A Synthesis of 5-Ethyl-5-(5′,5′-phenylhydantoin) Barbituric Acid

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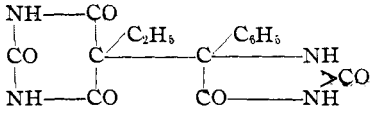
The use of hypnotics and sedatives is so wide that every development in that field assumes importance. Although barbiturates have been investigated intensively, the hydantoins with very pronounced sedative properties have been applied less successfully. Hydantoin derivatives, especially *5,5-phenylethyl-hydantoin*, have been employed in the treatment of chorea and epilepsy, but because of toxic effects consisting of eruptions, cyanotic swellings of the face and elevation of temperature, their use has been restricted.

The experimental work here described had as its objective the combination of the barbiturate and hydantoin structures, planning thereby to reduce the toxicity of the hydantoin through the formation of a larger molecule and increasing the hypnotic action of the barbiturate.

A compound of the following structural formula was thus created.

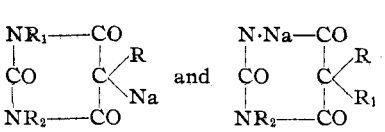


A number of difficult techniques for this synthesis are available. The most practical one is here described.

As starting materials for the preparation of this compound it was decided to use phenylbromohydantoin, which is known to have a very reactive bromine atom as has been shown by Gabriel,[1] and sodium ethyl-barbiturate which has an easily replaceable sodium atom.[2]

By bringing these two compounds together in a suitable solvent the condensation took place to 5-ethyl-5-(5-phenyl-hydantoin)-barbituric acid. This synthesis was accomplished readily by carrying out the reaction in glacial acetic acid at room temperature. The resulting compound is being investigated further pharmacologically.

As phenylbromohydantoin is very reactive it should also condense with all sodium salts of substituted barbituric acids having the general formulas



where R, R_1 and R_2 are either aliphatic, aromatic or alicyclic. These reactions are now under further investigation.

Experimental Part

Preparation of Mandelonitrile.—Mandelonitrile was used as the starting material in the preparation of phenylbromohydantoin and was prepared according to Spiegel[3] with several modifications thereby obtaining excellent yields. The following preparation is given as typical of the final procedure: 65 g. of potassium cyanide was moistened with a little water, covered with 106 g. of benzaldehyde, and cooled under mechanical stirring to about 5° with freezing mixture; 100 cc. of concentrated hydrochloric acid diluted with an equal volume of water was then dropped in slowly, care being taken that the vapor over the reaction mixture did not go above 12°. Mechanical stirring was continued during this operation and the time of dropping was about two hours. At the end of this procedure the reaction mixture should be a golden yellow. It was poured into a separatory funnel, the mandelonitrile forming the top layer. The aqueous layer was drained off and the oil washed with a large excess of water. Solid by-products mixed with the mandelonitrile were removed by filtering with suction. The filtrate was washed once more with water, giving a product pure enough to be used for the preparation of phenylhydantoin; yield, 114.5 g. (86%).

Preparation of Phenylhydantoin.—Phenylhydantoin was prepared according to Pinner.[4] Good yields were obtained, however, only when a mechanical stirrer was used during the condensation of the mandelonitrile with urea. The following procedure was found to give good yields: 145 g. of mandelonitrile and 60 g. of urea were heated together on a water-bath under mechanical stirring for five hours. The reaction mixture was then cooled below 40° and while still hot was poured into an excess of ether and violently stirred until an intimate mixture was obtained. It was then placed on ice overnight. The following day, the crystals of phenyl-ureido-nitrile were filtered off and washed by stirring up with several portions of ether. The yield was 80 g. or 46%.

The phenyl-ureido-nitrile was converted to phenylhydantoin by dissolving it in five volumes of 50% hydrochloric acid and then heating for twenty minutes further on the water-bath. The reaction mixture was then cooled with ice and the phenylhydantoin filtered off and washed with a little cold water; yield of 72 g. or 90%. Phenylhydantoin may be purified by recrystallization from six parts of boiling water; loss 10%; m. p. 178°.

Preparation of Phenylbromohydantoin.—Phenylbromohydantoin was prepared according to Gabriel.[1] Good yields were obtained only when the length of the bromination was proportional to the amount of material used. The following procedure is typical. Twenty grams of phenylhydantoin was dissolved in 60 cc. of glacial acetic

(1) Gabriel, *Ann.*, **350**, 118–34 (1906).
(2) E. A. Volwiler, THIS JOURNAL, **47**, 2236–40 (1925).
(3) A. Spiegel, *Ber.*, **14**, 238–40 (1881).
(4) A. Pinner, *ibid.*, **21**, 2320–9 (1888).

acid at about 80° and 30 g. of bromine in 40 cc. of glacial was then run in under stirring over a period of fifteen minutes. The reaction mixture was heated to 100° without stirring for two and one-half hours and then placed on ice overnight. On melting next day a precipitate was obtained which was filtered, washed with a little glacial acetic acid and then with absolute ether; yield 22 g. or 37%; m. p. 210°.

