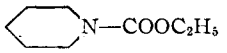
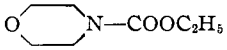
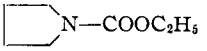
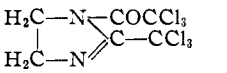
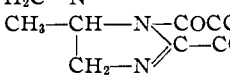
TABLE I

	M.p. or b.p. (mm.), °C.	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
Amides										
$Cl_3CCONHC_3H_7$-*i*	82.5–84	83	29.38	29.32	3.94	3.99	6.85	6.84	52.04	51.89
$Cl_3CCONHC_4H_9$-*n*	29–30	71–77	32.98	33.00	4.61	4.51	6.41	6.48	48.68	48.53
	96 (1)									
$Cl_3CCONHC_4H_9$-*t*	108–110	54	32.98	32.94	4.61	4.64	6.41	6.36	48.68	48.65
$Cl_3CCONHC_9H_{19}$	34–35	66	45.78	45.72	6.98	6.81	4.85	4.85	36.85	36.75
	133 (2)									
$Cl_3CCONHCH_2CH_2C_6H_5$	118–119[a]	94	45.07	45.14	3.78	3.89	5.26	5.29	39.89	39.72
$Cl_3CCONH(CH_2)_2CH_2N(CH_3)_2 \cdot HCl$	189–190	57	29.62	29.71	4.93	5.00	9.87	9.83	49.95	49.77
$F_3CCONHCH_2CH_2C_6H_5$	56–57	80–85	55.30	55.44	4.64	4.64	6.45	6.36		
Urethans										
	56 (1)[b]	65–70	61.12	61.04	9.61	9.53	8.91	8.98		
	60 (1)	73	52.61	52.55	8.19	8.03	8.76	8.45		
	63 (2)	50–60	58.71	58.66	9.14	9.32	9.78	9.72		
$(CH_3)_2N\text{-}COOC_2H_5$	74 (80)[c]	43	51.28	51.33	9.46	9.43	11.97	11.99		
Dihydroimidazoles										
	206–207	84	21.66	21.51	1.21	1.56	8.42	8.43	63.91	63.66
	196–197	91	24.25	24.14	1.74	1.94	8.09	8.03	61.34	61.43

[a] This compound, prepared by a different method, was reported to melt at 112–113° (J. v. Braun, F. Jostes and W. Munch, *Ann.*, **453**, 144, 1927). [b] Prepared by a different method, it was reported to boil at 211° at atmospheric pressure (C. Schotten, *Ber.*, **15**, 425, 1882). [c] Prepared by a different method, it was reported to boil at 147° at atmospheric pressure.[7]

amide gradually dissolved. The solution was then evaporated to dryness and 1.2 g. of a crystalline substance was obtained. The product was recrystallized from ethyl alcohol and water (10 ml. of ethyl alcohol and 3 ml. of water). The recrystallized product darkened at 300° and decomposed at about 327° without melting. The analytical results showed the compound to be ethylenediamine dihydrochloride.

Anal. Calcd. for $C_2H_{10}N_2Cl_2$: C, 18.06; H, 7.57; N, 21.07. Found: C, 18.17; H, 7.54; N, 20.99.

In contrast to the behavior of the above diamide with hydrochloric acid, the dihydroimidazole derivative obtained from ethylenediamine and ethyl trichloroacetate did not react with hydrochloric acid under similar conditions.

PHILADELPHIA, PENNSYLVANIA

[CONTRIBUTION FROM THE RESEARCH DIVISION, BRISTOL LABORATORIES, INC.]

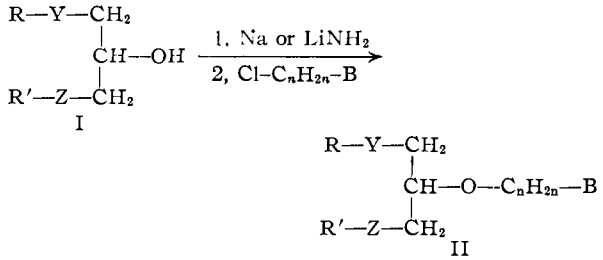
Glycerol Ethers. I. Alkaminoalkyl Ethers of 1,3-Bis-(aryloxy)-2-propanols and Related Compounds

BY WILLIAM F. MINOR, RICHARD R. SMITH AND LEE C. CHENEY

RECEIVED JANUARY 30, 1954

By the condensation of an alkali salt of a 1,3-diether of glycerol with an alkaminoalkyl chloride, a novel series of basic ethers has been prepared for pharmacological investigation. 2-[(1,3-Diphenoxy)-2-propoxymethyl]-imidazoline was obtained by heating ethyl [(1,3-diphenoxy)-2-propoxy]-acetate with ethylenediamine. Certain members of the group exhibit pronounced local anesthetic activity.

