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Muscle-paralyzing Compounds Related to Mephenesin

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A series of ring-substituted phenoxy alkanols and alkanediols structurally related to mephenesin (3-*o*-toloxy-1,2-propanediol) have been synthesized for pharmacological evaluation as muscle-paralyzing agents. The methods of preparation and the physical constants of these compounds are described.

Pharmacological investigations of the properties of mephenesin, 3-*o*-toloxy-1,2-propanediol, have disclosed that this compound possesses both muscle-paralyzing and anticonvulsant properties.[1] Compounds of the mephenesin type having predominantly one or the other of these properties have also been described.[2] In a search for drugs that produce a muscle-paralyzing action more intense and of longer duration than that exhibited by mephenesin, we have prepared and tested a number of structurally similar ethers of glycerol, propylene glycol and related alkanols.

Prior to and during the course of this investigation, there appeared several publications describing compounds of this general type.[3] Our study included in addition to many of these a number of compounds not previously disclosed in the chemical literature. This paper describes the preparation and physical properties of compounds synthesized for this study; the pharmacological data showing the correlation between muscle-paralyzing activity and chemical structure of these compounds will be published elsewhere.

In preparing these substituted phenoxyalkanols, variations were made in the nature and distribution of substituents in the aromatic nucleus, and modifications were made in the structure of the hydroxylated side chain.

The glycerol, propylene glycol and trimethylene glycol ethers were generally prepared by the condensation of the phenol or alcohol with the appropriate halohydrin in the presence of a suitable alkali. An aqueous or aqueous alcoholic medium was usually employed although most of the condensations could be effectively carried out in anhydrous alcohol using the corresponding sodium alkylate as the acid acceptor. Some of the ethers were prepared by the alkali-catalyzed condensation of the phenol and the appropriate epoxide, but this method of preparation was less satisfactory.

Fairbourne, *et al.*,[4] have presented evidence that reactions carried out with glycerol α-monochlorohydrin in alkaline medium involve the intermediate formation of glycidol which further reacts with phenols to form α-aryl ethers exclusively. Presumably, propylene chlorohydrin under similar conditions through the intermediate formation of propylene oxide would also yield in an analogous manner only α-ethers. This is substantiated by the findings of Sexton and Britton[5] who have shown that the reaction of phenols with propylene oxide in the presence of an alkaline catalyst leads to the formation of a secondary rather than a primary alcohol, and other investigators[6] who have obtained the secondary alcohol almost exclusively from the alkali-catalyzed reaction of propylene oxide and a variety of aliphatic alcohols.

Additional confirmation that the product obtained from propylene chlorohydrin is the 2-propanol rather than the 1-propanol isomer was afforded by obtaining one of the phenoxypropanols both by reduction of the corresponding ketone and by the usual condensation. 4-Chloro-3,5-dimethylphenoxyacetone on reduction with lithium aluminum hydride gave a product identical in every respect to that obtained by direct condensation of 4-chloro-3,5-xylenol with propylene chlorohydrin in alkaline medium.

On the basis of this evidence and the results of previous workers in this field, the assignment of the secondary alcohol (primary ether) structure to the glycerol and propylene glycol ethers appears justified.

Most of the ethers were obtained as readily distillable liquids, some of which solidified upon standing and could be purified by recrystallization. In general, the substituted 3-phenoxy-1,2-propanediols were isolated as white crystalline solids, while most of the corresponding monohydric compounds were obtained as high boiling liquids. Some of the liquid ethers were not analytically pure even after repeated fractional distillation. 3-(2,6-Dimethoxyphenoxy)-1,2-propanediol (VIII) which was obtained as a viscous oil after repeated fractional distillation, was prepared in a pure crystalline state by converting it to its dioxolane, purifying this derivative by fractional distillation and regenerating the diol by acid hydrolysis.

Highly branched ortho-substituted phenols gave low yields of phenolic ethers when the condensation was conducted by the usual procedures. 4,6-Di-*t*-butyl-*o*-cresol condensed with glycerol α-monochlorohydrin only to a limited degree under the most favorable reaction conditions. Consequently, the desired glycerol ether (VI) was prepared by oxidation of the corresponding allyl ether (XLIV), which was obtained in good yield by the reaction of allyl bromide with the sodium phenolate in anhydrous alcoholic medium.

Certain of the halogenated phenols gave unusu-

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(2) F. M. Berger, *Arch. intern. pharmacodynamie*, **85**, 474 (1951); F. M. Berger and B. J. Ludwig, *J. Pharmacol. Exptl. Therap.*, **100**, 27 (1950).

