 3.5 c/s ($-CH = CH-\underline{CH_2}-OH$), 4.25 m ($-\underline{CH} = \underline{CH}-$) 2.50 q ($SO_2-C_6\underline{H_4}-CH_3$).

Treatment of the alcohol with acetic anhydride in pyridine gave, after dilution with water, an oil, analysing to 3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-prop-2-en-1-yl acetate. Attempts to crystallise this substance failed.

Found : C, 58.7 ; H, 6.5 ; N, 4.4%.
$C_{16}H_{21}NO_4S$ requires : C, 59.4 ; H, 6.6 ; N, 4.3%.

The I.R. spectrum (liquid film) showed absorptions at :-
2950 cm^{-1} m (C-H), 1750 cm^{-1} s (C=O), 1600 cm^{-1} m and 1500 cm^{-1} m (C = C), 1445 cm^{-1} s and 1160 cm^{-1} s ($N-SO_2$), 1240 cm^{-1} s ($O-COCH_3$), 820 cm^{-1} m (p-disubstituted ring).

The P.M.R. spectrum (deuterochloroform solution) showed absorptions at (τ) :-
8.3 m ($-\underline{CH_2}-\underline{CH_2}-$), 7.95 s ($-CO\underline{CH_3}$), 7.66 s ($\phi-\underline{CH_3}$), 6.65 m ($CH_2-\underline{CH_2}N$), 5.85 m ($N-\underline{CH}-CH=CH$), 5.45 d, J = 4 c/s ($CH=CH-\underline{CH_2}-O$), 4.21 m ($-\underline{CH}=\underline{CH}-$), 2.48 q ($SO_2-C_6\underline{H_4}-CH_3$)

Two other substances, or mixtures of substances were eluted with ether/20% ethanol. The first was present only as a trace, but the second was the major product (2.6 g.).

3.25 Preparation of diborane

Sodium borohydride (20.0 g.) was suspended in dry diglyme (100 ml.) in a flask fitted with a sealed stirrer, nitrogen inlet tube, a pressure equalising dropping funnel and a gas outlet tube. This tube led into a flask cooled in an ice/salt freezing mixture and containing dry tetrahydrofuran (500 ml.). The exit gases from this flask were passed through a little acetone to destroy any unabsorbed diborane.

Boron trifluoride etherate (90 g.) was placed in the funnel, and the apparatus flushed out with nitrogen. The boron trifluoride was allowed to drip in slowly whilst the suspension was vigorously stirred and a moderate stream of nitrogen was passed into the apparatus. The addition took two hours. The reaction flask was then warmed to about 60° while the system was flushed for a further 60 minutes.

The tetrahydrofuran solution (530 ml.) was stored in a refrigerator and assayed by measuring the volume of hydrogen released on reaction with water.

A volume of 72 ml. (at STP) of hydrogen was released by 1 ml. of the solution, i.e. it was 1.07 molar in the diborane - tetrahydrofuran complex. The yield was 80.5%.

3.26 Preparation of *erythro*-2,3-dibromo-butan-1-ol.

Diborane solution (130 ml. of 0.81 M solution in tetrahydrofuran, 0.105 moles) was added dropwise, with voluminous evolution of hydrogen to a stirred solution of *erythro*-2,3-dibromobutanoic acid (15.0 g., .061 moles) in dry ether (50 ml.). The reaction mixture was cooled during the addition and then left at room-temperature for thirty-eight hours. Water was added to destroy the excess diborane, and after gas evolution had ceased most of the solvent was removed on a rotary evaporator.

Sufficient water (100 ml.) was added to dissolve the precipitated boric acid and the solution was extracted with ether (3 x 20 ml.). The extract was dried over anhydrous sodium sulphate and the solvent removed to give an oil. This was crystallised by dissolving in light petroleum (140 ml.) and cooling in a dry ice/acetone freezing mixture. The flaky crystals of 2,3-dibromo-butan-1-ol melted at 29 - 30°. The yield was 11.7 g., 83% (Charon, Ann. chim. phys. 1899 17 226 found m.p. 31°).