A series of glycerol triethers wherein the central alkoxy moiety bears an alkamine function (general formula II) has been prepared for biological investigation.



R, R′ = alkyl, aryl or substituted aryl groups
Y, Z = O or S; B = dialkylamino, piperidyl or imidazolyl

The intermediate symmetrical 1,3-bis-(aryloxy)-2-propanols (I) were prepared by a slight modification of the excellent method of Marple and Evans[1] (method A), utilizing the interaction of the appropriate phenol, sodium hydroxide and epichlorohydrin in a medium of dioxane. The yields varied from 61 to 95% with but four exceptions (Table I). Obviously this procedure was suitable only when R and R′ of I were the same. In the instances where they differed, methods B, C and D were employed.

The evidence that the ring openings in basic media of unsymmetrical epoxides by alcohols,[2] phe-

(1) K. E. Marple and T. W. Evans, U. S. Patent 2,351,025 (1944), Example V; *C. A.*, **38**, 5224 (1944).

(2) D. Swern, G. N. Billen and H. B. Knight, THIS JOURNAL, **71**, 1152 (1949).

TABLE I

2-PROPANOLS OF THE FORMULA R—Y—$CH_2CH(OH)CH_2$—Z—R′

R	R′	Y	Z	Method	Yield, %	M.p.,[h] °C.	B.p. °C.	Mm.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Phenyl	Phenyl	O	O	A,B	95, 30	82.5–84[a]			$C_{15}H_{16}O_3$				
o-Tolyl	o-Tolyl	O	O	A	61[d]		176–180	1	$C_{17}H_{20}O_3$	75.0	74.7	7.39	7.87
p-Tolyl	p-Tolyl	O	O	A	88[d]	89.5–91[a]			$C_{17}H_{20}O_3$	75.0	74.9	7.39	7.25
3,5-Xylyl	3,5-Xylyl	O	O	A	62	68–69[a,b]			$C_{19}H_{24}O_3$	75.9	76.1	8.04	7.83
p-Ethoxyphenyl	p-Ethoxyphenyl	O	O	A	89.5	95–96.5[a]			$C_{19}H_{24}O_5$	68.6	68.8	7.26	7.09
p-Nitrophenyl	p-Nitrophenyl	O	O	A	4[d]	146–147			$C_{15}H_{14}N_2O_7$				
p-Chlorophenyl	p-Chlorophenyl	O	O	A	89.5	91–92[a,g]			$C_{15}H_{14}Cl_2O_3$	57.5	57.8	4.52	4.32
2,4-Dichlorophenyl	2,4-Dichlorophenyl	O	O	A	80	128.5–129[a]			$C_{15}H_{12}Cl_4O_3$	47.1	47.3	3.16	3.52
2,4,5-Trichlorophenyl	2,4,5-Trichlorophenyl	O	O	A	12	124.5–127[a]			$C_{16}H_{10}Cl_6O_3$	39.9	40.0	2.23	2.30
4-Chloro-3,5-xylyl	4-Chloro-3,5-xylyl	O	O	A	74	89–90[b]			$C_{19}H_{22}Cl_2O_3$	61.9	61.8	6.00	5.96
Phenyl	Phenyl	S	S	A	64[c]		192–225	1–3.5	$C_{15}H_{16}OS_2$	65.1	65.2	5.83	5.68
o-Tolyl	o-Tolyl	S	S	A	73		208–218	<1	$C_{17}H_{20}OS_2$	67.0	67.2	6.61	7.00
o-Tolyl	Phenyl	S	O	B	20		184–191	<1	$C_{16}H_{18}O_2S$	70.0	70.2	6.61	6.75
o-Tolyl	Phenyl	O	S	C	60		205–210	3.5	$C_{16}H_{18}O_2S$	70.0	70.1	6.61	6.45
n-Butyl	Phenyl	O	O	D	39[e]		125–132	<1	$C_{13}H_{20}O_3$	69.5	68.4	8.97	8.93[f]
o-Tolyl	Ethyl	O	S	C	86		142–149	1	$C_{12}H_{18}O_2S$	63.6	64.6	8.00	7.86[f]

