[CONTRIBUTION FROM THE RESEARCH LABORATORY, DOMINION RUBBER CO. LTD.]

Macro Rings Containing Carbon, Oxygen and Sulfur

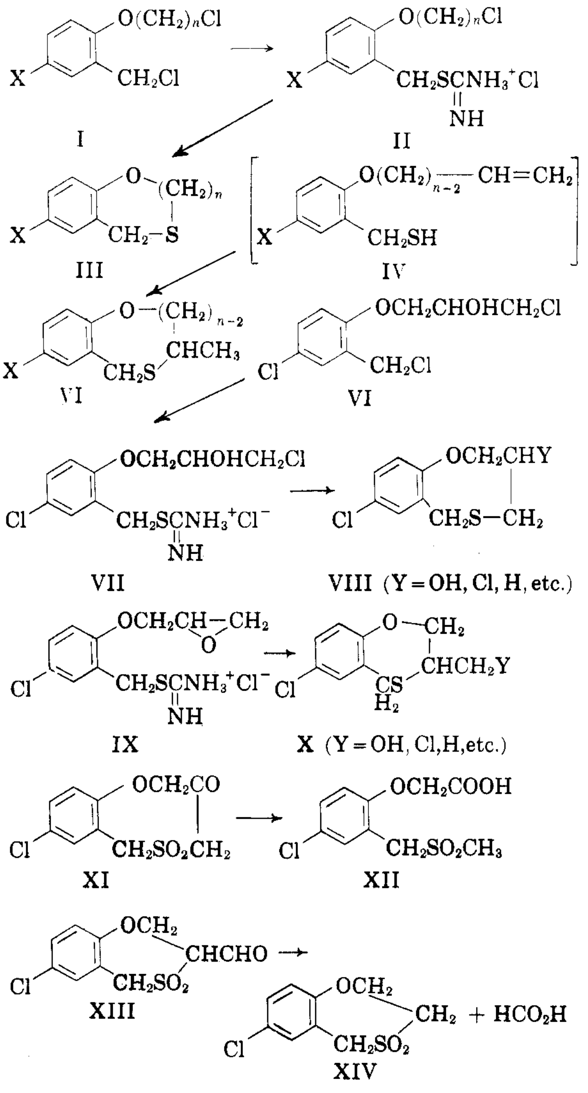
MARSHALL KULKA

Received September 11, 1956

Eight- and nine-membered ring compounds (III) have been synthesized in almost quantitative yields from the corresponding 2-chloroalkoxybenzylisothiuronium chlorides (II). Proof is provided to show that 2-(2-hydroxy-3-chloropropoxy)-5-chlorobenzylisothiuronium chloride (VII) undergoes degradation and cyclization in dilute alkali to form the eight-membered ring compound, namely 3-hydroxy-8-chloro-2,3-dihydrobenzo[g]-1,5-oxathiocin (VIII, Y = OH) and not the seven-membered cyclic compound X.

Recently it was found[1] that *o*-2-chloroethoxybenzylisothiuronium chlorides (II, n = 2) undergo simultaneous degradation and ring closure to form the 2,3-dihydrobenzo(f)-1,4-oxathiepins (III, n = 2) in almost quantitative yields when the principle of high dilution is employed. The remarkable ease with which these seven-membered heterocyclic compounds formed aroused interest in rings of larger size. Therefore *o*-chloropropoxy- (II, n = 3) and *o*-4-chlorobutoxy-(II, n = 4)benzylisothiuronium chlorides were prepared and subjected to the same conditions of cyclization. The larger ring compounds, namely the 2,3-dihydrobenzo(g)-1,5-oxathiocins (III, n = 3) and 2,3,4,5-tetrahydrobenzo-[h]-1,6-oxathionins (III, n = 4) were also obtained in almost quantitative yields. These observations are in harmony with those of Ziegler and Holl[2] who found that macro rings containing one or more hetero atoms are more easily formed than carbocyclic compounds. Apparently the different bond angles of oxygen and sulfur atoms make hetero ring formation easier than carbocyclization.