(3) F. M. Berger, *ibid.*, **93**, 470 (1948); W. A. Lott, *Trans. N. Y. Acad. Sci.*, [2] **11**, 1 (1948); C. H. Hine, H. E. Christensen, F. J. Murphy and H. Davis, *J. Pharmacol. Exptl. Therap.*, **97**, 414 (1949); A. F. Lindenstruth, J. H. Fellman and C. A. VanderWerf, THIS JOURNAL, **72**, 1886 (1950); H. L. Yale, E. J. Pribyl, W. Braker, F. H. Bergeim and W. A. Lott, *ibid.*, **72**, 3710 (1950); R. I. Meltzer and J. Doczi, *ibid.*, **72**, 4986 (1950); J. P. Lambooy, *ibid.*, **73**, 349 (1951).

(4) A. Fairbourne, C. P. Gibson and D. W. Stephens, *J. Soc. Chem. Ind.*, **49**, 1021 (1930); *J. Chem. Soc.*, 445 (1931); 1965 (1932).

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

(6) D. Swern, G. N. Billen and H. B. Knight, *ibid.*, **71**, 1152 (1949); W. Reeve and A. Sadle, *ibid.*, **72**, 1251 (1950).

TABLE I

Compd. No.	Compounds 3-Substituted-1,2-propanediols	Method of prepn.	Yield, %[a]	B.p. °C.	Mm.	$n^{25}D$	M.p., °C.[b]	Empirical formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
I	3-(β-Phenylethoxy)-	5	31	156–157	2.0	1.5203	.....	$C_{11}H_{16}O_3$	67.35	67.24	8.17	8.29
II	3-(2,3-Xylyloxy)-	2	50	.....	..	....	82.5–83[cm]	$C_{11}H_{16}O_3$	67.35	67.69	8.17	8.27
III	3-(2,4-Xylyloxy)-	2[d]	50	.....	..	....	92–93[cm]	$C_{11}H_{16}O_3$	67.35	67.70	8.17	8.16
IV	3-(2-t-Butyl-5-methylphenoxy)-	5	35	.....	..	....	78–79[cc]	$C_{14}H_{22}O_3$	70.58	70.13	9.24	9.26
V	3-(2,3,5-Trimethylphenoxy)-	4	25	.....	..	....	93–94[cm]	$C_{12}H_{18}O_3$	68.57	68.66	8.57	8.75
VI	3-(4,6-Di-t-butyl-2-methylphenoxy)-	[e]	12	.....	..	....	109–110[cc]	$C_{18}H_{30}O_3$	73.47	73.19	10.02	9.87
VII	3-(2,6-Dimethyl-4-isopropoxyphenoxy)-	1[e]	60	.....	..	....	60.5–62[cm]	$C_{14}H_{22}O_4$	66.14	65.83	8.66	8.28
VIII	3-(2,6-Dimethoxyphenoxy)-	[c,d,f]	76	.....	..	....	52–53.5[cm]	$C_{11}H_{16}O_5$	57.89	58.21	7.07	7.08
IX	3-(2-Chlorophenoxy)-	5[d]	80	.....	..	....	71–72[cm]	$C_9H_{11}O_3Cl$	53.45	53.33	5.48	5.44
X	3-(2,4-Dichlorophenoxy)-	5[d]	75	.....	..	....	80–81[cm]	$C_9H_{10}O_3Cl_2$		[g]		
XI	3-(2,6-Dichlorophenoxy)-	5	55	.....	..	....	80.5–81[cm]	$C_9H_{10}O_3Cl_2$	45.57	45.70	4.22	4.08
XII	3-(4-Chloro-2-methylphenoxy)-	2	42	.....	..	....	96–97.5[cb]	$C_{10}H_{13}O_3Cl$	55.42	55.36	6.00	6.09
XIII	3-(4-Chloro-3,5-dimethylphenoxy)-	1[d]	57	.....	..	....	89–90[cm]	$C_{11}H_{15}O_3Cl$	57.30	57.74	6.51	6.40
XIV	3-(4-Chloro-2,6-dimethylphenoxy)	2	77	.....	..	....	64.5–65[cm]	$C_{11}H_{15}O_3Cl$	57.30	57.40	6.51	6.43
XV	3-(2,6-Dichloro-4-methylphenoxy)-	4	10	.....	..	....	65–66[cm]	$C_{10}H_{12}O_3Cl_2$	47.81	47.72	4.78	4.98
XVI	3-(2,4-Dichloro-6-methylphenoxy)-	2	61	.....	..	....	67–68[cm]	$C_{10}H_{12}O_3Cl_2$	47.81	47.93	4.78	4.79