[a] Recrystallized from isopropyl alcohol. [b] Recrystallized from petroleum ether (b.p. 60–71°). [c] A small amount of diphenyl disulfide, m.p. 58–60°, was isolated from this reaction. [d] *Cf.* H. Lefebvre, E. Levas and Mme. E. Levas; *Compt. rend.*, **222**, 1439 (1946). [e] *Cf.* C. H. Hine, *et al.*, *J. Pharmacol. Exptl. Therapeutics*, **97**, Pt. I, 414 (1949). [f] These analytical results are slightly beyond the acceptable range, but others of analytical purity (Table II) were obtained from the alcohols. [g] W. Bradley, J. Forrest and O. Stephenson, *J. Chem. Soc.*, 1589 (1951), report m.p. 89–90°. [h] Melting points are uncorrected.

nols[3] and mercaptans[4,5] gives ecoindary alcohols predominantly, if not exclusively, lends substantial support for the 1,3-diether structure assigned to I. Furthermore, the relatively recent preparation of *sym*-diphenoxyacetone[6] has afforded a satisfactory structural proof for the product (I) derived from phenol and epichlorohydrin. This ketone was isolated by Munch-Peterson as a destructive distillation product of the β-keto ester derived from the self Claisen condensation of *t*-butyl phenoxyacetate. The same ketone was synthesized by the chromic acid oxidation of 1,3-diphenoxy-2-propanol (prepared from glycerol *sym*-dichlorohydrin, sodium ethoxide and phenol). The two samples of *sym*-diphenoxyacetone thus prepared were proven identical by "mixed melting point." The latter preparation constitutes the same proof of the secondary alcohol structure for 1,3-diaryloxy-2-propanols that Henze and Rogers[7] afforded for the 1,3-dialkoxy-2-propanols.

In general the basic ethers of type II were prepared in yields of 60–80% (Table II) by the condensation of dialkylaminoalkyl chlorides with sodium or lithium salts of I (methods E and F). In no case was an attempt made to determine the conditions of optimum yield.

The formation of the ethers proceeded smoothly, but the isolation of their hydrochlorides caused unexpected difficulty in several cases (Table II; numbers six through nine, twelve and thirteen). In these instances the addition of dilute hydrochloric acid to the toluene reaction mixtures (see method A) gave homogeneous solutions, with no separation of acidic aqueous phases. Further details of the isolation of these compounds will be found in the footnotes to Table II. The purified hydrochlorides were found to be remarkably soluble in hot toluene, although their solubilities in this solvent at room temperature were invariably less than 0.5%

Dr. H. L. Dickison and his associates have found that these compounds as a class are potent local anesthetic agents. Pharmacological details will be reported elsewhere.

(3) A. R. Sexton and E. C. Britton, THIS JOURNAL, **70**, 3606 (1948).

(4) H. Gilman and L. Fullhart, *ibid.*, **71**, 1478 (1949).

(5) T. K. Tudsen, C. B. Pollard and E. G. Rietz, *ibid.*, **72**, 4000 (1950).

(6) J. Munch-Peterson, *Acta Chem. Scand.*, **5**, 510 (1951); *C. A.*, **46**, 4711f (1952).

(7) H. R. Henze and B. G. Rogers, THIS JOURNAL, **61**, 433 (1939).

Experimental

Epoxides.—Epichlorohydrin and 1,2-epoxy-3-phenoxypropane were used as obtained from the Shell Chemical Corporation.

Phenols.—All phenols were procured from commercial sources and used without further purification.