In this investigation the question of preferred smaller ring formation arose. Thus, under the alkaline conditions of cyclization, might not the isothiuronium salt (II) undergo dehydrochlorination and degradation to form the intermediate alkene (IV) and then cyclize (by addition) to the compound V whose hetero ring is smaller than that of III by one carbon atom?[3] In the case of *o*-2-chloroethoxybenzylisothiuronium chloride (II, n = 2) this possibility of the six-membered ring formation is eliminated on the basis that the smaller ring compound (V, n = 2) obtained from II *via* IV would be a mixed acetal-mercaptal and therefore subject to acid hydrolysis. The compounds obtained from II by cyclization are stable to prolonged boiling with acid, and therefore must possess structure III (n = 2) as postulated previously.[1] With higher homologs of II (n > 2) the route to smaller ring formation exists but it is not the likely one to be followed because dehydrohalogenation of chloroalkyl ethers usually requires conditions more drastic than those used in the present cyclizations. The more probable route is first the conversion of the isothiuronium salt (II) to the *o*-chloroalkoxybenzyl mercaptan $\{o\text{-}[Cl(CH_2)_nO]C_6H_4CH_2SH\}$ which in the presence of alkali cyclizes to III by the chloride-mercaptan reaction. This mechanism is indicated from the study of the ring closure of 2-(2-hydroxy-3-chloropropoxy)-5-chlorobenzylisothiuronium chloride (VII).



---

[1] Kulka, *Can. J. Chem.*, **33**, 1442 (1955).

[2] Ziegler and Holl, *Ann.*, **528**, 143 (1937).

[3] Poshkus, Armstrong Cork Company, Lancaster, Pa., private communication.

Theoretically 2-(2-hydroxy-3-chloropropoxy)-5-chlorobenzylisothiuronium chloride (VII) which was obtained from the corresponding benzyl chloride (VI) can undergo simultaneous degradation and cyclization in two different ways. Degradation to the mercaptan and then cyclization would yield the eight-membered cycle VIII (Y = OH). On the other hand, VII could be first dehydrochlorinated under the alkaline conditions to form the ethylene oxide IX which then might undergo simultaneous degradation and cyclization to the seven-membered cycle X (Y = OH).

Actually the isothiuronium chloride VII when treated with dilute alkali yielded only one compound. In order to prove that the structure of this compound was VIII (Y = OH) and not the smaller cycle X (Y = OH), attempts were first made to replace the hydroxyl group by hydrogen. The chloro and bromo derivatives VIII (Y = Cl and Br), which were readily obtained from the cyclic alcohol VIII (Y = OH), did not react with magnesium to form the Grignard reagent and the halogens could not be eliminated successfully by reduction with chromous chloride, metal-acid combination or catalytically. Also the cyclic ketosulfone XI, which was obtained by a two step oxidation of VIII (Y = OH), failed to give the required product when subjected to the reduction methods of Wolff-Kishner and Clemmensen.

That the structure of the cyclic alcohol sulfide is VIII (Y = OH) and not X (Y = OH) was finally established in an indirect manner. This compound was first oxidized and then subjected to degradation. It is seen that oxidation of VIII (Y = OH) would lead to the ketosulfone XI while the smaller ring compound X (Y = OH) under the same treatment would produce the ketoaldehyde XIII. It is known that β-ketosulfones of the type XV undergo cleavage in the presence of alkali to form the methylsulfone XVI and an acid salt.[4–6]

$$\underset{\text{XV}}{\text{RSO}_2\text{CH}_2\text{COR}_1} + \text{NaOH} \longrightarrow \underset{\text{XVI}}{\text{RSO}_2\text{CH}_3} + \text{NaOCOR}_1$$

Therefore, the cyclic β-ketosulfone XI should cleave in the presence of alkali to form the acid sulfone XII while the β-aldehydrosulfone XIII would give the neutral sulfone XIV and formic acid. Actually when the cyclic carbonyl compound XI or XIII was treated with aqueous alkali the acid sulfone XII was formed in quantitative yield, showing that isothiuronium salt VII undergoes degradation and cyclization to form the eight-membered ring VIII and not the seven-membered ring compound X. This fact adds support to the belief that the larger rings III and not the smaller rings V are formed from the corresponding *o*-chloroalkoxybenzylisothiuronium chlorides (II).