XVII	3-(3,4-Dichloro-2,6-dimethylphenoxy)-	4	55	.....	..	....	75–76.5[cm]	$C_{11}H_{14}O_3Cl_2$	49.81	49.73	5.29	5.46
XVIII	3-(2,6-Dichloro-4-α-cumylphenoxy)-	4	15	200–202	0.3	1.5848	.....	$C_{18}H_{20}O_3Cl_2$		[h]		
XIX	3-(4-Benzylphenoxy)-	5	89	.....	..	....	81.5–82.5[cm]	$C_{13}H_{12}O_2$	74.42	74.03	6.97	7.12
XX	3-(4-α-Cumylphenoxy)-	2	26	200–202	.5	1.5756	.....	$C_{18}H_{22}O_2$	75.52	75.71	7.78	7.85
XXI	3-(3-Carbo-n-butoxyphenoxy)-	5	88	194–196	.4	1.5238	.....	$C_{14}H_{20}O_5$	62.70	62.28	7.46	7.15
XXII	3-(4-Carbo-n-butoxyphenoxy)-	2[d]	85	207–210	1.0	....	59–60[cc]	$C_{14}H_{20}O_5$	62.70	62.60	7.46	7.23
	1-Substituted-2-propanols											
XXIII	1-(2,6-Xylyloxy)-	3	83	95–100	1.0	1.5100	.....	$C_{11}H_{16}O_2$	73.33	73.10	8.98	9.00
XXIV	1-(4-α-Cumylphenoxy)-	4	21	170–175	0.8	1.5633	.....	$C_{18}H_{22}O_2$	80.00	80.05	8.15	7.91
XXV	1-(2-Ethoxyphenoxy)-	5	66	114–119	1.8	1.5151	.....	$C_{11}H_{16}O_3$	67.35	67.08	8.17	8.18
XXVI	1-(2,6-Dichlorophenoxy)-	5	50	96–97	0.7	1.5395	.....	$C_9H_{10}O_2Cl_2$	48.88	49.09	4.53	4.72
XXVII	1-(2,4,6-Trichlorophenoxy)-	4	67	124–126	1.6	....	41–42[cl]	$C_9H_9O_2Cl_3$	42.27	42.54	3.55	3.52
XXVIII	1-(2,3,4,6-Tetrachlorophenoxy)-	5	10	142–150	1.5	1.5680	.....	$C_9H_8O_2Cl_4$	37.25	37.08	2.76	2.81
XXIX	1-(4-Chloro-2-methylphenoxy)-	5	34	95–99	0.5	1.5341	.....	$C_{10}H_{13}O_2Cl$	59.85	59.55	6.48	6.68
XXX	1-(6-Chloro-2-methylphenoxy)-	2	38	109–110	2.5	1.5258	.....	$C_{10}H_{13}O_2Cl$		[i]		
XXXI	1-(4-Chloro-3-methylphenoxy)-	1	65	103–107	0.3	1.5350	.....	$C_{10}H_{13}O_2Cl$	59.85	59.94	6.48	6.41
XXXII	1-(2-Chloro-4-t-butylphenoxy)-	1	52	126–128	.5	1.5210	.....	$C_{13}H_{19}O_2Cl$	64.33	64.74	7.84	8.07
XXXIII	1-(2-Chloro-4-phenylphenoxy)-	5	12	.....	..	....	97–97.5[cc]	$C_{15}H_{15}O_2Cl$		[j]		
XXXIV	1-(2-Chloro-6-phenylphenoxy)-	1	30	138–146	.5	1.5941	.....	$C_{15}H_{15}O_2Cl$	68.56	68.51	5.71	5.86
XXXV	1-(4-Chloro-2,6-dimethylphenoxy)	2	10	104–108	.6	1.5254	.....	$C_{11}H_{14}O_2Cl_2$	61.54	61.72	6.98	7.39
XXXVI	1-(4-Chloro-3,5-dimethylphenoxy)-	[c]	85	110.5–112.5	.7	....	61–62[cm]	$C_{11}H_{14}O_2Cl_2$	61.54	61.26	6.98	6.73
XXXVII	1-(2,6-Dichloro-4-methylphenoxy)-	1	40	109–110	.5	1.5387	.....	$C_{10}H_{12}O_2Cl_2$		[k]		
XXXVIII	1-(2,4-Dichloro-6-methylphenoxy)-	2	26	.....	..	....	50–51[cc]	$C_{10}H_{12}O_2Cl_2$		[l]		
XXXIX	1-(2,6-Dichloro-4-α-cumylphenoxy)-	2	43	180–181	.8	1.5774	.....	$C_{18}H_{20}O_2Cl_2$		[m]		
XL	1-(2,6-Dibromo-4-t-butylphenoxy)-	5	20	144–147	.7	1.5572	.....	$C_{13}H_{18}O_2Br_2$[n]	42.62	42.85	4.92	5.14
XLI	1-(4-Carbo-n-butoxyphenoxy)-	5	58	153–157	.3	1.5249	.....	$C_{14}H_{20}O_4$	66.67	66.72	7.89	7.55

