The Addition of Dimethylamine to Propylene Sulphide

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The product of the reaction between dimethylamine and propylene sulphide in ether has been studied in several ways and found to be 2-dimethylamino-propanethiol. Based on a comparison with the opening of alkene oxide and alkene immonium rings, it is proposed that the opening of the propylene sulphide ring includes a cyclic sulphonium intermediate,

\[
\begin{array}{c}
\text{CH}_3\text{CH}_2\text{CH}_2\text{NH} \quad \text{S} \\
\text{R} \\
\end{array}
\]

For the preparation of derivatives of \(\alpha\)- and \(\beta\)-methyl-thiocholine esters 2-dimethylamino-propanethiol-(1) and 1-dimethylamino-propanethiol-(2) are useful starting materials\(^1\). As 2-dimethylamino-ethanethiol is easily obtained from ethylene sulphide and dimethylamine\(^2\), it seemed obvious to investigate if one of the dimethylamino-propanethiols could be prepared from propylene sulphide and dimethylamine. This paper describes the work carried out to find out which of the two possible thiols I and II was formed in this reaction\(^1\).

\[
\begin{array}{c}
\text{CH}_3\text{CH}_2\text{CH}_2\text{SH} \quad \text{(I)} \\
\text{CH}_3\text{CH}_2\text{NCH}_2\text{CH}_2\text{SH} \\
\end{array}
\]

The reaction between propylene sulphide and an amine is described in the literature, but nobody has shown how the ring ruptures. Reppe and Nicolai\(^3\) say that they have obtained a primary mercaptan by treating propylene sulphide with \(n\)-butylamine. On the other hand Snyder \textit{et al.}\(^4\) guess that they got a secondary thiol when di-\(n\)-amylamine reacted with propylene sulphide, because they could show that the same amine with \(\text{iso}\)-butylene sulphide gave a tertiary mercaptan.

Regarding other reactions with propylene sulphide it has been found that hydrogen chloride, acetyl chloride and acetyl bromide\(^5\) open the ring.
at the centre carbon atom, while acetic anhydride and lithium aluminium hydride destroy the bond between the sulphur atom and the terminal carbon atom. There is, in other words, no general rule for the opening of the propylene sulphide ring which can be applied to reactions between amines and propylene sulphide.

**EXPERIMENTAL**

*Propylene sulphide* was prepared from propylene oxide and thiourea. B. p. 74—76°. Addition of dimethylamine to propylene sulphide. The reaction was carried out in anhydrous ether as described in Ref. Physical data for the dimethylamino-propanethiol are b. p. 71°/88 mm; n_D^20 = 1.4538; d_20^2 = 0.8693 g/cm³.

The hydrochloride when crystallized from a mixture of isopropanol/ligroin gave needles which, after being dried in a vacuum desiccator, melted at 167°. (Found: C 38.6; H 9.1. Calc. for C_H_4CIN(S): C 38.6; H 9.1.) The picrate, recrystallized from isopropanol/petroleum ether and dried in air, melted at 94.5°. (Found: C 38.1; H 4.5. Calc. for C_H_4H_3N_2O_3S: C 37.9; H 4.6.)


2-Dimethylamino-1-chloropropane hydrochloride was prepared from thionyl chloride and 2-dimethylamino-propanol-(1) which was obtained by reducing ethyl-α-dimethylamino-propionate with lithium-aluminium hydride. M. p. 102°. Schultz and Sprague observed 103—104°.

*Isothiuronium compounds.* Dimethylamino-chloropropane hydrochloride and thiourea were refluxed in abs. ethanol. For the product from 1-dimethylamino-2-chloropropane hydrochloride see Ref.

From 2-dimethylamino-1-chloropropane hydrochloride a crude product in 54% yield was obtained, which, after recrystallization, melted at 153°. (Found: C 30.8; H 7.4. Calc. for C_H_4Cl_2N_4S: C 30.8; H 7.3.)

Hydrolysis of *isothiuronium salts.* The reaction was carried out as described in Ref.

For the hydrolysis of the isothiuronium compound from 1-dimethylamino-2-chloropropane hydrochloride see Ref. The hydrochloride of the hydrolysis product after precipitation by ether from a solution in absolute ethanol/ligroin (1:1) melted at 114—115°. (Found: C 38.5; H 9.4. Calc. for C_H_4CIN(S): C 38.6; H 9.1.)

The picrate, after recrystallization from absolute ethanol, melted at 165°. Renshaw et al. reported 159—166°. (Found: C 38.6; H 4.6. Calc. for C_H_4H_3N_2O_3S: C 37.9; H 4.6.)

The isothiuronium compound from 2-dimethylamino-1-chloropropane hydrochloride gave thiol in 48% yield. B. p. 55.5°/27 mm. n_D^20 = 1.4678. (Found: C 50.1; H 11.0. Calc. for C_H_4NS: C 50.4; H 10.8.)