EXPERIMENTAL[7]

Preparation of the phenoxyalkyl chlorides. These were prepared in 40–60% yields from the phenol and the alkylene dichloride by the same method as was 4-*p*-chlorophenoxybutyl chloride.[8] In each case the higher boiling diphenoxyalkane was the by-product. *4-p-Tolyloxybutyl chloride*[9] boiled at 140–142° (10 mm.). The *1,4-bis-p-tolyloxybutane* melted at 102–103° after crystallization from benzene-methanol.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 80.00; H, 8.15. Found: C, 80.13, 80.29; H, 8.22, 8.04.

4-p-t-Butylphenoxybutyl chloride distilled at 163–165° (10 mm.) as a colorless liquid, n_D^{24} 1.5100.

Anal. Calcd. for $C_{14}H_{21}ClO$: C, 69.85; H, 8.73. Found: C, 69.95, 69.50; H, 8.56, 8.54.

The residue from the distillation when crystallized from benzene-methanol yielded (11%) white prisms of *1,4-bis-p-t-butylphenoxybutane* melting at 111–112°.

Anal. Calcd. for $C_{24}H_{34}O_2$: C, 81.32; H, 9.60. Found: C, 81.57, 81.20; H, 9.50, 9.60.

3-p-t-Butylphenoxypropyl chloride distilled at 152–153° (10 mm.) as a colorless liquid, n_D^{24} 1.5115.

Anal. Calcd. for $C_{13}H_{19}ClO$: C, 68.87; H, 8.39. Found: C, 69.20, 69.11; H, 8.32, 8.54.

The residual *1,3-bis-p-t-butylphenoxypropane* after crystallization from benzene-methanol melted at 63–64°.

Anal. Calcd. for $C_{23}H_{32}O_2$: C, 81.18; H, 9.41. Found: C, 81.40, 81.46; H, 9.50, 9.34.

3-p-Chlorophenoxypropyl chloride distilled at 141–143° (10 mm.) as a colorless liquid, n_D^{25} 1.5380.

Anal. Calcd. for $C_9H_{10}Cl_2O$: C, 52.68; H, 4.88. Found: C, 53.10, 52.86; H, 5.15, 5.20.

The residual 1,3-bis-*p*-chlorophenoxypropane melted at 121–122° after crystallization from benzene.

Anal. Calcd. for $C_{15}H_{14}Cl_2O_2$: C, 60.60; H, 4.71. Found: C, 60.56, 60.80; H, 4.79, 5.00.

Preparation of o-(chloroalkoxy)benzyl chlorides. 2-(4-Chlorobutoxy)-5-methylbenzyl chloride, 2-(3-chloropropoxy)-5-t-butylbenzyl chloride, and *2-(4-chlorobutoxy)-5-t-butylbenzyl chloride* were prepared in 60–70% yields by the chloromethylation of the corresponding phenyl chloroalkyl ethers using the same procedure as that reported for 2-(2-chloroethoxy)-5-methylbenzyl chloride.[1] These chlorides boiled at 175–180° (10 mm.), 172–175° (10 mm.) and 188–193° (10 mm.), respectively, but pure samples could not be obtained for analyses. The contaminant was the starting phenyl chloroalkyl ether which did not interfere in the next step of the synthesis. *2-(3-Chloropropoxy)-5-chlorobenzyl chloride* and *2-(4-chlorobutoxy)-5-chlorobenzyl chloride* were also prepared by the chloromethylation of the corresponding *p*-chlorophenyl chloroalkyl ether using the same conditions as those reported for the preparation of 2-(2-chloroethoxy)-5-chlorobenzyl chloride.[10] These compounds boiled at 187–190° (10 mm.) and 197–200° (10 mm.), respectively, but again they were contaminated by the small quantities of starting material.

Preparation of the S-o-chloroalkoxybenzyl isothiuronium chlorides (II) (Table I). These were prepared from the benzyl chloride and thiourea by the same method as was used for the preparation of the S-*o*-2-chloroethoxybenzylisothiuronium chloride.[1]

Preparation of the 2,3-dihydroxybenzo[g]-1,5-oxathiocins (III, *n* = 3) *and the 2,3,4,5-tetrahydrobenzo[h]-1,6-oxathionins* (III, *n* = 4) (Table II). These were prepared by gradually adding the aqueous alcoholic solution of the *o*-

---

[4] Kulka, *J. Am. Chem. Soc.*, **72**, 1215 (1950).