	Substituted phenoxy alkanols and related compounds												
XLII	1-Acetoxy-3-(2,6-xylyloxy)-2-propanol	[c]	81	129–131	0.5	1.5070	.....	$C_{13}H_{18}O_4$	65.56	65.60	7.56	7.52
XLIII	3-(4-Carbo-*n*-butoxyphenoxy)-1-propanol	5	40	147–149	.1	1.5255	.....	$C_{14}H_{20}O_4$	66.67	65.69	7.89	7.57
XLIV	3-(4,6-Di-*t*-butyl-2-methylphenoxy)-1-propene	[c]	79	80–81	.2	1.5017	.....	$C_{18}H_{28}O$	83.04	83.10	10.77	10.72
XLV	3-(4-Chloro-3,5-dimethylphenoxy)-1-propanol	1	74	.....	..	....	54–55[cm]	$C_{11}H_{14}O_2Cl_2$	61.54	61.61	6.98	7.04
XLVI	3-(2,6-Dichloro-4-methylphenoxy)-1-propanol	2	13	125–127	.5	1.5448	.....	$C_{10}H_{12}O_2Cl_2$		[o]		
XLVII	2,6-Dichlorophenoxyacetone	6	33	78.5–79.5	.06	1.5380	.....	$C_9H_8O_2Cl_2$	49.32	49.62	3.65	3.80
XLVIII	1-(2,6-Dichlorophenoxy)-2,5-dimethyl-2-hexanol	7	24	135–137	.9	1.5134	.....	$C_{14}H_{20}O_2Cl_2$		[p]		
XLIX	4-Chloro-3,5-dimethylphenoxyacetone	6	84	132–135	.5	....	58–59[cl]	$C_{11}H_{13}O_2Cl$	62.11	62.08	6.12	6.14
L	1,3-Bis-(2,6-xylyloxy)-2-propanol	[c]	20	.....	..	....	81–82[ca]	$C_{19}H_{24}O_3$	76.00	76.27	8.05	7.75
LI	2-*n*-Amyl-2-methyl-4-*o*-toloxymethyl-1,3-dioxolane	[c]	86	164–165	4.0	1.4901	.....	$C_{17}H_{26}O_3$	73.39	73.45	9.41	9.37
LII	3-(6-Chloro-2-methylphenoxy)-1-propanol	1	30	116–119	1.5	1.5268	.....	$C_{10}H_{13}O_2Cl$		[q]		
LIII	2-Methyl-1-(4-chloro-3,5-dimethylphenoxy)-2-butanol	7	85	124–126	1.0	1.5240	.....	$C_{13}H_{19}O_2Cl$	64.30	64.30	7.83	7.56
LIV	2-Methyl-1-(2,6-xylyloxy)-2-butanol	7	60	88.5–90	0.7	1.5029	.....	$C_{12}H_{20}O_2$	75.00	75.10	9.61	9.94
LV	Succinic acid mono-(1-methyl-2-*o*-toloxyethyl) ester	[c]	33	.....	..	....	64–65[ca]	$C_{14}H_{18}O_5$	63.16	63.47	6.78	7.05
LVI	3-*o*-Toloxy-1-(2,2-diethyl-3-hydroxypropoxy)-2-propanol	[c]	73	153–155	.1	1.5056	.....	$C_{17}H_{28}O_4$	68.91	68.65	9.46	9.13
LVII	1-*o*-Toloxy-2,5-dimethyl-2-hexanol	7	50	105–106	.3	1.4964	.....	$C_{15}H_{24}O_2$	76.27	75.90	10.18	10.12

[a] Yields are based on material of reasonable purity and do not take into account the recovery of starting materials. [b] M.p. data are for analytically pure samples. Superscripts indicate crystallization solvent: [ca] alcohol; [cb] benzene; [cc] carbon tetrachloride; [ce] ether–petroleum ether; [cl] ligroin; [cm] ligroin–benzene; [cw] water. [c] The preparation of this compound is described in the Experimental section. [d] Some pharmacological properties of these compounds have been described by W. A. Lott, ref. 3, and by F. M. Berger (see ref. 3). [e] The preparation and physical constants were not described however. [f] The intermediate 2,6-dimethyl-4-isopropoxyphenol was supplied by Dr. Wilkins Reeve of the University of Maryland. [g] This compound has been reported as a liquid, b.p. 165–167° at 0.6 mm. by R. F. Meltzer and J. Doczi, ref. 3. [h] Calcd.: Cl, 29.94. Found: Cl, 29.90. [i] Calcd.: Cl, 20.00. Found: Cl, 20.15. [j] Calcd.: Cl, 17.68. Found: Cl, 17.93. [k] Calcd.: Cl, 13.52. Found: Cl, 13.48. [l] Calcd.: Cl, 30.21. Found: Cl, 30.24. [m] Calcd.: Cl, 30.21. Found: Cl, 30.06. [n] Calcd.: Cl, 20.91. Found: Cl, 20.34. [o] Calcd.: Br, 43.71. Found: Br, 43.63. [p] Calcd.: Cl, 30.21. Found: Cl, 29.99. [q] Calcd.: Cl, 24.40. Found: Cl, 23.90. [r] Calcd.: Cl, 17.68. Found: Cl, 17.21.

ally low yields of the desired phenolic ethers and in some cases crystallization of the product to a constant melting point and a satisfactory halogen content was accomplished only with difficulty. This behavior indicated that dehalogenation of the phenol was probably taking place under the alkaline conditions employed in the reaction.

