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SEVEN- AND EIGHT-MEMBERED RINGS CONTAINING CARBON AND TWO SULPHUR ATOMS[1]

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ABSTRACT

7-Chloro-2,3-dihydrobenzo(*f*)-1,4-dithiepin (IV) has been synthesized from 2-(2-chloroethylmercapto)-5-chlorobenzyl chloride (I). Attempts to synthesize the higher homologues of IV by this method failed because the required intermediates cleaved at the alkyl–sulphur bond. A reaction product of *p*-chlorothiophenol, formaldehyde, and hydrogen chloride has been identified as 2,8-dichloro-6H,12H-dibenzo(*b*,*f*)-1,5-dithiocin (VI), a tricyclic system with the eight-membered ring containing two sulphur atoms.

It has been previously shown (1, 2) that *o*-ω-chloroalkoxybenzyl isothiuronium chlorides (II, Y = O) undergo simultaneous degradation and cyclization in the presence of dilute alkali to form macrorings IV (Y = O) containing carbon, oxygen, and sulphur. It was also indicated that this reaction involves the intermediate III (Y = O). The ease with which these macrorings formed was attributed to the presence of the two heteroatoms which provided favorable bond angles.

In the present investigation it was decided to examine the preparation of rings containing two sulphur atoms. Accordingly *p*-chlorophenyl 2-chloroethyl sulphide was chloromethylated and the resulting 2-(2-chloroethylmercapto)-5-chlorobenzyl chloride (I, Y = S, $n = 2$) was treated with thiourea. This produced the required isothiuronium salt II (Y = S, $n = 2$) which when added to a large volume of hot dilute alkali yielded 7-chloro-2,3-dihydrobenzo(*f*)-1,4-dithiepin (IV, Y = S, $n = 2$). Attempts to synthesize the higher homologues of IV (Y = S, $n > 2$) failed because the required intermediates I (Y = S, $n > 2$) could not be obtained.

It was found that the sulphur–alkyl linkage of $p\text{-ClC}_6\text{H}_4\text{S(CH}_2)_n\text{Cl}$ (where $n > 2$), unlike the ether linkage of $p\text{-ClC}_6\text{H}_4\text{O(CH}_2)_n\text{Cl}$, was susceptible to cleavage under the acidic conditions of chloromethylation. Thus when *p*-chlorophenyl 4-chlorobutyl sulphide was subjected to the same chloromethylation conditions as were used in the preparation of 2-(2-chloroethylmercapto)-5-chlorobenzyl chloride (I, Y = S, $n = 2$) from *p*-chlorophenyl 2-chloroethyl sulphide, no reaction occurred. However, when the amount of condensing agent (zinc chloride) was increased, reaction did occur but I (Y = S, $n = 4$) was not the product. Instead, a high-melting, difficultly soluble compound was isolated. This compound was also formed when *p*-chlorothiophenol, bis(*p*-chlorophenylmercapto)-methane (3, 4), 1,2-bis(*p*-chlorophenylmercapto)ethane, and 1,4-bis(*p*-chlorophenylmercapto)butane but not 1,3-bis(*p*-chlorophenylmercapto)-2-chloropropane (5) were subjected to the more drastic chloromethylation. It became evident that *p*-chlorothiophenol was the intermediate in the formation of the high-melting compound and that the sulphides produced this intermediate by cleavage at the sulphur–alkyl bond. That 1,3-bis(*p*-chlorophenylmercapto)-2-chloropropane did not undergo cleavage under the acidic conditions of chloromethylation may be attributed to the steric hindrance offered by the alkyl chlorine atom. It is remarkable that bis(*p*-chlorophenyl) disulphide also remained unaltered under these conditions.

The structure of the unknown high-melting compound obtained from *p*-chlorothiophenol was determined in the following manner. Analyses revealed the empirical

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[1] *Manuscript received January 15, 1958.*
Contribution from the Dominion Rubber Company Limited Research Laboratories, Guelph, Ontario.

