

# BENZYL 2-CHLOROETHYL ETHERS<sup>1</sup>

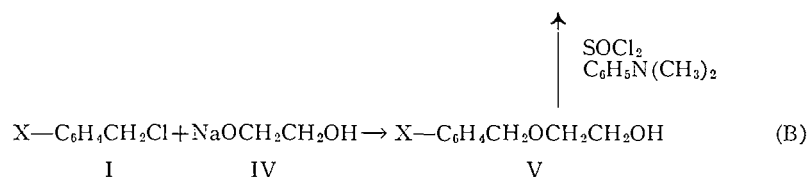
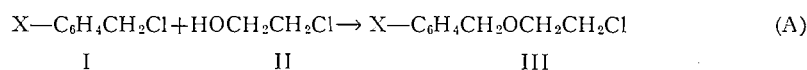
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## ABSTRACT

The solvolysis reaction between benzyl chlorides and ethylene chlorohydrin has been employed for the synthesis of a series of benzyl 2-chloroethyl ethers (III) required in insecticide screening tests. This method is limited to the synthesis of III which possesses a partially deactivated nucleus. Several new benzyl chlorides are recorded.

Several classes of compounds including derivatives of chlorobenzenesulphonic acid (8, 10), 2-hydroxybenzophenones (9), and phenoxymethyl 2-chloroethyl ethers (11) have been synthesized in this laboratory and screened for insecticidal value by Musgrave and Kukovica (14) at the Ontario Agricultural College. In continuation of the joint program of insecticide research this report deals with a class of compounds possessing the grouping  $-\text{CH}_2\text{OCH}_2\text{CH}_2\text{Cl}$ .

Genzer, Hutterer, and van Wessem (5) developed a method for the synthesis of benzyl 2-chloroethyl ether (III) and its *ortho* chloro-derivative which comprises treatment of benzyl chloride (I) with the monosodium salt of ethylene glycol (IV) followed by conversion of the resulting benzyl 2-hydroxyethyl ether (V) to III (Method B). Although this method was satisfactory in many cases, a more direct method was sought. The solvolysis reaction between benzyl halides (I) and ethylene chlorohydrin (II) to form III and hydrogen



chloride under the influence of heat (Method A) was found to be of preparative value though of limited scope. The failure of Method A in some cases can be attributed to the fact that benzyl halides are susceptible to polymerization under the influence of heat and acid catalyst and the extent of this side reaction is governed by the reactivity of the benzene nucleus. The following benzyl halides (I) gave polymers almost exclusively when heated with II: 2,4-dimethyl- (7), 2,4-dimethyl-5-chloromethyl (7), 3,4-dimethoxy- (12), 3-bromo-4-methoxy- (15), 2-nitro-4,5-dimethoxy-, 2-(2-chloroethoxy)-5-chloro-, 2,4-bis(chloromethyl)- (7), and *p*-nitrophenoxy- (17) benzyl chlorides

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as well as 6-chloro-8-chloromethyl-1,3-benzodioxane (1) and 1-chloromethylnaphthalene (2). The nuclei of the majority of these compounds are activated by alkyl or alkoxy substituents. Benzyl halides (I) possessing nuclear deactivating substituents such as chloro or nitro polymerized to a lesser extent when heated with ethylene chlorohydrin and formed the benzyl 2-chloroethyl ethers (III) (Table I). The reaction between I and II to form III was complete after heating under reflux for 24 to 48 hr. except in one case. Much of *p*-nitrobenzyl chloride remained unchanged after heating with II for four days.

The benzyl chlorides required for this investigation were prepared by chloromethylation of the appropriate aromatic compounds. It is interesting to note that 2-nitro-4,5-dimethoxybenzyl chloride, which was obtained from 3,4-dimethoxybenzyl chloride (12) by nitration, unlike the parent compound, is stable at room temperature. However it decomposes rapidly when warmed with alcoholic solutions of alkali or potassium cyanide to form resinous materials. Heating with ethanolic thiourea produced stable 2-nitro-4,5-dimethoxybenzyl isothiuronium chloride.