With the exception of 3-(β-phenylethoxy)-1,2-propanediol (I) and 3-(2,6-dimethoxyphenoxy)-1,2-propanediol (VIII) which possess abnormally high water solubilities, these compounds are relatively insoluble in water.

The substituted phenoxyalkyl butanols and hexanols were prepared by the reaction of the substituted phenoxyacetone with the appropriate Grignard reagent. The phenoxyacetones were prepared in good yield using the iodide-catalyzed potassium carbonate condensation of chloroacetone and the substituted phenol as described by Hurd and Perletz.[7]

1-Acetoxy-3-(2,6-xylyloxy)-2-propanol (XLII)[8] was prepared by the ferric chloride catalyzed addition of glacial acetic acid to 1-(2,6-xylyloxy)-2,3-epoxypropane. Succinoylation of 1-*o*-toloxy-2-propanol was accomplished by direct heating of the propanol with an equivalent amount of succinic anhydride at 125–130° for 30 minutes. Direct heating of the reactants in the absence of catalyst or solvent produced the desired half ester of succinic acid (LV) in crystalline form. 2-*n*-Amyl-2-methyl-4-*o*-toloxymethyl-1,3-dioxolane (LI) was prepared by the acid-catalyzed condensation of mephenesin with methyl *n*-amyl ketone in refluxing toluene with continuous removal of the water formed.

Experimental[9]

Preparation of Substituted Phenols.—The phenols obtained from commercial sources were used without further purification.[10] The methods of preparation of those not readily available are listed below.

2,3-Xylenol and 2,4-xylenol were obtained by diazotization of the corresponding xylidines following the procedure described for the preparation of *m*-nitrophenol.[11] 2,6-Dichlorophenol was prepared from *n*-butyl-*p*-hydroxybenzoate according to a previously described method.[12]

2,6-Dichloro-*p*-α-cumylphenol.—A mixture of 106 g. (0.5 mole) of *p*-α-cumylphenol and 203 g. (1.5 mole) of sulfuryl chloride was warmed on a steam-bath until the evolution of gas ceased. The excess sulfuryl chloride was re-

(7) C. D. Hurd and P. Perletz, THIS JOURNAL, **68**, 38 (1946).

(8) In naming this compound, the assumption is made that only the primary hydroxyl group is involved in the reaction. The high yield and relative homogeneity of the product indicate that it consists of a single isomer. Without further proof however, the exact designation of the compound as the 1-acetoxy- or 2-acetoxy-derivative cannot be made.

(9) All temperatures reported are uncorrected. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Middle Village, Long Island, N. Y.

(10) We are indebted to Koppers Co., Inc., and Dow Chemical Co. for samples of several of the phenols.

(11) R. H. F. Manske, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 404.

(12) D. S. Tarbell, J. W. Wilson and Paul E. Fanta, *Org. Syntheses*, **29**, 35 (1949).

moved and the residue distilled under diminished pressure, b.p. 133–137° (0.4 mm.). Recrystallization of the solidified distillate gave 105 g. (75%) of product, m.p. 69–70°. *Anal.* Calcd. for $C_{15}H_{14}OCl_2$: Cl, 25.25. Found: Cl, 25.26.

4-Chloro-2,6-xylenol, 2,6-dichloro-*p*-cresol, 4,6-dichloro-*o*-cresol and 3,4-dichloro-2,6-xylenol were obtained by chlorination of the appropriate cresol or xylenol with sulfuryl chloride essentially as described for the preparation of 2,6-dichloro-*p*-*α*-cumylphenol. It was necessary to add the sulfuryl chloride slowly to the cooled *o*-cresol because of the vigor of the reaction.

Preparation of Phenolic Ethers.—The general procedures employed in the preparation of the ethers described in Table I are given below. Those compounds which required special methods of preparation are described individually.

Procedure 1.—The phenol and 10% excess sodium hydroxide in 20% aqueous solution were stirred and refluxed to effect solution, then treated dropwise with an equimolar quantity of halohydrin over a period of 15 minutes. After refluxing and stirring for an additional three hours, the mixture was cooled and extracted with ether. The ether extracts were freed from unreacted phenol by washing with 5% sodium hydroxide solution, then washed with saturated sodium chloride solution, dried, and concentrated. The residue was either recrystallized to a constant melting point or purified by fractional distillation under reduced pressure.