*S-Acetylation and N-methylation of the dimethylamino-propanethiol.* The reactions with acetic anhydride and methyl bromide were carried out as reported in Ref. The dimethylamino-propanethiol from propylene sulphide gave a product melting at 188°. The dimethylamino-propanethiol from the isothiuronium salt gave a product melting at 185°. For analyses see Ref.

Treatment of the dimethylamino-propanethiols with a Raney nickel catalyst. To 2 ml of dimethylamino-propanethiol in 100 ml of absolute ethanol Raney nickel catalyst, W 5°, was added in portions, with shaking, until the gas evolution ceased. At the same time the red colour formed during the reaction disappeared. The catalyst was removed by filtration, and a saturated solution of picric acid in absolute ethanol was added. To avoid excess of picric acid the E.M.F. of a glass-calomel electrode system was plotted against the volume of the picric acid solution. When the curve showed that the equivalence point had almost been reached, the addition was stopped. The solution was evaporated to dryness under reduced pressure at a temperature below 40°. The residue was crystallized once from water. The yield of the crude product was about 50%.

The dimethylamino-propanethiol from the isothiuronium salt gave a product which melted at 110—115°. Recrystallization gave flakes which melted at about 110°. (Found: C 41.6; H 5.2. Calc. for C_H_4H_3N_2O_3S: C 41.8; H 5.1.)
The dimethylamino-propanethiol from propylene sulphide gave a product which melted at 130–150°. Recrystallization gave flakes which melted at about 110°. (Found: C 41.8; H 5.2. Calc. for C11H14N2O2 (316.3): C 41.8; H 5.1.)

**Treatment of quaternary nitrogen compounds with a Raney nickel catalyst.** One gram of the nitrogen compound and 20 g of catalyst were shaken for 1 h in 75 ml of absolute methanol. After filtration the solution was evaporated to dryness under reduced pressure at room temperature. The reaction was carried out with the two acetyl methyl-thiocholine iodides 1, acetyl choline iodide and choline iodide. In all cases the residues amounted to only a few mg.

**Dimethylpropylamine picrates.** One mole of propyl iodide was dissolved in 1.5 l of dry ether and cooled to −10°. Three moles of anhydrous dimethylamine were added, and the mixture was placed in an ice-water bath, which was allowed to come to room temperature. After 6 days a precipitate, consisting mainly of dimethylamine hydroiodide and possibly a little dimethyldipropylammonium iodide, was filtered off. The excess dimethylamine in the filtrate was bound as amide by adding acetic anhydride in portions until no increase in the temperature could be observed. The dimethylpropylamine was then precipitated with hydrogen chloride. The precipitate was filtered off by suction, washed with ether and dried in a vacuum desiccator. The picrate was obtained on cooling a solution of the crude hydrochloride and an equivalent amount of picric acid in the smallest possible amount of hot water. It was recrystallized once from water. Dimethyl-1-propylamine picrate: flakes, m. p. 109°. (Found: C 41.8; H 5.1. Calc. for C11H14N2O2 (316.3): C 41.8; H 5.1.) Dimethyl-isopropylamine picrate: needles, m. p. 239°. (Found: C 41.8 H 5.1. Calc. for C11H14N2O2 (316.3): C 41.8; H 5.1.)

**Infra-red spectra.** Samples were prepared from about 2 mg of the compound to be investigated and 300 mg of potassium bromide.

The spectra were recorded with a Perkin-Elmer spectrophotometer, Model 21, equipped with a rock-salt prism. The following settings of the instrument were used: resolution 0.027, response 2.1170, gain 6, scale 5 cm/μ, speed about 1 μ/min.

**RESULTS**

**Preparative work.** The addition of dimethylamine to propylene sulphide (reaction (1)) in ether gives a product which seems to consist of only one of the isomers I and II. It distils at constant temperature and the melting points of the hydrochloride and the picrate change only slightly on recrystallization (Table 1).

**Table 1.** Physical data for the products of the reactions (1) and (2) and derivatives.

<table>
<thead>
<tr>
<th>Product of reaction</th>
<th>B.p./mm Hg</th>
<th>nD</th>
<th>d25g/cm³</th>
<th>Melting-points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>hydrochloride</td>
</tr>
<tr>
<td>(1)</td>
<td>71°/88</td>
<td>1.4538</td>
<td>0.8693</td>
<td>167°</td>
</tr>
<tr>
<td>(2)</td>
<td>78.5°/70</td>
<td>1.4684</td>
<td>0.9046</td>
<td>114—115°</td>
</tr>
</tbody>
</table>

* Acetyl methyl-thiocholine bromide.