TABLE I  
PREPARATION OF BENZYL 2-CHLOROETHYL ETHERS (X—C<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>Cl, III) FROM THE CORRESPONDING BENZYL HALIDES (I)

III X =	Method of prep.	Yield, %	B.p. or m.p., °C.	$n_D^{20}$	Analyses			
					Calc.		Found	
					C	H	C	H
H	B (5) A	77 60	b <sub>13</sub> = 115	1.5200	63.33	6.45	63.26	6.15
<i>o</i> -Chloro (5)	B	49	b <sub>12</sub> = 132-136	1.5344				
<i>p</i> -Chloro	B	40	b <sub>12</sub> = 138-142	1.5348	52.69	4.88	52.35	4.84
2,4-Dichloro	A	40	b <sub>12</sub> = 158-161	1.5483	45.09	3.76	44.99	3.93
2,5-Dichloro	A	47	b <sub>12</sub> = 155-160	1.5362	45.09	3.76	44.83	4.36
3,4-Dichloro	B A	61 45	b <sub>12</sub> = 155-160	1.5498	45.09	3.76	45.36	3.69
2,3,4,5,6-Pentachloro	B	81	m.p. 71-72		31.49	1.75	31.90	1.97
<i>p</i> -β-Chloroethyl	A	40	b <sub>12</sub> = 170-175		56.65	6.01	56.72	5.80
<i>p</i> -Nitro	A	23	b <sub>12</sub> = 190-195		50.12	4.64	49.92	4.63
3-Nitro-4-methoxy	A	80	b <sub>1</sub> = 175-177	1.5535	48.88	4.88	49.30	4.81
3-Nitro-4- <i>n</i> -butoxy	A	78	b <sub>0,2</sub> = 160-163	1.5315	54.26	6.26	54.25	6.20
3-Nitro-4- <i>n</i> -dodecyloxy	A	82	b <sub>0,2</sub> = 235-240	1.5088	63.08	8.51	63.24	8.28
3-Chloro-6,β-chloroethoxy	A B	24 85	b <sub>12</sub> = 205-207	1.5452	46.56	4.58	46.82	4.46
3-Nitro-4-methyl	A	44	b <sub>12</sub> = 189-194	1.5452	52.29	5.23	52.49	5.09
3-Bromo-4-methoxy	B	84	b <sub>12</sub> = 186-188	1.5622	42.93	4.29	43.34	4.38
α-Naphthylmethyl 2-chloroethyl ether	B	85	b <sub>12</sub> = 188	1.5990	70.75	5.89	70.32	5.75

The benzyl 2-chloroethyl ethers (III) suffer degradation in the presence of acidic reagents. An attempt to chloromethylate benzyl 2-chloroethyl ether (III, X = H) resulted only in low-boiling materials. Similar results were obtained in attempts to chlorinate and nitrate III. The alkyl chlorine of III is far less reactive than the chlorine in bis(2-chloroethyl) sulphide (mustard gas), but like bis(2-chloroethyl) ether will react with alcoholic potassium thiocyanate after prolonged heating.

TABLE II  
PREPARATION OF BENZYL 2-HYDROXYETHYL ETHERS (X—C<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>OH, V) FROM THE CORRESPONDING BENZYL HALIDES (I) AND ETHYLENE GLYCOL

V, X =	Yield, %	B.p. or m.p., °C.	$n_D^{20}$	Analyses			
				Calc.		Found	
				C	H	C	H
H (5)	81	b <sub>0.25</sub> = 95	1.5209				
<i>o</i> -Chloro (5)	84	b <sub>0.03</sub> = 84	1.5348				
<i>p</i> -Chloro	52	b <sub>12</sub> = 151-154	1.5330	57.91	5.90	57.56	5.99
3,4-Dichloro	51	b <sub>12</sub> = 176-179	1.5502	48.87	4.52	48.65	4.34
2,3,4,5,6-Pentachloro*	20	m.p. 83-84		33.28	2.16	33.44	2.33
3-Chloro-6,β-chloro- ethoxy	64	b <sub>0.1</sub> = 148-150	1.5500	49.81	5.28	50.95	5.30
3-Bromo-4-methoxy	83	b <sub>12</sub> = 201	1.5655	45.98	4.98	46.07	4.87
α-Naphthylmethyl 2-hydroxyethyl ether	82	b <sub>12</sub> = 198	1.6045	77.23	6.93	77.24	6.93

\*In the preparation of this compound it was necessary to heat the reaction mixture for 18 hr. instead of 2 hr.