Procedure 2.—To a stirred and refluxing solution of the phenol and 10% excess sodium hydroxide (20% aqueous solution), there was added an equivalent quantity of halohydrin over a period of 15 minutes. Refluxing and stirring were continued for three hours with the occasional addition of sufficient ethyl alcohol to maintain a homogeneous solution. The ethanol was removed by distillation and the aqueous residue treated as in Procedure 1.

Procedure 3.—Molar quantities of the appropriate phenol and epoxy compound and 0.4 g. of potassium hydroxide in 4 ml. of water were allowed to stand for ten days at room temperature. The mixture was shaken with ether and the ethereal solution treated as in Procedure 1.

Procedure 4.—The halohydrin was introduced dropwise into a stirred, refluxing solution of an equimolar quantity of phenol and 10% excess sodium hydroxide in dioxane (ratio of sodium hydroxide to dioxane, 1:5). Refluxing and stirring were continued an additional three hours. The mixture was cooled, diluted with ether, filtered and the ether and dioxane removed by distillation. The residue was redissolved in ether and treated as in Procedure 1.

Procedure 5.—To a stirred and refluxing solution of the phenol and 10% excess sodium ethylate in absolute ethanol there was added an equivalent quantity of halohydrin over a period of 20 minutes. The mixture was refluxed and stirred for an additional six hours, cooled, filtered and the filtrate concentrated. The residue, following the addition of water, was extracted with ether and the ethereal extracts treated as in Procedure 1.

Procedure 6.—The aryloxyacetones were prepared according to the procedure of Hurd and Perletz.[7] These compounds were further purified by converting them to their solid bisulfite derivatives. The regenerated ketones, obtained by acid hydrolysis of the bisulfite compounds, were separated and fractionally distilled in the usual manner.

Procedure 7.—The Grignard reagent prepared from 0.5 mole of the appropriate halide and 12.0 g. (0.5 gram atom) of magnesium turnings in 350 ml. of anhydrous ether was introduced with stirring into a solution of 0.25 mole of the aryloxyacetone in 350 ml. of anhydrous ether maintained at 0–10°. The mixture was refluxed for one hour, cooled, poured onto a mixture of dilute hydrochloric acid and ice, and the ether layer separated. The aqueous layer was shaken with three 100-ml. portions of ether, the combined ether extracts washed first with saturated sodium chloride solution, and then with saturated sodium bicarbonate solution. The ether solution was dried, concentrated, and the residue fractionally distilled under diminished pressure.

1-(4-Chloro-3,5-dimethylphenoxy)-2-propanol (XXXVI) was prepared in 85% yield by condensation of 4-chloro-3,5-xylenol with propylene chlorohydrin according to Procedure 1. This compound was also obtained in 80% yield by the lithium aluminum hydride reduction of 4-chloro-3,5-dimethylphenoxyacetone (XLIX). Both products melted at 61–62° and their mixture gave no depression in melting point.

3-(2,6-Dimethoxyphenoxy)-1,2-propanediol (VIII).—This compound, prepared according to the procedure given by Meltzer and Doczi,[3] was obtained as a high boiling liquid which could not be further purified by fractional distillation. Since most aryl glycerol ethers in sufficiently pure form are crystalline solids, this liquid product was more rigidly purified in an attempt to isolate it as a solid compound.

A solution of 10 g. of liquid 3-(2,6-dimethoxyphenoxy)-1,2-propanediol, 33 g. of acetone, 35 g. of chloroform and 0.1 g. of *p*-toluenesulfonic acid was refluxed for 30 minutes, then slowly distilled. The high boiling residue was taken up in 30 ml. of ether, washed with 30 ml. of 2% aqueous sodium hydroxide followed by 30 ml. of water, dried over magnesium sulfate, and concentrated. Careful fractionation gave 6.0 g. (56%) of 2,2-dimethyl-4-(2,6-dimethoxyphenoxymethyl)-1,3-dioxolane, b.p. 132.5–136° (0.8 mm.).

Hydrolysis of this dioxolane derivative was accomplished by refluxing 6.0 g. of the compound with 10 ml. of water and 0.5 ml. of concentrated hydrochloric acid for 15 minutes. Upon removal of low boiling material under reduced pressure, the residue solidified. Recrystallization from benzene–petroleum ether gave 4.0 g. (78%) of solid product, m.p. 52–53.5°.