Found :	Br 68.8%
Calculated for $C_4H_8OBr_2$:	Br 69.0%

The I.R. spectrum (liquid film) showed absorptions at :- 3400 cm^{-1} s (O-H), 2950 cm^{-1} m (C-H), 1060 cm^{-1} s (C-OH).

The P.M.R. spectrum (deuterochloroform solution) showed absorptions at

8.11 d, J = 6.0 c/s ($-\underline{CH_3}$), 7.43 s ($-O\underline{H}$, disappeared on D_2O exchange), 5.92 m ($CH(Br)-CH_2-O-$), 5.70 m ($CH_3-\underline{CH}(Br).\underline{CH}(Br)-CH_2$).

3.27 Preparation of threo-1,2-epoxy-3-bromobutane.

A solution of potassium hydroxide (6.25 g.) in methanol (50 ml.) was added to 2,3-dibromo-butanol (19.5 g.) dissolved in methanol (50 ml.). The mixture was refluxed for ten minutes, cooled, added to water (120 ml.) and extracted with ether (3 x 60 ml.). The ether extracts were combined washed with water (3 x 30 ml.) and dried over anhydrous sodium sulphate. The ether was removed by distillation through a 10 cm. Vigreaux column, and the residue distilled under reduced pressure to give two fractions; the first b.p. 50 - 56°/16 mm. was the 1,2-epoxy-3-bromo-butane (8.5 g., 65%), the second b.p. 96 - 104°/16 mm. was unreacted 2,3-dibromobutanol (3 g.). The yield based on reacted starting material was 76%. (Waters and Van der Werf, J. Am. Chem. Soc. 1954 76 709 found b.p. 146°/741 mm.).

Found : C, 32.0 ; H, 4.8 ; Br, 52.3%.
Calculated for C_4H_7OBr : C, 31.8 ; H, 4.6 ; Br, 52.9%.

The I.R. spectrum (liquid film) showed absorptions at :- 2950 cm^{-1} m (C-H), 1250 cm^{-1} m (epoxide).

The P.M.R. spectrum (deuterochloroform) showed absorption at (τ) :-
8.32 d, J = 7 c/s ($-\underline{CH_3}$), 7.31 q and 7.11 q ($-CH-\underline{CH_2}-O$), 6.83 m ($-CHBr-\underline{CH}-O-$) 6.19 quintet ($CH_3-\underline{CHBr}-$).

3.28 Preparation of trans-2-methyl-3-benzyloxymethyl-1,4-dithiolan-5-thione.

A solution of 1,2-epoxy-3-bromo-butane (1.51 g.) in redistilled benzyl alcohol (4.25 ml.) was treated with boron trifluoride etherate (5 drops) and heated for five minutes in a boiling water bath. A little solid sodium bicarbonate was added, the mixture stirred for a few minutes and then filtered. Methanolic potassium hydroxide (13 ml. of a 1M solution) was added to the filtrate and the mixture refluxed for five minutes. Potassium methyl xanthate (4.5 g.) and methanol (20 ml.) were added and the solution heated under reflux for two hours, the colour becoming intensly yellow. The reaction mixture was concentrated on a rotary evaporator, diluted with water (50 ml.) and extracted with ether (3 x 20 ml.). The extract was dried over anhydrous sodium sulphate and the solvent removed under reduced pressure to give an oil that was chromatographed on a column of neutral alumina. The intensely yellow band that was eluted with ether/50% light petroleum was collected and the solvent removed to give the <u>trans</u>-2-methyl-3-benzyloxymethyl-1,4-dithiolan-5-thione as an oil (1.4 g., 54%) that crystallised on standing. A sample recrystallised from ether had m.p. 65-66°.

