Structure of some 1,2,3,4-Tetrahalogeno*cyclo*hexanes

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Tetrahalogeno*cyclo*hexanes obtained from 1,3-*cyclo*hexadiene 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-tetrabromo*cyclo*hexane of m. p. 142° investigated by E. Wang Lund[1] and which has the configuration eeee. 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.

Substances	Br_4	Br_4	Br_4	Br_3Cl_3	Cl_4
Melting point	142°	90°	156°	128°	112°
Dipole moment	2.89	2.82	3.66	3.81	2.95

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: eeee (3.4), eeea (4.9), eaee (3.4), eeaa (3.4), eaae (0) aeea (3.4), aeae (6.8). Considering the results earlier obtained for halogenated *cyclo*hexanes 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 tetrabromo*cyclo*hexane m. p. 142° has been shown to be the eeee compound. The two compounds with dipole moments of 3.7—3.8 D would then be expected to represent the configuration *eeea*. The alternative aeae 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 dichlorodibromo compound m. p. 128° form isomorphous crystals [2].

Before starting X-ray crystallographic work we have tried to elucidate the structures in question using electron diffraction technique. The $\sigma(r)/r$-curves thus obtained for the tetrabromo*cyclo*hexane (156°) and the dichlorodibromo*cyclo*hexane (128°) had important features in common. In Fig. 1 the $\sigma(r)/r$-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 aaee, eaae and aeea. If we consider the fact that no indication of a 1e, 4e-distance ($r = 6.7$ Å) is observed, the two conformations eeee and eaee should also be excluded. The two remaining possibilities, aeae and aeee, cannot easily be distinguished on the basis of electron diffraction experiments as both may be brought in good agreement with the observed $\sigma(r)/r$-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-

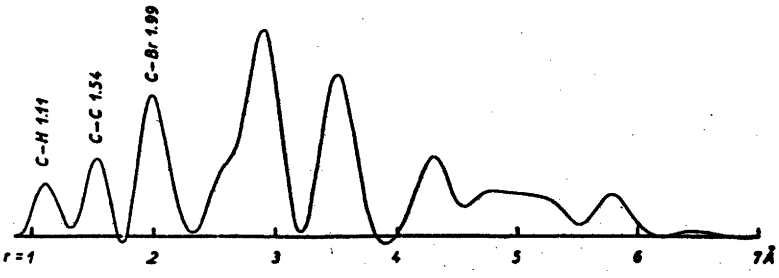

Fig. 1.

pound with the arrangement acce 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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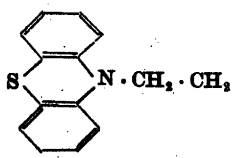
Previous investigations in this Laboratory have shown that certain derivatives of phenothiazine-10-carboxylic acid containing basic substituents possess strong spasmolytic and nicotinolytic properties [1]. As an extension of this work some new derivatives of the easily accessible β-10-phenothiazinepropionic acid were prepared (I—VI).



I. R = Cl
II. R = N⟨ ⟩
III. R = O—CH_2—CH_2—$N(CH_3)_2$
IV. R = O—CH_2—CH_2—$N(C_2H_5)_2$
V. R = S—CH_2—CH_2—$N(C_2H_5)_2$
VI. R = NH—CH_2—CH_2—$N(C_2H_5)_2$

The esters and amides were obtained *via* the acid chloride (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 [2] (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 62.6; H 3.97; Cl 12.0. $C_{15}H_{12}ClNOS$ requires C 62.2; 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 6.23; N 8.09. $C_{20}H_{22}N_2OS$ requires C 70.9; H 6.55; N 8.28 %).

β'-Dimethylaminoethyl β-10-phenothiazinepropionate (III). A solution of I (2.9 g, 0.01 mole) and β-dimethylaminoethanol (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 6.46; N 8.14. $C_{19}H_{22}N_2O_2S$ requires C 66.6; H 6.48; N 8.18%).

β'-Diethylaminoethyl 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 59.8; H 6.21. $C_{23}H_{28}N_2O_6S$ requires C 60.0; H 6.13 %).

β'-Diethylaminoethyl β-10-phenothiazinethiopropionate oxalate (V). Prepared from I and β-diethylaminoethyl mercaptan [3]. Yield 89 %; m. p. 121—122° (dec.) after recrystallisation from ethyl acetate. (Found: C 58.5; H 6.08; N 5.84. $C_{23}H_{28}N_2O_5S_2$ requires C 58.0; H 5.92; N 5.88 %).

N-(β-10-Phenothiazinepropionyl)-N^1,N^1-diethylethylenediamine oxalate (VI). Prepared from I and N,N-diethylethylenediamine [4] by the same method as for the esters. Yield 87 %; m. p. 130—131° (from acetone). (Found: C 59.8; H 6.14; N 8.78. $C_{23}H_{29}N_3O_5S$ requires C 60.1; H 6.36; N 9.14 %).

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