3-(4,6-Di-*t*-butyl-2-methylphenoxy)-1-propene (XLIV).—To a solution of 44.0 g. (0.2 mole) of 4,6-di-*t*-butyl-2-methylphenol in 200 ml. of absolute ethanol, there was added 11.9 g. (0.22 mole) of sodium methoxide (98% purity). The solution was refluxed with stirring for one hour, 24.2 g. (0.2 mole) of allyl bromide was added over a period of 30 minutes, and refluxing continued for two hours. The alcohol was removed by distillation and the residue shaken with 200 ml. of ether and 100 ml. of water. The ether solution, after drying over magnesium sulfate, was concentrated and the residual oil fractionated to give 41.1 g. (79%) of product, b.p. 80.0–81.0° (0.2 mm.), $n^{25}D$ 1.5017.

3-(4,6-Di-*t*-butyl-2-methylphenoxy)-1,2-propanediol (VI).—To a vigorously stirred solution of 26.0 g. (0.1 mole) of 3-(4,6-di-*t*-butyl-2-methylphenoxy)-1-propene (XLIV) dissolved in 2 l. of acetone, there was added over a period of six hours a 1% aqueous solution containing 31.6 g. (0.2 mole) of potassium permanganate, the temperature being maintained at 0–5° during the addition. The manganese dioxide was removed by filtration, and the acetone distilled from the filtrate. The residue was extracted with ether, the ether layer washed with a saturated solution of sodium chloride and the ether removed by distillation. Fractionation of the residue led to the recovery of 12.0 g. of unchanged allyl ether and 2.5 g. of product, an orange viscous oil, b.p. 146–148° (0.3 mm.), which solidified on standing. On recrystallization from carbon tetrachloride, a white, crystalline solid, m.p. 109–110°, was obtained.

1,3-Bis-(2,6-xylyloxy)-2-propanol (L).—This compound was obtained together with 1-(2,6-xylyloxy)-2,3-epoxypropane from the condensation of 2,6-xylenol and 1-chloro-2,3-epoxypropane. A solution of 61.0 g. (0.5 mole) of 2,6-xylenol, 46.3 g. (0.5 mole) of 1-chloro-2,3-epoxypropane and 25 ml. of dioxane was refluxed for 15 minutes. With vigorous stirring, there was added over a period of 30 minutes 24.0 g. (0.6 mole) of sodium hydroxide in 80 ml. of water and refluxing was continued for two hours. The mixture was cooled, the organic material taken up in 200 ml. of ether and the ether layer washed with 100 ml. of a saturated aqueous sodium chloride solution. After drying over sodium carbonate, the solution was concentrated and the residue fractionated under reduced pressure. A yield of 34 g. (38%) of the glycidyl ether, b.p. 77–79° (0.3 mm.), $n^{25}D$ 1.5158, was obtained as a colorless oil. Further distillation of the higher boiling residue gave a considerable yield of 1,3-bis-(2,6-xylyloxy)-2-propanol, b.p. 155–165° (0.3 mm.), which solidified in the receiver and on recrystallization from aqueous alcohol gave 31 g. (20%) of pure product, m.p. 81–82°.

1-Acetoxy-3-(2,6-xylyloxy)-2-propanol (XLII).[8]—A mixture of 29.0 g. (0.16 mole) of 1-(2,6-xylyloxy)-2,3-epoxypropane, 10.8 g. (0.18 mole) of glacial acetic acid and 0.1 g. of ferric chloride was heated at 130° for 30 minutes, then at 190° for 20 minutes. A yield of 31.5 g. (81%) of product, b.p. 129–131° (0.5 mm.), was obtained on distillation of the reaction mixture.

Succinic Acid Mono-(1-methyl-2-*o*-toloxyethyl) Ester (LV).—A mixture of 24.9 (0.15 mole) of 1-*o*-toloxy-2-propanol and 15.0 g. (0.15 mole) of succinic anhydride was warmed slowly to 125°. The source of heat was then removed while the temperature rose spontaneously to 210°

and after the reaction subsided, a temperature of 125° was maintained for one hour. The viscous yellow solution solidified on cooling. On recrystallization from a 50% aqueous alcohol solution, the product was obtained in pure form, m.p. 64–65°.

2-*n*-Amyl-2-methyl-4-*o*-toloxymethyl-1,3-dioxolane (LI).—A mixture of 91.0 g. (0.5 mole) of 3-*o*-toloxy-1,2-propanediol, 57.0 g. (0.5 mole) of methyl *n*-amyl ketone, 1.0 g. of *p*-toluenesulfonic acid and 300 ml. of toluene was refluxed in a flask fitted with a water-separating reflux condenser. After refluxing for five hours (98% of the theoretical amount of water was collected in the first two hours) the reaction mixture was cooled and extracted twice with 100 ml. of 5% sodium carbonate solution followed with 100 ml. of water. The toluene was distilled at reduced pressure and the residue yielded 119 g. (86%) of product, b.p. 164–165° (4.0 mm.).

