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GLYCOL ESTERS OF CERTAIN AROMATIC ACIDS

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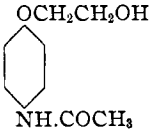
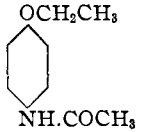
The introduction of an hydroxyl group into an aliphatic compound or side chain usually results in a diminution of physiological activity and of toxicity. This effect is roughly proportional to the number of hydroxyl groups introduced, provided the substitution of hydroxyl for hydrogen does not take place more than once on any one carbon atom.

There appears to be no reason to believe that reduction of the toxicity and of the desirable pharmacodynamic action of a given compound effected by the introduction of an hydroxyl group will be equal. It may, then, be possible to prepare hydroxyl derivatives of medicinal substances which, while possessing the desired effect to a somewhat lessened degree, will be so much less toxic than the parent substance as to produce the desired effect with greater latitude between effective and toxic dosages. Other effects which may be undesirable under given conditions, may also be diminished. The results of a comparative study of phenacetin and "pertonal" made by Douglas Cow[1] are interesting in this connection. The structural relationship of the compounds is shown in Formulas I and II. Pertonal



I. Pertonal



II. Phenacetin

was found to be one-half as strongly antipyretic, one-half as toxic, and one-fifteenth as narcotic as phenacetin.

In order to study further the effect of substitution of hydroxy-ethyl for hydrogen, alkyl and substituted alkyl groups, it has been necessary to prepare a number of glycol esters of aromatic acids. But few esters of this series have been prepared previously. The methods of synthesis and the physical constants of the glycol mono-esters hitherto described are to be found in the patent literature and leave much to be desired from the standpoint of both utility and accuracy.

A number of these compounds and a method generally applicable to their preparation are described below. The physiological action of one product, glycol mono-*p*-aminobenzoate, is also given.

The study of hydroxy derivatives in general is being continued.

[1] Cow, *J. Pharmacol.*, **12**, 343 (1919).

Experimental Part

Glycol Mono-esters.—The method of synthesis of the various glycol mono-esters described in Table I, with the exception of *p*-aminobenzoate, was as follows.

One molecular proportion of the thoroughly dried sodium salt of the acid was intimately mixed with 3 molecular proportions of dry ethylene chlorohydrin and an amount of diethylamine[2] corresponding to about 1% of the weight of sodium salt. The mixture was then heated in an oil-bath, with good agitation. To prepare the benzoate, salicylate and *p*-nitrobenzoate, the reaction was allowed to continue for four hours at 130°, and for the phenylcinchoninate, for two hours at 160°. The product was then cooled. When the ester formed was liquid, the sodium chloride was removed by filtration and washed with ethyl ether; the liquid was then distilled under reduced pressure. When the ester was solid, water was added, and the ester extracted with ether; after removal of the ether, the compound was purified by crystallization from benzene.

Glycol Mono-*p*-aminobenzoate, $C_6H_4NH_2COOCH_2CH_2OH$.—This ester was prepared by reducing the *p*-nitrobenzoate in the following manner. To an intimate mixture of 20 g. of glycol *p*-nitrobenzoate, made into a paste with water, and 50 g. of iron powder in a small beaker were added 8 drops of concd. hydrochloric acid; after this mixture had been stirred for ten minutes, it became hot and was cooled to about 55° by the addition of a small amount of ice. Iron was then added at such a rate as to keep the temperature between 50° and 60°. After 40 minutes, when about 100 g. of iron had been added, further addition caused no liberation of heat and the reaction was considered complete. One-half g. of sodium bicarbonate was then stirred into the mixture and the mass was thrice extracted with hot alcohol. The alcoholic solution was evaporated to dryness and the residue dissolved in absolute alcohol. A calculated amount of 36% hydrochloric acid was added, and the hydrochloride completely precipitated by addition of

TABLE I

GLYCOL MONO-ESTERS PREPARED

Esters	Formula	Yield %	M. p. °C.	B. p. °C.	d_{15}^{15}	Percentage composition C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
Benzoate[a]	$C_9H_{10}O_3$	85		173 (21 mm.)	1.0937	65.06	65.14	6.02	6.25		
Salicylate[b]	$C_9H_{10}O_4$	75		172 (12 mm.)	1.2537	59.34	59.09	5.50	5.53		
Phenylcinchoninate	$C_{18}H_{15}O_3N$	70	90							4.77	4.67
p-Nitrobenzoate[c]	$C_9H_9O_5N$	83	77			51.18	51.15	4.26	4.41	6.6	6.6
p-Aminobenzoate	$C_9H_{11}O_3N$	80	132			59.6	59.2	6.08	6.05	7.6	7.7

[a] This compound was previously prepared by Gabriel and Heymann [*Ber.*, **23**, 2493 (1890)]. Only a small amount was obtained and it was not analyzed nor were its physical constants determined. In Ger. pat. 245,532 (1910) it was described as a solid melting at 45°. Our samples showed no tendency to crystallize when cooled to 0°, nor on standing for many months at room temperature.

[b] Previously mentioned in Ger. pat. 164,128 (1903); 173,776 (1905).