Dialkylaminoalkyl Chlorides.—β-Dialkylaminoethyl chloride hydrochlorides were prepared by the treatment of a benzene solution of the corresponding aminoalcohols with an excess of thionyl chloride.[8]

γ-1-Piperidylneopentyl chloride hydrochloride was made by a reported procedure.[9] Previous work[10] has adduced strong evidence that the subsequent alkylation of I with this chloride did not involve rearrangement. The dialkylaminoalkyl chlorides were prepared immediately before use by treating the corresponding hydrochlorides with strong alkali, extracting with toluene and drying over anhydrous potassium carbonate.

Method A. 1,3-Bis-(aryloxy)-2-propanols (Table I).—These compounds were synthesized by the following modification of the method of Marple and Evans.[1]

A stirred mixture of 2.2 moles of the phenol and 1.2 moles of flake sodium hydroxide in 200 ml. of dioxane was heated and stirred on the steam-bath for approximately one hour or until the majority of the sodium hydroxide was dissolved. To the heated and stirred mixture was added one mole of epichlorohydrin at a rate which maintained reflux, the addition usually requiring about 45 minutes. The mixture was heated and stirred for an additional 5.5 hours and was poured into 800 ml. of cold water. Whenever the precipitated oil crystallized it was collected by suction, dried and recrystallized from isopropyl alcohol or petroleum ether (b.p. 85–100°). If the oil did not crystallize on standing overnight at 5–10°, it was extracted into chloroform and washed in turn with 5% sodium hydroxide solution, water and a saturated solution of sodium chloride. After filtration through anhydrous magnesium sulfate this chloroform solution was distilled (Table I).

Method B. 1-Phenoxy-3-*o*-tolylmercapto-2-propanol.—To a stirred solution of 56.5 g. (0.455 mole) of *o*-thiocresol in 110 ml. of dioxane at 100° was added 65.0 g. (0.432 mole) of 1,2-epoxy-3-phenoxypropane during a 45-minute period.

(8) K. H. Slotta and R. Behnisch, *Ber.*, **68**, 754 (1935).

(9) C. Mannich and G. Baumgarten, *ibid.*, **70**, 210 (1937).

(10) W. B. Wheatley and L. C. Cheney, THIS JOURNAL, **74**, 1359 (1952).