3-*o*-Toloxy-1-(2,2-diethyl-3-hydroxypropoxy)-2-propanol (LVI). **3-Chloro-1-(2,2-diethyl-3-hydroxypropoxy)-2-propanol.**—To a stirred mixture of 92.5 g. (1.0 mole) of 1-chloro-2,3-epoxypropane and 264 g. (2.0 mole) of 2,2-diethyl-1,3-propanediol heated to 40°, was added 4.3 ml. of concentrated sulfuric acid over a period of half an hour. When the reaction commenced it was necessary to cool the mixture in order to maintain the temperature at 40–50°. The mixture was kept at 100° for five hours after the spontaneous reaction had ceased. The sulfuric acid was neutralized with sodium carbonate and the product distilled directly from the reaction mixture. A forerun of 150 g. of the original diol, b.p. 91–93° (1.0 mm.), and 110 g. (49%) of product, b.p. 112–115° (0.1 mm.), were obtained. *Anal.* Calcd. for $C_{16}H_{21}O_3Cl$: C, 53.25; H, 9.36. Found: C, 53.50; H, 9.08.

A solution of 10.8 g. (0.1 mole) of *o*-cresol, 4.4 g. (0.11 mole) of sodium hydroxide and 50 ml. of water was refluxed for ten minutes. A solution of 22.5 g. (0.1 mole) of 3-chloro-1-(2,2-diethyl-3-hydroxypropoxy)-2-propanol in 30 ml. of ethanol was introduced to the stirred solution over a period of half an hour, and refluxing continued for four hours. After removal of the alcohol by distillation, the oil was taken up in 100 ml. of ether, washed with 40 ml. of a saturated sodium chloride solution, concentrated and the residue distilled, collecting the fraction, b.p. 145–158° (0.1 mm.). Refractionation gave 20.0 g. (73%) of 3-*o*-toloxy-1-(2,2-diethyl-3-hydroxypropoxy)-2-propanol, b.p. 153–155° (0.1 mm.).

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Preparation and Polymerization of Unsaturated Quaternary Ammonium Compounds. III. Vinyloxyethyl Derivatives[1,2]

BY GEORGE B. BUTLER AND ROBERT L. GOETTE

Several new tertiary amines and unsaturated quaternary ammonium bromides containing the β-vinyloxyethyl group have been prepared and characterized. The unsaturated quaternary ammonium salts were polymerized under the influence of *t*-butyl hydroperoxide to yield water soluble polymers from those compounds containing only two unsaturated groups in addition to the β-vinyloxyethyl group, and water insoluble polymers from those compounds containing three unsaturated groups in addition to the β-vinyloxyethyl group. The water insoluble polymers were found to undergo ion exchange reactions. These polymers had a high coefficient of swelling and ion-exchange capacity equal to 88.8% of the theoretical. It was found that the β-vinyloxyethyl group did not enter into the polymerizations under the conditions used.

Polymerization of unsaturated quaternary ammonium compounds has been found[3] to produce water insoluble polymers suitable for strongly basic ion exchange resins. However, because of the low tensile strength and brittleness of these materials, apparently due to a low degree of polymerization, an effort to improve these properties seemed important. Polymerization studies of unsaturated quaternary ammonium salts containing halogenated allyl derivatives[4] resulted in the formation of improved capacities, apparently as the result of a higher coefficient of swelling, but no improvement in physical properties.

It has been shown by a number of workers[5,6] that vinyl ethers can be polymerized by a cationic mechanism to give polymers of high molecular weight. It has also been shown[7] that vinyl ethers of unsaturated alcohols such as allyl alcohol can be made to undergo a two-stage polymerization in which the ether is converted to an unsaturated linear polymer through the vinyl groups by a cationic mechanism and this polymer cross-linked through the unsaturated linkages by a free radical catalyzed mechanism. Also, in this work, cross-linked polymers were obtained by a free radical catalyzed polymerization of ethylene glycol vinyl allyl ether, indicating that the vinyloxy group undergoes copolymerization with the allyl group. Many other examples of copolymerization of vinyloxy groups may be cited. It has been shown[8] that 2-alkoxy-1,3-butadienes, compounds which are both vinyl and allyl ethers, undergo polymerization as the result of peroxide catalysis, as well as by light, heat and other catalysts. Divinyl ether[9,10] has been used as a cross-linking agent for vinyl acetate and methyl methacrylate. Vinyl chloride copolymerizes with the trivinyl ether of glycerol[11] in ratios of 0.1–10% in presence of benzoyl peroxide catalyst to produce a brittle copolymer decomposing from 174–200° depending on the amount of cross-linking agent used. Vinyl ethers have been copolymerized with maleic anhydride and related compounds in presence of per-

(1) An abstract of a thesis presented by Robert L. Goette to the Graduate School of the University of Florida in partial fulfillment of the requirements for the degree of Master of Science.

(2) This material was presented before the Meeting-in-Miniature, Florida Section, American Chemical Society, Orlando, Florida, May, 1951.

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