[5] Otto and Otto, *J. prakt. Chem.*, (2) **36**, 401 (1887).

[6] Ziegler and Connor, *J. Am. Chem. Soc.*, **62**, 1049 (1940).

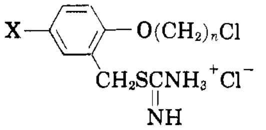
[7] All melting points are corrected.

[8] Kulka, *Can. J. Chem.*, **34**, 1093 (1956).

[9] Genzer, Huttrer and Van Wessem, *J. Am. Chem. Soc.*, **73**, 3159 (1951).

[10] Kulka and Van Stryk, *Can. J. Chem.*, **33**, 1130 (1955).

TABLE I

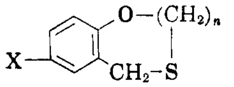


II

Isothiuronium chloride (II)

					Analyses			
		M.P.,	%		Calcd.		Found	
X	*n*	°C.	Yield	Formula	C	H	C	H
t-Butyl	3	181–183	60	$C_{15}H_{24}Cl_2N_2OS$	51.29	6.82	51.38	6.86
Chloro	3	187–188	26	$C_{11}H_{15}Cl_3N_2OS$	40.06	4.55	40.28	4.44
Methyl	4	168–169	52	$C_{13}H_{20}Cl_2N_2OS$	48.30	6.19	48.51	6.19
t-Butyl	4	167–168	55	$C_{16}H_{26}Cl_2N_2OS$	52.60	7.12	52.92	7.14
Chloro	4	167–168	63	$C_{12}H_{17}Cl_3N_2OS$	41.93	4.95	42.63	5.21

TABLE II

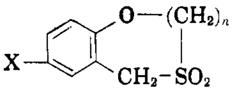


III

Compound III

					Analyses			
		M.P., °C.	%		Calcd.		Found	
X	*n*	or B.P.	Yield	Formula	C	H	C	H
t-Butyl	3	B_{11} = 174–175	85	$C_{14}H_{10}OS$	71.19	8.47	70.77	8.38
Chloro	3	46–47	90	$C_{10}H_{11}ClOS$	55.94	5.13	55.99	5.38
Methyl	4	75–76	78	$C_{12}H_{16}OS$	69.23	7.69	69.43	7.83
t-Butyl	4	B_{10} = 185–187	73	$C_{15}H_{22}OS$	72.00	8.80	71.11	8.71
Chloro	4	71–72	83	$C_{11}H_{13}ClOS$	57.77	5.69	58.02	5.75

TABLE III



Sulfone

					Analyses			
		M.P.,	%		Calcd.		Found	
X	*n*	°C.	Yield	Formula	C	H	C	H
t-Butyl	3	179–178	95	$C_{14}H_{20}O_3S$	62.69	7.46	63.07	7.52
Chloro	3	184–185	90	$C_{10}H_{11}ClO_3S$	48.69	4.46	48.92	4.59
Methyl	4	111–112	90	$C_{12}H_{16}O_3S$	60.00	6.67	60.40	6.70
t-Butyl	4	132–133	78	$C_{15}H_{22}O_3S$	63.83	7.80	63.62	7.73
Chloro	4	168–169	95	$C_{11}H_{13}ClO_3S$	50.67	4.99	50.96	4.94

chloroalkoxybenzylisothiuronium chloride (II) to hot dilute aqueous alkali as previously described.[1]

Preparation of 2,3-dihydrobenzo[g]-1,5-oxathiocin-5,5-dioxides and 2,3,4,5-tetrahydrobenzo[h]-1,6-oxathionin-6,6-dioxides (Table III). The cyclic sulfides III were oxidized to the corresponding sulfones by means of hydrogen peroxide in acetic acid.[1]

2-(2-Hydroxy-3-chloropropoxy)-5-chlorobenzyl chloride (VI). A mixture of acetic acid (600 ml.), paraformaldehyde (21 g.) and zinc chloride (21 g.) was saturated with hydrogen chloride. Then 2-hydroxy-3-chloropropyl p-chlorophenyl ether[11] (100 g.) was added and the resulting solution was heated at 80–90° for 20 hr. About three quarters of the acetic acid was distilled off *in vacuo*. To the residue was added dilute hydrochloric acid, and the precipitated oil was extracted with benzene. The benzene solution was washed with water, with aqueous sodium bicarbonate, and with water. The solvent was removed and the residue distilled, b.p. (10 mm.) 210–215°. This colorless distillate (105 g.) was contaminated with a small quantity of the starting material and thus gave slightly high analytical figures for carbon and hydrogen.