Found :	C, 53.2 ; H, 5.1 ; S, 35.2%.
$C_{12}H_{14}OS_3$ requires :	C, 53.3 ; H, 5.2 ; S, 35.6%.

The I.R. spectrum (liquid film) showed absorptions at :- 2900 cm^{-1} m (CH), 1500 cm^{-1} m and 1450 cm^{-1} m (C=C), 1085 cm^{-1} vs, 1060 cm^{-1} vs and 1035 cm^{-1} m (C-O-C or dithiolane-thione bands), 880 cm^{-1} s, 738 cm^{-1} vs, and 698 cm^{-1} vs (aromatic ring).

The P.M.R. spectrum (deuterochloroform solution) showed absorptions at (τ) :-

8.40 d, J = 7 c/s, ($-\underline{CH_3}$), 5.5 - 6.4 complex multiplet ($CH_3-{}'\underline{CH}-{}'\underline{CH}-\underline{CH_2}-O$), 5.44 s ($O-\underline{CH_2}-\phi$), 2.69 s ($-CH_2-C_6\underline{H_5}$).

The U.V. spectrum (ethanol solution) showed absorptions at:-

λ_{max} 212 nm. ε_{max} 8700, λ_{max} 316 nm. ε_{max} 15,300 (shoulder 298 nm., ε 11,600).

3.29 Preparation of erythro-2,3-dibromo-3-phenyl-propan-1-ol.

Diborane (45 ml. of a 0.81M solution in tetrahydrofuran) was added cautiously to a solution of erythro-2,3-dibromo-3-phenyl-propanoic acid (16.4 g.) in dry ether (40 ml.). The mixture was left for thirty-six hours at room-temperature, the excess diborane destroyed by the cautious addition of water and the solvent removed under reduced pressure. Water was added to the residue to dissolve the boric acid and the mixture was extracted with chloroform (2 x 30 ml.). The extract was dried over anhydrous sodium sulphate and the solvent removed to give crystals of the crude dibromo-alcohol (13 g., 83%). Recrystallisation from ethanol/water yielded 2,3-dibromo-3-phenyl-propan-1-ol, 11.2 g., m.p. 68 - 70° (Grimaux, Bl.[2] 20 120 found m.p. 74°).

Found : Br 54.9%

Calculated for $C_9H_{10}O\,Br_2$: Br 54.4%.

The I.R. spectrum (K Br disk) showed absorptions at :- 3350 cm^{-1} s (-OH), 1595 cm^{-1} m and 1500 cm^{-1} m (aromatic C=C), 764 cm^{-1} and 696 cm^{-1} vs (mono-substituted benzene ring).

3.30 Hydrolysis of L-ethyl 3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-prop-2-enoate.

L-Ethyl 3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-prop-2-enoate (3.2 g.) was refluxed with methanolic (10 ml.), for ten minutes. The mixture was diluted with water (20 ml.) and extracted with dichloromethane (2 x 30 ml.). The dichloromethane layers were washed with water (50 ml.) and the acidic material extracted into saturated aqueous sodium bicarbonate solution (50 ml.). This was acidified and extracted with dichloromethane (2 x 50 ml.), the extract washed with water (50 ml.), dried over anhydrous sodium sulphate and the solvent removed under reduced pressure to give an oil (2.6 g.). This was crystallised from ethanol/water (0.9 g.). The product was recrystallised from ethanol/water as flakes m.p. 119 - 120^{0}, identified as 3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-3-hydroxy-propanoic acid.

Found : C, 53.8 ; H, 6.0 ; N, 4.5%.

$C_{14}H_{19}NO_5S$ requires : C, 53.7 ; H, 6.1 ; N, 4.5%.

The I.R. spectrum (K Br) showed absorptions at :- 3220 cm^{-1} m (bonded -OH), 2950 cm^{-1} m (C - H), 172o cm^{-1} s (C = O), 1335 cm^{-1} m and 1160 cm^{-1} s (N-SO$_2$), 940 cm^{-1} s , 815 cm^{-1} s (p-disubst. ring).