#### EXPERIMENTAL

##### 2-Nitro-4,5-dimethoxybenzyl Chloride

To a solution of 3,4-dimethoxybenzyl chloride (12) (46 gm.) in acetic acid (120 ml.) kept at 8-10° was added dropwise with stirring concentrated nitric acid ( $d = 1.42$ ) (37 gm.) over one-half hour. After the reaction mixture was stirred at 8-10° for two hours it was poured into cold water. The yellow precipitate was filtered, washed, and crystallized from methanol. The yellow prisms weighed 26 gm. (50%) and melted at 87-88°. Anal. calc. for C<sub>9</sub>H<sub>10</sub>NO<sub>4</sub>Cl: C, 46.65; H, 4.32; N, 6.05. Found: C, 47.08, 46.86; H, 4.43, 4.42; N, 6.23. Heating with thiourea in methanol under reflux produced *S*-2-nitro-4,5-dimethoxybenzyl isothiuronium chloride in 90% yield. The light-yellow needles melted at 215-216° with decomposition. Anal. calc. for C<sub>10</sub>H<sub>14</sub>N<sub>3</sub>O<sub>4</sub>ClS: C, 39.03; H, 4.55. Found: C, 38.64; H, 4.82.

##### 3-Nitro-4-*n*-butoxybenzyl Chloride

This is essentially the method previously used for the preparation of 3-nitro-4-methoxybenzyl chloride (4). Into a suspension of trioxymethylene (16 gm.), zinc chloride (25 gm.), and acetic acid (350 ml.) dry hydrogen chloride was passed until saturated. Then *o*-nitro-*n*-butoxybenzene (100 gm.) was added and the resulting solution was heated at 75-80° for 72 hr. The

solution was added to water, extracted with benzene, and the benzene extract washed with water, with aqueous sodium bicarbonate, and with water. Removal of the solvent and distillation of the residue yielded a yellow oil (80 gm. or 64%) boiling at 140° (0.3 mm.) or 200° (12 mm.),  $n_D^{20} = 1.5450$ . Anal. calc. for  $C_{11}H_{14}NO_3Cl$ : C, 54.21; H, 5.75. Found: C, 54.66; H, 5.70.

#### 3-Nitro-4-( $\beta$ -bromoethoxy)benzyl Chloride

This was prepared in 54% yield by the same method as was 3-nitro-4-*n*-butoxybenzyl chloride above from *o*-nitro- $\beta$ -bromoethoxybenzene which was obtained from *o*-nitrophenol and ethylene dibromide. The product distilled at 150–170° (0.3 mm.) and crystallized from methanol as white needles melting at 78–79°. Anal. calc. for  $C_9H_9NO_3ClBr$ : C, 36.67; H, 3.06. Found: C, 36.57; H, 3.09.

#### 3-Nitro-4-*n*-dodecyloxybenzyl Chloride

This was prepared in 56% yield by the same method as was 3-nitro-4-*n*-butoxybenzyl chloride above from *o*-nitrododecyloxybenzene. It crystallized as white needles from methanol and from ethyl acetate and melted at 55–56°. Anal. calc. for  $C_{19}H_{30}NO_3Cl$ : C, 64.13; H, 8.44. Found: C, 64.01; H, 8.58.

#### 3-Chloro-6-( $\beta$ -chloroethoxy)benzyl Chloride

This was prepared in 65% yield by the method used for the preparation of 3-nitro-4-*n*-butoxybenzyl chloride above from  $\beta$ -chloroethyl *p*-chlorophenyl ether (3). In this case it was not necessary to heat for 72 hr.; 20 hr. was sufficient and the amount of zinc chloride should be reduced by 30%. The product distilled at 165–175° (12 mm.), crystallized as white prisms from methanol, and melted at 34–35°. Anal. calc. for  $C_9H_9Cl_3O$ : C, 45.09; H, 3.76. Found: C, 45.25, 45.26; H, 3.79, 3.85.