TABLE II

TRIETHERS OF THE FORMULA R—Y—CH_2—CH(O—A)—CH_2—Z—R′

No.	R	R′	Y	Z	A	Method	Yield,[a] %	B.p. °C.	B.p. Mm.	M.p. of salt (uncor.), °C.	Recryst. from	Formula of salt[b]	Analyses,[c] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	Phenyl	Phenyl	O	O	$CH_2CH_2N(CH_3)_2$	E, F	61	152–160	<1	131 –132[d]	MeCOBu-*i*	$C_{19}H_{26}ClNO_3$	64.8	64.7	7.46	7.91
2	Phenyl	Phenyl	O	O	$CH_2CH_2N(C_2H_5)_2$	E	87.5	168–174	<1	109.5–111[d,g]	EtOAc	$C_{21}H_{30}ClNO_3$	66.4	66.7	7.97	8.12
3	Phenyl	Phenyl	O	O	$CH_2CH_2N(i\text{-}C_3H_7)_2$	E	87	195–197	1			$C_{23}H_{33}NO_3$	74.5	74.5	8.98	9.05
4	Phenyl	Phenyl	O	O	$CH_2CH_2NC_5H_{10}$[h]	E	79	180–185	<1	97 –98.5[d,k]	EtOAc	$C_{22}H_{30}ClNO_3$	67.5	67.9	7.73	7.69
5	Phenyl	Phenyl	O	O	$CH_2C(CH_3)_2CH_2NC_5H_{10}$[h]	E	79	202–206	1			$C_{25}H_{35}NO_3$	75.5	75.8	8.90	9.10
6	*o*-Tolyl	*o*-Tolyl	O	O	$CH_2CH_2N(CH_3)_2$	E[p]	79	187–192	1			$C_{21}H_{29}NO_3$	73.5	73.5	8.51	8.50
7	*p*-Tolyl	*p*-Tolyl	O	O	$CH_2CH_2N(CH_3)_2$	E[p]	79	192–194	1	123 –124.5[d,f]	Me_2CO	$C_{21}H_{30}ClNO_3$	66.4	66.6	7.95	8.08
8	3,5-Xylyl	3,5-Xylyl	O	O	$CH_2CH_2N(C_2H_5)_2$	E[q]	63			90 –92[d,f]	EtOAc	$C_{25}H_{38}ClNO_3$	68.7	68.0	8.78	9.12[l]
9	*p*-Ethoxyphenyl	*p*-Ethoxyphenyl	O	O	$CH_2CH_2N(CH_3)_2$	E[p]	74	230–232[j]	1	94.5–96[d,f]	EtOAc	$C_{23}H_{34}ClNO_5$	62.8	62.7	7.80	7.81
10	*p*-Nitrophenyl	*p*-Nitrophenyl	O	O	$CH_2CH_2N(C_2H_5)_2$	F	36.5	[i]			EtOH, EtOAc	$C_{21}H_{27}N_3O_7$	58.1	58.5	6.29	6.35
11	*p*-Chlorophenyl	*p*-Chlorophenyl	O	O	$CH_2CH_2N(C_2H_5)_2$	F	43			122 –123[e]	Me_2CO, EtOH	$C_{27}H_{35}Cl_2NO_{10}$	53.6	53.7	5.84	5.65
12	2,4-Dichlorophenyl	2,4-Dichlorophenyl	O	O	$CH_2CH_2N(C_2H_5)_2$	E[r]	60			108.5–110[d,f]	MeCOBu-*i*	$C_{21}H_{26}Cl_5NO_3$	48.7	49.0	5.06	5.04[m]
13	4-Chloro-3,5-xylyl	4-Chloro-3,5-xylyl	O	O	$CH_2CH_2N(C_2H_5)_2$	E[s]	85			135.5–137.5[d]	EtOAc	$C_{25}H_{31}Cl_3NO_3$	59.6	59.5	7.01	7.16[n]
14	*n*-Butyl	Phenyl	O	O	$CH_2CH_2N(C_2H_5)_2$	E	85.5	152–162	<1–1			$C_{19}H_{33}NO_3$	70.5	70.2	10.03	10.32
15	Phenyl	Phenyl	S	S	$CH_2CH_2N(C_2H_5)_2$	E	70			91 –92.5[e,f]	EtOH, Me_2CO	$C_{27}H_{37}NO_9S_2 \cdot {}^1/_2H_2O$	56.2	56.1 56.3	6.64	6.68 6.38
16	*o*-Tolyl	*o*-Tolyl	S	S	$CH_2CH_2N(CH_3)_2$	E	36	193–199	<1	103 –105[d,f]	EtOAc	$C_{21}H_{30}ClNOS_2$	61.2	60.9	7.34	7.36
17	*o*-Tolyl	Phenyl	O	S	$CH_2CH_2N(CH_3)_2$	E	53	208–217	<1–1.5			$C_{20}H_{27}NO_2S$	69.5	69.6	7.87	7.96
18	*o*-Tolyl	Phenyl	S	O	$CH_2CH_2N(C_2H_5)_2$	E	46	186–189	<1	112 –113.5[e,f]	*i*-PrOH	$C_{28}H_{39}NO_3S$	59.5	59.5	6.95	6.85
19	*o*-Tolyl	Ethyl	O	S	$CH_2CH_2N(CH_3)_2$	E	83.5	146–153	1	89 –90[e,f]	MeCOBu-*i*	$C_{24}H_{39}NO_3S$	55.7	55.7	7.59	7.76
20	Phenyl	Phenyl	O	O	$CH_2COOC_2H_5$	E	85	210–214	1.5			$C_{19}H_{22}O_5$	69.0	69.3	6.70	6.61
21	Phenyl	Phenyl	O	O	CH_2—C(=N—CH_2—CH_2—NH)		32	238–241	2	168 –168.5[d]	*i*-PrOH	$C_{19}H_{23}ClN_2O_3$	62.9	62.9	6.38	6.52
22	Phenyl	Phenyl	O	O	$CH_2CH_2N(CH_3)_2 \cdot C_2H_5I$		62.5			75 –76.5	EtOH–EtOAc	$C_{21}H_{30}INO_3$	53.5	53.6	6.41	6.34
23	Phenyl	Phenyl	O	O	$CH_2CH_2N(i\text{-}C_3H_7)_2 \cdot CH_3I$		92			95.5–97[f]	EtOH–Et_2O	$C_{24}H_{36}INO_3$	56.1	56.3	7.07	7.24
24	Phenyl	Phenyl	O	O	$CH_2CH_2NC_5H_{10} \cdot CH_3I$[h]		66			78.8[f]	EtOH–Et_2O	$C_{23}H_{32}INO_3$	55.5	55.6	6.49	6.59
25	*o*-Tolyl	*o*-Tolyl	O	O	$CH_2CH_2N(CH_3)_2 \cdot CH_3I$		95			86 –87[f]	Me_2CO–Et_2O	$C_{22}H_{32}INO_3$	54.4	54.4	6.65	6.84