As the analytical literature gives no test that is characteristic for primary or secondary thiols, an attempt was made to synthesize I and II. A possible way for the dimethylamino-propanethiols was to synthesize them from the hydrochlorides of the corresponding chlorides, III and IV. However, when

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these compounds were refluxed with thiourea in ethanol the resulting \textit{iso}-thiuronium compounds were found to be identical (from III m.p. 152°; from IV m.p. 154°). The refractive index of the thiols formed on hydrolysis of the \textit{iso}thiuronium salts also indicated the formation of only one isomer (from III $n_2^\infty = 1.4678$; from IV $n_2^\infty = 1.4684$).

The fact that only one \textit{iso}thiuronium salt was obtained from III and IV is not astonishing, as Schultz and Sprague have found that III when melted rearranges into IV. As IV is the stable isomer, it seems most likely that an isomerisation occurs in the reaction between III and thiourea giving a compound with the \textit{iso}thiuronium group bonded to the centre carbon atom. However, the possibility of an isomerisation in the reaction with IV could not be excluded at this point.

As the dimethylamino-propanethiols resulting from the reactions (1) and (2) have different physical properties themselves and as salts (Table 1), one of the thiols must have the structure I and the other II. By treatment first with acetic anhydride and then with methyl bromide they were transformed into N-(S-acetyl-mercaptopropyl)-trimethylammonium bromides (acetyl methyl-thiocholine bromides) and a comparison could thus be made with the product of reaction (3) (m.p. 187°). $\text{V}$ was known to be acetyl $\alpha$-methyl-thiocholine bromide, as Davies and Savige have been able to elucidate the direction of the first step of reaction (3). From the values in Table 1 the conclusion can be drawn that the product of reaction (1) has the structure I and that (2) gives II. A study of the infra-red spectra of the acetyl methyl-thiocholine bromides confirms the correctness of the conclusion.

\textit{Degradations with a Raney nickel catalyst.} In the hope of finding other ways of confirming the structures of the dimethylamino-propanethiols they were hydrogenated with a Raney nickel catalyst, a method that has been widely used for replacing the sulphur atom of organic sulphur compounds.

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with hydrogen atoms\textsuperscript{10,11}. The amines formed were isolated as picrates and compared with the picrates of the tertiary amines of reaction (4).

\[
2(\text{CH}_3)_2\text{NH} + RI \rightarrow RN(\text{CH}_3)_2 + [(\text{CH}_3)_2\text{NH}I]_2
\]

\[R = n\text{-propyl or isopropyl}\]

Contrary to the picrates of (4) (\textit{n\text{-propyl} m.p. 109\textdegree; \textit{isopropyl} m.p. 239\textdegree}) the two picrates from the hydrogenation reactions showed no distinct melting-points indicating that they were not pure. After one recrystallization from water both melted at about 110\textdegree. The melting-points and the analyses indicate a rearrangement of the \textit{isopropylamine} derivative into the \textit{n\text{-propyl}} one during the hydrogenation. Further confirmation for the rearrangement was obtained from the infrared spectra of the four picrates.

No rearrangement has been observed on treating benzoyl-\textit{L}(-)-cystine with Raney nickel, and benzoyl-\textit{L}(+)\textendash;alanine is formed\textsuperscript{11}. A possible explanation of the difference between the reactions lies in the character of the unshared electron pair of the nitrogen atom, which in benzoyl-cystine is strongly attrac-

\[\text{Fig. 1. Infra-red spectra of acetyl thiocholine iodide (first spectrum) and of the acetyl methyl-thiocholine iodides prepared from the dimethylamino-propanethiols derived from propylene sulphide and dimethylamine (second spectrum) and from S-(dimethylamino-propyl)-isothiuronium chloride hydrochloride.}\]

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Fig. 2. Infra-red spectra of some derivatives of choline and of some tetraalkylammonium iodides.

ted by the benzoyl and the carboxylic groups and thus has a reduced ability to take part in reactions. If all the electron pairs of the nitrogen atom are occupied, as in a quaternary ammonium compound, no rearrangement would be expected. The acetyl methyl-thiocholine iodides prepared from the two dimethylamino-propanethiols\(^1\) were therefore treated in ethanol solution with Raney nickel. The reactions were supposed to give \(n\)-propyl- and iso-propyltrimethylammonium iodide. However, when the solutions were evaporated to dryness at room temperature almost no residue was left, showing that the quaternary ammonium group must have been degraded by the Raney nickel. This behaviour was also found on treating choline iodide and acetyl choline iodide with Raney nickel. Consequently, the hydrogenation reactions could not give any information on the structures of the dimethylamino-propanethiols.