3.31 The preparation of (+)-3-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl] - prop-2-enoic acid.

Malonic acid (7.4 g.) and piperidine (1.0 ml.) were added to a solution of 1-(p-toluenesulphonyl)-pyrrolidine-2-aldehyde (8.2 g.)

in dry pyridine (100 ml.). The solution was left at room-temperature overnight, protected by a calcium chloride tube, and then heated on an oil-bath at a rate of 20° per hour until 80° was attained. The temperature was kept constant at this value until the evolution of carbon dioxide had almost ceased (about 9 to 10 hours after commencing heating).

Most of the pyridine was removed under reduced pressure, the residue made strongly acid with hydrochloric acid and extracted with chloroform (3 x 50 ml.). Acidic material was extracted from the chloroform solution with saturated sodium bicarbonate solution (2 x 100 ml.); this was acidified and extracted with chloroform (2 x 50 ml.). The extract was dried over anhydrous sodium sulphate and the solvent removed to give the crude crystalline acid (7.65 g., 76% yield). This was recrystallised from dichloromethane/light petroleum to give crystals (5.5 g., 55% yield) of the (±)-3-[1'-(*p*-toluenesulphonyl)-pyrrolidin-2'-yl]-prop-2-enoic acid, m.p. 169 - 171° $[\alpha]_D$-0.6° in chloroform.

Found : C, 56.5 ; H, 6.3 ; N, 4.7 ; S, 11.2%.
Calculated for $C_{14}H_{17}NO_4S$: C, 56.9 ; H, 5.8 ; N, 4.7 ; S, 10.8%.

The I.R. Spectrum (K Br disk) showed absorptions at :- 3000 cm^{-1} v broad (-OH), 1690 cm^{-1} s (C = O), 1645 cm^{-1} s (-CH=CH-), 1600 cm^{-1} 4 (aromatic C=C), 1340 cm^{-1} s and 1160 cm^{-1} s (,N-SO_2-), 820 cm^{-1} s (*p*-disubst. ring).

An S-benzyl-*iso*-thiouronium salt was prepared; it was recrystallised from ethanol/water as flakes m.p. 181 - 182°.

Found : C, 56.6 ; H, 6.1 ; N, 9.2%.

$C_{22}H_{27}N_3O_4S_2$ requires : C, 57.2 ; H, 5.9 ; N, 9.1%.

The P.M.R. spectrum (hexadextero-acetone solution) showed absorptions at (τ) :-
8.2 m ($-\underline{CH_2}-\underline{CH_2}$), 7.55 s ($Ø-\underline{CH_3}$), 6.6 m ($-\underline{CH_2}-N-$), 5.85 sextet, t J = 6 c/s split J = 3 c/s ($N-\underline{CH}-CHBr-CHBr-$), 5.57 d, J = 12 c/s ($N-CH-CHBr-\underline{CHBr}-COOH$), 4.79 dd, J = 12 c/s and 3 c/s ($N-CH-\underline{CHBr}-CHBr-$), 3.95 broad singlet ($COO\underline{H}.\underline{H_2}O$; disappeared on D_2O exchange), 2.36 q ($-SO_2-C_6\underline{H_4}-CH_3$).

A sample was dried by heating at 100°/1 mm for four hours to give the anhydrous acid m.p. 175 - 178°.

Found : C, 37.2; H, 3.6; N, 3.2; S, 7.1; Br, 34.9%.
$C_{14}H_{17}NO_4SBr_2$ requires : C, 37.0; H, 3.8; N, 3.1; S, 7.0; Br, 35.1%.

The I.R. spectrum (K Br disk) showed absorptions at :-
3000 cm^{-1} s, broad (-OH), 1720 cm^{-1} s (C = O), 1595 cm^{-1} m (C = C), 1445 cm^{-1} s and 1160 cm^{-1} s ($N-SO_2$), 812 cm^{-1} s (*p*-disubstituted ring).