[a] The yield is of the base whenever it was isolated. [b] The formula and analysis of the base are given when no salt was prepared. [c] Analysis of the addition salt when it was prepared. [d] Hydrochloride. [e] Dihydrogen citrate. [f] Melts with decomposition. [g] The dihydrogen citrate was also obtained, m.p. 113–114° dec. from water–isopropyl alcohol. *Anal.* Calcd. for $C_{27}H_{37}NO_{10}$: C, 60.5; H, 6.96. Found: C, 60.8; H, 7.22. [h] $-NC_5H_{10}$ represents 1-piperidyl. [i] This product was not distilled; m.p. 98–100°. [j] The amine crystallized after distillation; m.p. 60–61.5°. [k] In a second preparation the composition of the hydrochloride approached that of a monohydrate: *Anal.* Calcd.: H_2O, 4.40. Found: H_2O, 3.78; m.p. 74.5–76°. [l] Calcd.: N, 3.2. Found: N, 3.0. [m] Calcd.: Cl, 33.6; N, 2.7. Found: Cl, 33.5; N, 3.1. [n] Calcd.: Cl, 21.2. Found: Cl, 20.8. [p] The amine could not be extracted from the reaction mixture with dilute hydrochloric acid, a single-phase system resulting. However, the addition of ether caused the separation of an acidic, aqueous layer that contained the amine hydrochloride. [q] Acid extraction of the toluene reaction mixture yielded no product; when the toluene was removed by steam distillation the hydrochloride crystallized from the cooled aqueous residue. [r] An attempted isolation as in *p* gave no acidic aqueous layer upon the addition of ether; after the removal of all solvents the hydrochloride crystallized and was separated from unreacted starting material by trituration with ether. [s] All toluene was removed from the reaction mixture by steam distillation, and the organic residue was extracted into ether. An attempted extraction of this ether solution with dilute hydrochloric acid yielded no aqueous hydrochloride layer. After removal of the ether by distillation the residue crystallized slowly and the hydrochloride was isolated by trituration of the mass with boiling ether.

The solution was heated for 19 hours, cooled and extracted thrice with 5% sodium hydroxide solution to remove excess *o*-thiocresol. After being washed with water and saturated sodium chloride solution, the mixture was filtered through anhydrous sodium sulfate and distilled. The product, a viscous yellow oil, was collected at 184–191° at less than 1 mm.; yield 24 g. (20%).

Method C. 1-Phenylmercapto-3-(*o*-toloxy)-2-propanol.—A mixture of 37.4 g. (0.34 mole) of thiophenol and 16 g. (0.40 mole) of flake sodium hydroxide in 100 ml. of dioxane was heated and stirred for one hour on the steam-bath. To the resultant homogeneous mixture was added 66.5 g. (0.33 mole) of 1-chloro-3-(*o*-toloxy)-2-propanol[11] over a 25-minute period. After the initial vigorous reaction subsided, the mixture was heated for two hours and poured into water. The precipitated oil was extracted into chloroform and the combined extracts were washed with water and saturated sodium chloride solution. The chloroform solution was filtered through anhydrous magnesium sulfate and distilled to obtain 55 g. (60%) of product; b.p. 183° at 1 mm. to 210° at 3.5 mm.

1-Ethylmercapto-3-(*o*-toloxy)-2-propanol was prepared in the same manner, except that a temperature of only 50° was employed for the preparation of the sodium salt of ethyl mercaptan.