[c] In Ger. pat. 245,532 (1910) it is said to melt at 63°.

[2] Compare Cretcher and Pittenger, THIS JOURNAL, **47**, 163 (1925). Cretcher, Koch and Pittenger, *ibid.*, **47**, 1175 (1925).

ethyl acetate. After the hydrochloride had been filtered off and dried it was dissolved in water and the free base precipitated by addition of aqueous ammonia. This ester is soluble in water to the extent of 0.24% at 25°. It is very slightly soluble in olive oil. The hydrochloride, prepared as described, melts at 162–163° with effervescence.

Anal. Calcd. for $C_9H_{11}O_3N.HCl$: HCl, 16.7. Found: 16.6.

The Phenylurethan of Glycol Monobenzoate, $C_6H_5NH.COOCH_2CH_2OCOC_2H_5$.— Two cc. of glycol monobenzoate was added to a like amount of phenylisocyanate and the mixture heated for two minutes. The solid formed on cooling was recrystallized several times from alcohol; m. p., 115°.

Anal. Calcd. for $C_{16}H_{16}O_4N$: N, 4.91. Found: 4.91.

Behavior of Glycol Mono-esters when Heated; Glycol Di-esters

When Gabriel and Heymann[3] attempted to purify the product made by treating β-amino-ethyl benzoate with nitrous acid, they obtained, on distillation, an oily liquid that partially solidified on cooling. The solid material was purified and identified as glycol dibenzoate.

In order to determine the extent to which glycol monobenzoate when heated undergoes decomposition to the dibenzoate, and to ascertain whether or not glycol is simultaneously formed, 100 g. of the monobenzoate was distilled at atmospheric pressure. About 1 cc. of water was collected at 100°. The temperature then rose gradually to 275°. Between this temperature and 285° a considerable fraction was obtained, the temperature then rising rapidly to 350°. The material boiling below 335° was subjected to six redistillations, whereupon it separated completely into two fractions, one distilling at 198–200°, and the other above 335°. The higher-boiling fraction solidified and on recrystallization from methyl alcohol melted at 73°. The melting point and analysis identified it as glycol dibenzoate.

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.1; H, 5.25. Found: C, 70.74; H, 5.07.

The lower-boiling fraction was dissolved in water containing two equivalents of sodium hydroxide and shaken with twice the calculated amount of benzoyl chloride. The reaction product was crystallized from methyl alcohol; m. p., 73°. Glycol monobenzoate, therefore, when distilled at atmospheric pressure forms glycol dibenzoate and ethylene glycol practically quantitatively. This reaction seems to be a general one in this series.

Glycol monosalicylate and the *p*-nitrobenzoate were converted into the

TABLE II

GLYCOL DI-ESTERS

Esters	Formula	M. p. °C.	Percentage composition C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
Disalicylate	$C_{16}H_{14}O_6$	78.5	63.57	63.64	4.63	4.68		
Di-*p*-nitrobenzoate	$C_{16}H_{12}O_8N$	140					7.77	7.60

[3] Table I, Ref. a, p. 2498.

corresponding di-esters when heated for a few minutes at about 300° in a metal bath. The yields corresponded practically to the calculated amounts. The mono-*p*-amino ester decomposed below the temperature necessary for the formation of the di-ester. The esters prepared are described in Table II.

Physiological Behavior of Glycol *p*-Aminobenzoate

A 5% aqueous solution of the hydrochloride produces no precipitate when added to 1% solutions of egg white, horse serum or peptone.

Toxicity.—The m. l. d. for the rat, when injected into the saphenous vein, was found to be 450 mg. per kg. of body weight as compared to 40 mg. for novocaine. Novocaine is, therefore, eleven times as toxic.

The effects noted after intravenous injection indicate that this substance possesses, qualitatively, the same toxic properties as novocaine, that is, it paralyzes the respiratory center. This action is shown by the increased rate of respiration, extensor spasms, followed by shallow breathing and flaccid paralysis and continued auricular contractions for some time after respiration has ceased. The recovery from any sublethal dose is prompt and complete.

Anesthetic Value.—Neither the free base (up to a 25% mixture with talc) nor a solution of the hydrochloride (up to 5% concentration) produces anesthesia of the rabbit's eye when applied continuously for 45 minutes.

When injected subcutaneously, the hydrochloride is approximately equivalent to novocaine in anesthetic effect, but it produces anesthesia less rapidly. From seven to ten minutes is required for complete anesthesia in doses and concentrations which produce complete anesthesia with novocaine in five minutes.

Local After-effects.—A 3% solution of the hydrochloride, that is, the minimum effective concentration of this substance as well as of novocaine, after subcutaneous injection produces marked edema, bloody transudate and induration. Stronger solutions cause necrosis. This compound is, therefore, not suitable for use as a local anesthetic.

The authors are indebted to Mr. Horace A. Holaday, of the Research Laboratories of E. R. Squibb and Sons, for the data here recorded on the physiological behavior of this substance.

Summary

1. The preparation and properties of several glycol esters of aromatic acids have been described.

2. The physiological effects of glycol *p*-aminobenzoate have been presented.

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