Preparation of Sodium Ethyl Barbiturate.—Sodium ethyl barbiturate was prepared according to Merkatz,[5] about four hours of boiling giving a maximum yield.

Preparation of 5-Ethyl-5′-(5′,5′-phenylhydantoin)-barbituric Acid.—Six grams of sodium ethyl barbituric acid was dissolved in 50 cc. of glacial acetic acid at room temperature with the aid of mechanical stirring. After solution was complete, 8.6 g. (1 equivalent) of phenylbromohydantoin was added slowly, the mechanical stirring being continued during this addition. This should take about ten minutes. Although phenylbromohydantoin is not soluble in glacial acetic acid at room temperature, it was dissolved readily in the presence of the barbiturate. Almost immediately after complete solution, a white precipitate began to come down. By allowing the reaction mixture to stand for several hours at room temperature and then on ice overnight, a maximum yield of 6.5 g. was obtained. The precipitate was filtered by suction and washed with a little glacial acetic acid. The material is soluble in hot water and hot glacial acetic acid, and insoluble in chloroform, acetone, alcohol and benzene. For analysis it was recrystallized twice from glacial acetic acid and dried *in vacuo* over sulfuric acid, m. p. 215–218°.

Anal. Calcd. for $C_{15}H_{14}O_5N_4$: C, 54.54; H, 4.25; N, 16.97. Found: C, 54.86; H, 4.45; N, 17.09.

(5) A. Merkatz, *Ber.*, **52**, 869–8 (1919).

Summary

1. The method for the preparation of phenylbromohydantoin has been improved.

2. A method for the synthesis of 5-ethyl-5′-(5′,5′-phenylhydantoin)-barbituric acid has been given.

3. The use of phenylbromohydantoin as a means of introducing the hydantoin ring into the barbituric acid ring is described.

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The Preparation of Benzyloxyalkyl *p*-Toluenesulfonates

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Much time has been spent in this Laboratory on the study of the alkylation of cinchona alkaloids with toluenesulfonates and these esters were found to give, in general, excellent results.[1] However, attempts to hydroxyalkylate at the phenolic hydroxyl group of hydrocupreine and apocupreine, using hydroxyalkyl *p*-toluenesulfonates, were less successful. Yields were very low and isolation of the desired products was difficult. A method which was far more efficient was found in alkylation with benzyloxyalkyl *p*-toluenesulfonates; the resulting benzyloxyalkyl ethers were hydrolyzed to hydroxyalkyl derivatives. The use of these reagents in the hydroxyalkylation of cinchona alkaloids and other basic phenolic substances will be discussed in future papers.

The preparation of benzyloxyalkyl *p*-toluenesulfonates offered no difficulties. Monobenzylation of ethylene, propylene and trimethylene glycols with benzyl chloride took place readily,[2] as did also the esterification of the hydroxyalkyl benzyl ethers with *p*-toluenesulfonyl chloride. Glycerol α,γ-dibenzyl ether,[3] prepared from glycerol α,γ-dichlorohydrin and a solution of potassium hydroxide in an excess of benzyl alcohol, reacted readily with *p*-toluenesulfonyl chloride giving β,β'-dibenzyloxyisopropyl *p*-toluenesulfonate.

(1) Butler, Renfrew, Cretcher and Souther, THIS JOURNAL, **59**, 227 (1937); Butler, Hostler and Cretcher, *ibid.*, 2354.

(2) Bennett, *J. Chem. Soc.*, **127**, 1277 (1925); Danilov, *et al.*, *Plasticheskie Massui*, **2**, 11 (1934); *C. A.*, **28**, 6300 (1934).

Experimental

Glycol Monobenzyl Ethers.—One hundred thirty-three grams of 85% potassium hydroxide (2 moles) was dissolved in 5 moles of the desired glycol in a 3-necked, 1-liter round-bottomed flask. After distilling a small amount of water from the solution, the flask was equipped with a mechanical stirrer and a thermometer. Two hundred fifty-three grams of benzyl chloride (2 moles) was then added with stirring, during a period of two hours, keeping the temperature of the reaction mixture at about 90°. The temperature was then raised to 130° and kept at this point for two hours longer.

The cooled mixture was diluted with a liter of water and the insoluble oily reaction product was extracted with ether. The extract was dried and after distilling off the solvent the glycol monobenzyl ether was separated and purified by fractional distillation. Yields were from 66–72% of the theoretical.

The propylene derivative consisted mainly of the 1-

(3) Fairbourne, Gibson and Stephens, *J. Chem. Soc.*, 456 (1931).