[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SCHIEFFELIN & CO.]

Aromatic Glycols

BY ANTHONY J. SHUKIS AND RALPH C. TALLMAN

In order to extend a previous investigation on glycol mercurials,[1] through the introduction of a phenyl group into the glycol molecule, a series of glycols containing a substituted or an unsubstituted phenyl group, was prepared. The commercially available 2-phenoxyethanol, $C_6H_5OCH_2CH_2OH$, the monophenyl ether of ethylene glycol, was selected as a suitable aromatic glycol which would lend itself readily to variations in structure.

The basic structure was varied in three ways: (I) extension of the side chain, $C_6H_5(OCH_2CH_2)_nOH$; (II) substitution in the ring, p-$XC_6H_4OCH_2CH_2OH$, where X is CH_3, Br, OH, NO_2, NH_2; (III) introduction of another β-hydroxy-ethoxy group into the ring, $HOCH_2CH_2OC_6H_4OCH_2CH_2OH$.

The general method of treating the sodium salt of the appropriately substituted phenol in absolute alcohol with ethylene chlorohydrin.[3]

The mercurials which were prepared from the aromatic glycols listed herein are reported in the paper immediately following.

Experimental

The 2-phenoxyethanol ("Phenyl Cellosolve," U. C. C.) used as starting material for the first series of compounds was purchased and redistilled before use. The para substituted phenols were of the Eastman grade purchased from Eastman Kodak Co.

Monophenyl Ether of Diethylene Glycol.[2]—To anhydrous 2-phenoxyethanol (345.4 g., 2.5 moles) in a one-liter flask on a steam-bath, 23 g. of sodium was added with stirring. When all the sodium had reacted, anhydrous ethylene chlorohydrin (96.6 g., 1.2 moles) was added dropwise by means of a dropping funnel. During the addition and for an additional two hours the mixture was stirred and heated as the sodium chloride precipitated. The sodium chloride was filtered off by means of suction using a Buchner funnel; the filtrate was transferred to a 500-ml. Claisen flask having a modified neck, and distilled carefully under reduced pressure. The fraction coming over at 121–125° at 2 mm. was collected; yield 109.4 g. (60%); $n^{20}D$ 1.5243; d_{20} 1.1176; MR_D calcd. 49.73, found 49.91.

TABLE I

PHYSICAL CONSTANTS, FORMULAS, ANALYSES, DERIVATIVES

No.	n	B. p., °C. (uncor.)	Yield, %	Analyses,[k] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	M. p., °C. (uncor.) Trityl Ether[b]
		Type I: $C_6H_5(OCH_2CH_2)_nOH$						
1	1[a]	110–112, 4 mm.	..	...	...	..	..	124[b]
2	2	121–123,[c] 2 mm.	60	65.91	65.64	7.74	8.11	91[j,k]
3	3	135–137, 2 mm.	55	63.70	63.54	8.02	8.24	82[j,k]
		Type II: $XC_6H_4OCH_2CH_2OH$						
	X	M. p., °C. (uncor.)						
4	CH_3	42	80	71.03	70.93	7.95	8.16	73[j,k]
5	Br	55	66	44.26	44.25	4.18	4.37	116[j,k]
6	NO_2	92[d]	46	52.46	52.52	4.95	5.00	Benzoate, 113[e]
7	NH_2[f]	72	80	62.72	62.62	7.24	7.44	Diacetate, 130
8	OH	88[g]	80	62.36	62.58	6.54	6.58	....
		Type III: $HOCH_2CH_2O$-(4,3,2)-OCH_2CH_2OH						
	$HOCH_2CH_2O$— at position							
9	3	90	h	60.59	60.79	7.12	6.92	Dityrityl, 175[j,k]
10	4	105	i	60.59	60.84	7.12	6.82	Dityrityl, 200[j,k]

[a] Commercially available as Phenyl Cellosolve, U. C. C. [b] Seikel and Huntress, THIS JOURNAL, **63**, 593 (1941). [c] Palfray, *et al.*, *Compt. rend.*, **208**, 299 (1939), report b. p. (15 mm.) 140–142°. [d] Reported m. p. 102°, Katrak, *J. Ind. Chem. Soc.*, **13**, 334 (1936). [e] Reported m. p. 116°, *ibid.* [f] Butler and Renfrew, THIS JOURNAL, **60**, 1582 (1938), prepared the compound by a somewhat more complex synthesis requiring special reagents. [g] Reported as an oil, b. p. (14 mm.) 202–205° by Read and Miller, *ibid.*, **54**, 1195 (1932). [h] Obtained by fractional crystallization of mother liquors 2-(*m*-hydroxyphenoxy)-ethanol. [i] Obtained by fractional crystallization of mother liquors of 8 above, the 2-(*p*-hydroxyphenoxy)-ethanol. [j] Analyzed satisfactorily for C and H. [k] Microanalyses by Dr. C. Tiedcke, N. Y.

The compounds of series I (see table) were prepared by an extension, to the aromatic glycols, of the method of Cretcher and Pittenger,[2] wherein the sodium salt of the glycol, in excess glycol, is treated with ethylene chlorohydrin. Compounds of series II and III (see table) were prepared by

(1) Shukis and Tallman, THIS JOURNAL, **65**, 2365 (1943).

(2) Cretcher and Pittenger, *ibid.*, **46**, 1503 (1924).

