Structure of some 1,2,3,4-
Tetrahalogenocyclohexanes

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Tetrahalogenocyclohexanes obtained from
1,3-cyclohexadiene and halogens are usually considered to be 1,2,3,4-derivatives. This is probably correct, but the first step is not necessarily a Thiele addition and when different halogens are used in the two steps the structure formula of the final product must be determined in each separate case. We are interested also in the steric forms of tetrahalogeno compounds and have carried out some preliminary investigations in the field. The only member of the series the structure of which has been definitively settled is the 1,2,3,4-tetra-
bromocyclohexane of m.p. 142° investigated by E. Wang Lund and which has the configuration eee e. Besides this compound we had four more representatives of this group at our disposal (cf. Table 1) and the results of the determination of the dipole moments of all five substances are listed in Table 1.

Table 1.

<table>
<thead>
<tr>
<th>Substances</th>
<th>Br₄</th>
<th>Br₃</th>
<th>Br₂Cl₂</th>
<th>Cl₄</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melting point</td>
<td>142°</td>
<td>90°</td>
<td>156°</td>
<td>128°</td>
</tr>
<tr>
<td>Dipole moment</td>
<td>2.89</td>
<td>2.82</td>
<td>3.66</td>
<td>3.81</td>
</tr>
</tbody>
</table>

If "theoretical" dipole moments are calculated assuming the partial electric moments of both C—Cl and C—Br bonds to be 2.1 D and all valency angles "tetrahedral" the following moments are found: eee (3.4), eee e (4.9), eee (3.4), eee a (3.4), eee (0) aee a (3.4), aee a (5.8). Considering the results earlier obtained for halogenated cyclohexanes it seems very probable that the substances with a measured dipole moment of about 2.9 D all belong to the group with theoretical values 3.4 D. This is substantiated by the fact that the tetrabromocyclohexane m.p. 142° has been shown to be the eee compound. The two compounds with dipole moments of 3.7—3.8 D would then be expected to represent the configuration eee a. The alternative eee a would probably demand a still higher experimental dipole moment and would also be less stable and more unlikely to result from the reaction mentioned above. Furthermore, it has already been shown by X-ray analysis that the tetrabromo compound m.p. 156° and the dichlordibromo compound m.p. 128° form isomorphous crystals.

Before starting X-ray crystallographic work we have tried to elucidate the structures in question using electron diffraction technique. The σ(r)/r-curves thus obtained for the tetrabromocyclohexane (156°) and the dichlordibromocyclohexane (128°) had important features in common. In Fig. 1 the σ(r)/r-curve of the tetrabromo compound has been reproduced. The pronounced peak at r = 5.8 Å can only be due to a 1e, 3e-Br-Br-distance which would exclude the conformations eee e, eee e and eee a. If we consider the fact that no indication of a 1e, 4e-distance (r = 6.7 Å) is observed, the two conformations eee e and eee a should also be excluded. The two remaining possibilities, eee e and eee a, cannot easily be distinguished on the basis of electron diffraction experiments as both may be brought in good agreement with the observed σ(r)/r-curves.

In order to decide whether the first reaction step is a Thiele addition or not it appears necessary to complete the crystal structure determination of the 128° substance. In the first case only one com-

Fig. 1.
pound with the arrangement seen is possible, in the second case two different substances may arise.

We wish to thank cand. real. A. Munthe-Kaas for his valuable assistance in carrying out dipole moment measurements.