#### *p*-( $\beta$ -Chloroethyl)benzyl Chloride

Into a stirred reaction mixture of  $\beta$ -chloroethylbenzene (50 gm.), ethylene dichloride (100 ml.), paraformaldehyde (10 gm.), and zinc chloride (10 gm.) hydrogen chloride was passed for three hours. The temperature was maintained at 40° by cooling at first and warming later. After standing overnight, the reaction mixture was washed with water, with aqueous sodium bicarbonate, and with water. The solvent was removed and the residue was distilled and the fraction (32 gm.) boiling at 140° (12 mm.),  $n_D^{20} = 1.5550$ , was collected. Anal. calc. for  $C_9H_{10}Cl_2$ : C, 57.14; H, 5.29. Found: C, 57.39, 57.14; H, 5.39, 5.14.

#### 3-Nitro-4-methylbenzyl Chloride

This was prepared by a method similar to that of Matsukawa and Shirakawa (13). To stirred 20% oleum (475 gm.) was added dropwise a solution of *o*-nitrotoluene (137 gm.) and crude methylchloromethyl ether (100 gm.) over one and a half hours, the temperature being kept at 5–10° by cooling. After it was stirred for an additional two hours at 5–10° the dark reaction mixture was poured onto cracked ice. The precipitated oil was extracted with benzene, the extract washed with water, and the solvent removed. The residue was

distilled and the fraction (39 gm.) boiling at 140–150° (12 mm.) was collected. This solidified on standing and was crystallized from methanol, m.p. 44–45°; literature (18) m.p. 45°.

*2,5-Dichlorobenzyl Chloride and 2,5-Dichloro-p-xylylene Dichloride*

To stirred 20% oleum (500 gm.) kept at 0–5° by cooling was added dropwise a solution of *p*-dichlorobenzene (74 gm.) in 150 gm. of crude methyl chloromethyl ether over one hour. The reaction mixture was stirred at 0–5° for two hours, let stand overnight at 8–10°, and then poured on cracked ice. The reaction mixture was extracted with chloroform, the extract was washed with water, and the solvent was then removed. The residue was fractionally distilled and two main fractions were collected. The first fraction, a colorless liquid (14 gm.) which was *2,5-dichlorobenzyl chloride*, boiled at 122–124° (15 mm.),  $n_D^{20} = 1.5750$ . Anal. calc. for  $C_7H_5Cl_3$ : C, 42.97; H, 2.56. Found: C, 42.29; H, 2.61.

The second fraction boiled at 165–180° (15 mm.) and the distillate (16 gm.) which solidified was crystallized from ethanol. The colorless rhombohedrons of *2,5-dichloro-p-xylylene dichloride* (13 gm.) melted at 98–99°. Anal. calc. for  $C_8H_6Cl_4$ : C, 39.35; H, 2.46. Found: C, 39.68; H, 2.48.

The *S,S'*-*2,5-dichloro-p-xylylene bis-isothiuronium chloride* was prepared by boiling the *2,5-dichloro-p-xylylene dichloride* with thiourea in ethanol. It melted at 289–292° (with decomposition) after crystallization from water. Anal. calc. for  $C_{10}H_{14}N_4Cl_4S_2$ : C, 30.30; H, 3.54. Found: C, 30.02; H, 3.72.

*Preparation of Benzyl 2-Chloroethyl Ethers by Method A*

Some of the benzyl 2-chloroethyl ethers listed in Table I were prepared by a method used for the preparation of *p-xylylene bis-2-chloroethyl ether* which follows: A solution of *p-xylylene dichloride* (7) (20 gm.) in dry ethylene chlorohydrin (100 ml.) was heated under reflux for 24 hr. The hydrogen chloride gas was allowed to escape through a condenser kept at about 60°. The excess ethylene chlorohydrin was removed and the residue distilled. The colorless liquid boiled at 200–203° (12 mm.),  $n_D^{20} = 1.5260$ . The yield was 26 gm. or 85%. Anal. calc. for  $C_{12}H_{16}O_2Cl_2$ : C, 54.75; H, 6.08. Found: C, 55.12, 55.13; H, 5.97, 5.99.

*o-Xylylene bis-2-chloroethyl ether*.—This was prepared in 68% yield by Method A from *o-xylylene dichloride* (7). The colorless liquid boiled at 190–195° (14 mm.). Anal. calc. for  $C_{12}H_{16}O_2Cl_2$ : C, 54.75; H, 6.08. Found: C, 54.44, 54.49; H, 5.53, 5.60.