Infra-red spectra. The spectra of the acetyl methyl-thiocholine iodides derived from the two dimethylamino-propanethiols and of acetyl thiocholine iodide\(^2\) are shown in Fig. 1. The compounds are differently substituted in the carbon chain between the nitrogen and the sulphur atoms and must therefore exhibit dissimilarities in the C—N\(^+\) and C—S(—CO) bands. The C—S stretching bands which are expected to appear at 600—660 cm\(^{-1}\) (15—

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17 \mu\textsuperscript{12} could not be recorded. As tetramethylammonium iodide has strong absorption in the range 900—1 000 cm\textsuperscript{-1} (11—10 \mu) which can be ascribed to the C—N\textsuperscript{+} bond, this range has also been recorded (Fig. 2) for some other compounds related in the same way as the thiocholine esters. In all cases the compounds with the simplest structure have the simplest spectra in this range, while the most complicated spectra are found for the compounds having an additional methyl group at the carbon atom adjacent to the nitrogen atom. This result shows that the infra-red spectra give some information about the actual structures and is a support for the formation of 2-dimethylamino-propanethiol-(1) in the addition of dimethylamine to propylene sulphide.

DISCUSSION

The only direct proof that the opening by dimethylamine of the propylene sulphide ring leads to a primary mercaptan (1) is the identification, by comparison of the melting-points, of the acetyl methyl-thiocholine bromide obtained from the reaction product with that obtained from the addition product of propylene sulphide and acetylbromide (3). This result is, however, more or less clearly supported by the other experiments, and nothing points to a rupture of the terminal C—S-bond. Only the rates of hydrolysis of the two acetyl methyl-thiocholine bromides, which have been studied by Heilbronn \textsuperscript{13,14}, seem strange. She found that the compound prepared from the product of (2) was hydrolyzed somewhat faster than \( V \), while the reverse relationship was observed for the corresponding oxygen compounds. No explanation of the difference has been found.

It is interesting to compare the ring opening of propylene oxide and propylene sulphide. The propylene oxide ring is, in almost every reaction, destroyed at the terminal carbon atom, while the propylene sulphide ring generally ruptures at the centre carbon atom. The difference is probably due to different reaction mechanisms. The first step in the addition to propylene oxide is often a nucleophilic attack, for instance the additions of acetic acid \textsuperscript{15}, phenol \textsuperscript{16} and methanol \textsuperscript{17} which all are catalyzed by alkali.

As sulphur atoms giveonium compounds much more easily than oxygen atoms, it seems probable that additions to propylene sulphide involve the formation of an intermediate cyclic sulphonium ion, \( \text{CH}_3\text{CH}=\text{CH}_2 \)

\[
\begin{array}{c}
\text{S}^+ \\
\downarrow \\
\text{R}
\end{array}
\]

which then opens at the centre carbon atom while capturing a negative ion. Support for this theory is obtained from ring ruptures of nitrogen compounds. Schultz and Sprague \textsuperscript{7} found that (1-chloropropyl-(2))-dimethylamine cannot be distilled without rearrangement to (2-chloropropyl-(1))-dimethylamine. It is very likely that this rearrangement involves the formation of the cyclic quaternary ammonium ion, \( \text{CH}_2\text{CH}=\text{CH}_2 \)

\[
\begin{array}{c}
\text{N(\text{CH}_3)_2} \\
\downarrow \\
\text{CH}_3
\end{array}
\]

which opens at the centre carbon atom.

Another reaction showing that an isopropyl amino compound is less stable than a \( n \)-propyl amino compound is the reaction of 2-dimethylamino-propane-

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thiol-(1) with Raney nickel catalyst, Ni(H₂), which gives dimethyl-n-propyl-
amine as described above. This reaction also throws some light on the mecha-
nism of the removal of the sulphur atom by the Raney nickel catalyst. The

\[
\text{CH}_2\text{CH}_2\text{CH}_2\text{NiCH}_2\text{NiCH}_2\text{NiCH}_2\text{NiCH}_2 \quad \text{(5)}
\]

first step seems to be a rupture of the C—S-bond in such a way that the
shared electron pair goes to the sulphur atom. Thus a carbonium ion is formed
which can react with the unshared electron pair of the nitrogen atom, resulting
in a cyclic quaternary immonium ion. This finally opens at the centre carbon
atom.

The formation of a cyclic sulphonium ion intermediate in some addition
reactions with propylene sulphides has also been proposed by Davies and
Savige ⁶,¹⁸. For the reaction between propylene sulphide and an amine they
propose, however, a ring-opening at the terminal carbon atom. It is certainly
difficult to find a source for the first hydrogen ions required for the inter-
mediate sulphonium ion CH₃CH—CH₂, but once some mercaptan has formed

\[
\text{S} \quad \text{H}
\]

it can give rise to the hydrogen ions necessary.

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REFERENCES

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