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Derivatives of β-10-Phenothiazinepropionic Acid

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Previous investigations in this laboratory have shown that certain derivatives of phenothiazine-10-carboxylic acid containing basic substituents possess strong spasmolytic and nicotinolytic properties. As an extension of this work some new derivatives of the easily accessible β-10-phenothiazinepropionic acid were prepared (I-VI).

\[
\begin{align*}
& S \quad \text{N} \cdot \text{CH}_3 \cdot \text{CH}_3 \cdot \text{CO} \cdot \text{R} \\
& \text{I. } \text{R} = \text{Cl} \\
& \text{II. } \text{R} = \text{N} \\
& \text{III. } \text{R} = \text{O} - \text{CH}_3 - \text{CH}_3 - \text{N(CH}_3)_2 \\
& \text{IV. } \text{R} = \text{O} - \text{CH}_3 - \text{CH}_3 - \text{N(C}_6\text{H}_5)_2 \\
& \text{V. } \text{R} = \text{S} - \text{CH}_3 - \text{CH}_3 - \text{N(C}_6\text{H}_5)_2 \\
& \text{VI. } \text{R} = \text{NH} - \text{CH}_3 - \text{CH}_3 - \text{N(C}_6\text{H}_5)_2 \\
\end{align*}
\]

The esters and amides were obtained via the acid chlorides (I). The compounds III-VI were tested for cholinolytic and antihistaminic effect but their activity was rather weak.

Experimental. β-10-Phenothiazinepropionyl chloride (I). A mixture of β-10-phenothiazinepropionic acid (5.42 g, 0.02 mole), pyridine (1.58 g, 0.02 mole), and ether (60 ml) was cooled to -5° and thionyl chloride (2.38 g, 0.02 mole) was added drop by drop with stirring. The mixture was kept at room temperature overnight. The separated pyridine hydrochloride was then filtered off and the ether was evaporated in vacuo. The residue (5.4 g, 93%) was recrystallised twice from ether; m. p. 117—119°. (Found: C 62.8; H 3.97; Cl 12.0. C₁₅H₁₂NClO₃ requires C 62.8; H 4.18; Cl 12.2%).

N-(β-10-Phenothiazinepropionyl)-piperidine (II). The acid chloride obtained above (1.45 g) was dissolved in ether (15 ml) and treated with piperidine (1.1 g) at room temperature. The mixture was filtered and the filtrate washed with water and evaporated to dryness. The residue (0.9 g, 53%) was recrystallised from ethanol; m. p. 127—128°. (Found: C 70.4; H 6.53; N 8.09. C₁₅H₁₄N₂O₂ requires C 70.9; H 6.55; N 8.28%)

β’-Dimethylaminooethyl β-10-phenothiazinepropionate (III). A solution of I (2.9 g, 0.01 mole) and β’-dimethylaminooethyl (2.2 g, 0.025 mole) in toluene (25 ml) was refluxed for two hours. After cooling the mixture was filtered and the filtrate washed with water and extracted with 2 N hydrochloric acid. The extract was made alkaline with sodium carbonate solution and the oily base extracted with ether. The ether was then evaporated giving a solid residue (2.0 g, 60%) which melted at 81—83° after recrystallisation from ether. (Found: C 66.5; H 8.46; N 8.4. C₁₅H₁₄N₂O₂S requires C 66.6; H 6.48; N 8.18%)

β’-Diethylaminooethyl β-10-phenothiazinepropionate oxalate (IV). Prepared by the same method as III. The oily base was isolated as the oxalate. Yield 55%; m. p. 118—120° (from acetone). (Found: C 59.3; H 6.21. C₁₅H₁₆N₂O₄ requires C 60.0; H 6.13%)

β’-Diethylaminooethyl β-10-phenothiazinepropionate oxalate (V). Prepared from I and β’-diethylaminooethyl mercaptan. Yield 89%; m. p. 131—132° (dec.) after recrystallisation from ethyl acetate. (Found: C 58.5; H 6.08; N 5.84. C₁₅H₁₄N₂O₄S requires C 58.8; H 5.92; N 5.88%)

N-(β-10-Phenothiazinepropionyl) - N’-N’’-diethylthelylenediamine oxalate (VI). Prepared from I and N,N-diethylthelylenediamine by the same method as for the esters. Yield 87%; m. p. 130—131° (from acetone). (Found: C 58.9; H 6.14; N 8.78. C₁₅H₁₅N₂O₄S requires C 60.1; H 6.36; N 9.14%)


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