2-(2-Hydroxy-3-chloropropoxy)-5-chlorobenzylisothiuronium chloride (VII). A reaction mixture of the crude benzyl chloride VI (105 g.), thiourea (40 g.) and ethanol (300 ml.) was heated under reflux for 3 hr. The ethanol was removed *in vacuo* and warm water (250 ml.) was added to the residue. The water-insoluble material was extracted with benzene and discarded. The isothiuronium salt VII was very soluble in water and could not be isolated even after concentration

---

(11) Stephenson, *J. Chem. Soc.*, 1571 (1954).

of the solution. The aqueous solution was therefore used directly in the next experiment.

8-Chloro-3-hydroxy-2,3-dihydrobenzo[g]-1,5-oxathiocin (VIII, Y = OH). The above solution of the isothiuronium salt VII was added dropwise over 2 hr. to a stirred solution of sodium hydroxide (30 g.) in water (1750 ml.) heated on the steam bath. After stirring for an additional one-half hour, the reaction mixture containing precipitated VIII (Y = OH) was cooled and extracted with benzene. The benzene solution was washed with water, the solvent removed, and the residue distilled, b.p. (12 mm.) 210°. The distillate (51 g.) solidified and was crystallized from methanol. The white prisms (42 g. or 50% over-all yield based on the crude benzyl chloride VI) melted at 84–85°.

Anal. Calcd. for $C_{10}H_{11}ClO_2S$: C, 52.07; H, 4.77. Found: C, 51.86; H, 4.86.

8-Chloro-3-hydroxy-2,3-dihydrobenzo[g]-1,5-oxathiocin-5,5-dioxide. The cyclic sulfide VIII (Y = OH) was oxidized with 30% hydrogen peroxide in acetic acid. The white needles which were obtained in 90% yield melted at 191–192°.

Anal. Calcd. for $C_{10}H_{11}ClO_4S$: C, 45.72; H, 4.19. Found: C, 46.13, 46.07; H, 4.43, 4.28.

3-Oxo-8-chloro-2,3-dihydrobenzo[g]-1,5-oxathiocin-5,5-dioxide (XI). 3-Hydroxy-8-chloro-2,3-dihydrobenzo[g]-1,5-oxathiocin-5,5-dioxide (10 g.) was dissolved in acetic acid (100 ml.) at 60° and then chromic oxide (5 g.) was added portionwise with cooling in order to keep the reaction temperature at 60–70°. The resulting solution was heated on the steam bath for 2 hr., then concentrated *in vacuo* to half the original volume. Cold water was added to the residue, the precipitate was filtered, washed with dilute hydrochloric acid and with water, and crystallized from methanol. The white prisms (6.1 g.) melted at 191–192°. This compound was insoluble in aqueous sodium bicarbonate and depressed the melting point of the starting alcohol.

Anal. Calcd. for $C_{10}H_9ClO_4S$: C, 46.07; H, 3.45. Found: C, 46.50, 46.44; H, 3.88, 3.68. The *semicarbazide* of this ketone XI melted at 250° with decomposition.

Anal. Calcd. for $C_{11}H_{12}ClN_3O_4S$: N, 13.22. Found: N, 13.40.

3,8-Dichloro-2,3-dihydrobenzo[g]-1,5-oxathiocin (VIII, Y = Cl). To a solution of 3-hydroxy-8-chloro-2,3-dihydrobenzo-[g]-1,5-oxathiocin (VIII, Y = OH) (10 g.) in benzene (25 ml.) was added thionyl chloride (10 ml.) and the solution was heated under reflux for 2 hr. The solvent and excess thionyl chloride were removed *in vacuo* and the residue which solidified was crystallized from ethanol. The colorless prisms (10 g.) melted at 88–89°.