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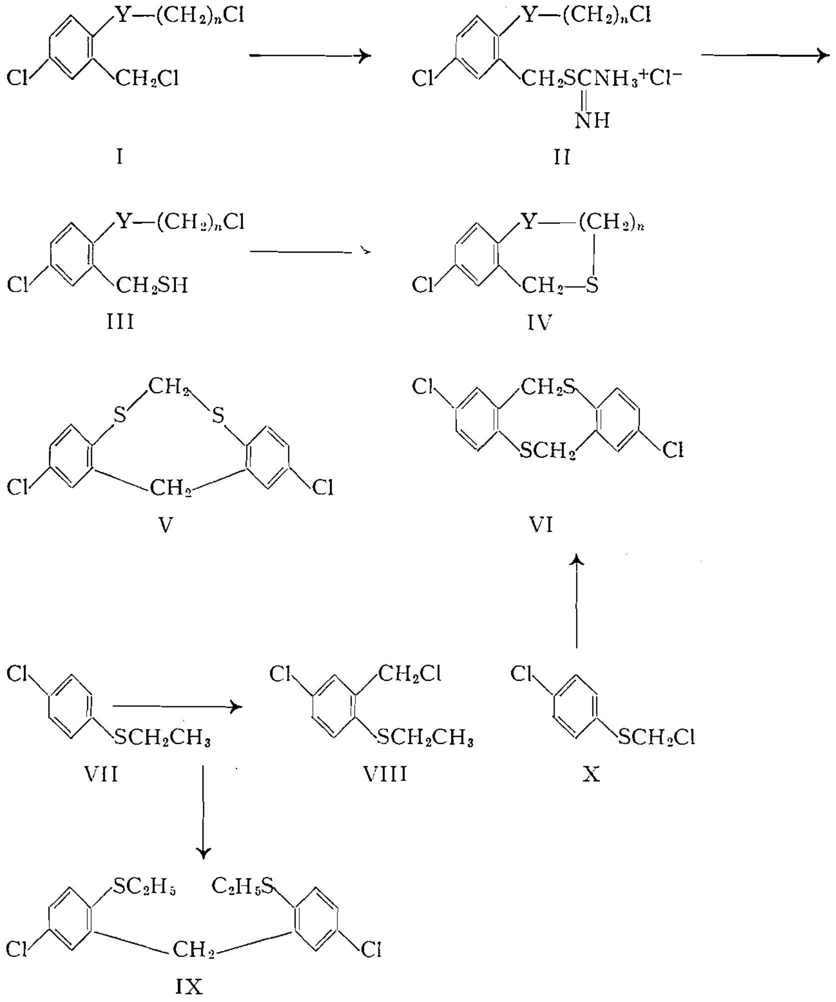

formula $C_{14}H_{10}Cl_2S_2$. A low molecular weight was indicated from the fact that the compound could be sublimed *in vacuo*, and a determination according to the method of Rast gave a figure of 315. On the basis of the properties and the origin of the compound, two possible structures, V and VI, were proposed. Further examination of the unknown compound showed that it was stable under a variety of acidic conditions and this finding eliminated the structure V, which is a mercaptal and therefore susceptible to acid hydrolysis. An attempt to synthesize V by preparing 2,2′-bis(ethylmercapto)-5,5′-dichlorodiphenylmethane (IX) from VII and VIII and subjecting it to chloromethylation resulted only in resinous material.

There are two possible routes by which the compound of structure VI could form from *p*-chlorothiophenol, formaldehyde, and hydrogen chloride in the presence of zinc chloride. Firstly, C-chloromethylation could occur to form 2-mercapto-5-chlorobenzyl chloride, two molecules of which could then react with each other in the presence of zinc chloride to form VI. Secondly, S-chloromethylation could occur to form *p*-chlorophenyl chloromethyl sulphide (X), two molecules of which could then undergo a Friedel–Crafts reaction with each other to form VI. That VI was formed via the second route was shown

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by synthesis. *p*-Chlorothiophenol was treated with formaldehyde and hydrogen chloride according to the method of Scherer and Fink (6) to form *p*-chlorophenyl chloromethyl sulphide (X). Then when X was heated with zinc chloride in acetic acid 2,8-dichloro-6H,12H-dibenzo(*b*,*f*)-1,5-dithiocin (VI) was formed in high yield. On the other hand 2-ethylmercapto-5-chlorobenzyl chloride (VIII) when heated with zinc chloride in acetic acid saturated with hydrogen chloride did not produce VI.

The reaction of *p*-chlorothiophenol with formaldehyde and hydrogen chloride follows a course unlike that of its oxygen analogue. Thus when *p*-chlorophenol was treated with formaldehyde and hydrogen chloride under the conditions used in the preparation of VI, there was formed 6-chloro-8-chloromethyl-1,3-benzodioxane (7). This is obviously a reaction product of only one molecule of *p*-chlorophenol. *p*-Thiocresol did not produce a dithiocin of the type VI when subjected to chloromethylation. The product was a resin.

The chloromethylation of *p*-chlorothiophenol now provides an easy access to the ring system VI, which up to the present time was available only in the form of dibenzo(*b*,*f*)-1,5-dithiocin-6,12-dione, a dehydration product of thiosalicylic acid (8).