Method D. 1-Butoxy-3-phenoxy-2-propanol.—To a mixture of 500 ml. of butyl alcohol and 0.5 ml. of stannic chloride as catalyst,[12] stirred and heated on the steam-bath with calcium chloride protection from moisture, was added 75.1 g. (0.50 mole) of 1,2-epoxy-3-phenoxypropane during a 30-minute period. After being stirred and heated for 7.5 hours the mixture was filtered. One and eight-tenths grams of anhydrous potassium carbonate was added and the mixture was distilled. Forty and six-tenths grams (39%) of colorless oil was collected at 125–132° at 1 mm.

Method E. Basic Ethers (Table II).—The mode of preparation of the sodium alkoxide was dependent upon the degree of solubility of the glycerol diether (I) in toluene. Whenever the solubility permitted, the alkoxide was prepared by the addition of a toluene solution of the alcohol to a stirred mixture of molten sodium in toluene at a rate to maintain reflux. Since the alcohols were usually not too soluble in toluene at room temperature, the majority of the sodium alkoxides were prepared by the piecewise addition of sodium to a 10–20% excess of the alcohol in hot toluene. This reaction was invariably a vigorous one. The mixture was refluxed and stirred until the sodium was consumed (5–9 hours), the length of time necessary for this salt formation being materially decreased by the use of a large excess of the alcohol. If decomposition was evident, a nitrogen atmosphere was used.

When the salt formation was complete a dried toluene solution of 10–15% excess of the dialkylaminoalkyl chloride was added rapidly, the reaction not being noticeably exothermic. Refluxing and stirring were continued for 10 to 17 hours. To ensure the destruction of all sodium, 5 to 10 ml. of methanol was added, followed by enough water to dissolve all inorganic material (alternatively the toluene was sometimes removed by steam distillation, and the organic residue was extracted into ether). If no addition salt could be prepared from the washed toluene layer, then acid extraction and subsequent neutralization of the extracts yielded the product, which was taken up in ether, dried and distilled. Addition salts were prepared from the crude amines when possible, hydrochlorides and dihydrogen citrates being the salts of choice.

Method F.—Lithium amide was added in one portion to a warm toluene solution of a slight excess of the alcohol (I). The resultant mixture was stirred and refluxed for four hours, with copious evolution of ammonia throughout this period. A toluene solution of the dialkylaminoalkyl chloride was added over a 30-minute period and the mixture was refluxed and stirred for 17–19 hours. The product was then isolated in the manner of method E.

Ethyl [(1,3-Diphenoxy)-2-propoxy]-acetate.—This compound was prepared essentially by method E, using 101.0 g. (0.41 mole) of 1,3-diphenoxy-2-propanol, 7.8 g. (0.34 mole) of sodium, 550 ml. of dry toluene and 45.3 g. (0.37 mole) of ethyl chloroacetate in 200 ml. of toluene. After a final reflux of 14 hours, methanol and water were added as previously described (method E). The toluene layer was separated, washed with water and saturated sodium chloride solution and dried over anhydrous sodium sulfate. Distillation yielded 95.0 g. (85%) of viscous oil; b.p. 210–214° at 1.5 mm.

2-[(1,3-Diphenoxy)-2-propoxymethyl]-imidazoline.—A mixture of 33.0 g. (0.10 mole) of ethyl [(1,3-diphenoxy)-2-propoxy]-acetate and 30.0 g. (0.50 mole) of anhydrous ethylenediamine was heated on the steam-bath for 89 hours with calcium chloride protection from moisture. Water, alcohol and excess ethylenediamine were removed by distillation under a water aspirator and the residue was distilled *in vacuo*. Ten and five-tenths grams (32%) of reddish oil was collected at 238–241° and 1 mm. The hydrochloride was prepared in ether.

Quaternary Ammonium Halides.—The quaternaries were prepared by reaction of the amines with the corresponding halides in methyl or isopropyl alcohol at room temperature, subsequent removal of the solvent *in vacuo* and recrystallization of the residues from suitable solvents.

Acknowledgment.—The authors are indebted to Mr. Richard M. Downing for the microanalyses reported in this paper.

SYRACUSE, NEW YORK

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