*Preparation of Benzyl 2-Chloroethyl Ethers by Method B*

Some of the benzyl 2-chloroethyl ethers listed in Table I were prepared by Method B. This method, which was used by Genzer *et al.* (5), is further exemplified by the preparation of *2,5-dichloro-p-xylylene bis-2-chloroethyl ether*.

(a) *2,5-Dichloro-p-xylylene bis-2-hydroxyethyl ether*.—To a solution of dry ethylene glycol (50 ml.), xylene (25 ml.), and sodium (2.5 gm.) was added a solution of *2,5-dichloro-p-xylylene dichloride* (12 gm.) in xylene (25 ml.).

The reaction mixture was heated under reflux for two hours, most of the xylene and glycol were removed *in vacuo*, and the residue was treated with water. The white solid was filtered and crystallized from methanol. The white crystals (12 gm.) melted at 120–121°. Anal. calc. for  $C_{12}H_{16}O_4Cl_2$ : C, 48.82; H, 5.42. Found: C, 49.32; H, 5.47.

(b) *2,5-Dichloro-p-xylylene bis-2-chloroethyl ether*.—To a stirred suspension of 2,5-dichloro-*p*-xylylene bis-2-hydroxyethyl ether (10 gm.), dimethylaniline (10 ml.), and dry chloroform (25 ml.) was added dropwise with cooling a solution of thionyl chloride (6 ml.) in chloroform (10 ml.), the temperature being kept at 20–30°. The dark reaction mixture was heated under reflux for one-half hour and then poured into cold dilute hydrochloric acid. This was extracted with chloroform, the extract was washed with dilute hydrochloric acid and with water, and the solvent was removed. The residue was crystallized from methanol and from petroleum ether (30–60°) yielding 9 gm. (80%) of white needles which melted at 70–71°. Anal. calc. for  $C_{12}H_{14}O_2Cl_4$ : C, 43.38; H, 4.22. Found: C, 43.81, 43.77; H, 4.33, 4.32.

*p,p'*-Dichlorobenzhydrol 2-Chloroethyl Ether

A method simpler than A or B which was employed by Kato *et al.* (6) was followed in this case.

To a hot solution of *p,p'*-dichlorobenzhydrol (16) (10 gm.) in ethylene chlorohydrin (40 ml.) was added a solution of concentrated sulphuric acid (2 ml.) in water (10 ml.) and the resulting solution was heated at 80° for six hours. The reaction mixture containing a precipitated oil was poured into water, extracted with benzene, the benzene extract washed with water, and the solvent removed. The residue distilled at 167–170° (0.2 mm.) giving a colorless liquid (15 gm.),  $n_D^{20} = 1.5830$ . Anal. calc. for  $C_{15}H_{13}OCl_3$ : C, 57.06; H, 4.12. Found: C, 57.00; H, 4.14.

*o,p'*-Dichlorobenzhydrol 2-Chloroethyl Ether

This was prepared in 90% yield as above from *o,p'*-dichlorobenzhydrol. The colorless liquid distilled at 155–160° (0.2 mm.),  $n_D^{20} = 1.5835$ . Anal. calc. for  $C_{15}H_{13}OCl_3$ : C, 57.06; H, 4.12. Found: C, 57.52; H, 4.25.

3-Nitro-4-methoxybenzyl 2-Thiocyanatoethyl Ether

A solution of 3-nitro-4-methoxybenzyl 2-chloroethyl ether (13 gm.) in ethanol (150 ml.) and potassium thiocyanate (6 gm.) was heated under reflux for 40 hr. The precipitated potassium chloride was filtered and the ethanol was distilled off from the filtrate. The residue was dissolved in benzene and washed with water. The solvent was removed and the residue distilled yielding a malodorous yellow liquid (8 gm.), b.p. = 165–170 (1 mm.). Anal. calc. for  $C_{11}H_{12}N_2O_4S$ : C, 49.25; H, 4.48. Found: C, 48.82, 48.78; H, 4.81, 4.74.

*p*-Chlorobenzyl 2-Thiocyanatoethyl Ether

This was prepared in 65% yield as above. It boiled at 187–192° (12 mm.),  $n_D^{20} = 1.5358$ . Anal. calc. for  $C_{10}H_{10}NOCIS$ : C, 52.75; H, 4.39. Found: C, 52.45; H, 4.83.

## ACKNOWLEDGMENT

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