EXPERIMENTAL

2-(2-Chloroethylmercapto)-5-chlorobenzyl Chloride (I, Y = S, n = 2)

A reaction mixture of acetic acid (300 ml.), paraformaldehyde (10 g.), zinc chloride (15 g.), and 2-chloroethyl *p*-chlorophenyl sulphide (60 g.) (5) was saturated with hydrogen chloride and then heated at 85°–90° for 3 days. The reaction mixture was concentrated *in vacuo* to about half its original volume and then diluted with dilute hydrochloric acid. The precipitated oil was extracted with benzene, the benzene solution washed with water, with aqueous sodium bicarbonate, and with water. The solvent was removed and the residue fractionally distilled. Fraction 1, b.p. (12 mm.) = 150°–170°, 20 g.; fraction 2, b.p. (12 mm.) = 170°–185°, 13 g.; and fraction 3, b.p. (12 mm.) = 185°–190°, 25 g. Fraction 3, which was the required product, was not purified but was used directly in the formation of the isothiuronium salt (see below).

2-(2-Chloroethylmercapto)-5-chlorobenzyl Isothiuronium Chloride (II, Y = S, n = 2)

A solution of crude 2-(2-chloroethylmercapto)-5-chlorobenzyl chloride (fraction 3 above) (20 g.), thiourea (10 g.), and ethanol (120 ml.) was heated under reflux for 3 hours. The solvent was removed *in vacuo*, the residue dissolved in hot water (50 ml.), and the solution was allowed to cool. The white precipitate (15 g.) was filtered, washed with cold water and with benzene, and crystallized from water, yielding white prisms melting at 143°–145°. Anal. Calc. for $C_{10}H_{13}N_2Cl_3S_2$: C, 36.20; H, 3.92. Found: C, 36.01; H, 4.04.

7-Chloro-2,3-dihydrobenzo(f)-1,4-dithiepin (IV, Y = S, n = 2)

A solution of 2-(2-chloroethylmercapto)-5-chlorobenzyl isothiuronium chloride (8 g.) in methanol (50 ml.) and water (50 ml.) was added dropwise to a stirred hot solution of sodium hydroxide (5 g.) in water (500 ml.) heated on the steam bath. The addition time was approximately $\frac{1}{2}$ hour and the reaction mixture was heated for an additional $\frac{1}{2}$ hour. The precipitated yellow oil was extracted with benzene, the solution washed with water, and the solvent removed. The residue distilled at 180°–182° (12 mm.) and the distillate when crystallized from methanol yielded golden prisms (1.9 g. or 35%) melting at 91°–92°. Anal. Calc. for $C_9H_9ClS_2$: C, 49.87; H, 4.14. Found: C, 50.23, 49.96; H, 4.15, 3.94.

p-Chlorophenyl 4-Chlorobutyl Sulphide

To a solution of potassium hydroxide (30 g.) in methanol (100 ml.) was added *p*-chlorothiophenol (73 g.) and 1,4-dichlorobutane (300 ml.), and the resulting reaction mixture was heated on the steam bath for $\frac{1}{2}$ hour. There was a slight exothermic reaction at the beginning. Water was added to dissolve the precipitated salt and the organic layer was washed with aqueous alkali and with water. The excess 1,4-dichlorobutane was removed *in vacuo* and the residue was distilled, yielding a colorless liquid (92 g.) boiling at 180° (12 mm.), n_D^{20} = 1.5793. Anal. Calc. for $C_{10}H_{12}Cl_2S$: C, 51.07; H, 5.11. Found: C, 51.58; H, 5.27.

The residue from the distillation when crystallized from methanol gave white prisms of *1,4-bis(p-chlorophenylmercapto)butane* (6 g.) melting at 73°–74°. Anal. Calc. for $C_{16}H_{16}Cl_2S_2$: C, 55.98; H, 4.67. Found: C, 55.74; H, 4.48.

2,8-Dichloro-6H,12H-dibenzo(b,f)-1,5-dithiocin (VI)

(*a*) *From p-chlorothiophenol.*—A reaction mixture of *p*-chlorothiophenol (50 g.), zinc chloride (40 g.), paraformaldehyde (20 g.), and acetic acid (350 ml.) was saturated with hydrogen chloride and then heated on the steam bath for 16 hours. The resulting white precipitate was filtered from the cooled reaction mixture, washed with acetic acid, with concentrated hydrochloric acid, and with water, and dried. The crude product (35 g.) melted at 244°–246° and was insoluble in most organic solvents. When crystallized from benzene or N,N-dimethylformamide it melted at 254°–255°. Its melting point was not depressed by the products obtained in (*b*) or (*c*) (see below). Anal. Calc. for $C_{14}H_{10}Cl_2S_2$: C, 53.68; H, 3.19; Cl, 22.70; S, 20.45. Found: C, 53.87, 53.41; H, 2.92, 3.12; Cl, 23.37; S, 20.66, 20.85.

