In the case of the first two solvents solubility was complete when the mixture was warmed. The butyrates could be "recrystallized" from ethanol or *n*-butanol (2% concentration). The caproyl esters were completely soluble in pyridine only but partially soluble in most other organic solvents. Palmitate esters were the most insoluble of all and were not completely soluble in any single solvent tried. They were partially soluble in chloroform, ethyl acetate, benzene, ether, petroleum ether, butanol and diethyl Cellosolve.

By contrast to the foregoing, whole starch esters prepared from liquid ammonia pretreated starch, or any esters prepared by the Mullen and Pacsu procedure, were much less soluble in organic solvents and the solubility differences between ester classes were non-existent. Acetates, propionates, butyrates and benzoates of the polysaccharides prepared by this method were insoluble in ether, diethyl Cellosolve, petroleum ether and the lower alcohols, and partially soluble in the other solvents. The esters were not completely soluble in any solvent.

In many cases the esters were highly swollen in organic liquids even though completely insoluble in those liquids. The large number of instances of "partial solubility" is analogous to the behavior of pectin esters noted by Carson and Maclay.[14]

Optical Rotations.—Since many of the esters were only partially soluble in chloroform when direct solution was attempted, the rotations were taken in a manner similar to that described by Mullen and Pacsu.[2] A 1 or 2% dispersion of the ester in chloroform was prepared in a Waring Blendor. This dispersion was filtered through a coarse-fritted glass funnel, the rotation taken, and the concentration determined by evaporating a 10-ml. aliquot to dryness and to constant weight under an infrared lamp. Where comparisons were possible, rotations obtained by this method agreed closely with those obtained by the direct-solution procedure. Noteworthy in Table I are the higher rotations of the amylose esters[15] compared with the same amylopectin ester and the approximate constancy of the molecular rotations with increasing length of the acyl radical.

The use of trade names in this publication does not necessarily constitute endorsement of these products nor of the manufacturers thereof.

Acknowledgment.—We are indebted to C. H. Van Etten and to T. A. McGuire for carrying out many of the acyl analyses. Dr. A. Jeanes developed the technique described for obtaining "disintegrated" starch.

Summary

1. Satisfactory techniques have been described for the preparation of whole corn starch, amylose and amylopectin triacetate, tripropionate, tributyrate, tricaproate, tripalmitate and tribenzoate.

2. Solubilities of the esters in a number of organic solvents were qualitatively determined. Solubility of an ester was shown to be dependent on the method used for pretreating the polysaccharide prior to its esterification.

3. The optical rotations of the triesters of amylose were higher than those of whole starch and amylopectin. The molecular rotations of the various aliphatic acid esters of the polysaccharides were approximately constant.

(14) Carson and Maclay, THIS JOURNAL, **67**, 787 (1945).

(15) A. Jeanes of this Laboratory (unpublished work) has previously measured the rotations of the acetates of amylose, amylopectin and disintegrated corn starch.

PEORIA, ILLINOIS RECEIVED JUNE 3, 1950

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGY AND VITAL ECONOMICS, UNIVERSITY OF ROCHESTER SCHOOL OF MEDICINE AND DENTISTRY]

Physiologically Active Substituted α-Glyceryl Phenyl Ethers[1]

BY JOHN P. LAMBOOY

The search for active analogs of 3-(*o*-toloxy)-1,2-propanediol which possess increased solubility or increased potency has not produced compounds which show therapeutic promise. As a result of interest in our department concerning the site and mode of action of the α-glyceryl phenyl ethers we undertook the preparation of analogs which might show greater solubility or potency. Any compound showing increased solubility would facilitate the study of permeability of this class of compounds and one of greater potency would reduce the complications introduced by disturbing the osmotic conditions which normally prevail in tissue.

It was felt that 3-(*o*-ethylphenoxy)-1,2-propanediol was worthy of more detailed study. Preliminary studies[2] had already been made on this compound but its synthesis had not been reported.

In view of the abnormal solubility of fluorobenzene when compared with the other halobenzenes it was thought that 3-(*o*-fluorophenoxy)-1,2-propanediol might show increased solubility. This compound was found to be soluble in less than an equal weight of water.

Since 3-(*o*-toloxy)-1,2-propanediol and 3-(*o*-chlorophenoxy)-1,2-propanediol had been found[2] to be about equal in potency we thought that their combination into 3-(2-methyl-6-chlorophenoxy)-1,2-propanediol might produce a compound of greater potency. This compound was found to be twice as potent as 3-(*o*-toloxy)-1,2-propanediol.

As can be seen in the summary of the pharmacological data (Table I), 3-(*o*-ethylphenoxy)-1,2-propanediol and 3-(2-methyl-6-chlorophenoxy)-1,2-propanediol are more potent and more toxic than 3-(*o*-toloxy)-1,2-propanediol, and these changes are accompanied by a somewhat reduced solubility.