The 3-[1'-(*p*-toluenesulphonyl)-pyrrolidin-2'-yl]-2,3-dibromopropionic acid gave an S-benzyl-*iso*thiouronium salt which was recrystallised from ethanol/water; m.p. 149 - 150°.

Found : C, 4218; H, 4.7; N, 6.7; S, 10.5; Br, 26.3%.
$C_{22}H_{27}N_3O_4S_2Br_2$ requires: C, 42.5; H, 4.3; N, 6.8; S, 10.3; Br, 25.8%.

3.33 Preparation of (±)-1,2-*erythro*-1-[1'-(*p*-toluenesulphonyl)-pyrrolidin-2'yl]-1,2-dibromo-3-hydroxypropane.

Diborane (30 ml. of a 1.07 M solution in tetrahydrofuran) was added to (±)-2,3-*erythro*-3-[1'-(*p*-toluenesulphonyl)-pyrrolidin-2'-yl]-2,3-dibromopropanoic acid hydrate (5.0 g.) dissolved in tetrahydrofuran (30 ml.). The mixture was left at room-temperature for 42 hours. The excess diborane was destroyed by the addition of water and the solvent removed under reduced pressure to give a solid residue that was lixiviated with acetone (3 x 40 ml.). The extracts were combined, concentrated to 25 ml. and diluted with light petroleum(100 ml.). Crystals of (±)-1,2-*erythro*-1-[1'-(*p*-toluenesulphonyl)-pyrrolidin-2'-yl)-1,2-dibromo-3-hydroxypropane precipitated (3.9 g., 84% yield). A sample recrystallised from dioxane/light petroleum had m.p. 190 - 191°.

Found : C, 38.2; H, 4.4; S, 7.5 ; Br, 36.1%.

$C_{14}H_{19}NO_3SBr_2$ requires : C, 38.1; H, 4.3; S, 7.3; Br, 36.3%.

The I.R. spectrum showed absorptions at :- 3500 cm^{-1} s (-OH), 2900 cm^{-1} m (C-H), 1600 cm^{-1} m and 1500 cm^{-1} m (C = C), 1340 cm^{-1} s and 1155 cm^{-1} s ($N-SO_2$), 1050 cm^{-1} m (C-OH), 825 cm s (*p*-disubstituted ring).

An acetate was prepared by heating a portion of the 1-[1'-(*p*-toluenesulphonyl)-pyrrolidin-2'-yl]-1,2-dibromo-3-hydroxypropane with a large excess of acetic anhydride on a boiling-water bath for five minutes and then diluting with water. The 1-[1'-(*p*-toluenesulphonyl)-pyrrolidin-2'-yl]-1,2-dibromo-propan-3-yl acetate crystallised on standing and was recrystallised from dioxane/light petroleum as prisms m.p. 133 - 135°.

Found : C, 39.7; H, 4.6; S, 6.8; Br, 32.7%.

$C_{16}H_{21}NO_4SBr_2$ requires : C, 39.8; H, 4.4; S, 6.6; Br, 33.1%.

3.34 Preparation of (+)-1,2-threo-1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-1-bromo-2,3-epoxypropane.

Methanolic potassium hydroxide (13 ml. of a 1M solution) was added to a suspension of (+)-1,2-erythro-1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-1,2-dibromo-propan-3-ol (4.41 g.) in dioxane (10 ml.). The mixture was refluxed for 15 minutes, diluted with water (50 ml.) and extracted with dichloromethane (3 x 20 ml.). The extracts were combined and washed with water (2 x 20 ml.), dried over anhydrous sodium sulphate and the solvent removed to give the crude epoxide (3.69 g.). This was recrystallised from tetrahydrofuran/light petroleum. The yield of (+)-1,2-threo-1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-1-bromo-2,3-epoxypropane m.p. 109 - 110° was 2.23 g., 62%.