(3) Read and Miller, *ibid.*, **54**, 1195 (1932).

Monophenyl ether of triethylene glycol[3] was prepared as above using the phenyl ether of diethylene glycol prepared above and a similar ratio of reactants. The yield was 55%; b. p. 135–137° at 2 mm.; $n^{20}D$ 1.5200; d_{20} 1.1132; MR_D calcd. 60.62, found 61.79.

p-X-C_6H_4-OCH_2CH_2OH (X = CH_3, NO_2 Br, OH).—In general 50 g. of the *para*-substituted phenol was dissolved in 250 ml. of absolute alcohol in a 500-ml. three-necked flask fitted with a mechanical stirrer, a condenser with a drying tube and a cork in the third neck. An equivalent quantity of sodium shavings was added. Upon solution of the sodium the mixture was refluxed for an hour to ensure the formation of the sodium salt of the phenol. The cork was replaced by a dropping funnel from which 1.1 equivalents of anhydrous ethylene chlorohydrin was introduced dropwise while the mixture was stirred; when all the halohydrin had been added the solution was refluxed for twelve to twenty-four hours. The precipitate of sodium chloride was filtered off, the filtrate transferred to a Claisen flask, the alcohol removed and the residue distilled under reduced pressure. The distillate usually solidified in the receiver and was recrystallized from methanol or benzene.

***p*-Aminophenyl Ether of Ethylene Glycol.**—A mixture of 5.6 g. (0.0306 mole) of 2-(*p*-nitrophenoxy)-ethanol (see above), 100 ml. of absolute alcohol and 0.050 g. of platinum oxide catalyst was hydrogenated at atmospheric pressure. The reaction took up 2,315 ml. of hydrogen in an hour; calculated 2,410 ml. ($3H_2$ per mole of NO_2). (After the addition of 1400 ml. of hydrogen, the pressure bottle had to be cooled externally.) The catalyst was filtered off and the alcoholic solution concentrated to one half the original volume. The theoretical quantity of hydrogen chloride gas, 1.1 g., was added to the solution whereupon the amine hydrochloride precipitated out. Sufficient absolute alcohol to dissolve the hydrochloride was added and the solution chilled; yield, 5.7 g. of the hydrochloride (calcd. 5.77 g.), m. p. 200–205° dec. The theoretical quantity of ammonia, 4.6 ml. of 28% ammonium hydroxide solution, was added to the hydrochloride followed by 10–20 ml. of distilled water, and the mixture warmed to effect solution. On chilling there was obtained 3.5 g. of a salmon pink, leafy, crystalline solid, m. p. 71–72°; yield 80%.

Summary

Three series of aromatic glycols were prepared and characterized by means of derivatives.

NEW YORK, N. Y. RECEIVED JUNE 1, 1944

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Aromatic Glycol Mercurials

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Our study on glycol mercurials[1] has been extended to the series of aromatic glycols described in the preceding paper.[2]

The mercuration of these compounds, the aromatic glycols, afforded an opportunity to introduce a mercury residue either into the ring (see Table I) or the side chain (see Table II) and to study the consequent effect produced on the antibacterial activity. It was desirable to prepare, for each glycol, both the ring mercurial and the corresponding chain substituted mercurial. This plan was followed as far as practicable, being limited by experimental difficulties in certain of the attempted chain mercurations; in these instances, either the glycol was recovered unchanged (no reaction), or the mercurial could not be purified without decomposition.

In general, the mercury residue was introduced into the side chain by the method previously described, namely, the interaction of the glycol with mercuric acetate and ethylene.[1] In those instances where a solid glycol was used the procedure was modified by conducting the reaction above the melting point of the glycol or by using a solvent. Ring mercuration occurred when the aromatic glycol was treated with mercuric acetate in alcohol containing 5% glacial acetic acid. Those aromatic glycols which contain no other substituent in the benzene ring yielded monomercurials. By controlling conditions, either one or two mercury residues could be introduced into compounds where more than one ring substituent was already present.

In the series of ring mercurials, the effect of substituting at the phenyl group (see Table I) was an increase in the antibacterial potency of the compounds. For *para* substituents, this enhancement by the various groups decreases in the following sequence: $NH_2 > NO_2 > OH > Br > CH_3 > H$. The effect of position isomerism, where the group studied was OH, follows the order para > meta > ortho. The monomercurial was more active than the dimercurial of the same compound in this series.

In the chain mercurial series (see Table II) the effect of substituents on the benzene ring was the opposite of that observed with the ring mercurials. The order of decreasing activity found was H > Br > *p*-OH > NO_2 > *o*-OH > CH_3. In regard to position isomerism in the two instances studied the order para > ortho prevailed.

In general, in this investigation, we found that the chain mercurials were more effective bactericides than their ring analogs. The ring mercurials, compounds 4, 7, 9, 13, were less effective than their respective chain analogs, compounds 21, 20, 19, 24 (see Tables I and II, respectively). However, in the pairs of analogs 1–18, and 10–22 the reverse seems true. Attempts to prepare the chain analog of compound 11 met with no success. Should the general pattern be followed, this member, the corresponding chain mercurial, should prove to be an efficient bactericide. Also the attempt to prepare α-chloromercuri-β-phen-

(1) Shukis and Tallman, THIS JOURNAL, **65**, 2365 (1943).

(2) Shukis and Tallman, *ibid.*, **66**, 1461 (1944).