(*b*) *From sulphides.*—When bis(*p*-chlorophenylmercapto)methane (3, 4), 1,2-bis(*p*-chlorophenylmercapto)ethane (5), and 1,4-bis(*p*-chlorophenylmercapto)butane were subjected to chloromethylation as in (*a*) in each case a product was obtained melting at 254°–255° alone or in admixture with the 2,8-dichloro-6H,12H-dibenzo(*b,f*)-1,5-dithiocin (VI) obtained in (*a*).

(*c*) *From p-chlorophenyl chloromethyl sulphide (X).*—A solution of *p*-chlorophenyl chloromethyl sulphide (X) (6) (5 g.) in acetic acid (50 ml.) and zinc chloride (20 g.) was heated on the steam bath for 2 days. The white precipitate was filtered, washed with acetic acid and with methanol, and crystallized from N,N-dimethylformamide. The white needles (3.5 g. or 86%) melted at 251°–254° alone or in admixture with the compound obtained from *p*-chlorothiophenol (see Section (*a*)).

p-Chlorophenyl Ethyl Sulphide (VII)

This was prepared in quantitative yield by treating a hot alkaline solution of *p*-chlorothiophenol with diethyl sulphate in the usual manner. It boiled at 123° (18 mm.), n_D^{20} = 1.5800. Anal. Calc. for C_8H_9ClS: C, 55.67; H, 5.22. Found: C, 56.35; H, 5.72.

2-Ethylmercapto-5-chlorobenzyl Chloride (VIII)

A mixture of *p*-chlorophenyl ethyl sulphide (45 g.), acetic acid (200 ml.), paraformaldehyde (10 g.), and zinc chloride (10 g.) was saturated with hydrogen chloride and the resulting solution was heated on the steam bath for 20 hours. The reaction mixture was concentrated *in vacuo* to about one-half of its original volume and the residue treated with water and then extracted with benzene. The benzene extract was washed with water, with aqueous sodium bicarbonate, and with water, and the solvent removed. The residue was distilled yielding three fractions: fraction 1, b.p. (11 mm.) = 110°–135°, 4 g.; fraction 2, b.p. (11 mm.) = 135°–170°, 30 g.; and fraction 3, b.p. (11 mm.) = 200°–250°, 8 g. Fraction 2 was redistilled yielding a colorless liquid (20 g.) of VIII boiling at 150°–152° (11 mm.), n_D^{20} = 1.5933. Anal. Calc. for $C_9H_{10}Cl_2S$: C, 48.87; H, 4.52. Found: C, 49.23, 49.61; H, 4.41, 4.73.

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Fraction 3 was crystallized from benzene yielding white prisms (0.7 g.) melting at 250°–252° alone or in admixture with *2,8-dichloro-6H,12H-dibenzo(b,f)-1,5-dithiocin* (*VI*) prepared from *p*-chlorothiophenol.

The mother liquors from the crystallization of fraction 3 were taken to dryness and the residue crystallized from methanol yielding white prisms (1 g.) melting at 96°–98° alone or in admixture with *2,2′-bis(ethylmercapto)-5,5′-dichlorodiphenylmethane* prepared from VII and VIII (see below).

2-Ethylmercapto-5-chlorobenzyl Isothiuronium Chloride

2-Ethylmercapto-5-chlorobenzyl chloride (16 g.), thiourea (5 g.), and ethanol (100 ml.) were heated together under reflux for 3 hours. The solvent was removed *in vacuo*, the residue was dissolved in warm water (300 ml.), the solution washed with benzene and then concentrated *in vacuo* to about 25 ml. The white needles (12 g.), which precipitated when the solution was cooled, were filtered, washed, and dried, m.p. 204°–206°. Anal. Calc. for $C_{10}H_{14}N_2Cl_2S_2$: C, 40.40; H, 4.71; N, 9.42. Found: C, 40.73, 40.73; H, 4.88, 4.85; N, 9.91, 9.99.

2,2′-Bis(ethylmercapto)-5,5′-dichlorodiphenylmethane (*IX*)

A reaction mixture of 2-ethylmercapto-5-chlorobenzyl chloride (VIII) (5 g.), *p*-chlorophenyl ethyl sulphide (VII) (5 g.), zinc chloride (12 g.), and acetic acid (25 ml.) was heated under reflux for 1 hour and then poured into dilute hydrochloric acid. The precipitated oil was extracted with benzene, the benzene solution was washed with water, and the solvent removed. The residue was distilled and the fraction boiling at 175°–190° (0.5 mm.) collected. When this distillate was crystallized twice from methanol it yielded white prisms (3.5 g.) melting at 95°–97°. Anal. Calc. for $C_{10}H_{14}N_2Cl_2S_2$: C, 57.13; H, 5.04. Found: C, 57.06, 57.31; H, 5.27, 5.17.

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