Found :	C, 46.4; H, 5.1; S, 9.1; Br, 23.0%.
$C_{14}H_{18}NO_3Br$ requires :	C, 46.7; H, 5.1; S, 8.9; Br, 22.2%.

The I.R. spectrum (K Br disk) showed absorptions at :- 2950 cm^{-1} m (C-H), 1600 cm^{-1} m (C = C), 1345 cm^{-1} s ($N-SO_2$), 1250 cm^{-1} m (epoxide), 1160 cm^{-1} s ($N-SO_2$), 1090 cm^{-1} s (C-O-C ?), 820 cm^{-1} s (p-disubst. ring).

3.35 Attempted hydrolysis of (+)-1,2-threo-1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-1-bromo-2,3-epoxy propane.

A solution of (+)-1,2-threo-1-[1'-(p-toluenesulphonyl)-pyrrolidin-2'-yl]-1-bromo-2,3-epoxy propane (200 mg.) in dioxane (5 ml.) was refluxed with 10% aqueous hydrochloric acid (5 ml.) for ten minutes. The mixture was diluted with water (10 ml.) and extracted with dichloromethane (2 x 10 ml.).

The extract was dried over anhydrous sodium sulphate and taken to dryness. The product was recrystallised from dichloromethane/ light petroleum as needles m.p. 144 - 145°. The yield was 155 mg. The analysis was consistent with this being 1-[1'-(*p*-toluenesulphonyl)-pyrrolidin-2'-yl]-1-bromo-3-chloro-propan-2-ol.

Found : C, 42.7; H, 4.8; S, 8.3; Hal.as Br, 40.0%.

$C_{14}H_{19}NO_3SClBr$ requires : C, 42.6; H, 4.8; S, 8.1; Hal.as Br, 40.5%.

The I.R. spectrum (K Br disk) showed absorptions at :- 3500 cm^{-1} s (OH), 2950 cm^{-1} m (C-H), 1600 cm^{-1} m (C=C), 1340 cm^{-1} s and 1160 cm^{-1} s ($N-SO_2$), 1090 cm^{-1} s (C-OH), 820 cm^{-1} s (*p*-disubstituted ring), 760 cm^{-1} s (C-Cl ?).

The P.M.R. spectrum (deuterochloroform solution) showed absorptions at (τ) :-

8.5 m ($-\underline{CH_2}-\underline{CH_2}-$), 7.55 s ($\text{Ø}-\underline{CH_3}$), 6.6 m, ($N-\underline{CH_2}-CH_2$), 6.40 d ($CH-\underline{CH_2}Cl$), 6.29 s (O-$\underline{H}$ disappeared on D_2O exchange), 5.6 m ($N-\underline{CH}-\underline{CH}(Br)-\underline{CH}(OH)-$) 2.45 q ($-SO_2-C_6\underline{H_4}-CH_3$).

3.36 Preparation of (±)-1,2-*threo*-1-[1'-(*p*-toluenesulphonyl)-pyrrolidin-2'-yl]-1-bromo-3-benzyloxy-propan-2-ol.

A solution of (±)-1,2-*threo*-1-[1'-(*p*-toluenesulphonyl)-pyrrolidin-2'-yl]-1-bromo-2,3-epoxypropane (1.0 g.) and redistilled benzyl alcohol (3.0 ml.) in tetrahydrofuran (3 ml) was treated with boron trifluoride etherate (2 drops) and heated under reflux for five minutes. Water (50 ml.) was added and the mixture distilled until no further benzyl alcohol was coming over in the distillate. The residue was extracted with dichloromethane (2 x 20 ml.). The extract was dried over anhydrous sodium sulphate, concentrated to 5 ml. and diluted with light petroleum (25 ml.) when the (±)-1,2-*threo* 1-[1'-(*p*-toluenesulphonyl)-pyrrolidin-2'-yl]-1-bromo-3-benzyloxy-propan-2-ol, (1.11 g., 86%), crystallised. A sample recrystallised from dichloromethane/light petroleum had m.p. 75 - 76°.