A detailed report of the physiological properties of these compounds will be published by Dr. E. Wright and others in the near future.

The procedure outlined by Wheeler and Willson[3] was used for the preparation of the α-glyceryl phenyl ethers. The procedure was modified only in respect to purification and isolation of the product. *o*-Ethylphenol was prepared from *o*-nitroethylbenzene by reduction to the aniline and hydrolysis of the diazonium salt. 6-Chloro-*o*-cresol was prepared from *o*-cresol by adaptation of the method used by Brubaker and Adams[4] for the preparation of *o*-bromo-*o*-cresol with the result that the yield of

(1) This study was supported in part by a grant-in-aid from the Fluid Research Fund Committee of the University of Rochester School of Medicine and Dentistry.

(2) Berger, *J. Pharmacol.*, **93**, 470 (1948).

(3) Wheeler and Willson, "Organic Syntheses," Coll. Vol. I, John Wiley & Sons, Inc., New York, N. Y., 1932, p. 290.

(4) Brubaker and Adams, THIS JOURNAL, **49**, 2290 (1927).

TABLE I

SUMMARY OF PHARMACOLOGICAL DATA

-1,2-propanediols	mM./kg. ED_{50} ± S.E.	mM./kg. LD_{50} ± S.E.	mg./kg. ED_{50} ± S.E.	mg./kg. LD_{50} ± S.E.	Ratio LD_{50}/ED_{50}
3-(*o*-Toloxy)-	0.90 ± 0.05	3.00 ± 0.14	164 ± 9.1	546 ± 25.5	3.3
3-(*o*-Ethylphenoxy)-	0.64 ± 0.01	2.00 ± 0.04	125 ± 2.0	392 ± 7.8	3.1
3-(*o*-Fluorophenoxy)-	1.86 ± 0.08	6.49 ± 0.04	346 ± 14.9	1209 ± 7.4	3.5
3-(2-Methyl-6-chlorophenoxy)-	0.42 ± 0.01	1.64 ± 0.06	91 ± 2.2	354 ± 13.0	3.9

the desired product has been increased. *o*-Fluorophenol was generously supplied by Dr. G. C. Finger, State Geological Survey Division, Urbana, Illinois.

Experimental

6-Chloro-*o*-cresol.—This material was prepared by the following modification of the procedure outlined by Brubaker and Adams.[4] Following the sulfonation of 108 g. (1.0 mole) of *o*-cresol the product was poured onto 300 g. of ice and divided into four one-fourth mole lots. Each lot was then diluted to 600 ml. with water and 70 g. of barium carbonate added. The product was filtered and placed in a suitable container for chlorination. The temperature was kept between 20–25° while dry chlorine gas was added to the vigorously stirred solution. After the gain in weight of the flask indicated that 17.8–18.0 g. of chlorine had been absorbed the chlorination was stopped and the product filtered. To the filtrate was added 50 g. of barium chloride to obtain a second crop of the chlorinated barium salt. The yield of product varied between 56–60 g., or 77–82% of the theoretical amount, of light tan powder.[5]

The chlorinated barium salt, 78.9 g. (0.136 mole), was added to a solution of 275 ml. of water and 236 ml. of concentrated sulfuric acid and hydrolyzed as described,[4] to yield 26.5–28.0 g. of crude 6-chloro-*o*-cresol. The crude 6-chloro-*o*-cresol, 94 g., obtained from 274 g. of the chlorinated barium salt, was fractionated through a saddle packed column 50 cm. long and 1.8 cm. i.d., equipped with a cutter head, to yield 75.3 g., or 56% of the theoretical amount of pure 6-chloro-*o*-cresol, b.p. 188–189° at 748 mm. The residue was distilled under reduced pressure to yield 6.5 g. of material b.p. 129–132° at 40 mm. Following recrystallization from dilute ethanol it melted at 53–54°,[6] and was thus identified as 4,6-dichloro-*o*-cresol.[7]

α-Glyceryl Phenyl Ethers.—The procedure outlined by Wheeler and Willson[3] was used with the following modifications. Following the removal of the alcohol from the condensation product the material was distilled under reduced pressure. The distillate was then subjected to steam distillation until the phenol odor was no longer detectable in the distillate. The phenol free product was then taken up in ether and isolated in the usual manner and purified by recrystallization from mixtures of benzene and ligroin.

3-(*o*-Ethylphenoxyl)-1,2-propanediol.—*o*-Ethylphenol,[8] 24.4 g. (0.2 mole), produced 26.0 g. (66%) of the α-glyceryl phenyl ether, b.p. 185–187° at 14 mm. Following repeated recrystallizations, 15.9 g. (41%) of material was obtained as white needles which melted 56–57°. This product, which is only slightly less soluble in water than 3-(*o*-toloxy)-1,2-propanediol does not crystallize out of water solution at room temperature but remains for some time as a finely divided suspension and eventually settles out as an oil.