Anal. Calcd. for $C_{10}H_{10}Cl_2OS$: C, 48.19; H, 4.01. Found: C, 48.54; H, 4.33.

3-Bromo-8-chloro-2,3-dihydrobenzo[g]-1,5-oxathiocin (VIII, Y = Br). To a solution of phosphorus tribromide (5 ml.) in chloroform (10 ml.), 2.2 ml. bromine was added dropwise with cooling. Then VIII (Y = OH) (10 g.) was added portionwise with cooling on a water bath to the reaction mixture containing the precipitated phosphorus pentabromide. The reaction mixture was allowed to stand at room temperature for 0.5 hr. The resulting solution was diluted with chloroform and washed with water, with aqueous sodium hydroxide and again with water. The solvent was removed and the residue was crystallized first from ethanol and then from benzene. The bromide is not very stable in hot ethanol since it liberates hydrogen bromide. The white prisms (9.1 g.) melted at 100–101°.

Anal. Calcd. for $C_{10}H_{10}BrClOS$: C, 40.89; H, 3.41. Found: C, 40.92; H, 3.62.

3-Thiocyanato-8-chloro-2,3-dihydrobenzo[g]-1,5-oxathiocin (VIII, Y = SCN). A solution of 3,8-dichloro-2,3-dihydrobenzo[g]-1,5-oxathiocin (VIII, Y = Cl) (4 g.), sodium thiocyanate (3 g.) and ethanol (100 ml.) was heated under reflux for 2 hr. The precipitated sodium chloride was filtered off and the filtrate taken to dryness *in vacuo.* The residue (4 g.) which solidified on standing was crystallized from methanol. The white prisms melted at 49–50°.

Anal. Calcd. for $C_{11}H_{10}ClNOS_2$: C, 48.62; H, 3.68. Found: C, 48.94; H, 3.57.

3-(N,N-Dimethyldithiocarbamato)-8-chloro-2,3-dihydrobenzo[g]-1,5-oxathiocin [VIII, Y = $S_2CN(CH_3)_2$]. A solution of VIII (Y = Cl) (6 g.), sodium N,N-dimethyldithiocarbamate[8] (6 g.) and acetone (150 ml.) was heated under reflux for 1 hr. The acetone was distilled off, the residue was treated with water and extracted with benzene. The benzene extract was washed with water and the solvent removed. The residue which solidified was crystallized from methanol-benzene, yielding white prisms (6.1 g.) melting at 124–125°.

Anal. Calcd. for $C_{13}H_{16}ClNOS_3$: C, 46.78; H, 4.80. Found: C, 46.80; H, 4.79.

3-Mercapto-8-chloro-2,3-dihydrobenzo[g]-1,5-oxathiocin (VIII, Y = SH). A solution of the dithiocarbamate (VIII, Y = $S_2CN(CH_3)_2$) (3 g.), 85% hydrazine hydrate (10 ml.) and ethanol (75 ml.) was heated under reflux for 40 hr.[8] The solvent was removed *in vacuo*, the residue dissolved in benzene and then washed with dilute hydrochloric acid and with water. The solvent was removed and the residue distilled, b.p. (11 mm.) 220°. The distillate (1.4 g.) solidified and was pulverized and washed with petroleum ether and dried, m.p. 56–57°.

Anal. Calcd. for $C_{10}H_{11}ClOS_2$: C, 48.68; H, 4.46. Found: C, 49.12, 48.94; H, 4.51, 4.38.

2-(Methylsulfonylmethyl)-4-chlorophenoxyacetic acid (XII). To a stirred solution of sodium hydroxide (2 g.) in water (25 ml.) at 40° was added 3-oxo-8-chloro-2,3-dihydrobenzo-[g]-1,5-oxathiocin-5,5-dioxide (XI) (1 g.). The β-ketosulfone XI dissolved in a few minutes. The light yellow solution was heated to 90°, acidified and allowed to cool slowly. The white prisms (1 g.) were filtered, washed, and dried, m.p. 193–194°. This compound depressed the melting point of the starting ketone XI and was soluble in aqueous sodium bicarbonate.

Anal. Calcd. for $C_{10}H_{11}ClO_5S$: C, 43.09; H, 3.95. Found: C, 43.26; H, 4.17.

GUELPH, ONT., CANADA