Found : C, 53.5; H, 5.5; S, 6.9; Br, 16.8%.

$C_{21}H_{26}NO_4SBr$ requires : C, 53.8; H, 5.6; S, 6.8; Br, 17.1%.

The I.R. spectrum (K Br disk) showed absorptions at :- 3500 cm^{-1} s (O-H), 2900 cm^{-1} m (C-H), 1595 cm^{-1} m (C=C), 1335 cm^{-1} s and 1160 cm^{-1} s ($N-SO_2$), 1090 cm^{-1} s (C-O-C), 820 cm^{-1} s (*p*-disubst. ring), 743 cm^{-1} s (mono-subst. ring).

The P.M.R. spectrum (deuterochloroform solution) showed absorptions at (τ) :-
8.4 m ($-\underline{CH}_2-\underline{CH}_2-$), 7.59 s ($Ø-\underline{CH}_3$), 6.81 s ($O\underline{H}$, disappeared on D_2O exchange), 6.5 m ($N-\underline{CH}_2-CH_2$), 6.35 m ($-\underline{CH}_2-O-CH_2\ Ø$), 5.8 m ($N-\underline{CH}-\underline{CH}(Br)-\underline{CH}(OH)-CH_2-O$), 5.46 s ($O-\underline{CH}_2-Ø$), 2.70 s ($O-CH_2-C_6\underline{H}_5$), 2.47 q ($-SO_2-C_6\underline{H}_4-CH_3$).

3.37 Preparation of (±)-*cis*-1-[1'-(*p*-toluenesulphonyl)-pyrrolidin-2'-yl]-1,2-epoxy-3-benzyloxypropane.

A solution of *threo*-1-[1'-(*p*-toluenesulphonyl)-pyrrolidin-2'-yl]-1-bromo-3-benzyloxypropan-2-ol (1.2 g.) in methanol (5 ml.) was refluxed for 15 minutes with mathanolic potassium hydroxide (3.4 ml. of a 1M solution). The solution was diluted with water (20 ml.)

and extracted with dichloromethane (2 x 20 ml.). The extract was washed with water (1 x 20 ml.), dried over anhydrous sodium sulphate and taken to dryness. The residue of (±)-*cis*-1-[1'-(*p*-toluenesulphonyl)-pyrrolidin-2'-yl]-1,2-epoxy-3-benzyloxypropane was recrystallised from dioxane/light petroleum, m.p.78-80° (0.72 g., 72.4%).

Found: C, 65.0; H, 6.5; S, 8.5%.

$C_{21}H_{25}NO_4S$ requires : C, 65.1; H, 6.5; S, 8.3%.

The I.R. spectrum (K Br disk) showed absorptions at :- 2950 cm^{-1} m (C-H), 1595 cm^{-1} m (C=C), 1435 cm^{-1} s and 1165 cm^{-1} s ($N-SO_2$), 1250 cm^{-1} w (epoxide), 1100 cm^{-1} s (C-O-C), 825 cm^{-1} s (*p*-disubstituted ring), 742 cm^{-1} s (benzyl ring).

The P.M.R. spectrum (deuterochloroform solution) showed absorptions at (τ):-

8.2 m $(-\underline{CH_2}-\underline{CH_2}-)$, 7.60 s $(Ø-\underline{CH_3})$, 6.4 - 7.1 c.m. $(-\underline{CH_2}-N-\underline{CH}-\underline{CH}-\underline{CH}-)$, 6.31 d, J = 5 c/s $(CH-\underline{CH_2}-O-CH_2Ø)$, 5.41 s $(O-\underline{CH_2}-Ø)$, 2.69 s $(-O-CH_2-C_6\underline{H_5})$, 2.50 q $(CH_3-C_6\underline{H_4}-SO_2)$.

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