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.51; H, 7.88.

3-(*o*-Fluorophenoxy)-1,2-propanediol.—*o*-Fluorophenol, 39.0 g. (0.348 mole), produced 42.6 g. (66%) of the α-glyceryl phenyl ether, b.p. 183–184° at 15 mm. Following repeated recrystallizations, 30.9 g. (48%) of material was obtained as white needles which melted 52–54°. Further recrystallization induced by the gradual evaporation of the solvents at room temperature produced material which melted 56–57°. One gram of this product was completely soluble at room temperature in less than one gram of water.

Anal. Calcd. for $C_9H_{11}FO_3$: C, 58.06; H, 5.96. Found: C, 58.5; H, 6.2.

3-(2-Methyl-6-chlorophenoxy)-1,2-propanediol.—6-Chloro-*o*-cresol, 14.3 g. (0.1 mole), produced 18.4 g. (85%) of the α-glyceryl phenyl ether, b.p., 196–197° at 15 mm. Following repeated recrystallizations, 16.2 g. (75%) of material was obtained as white needles which melted 74–75°. This product is less soluble than 3-(*o*-toloxy)-1,2-propanediol in that only 1.25–1.4 g. is soluble in 100 ml. of water at 35°.

Anal. Calcd. for $C_{10}H_{13}ClO_3$: C, 55.43; H, 6.05; Cl, 16.37. Found: C, 55.8; H, 6.2; Cl, 16.3.

Pharmacological Data

Wistar Swiss Strain male mice weighing between 17 and 23 g. were used for the determination of the paralyzing dose and the lethal dose. The paralyzing dose (ED_{50}) was found by using as the criterion the loss of the righting reflex for 60 continuous seconds. All injections were made intraperitoneally and paralysis was produced within one minute at higher levels and within 5 minutes at levels near the ED_{50} dose. Deaths followed within two hours after administration and no animals died within 72 hours once they had overcome the paralysis.

3-(*o*-Ethylphenoxy)-1,2-propanediol and 3-(2-methyl-6-chlorophenoxy)-1,2-propanediol were too insoluble to prepare as a 2% solution for injections, therefore, they were suspended in 1% "Tween-80." Preliminary tests showed that 1% "Tween-80" given at a level of 10% of the body weight either subcutaneously or intraperitoneally produced no paralytic or lethal effects. Under the conditions of testing the highest dose of "Tween-80" containing solution amounted to only 2.1% of the body weight. 3-(*o*-Toloxy)-1,2-propanediol[9] and 3-(*o*-fluorophenoxy)-1,2-propanediol were completely soluble at a level of 2% at 37°.

Groups of from two to seven animals were used in preliminary studies to discover the approximate ED_{50} and LD_{50} levels for each compound. Once the approximate levels had been determined, four to six groups of five animals were used to obtain the necessary data. The experimental data were analyzed by the method described by Miller and Tainter.[10]

Summary

1. The synthesis of three new active α-glyceryl phenyl ethers, 3-(*o*-ethylphenoxy)-1,2-propanediol, 3-(*o*-fluorophenoxy)-1,2-propanediol and 3-(2-methyl-6-chlorophenoxy)-1,2-propanediol has been described. An improved synthesis of 6-chloro-*o*-cresol has also been described.

2. These new α-glyceryl phenyl ethers possess properties which make them useful for studies involving the mode and site of action by making available one compound much more potent than and one much more soluble than 3-(*o*-toloxy)-1,2-propanediol.

3. Basic pharmacological data have been reported for the effective dose and the lethal dose.

ROCHESTER, NEW YORK RECEIVED JULY 12, 1950

(5) Addition of either more or less than the theoretical amount of chlorine reduced the yield of desired product.

(6) All melting points observed on calibrated thermometers.

(7) Huston and Neeley, THIS JOURNAL, **57**, 2177 (1935).

(8) *o*-Nitroethylbenzene was reduced in alcohol over platinum oxide to produce 92–96% of the theoretical amount of *o*-ethylaniline. The *o*-ethylphenol was obtained in 88% yield by the hydrolysis of the diazonium salt by an improved method developed in this Laboratory: cf. THIS JOURNAL, **72**, 5327 (1950); *o*-ethylphenol, b. p., 201–203° at 750 mm., $n^{20}D$ 1.5360.

(9) "Tolserol," E. R. Squibb and Sons, was used.

(10) Miller and Tainter, *Proc. Soc. Exptl. Biol. and Med.*, **57**, 261 (1944).