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.

351 WEST 86TH ST.
NEW YORK, N. Y.

RECEIVED MARCH 23, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY, MELLON INSTITUTE OF INDUSTRIAL RESEARCH]

The Preparation of Benzyloxyalkyl *p*-Toluenesulfonates

BY C. L. BUTLER, ALICE G. RENFREW AND MARY CLAPP

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).

monobenzyl ether. A small amount of 2-benzyl ether (probably less than 2%) was separated from the product by applying the phthalic anhydride method for separating primary and secondary alcohols.[4]

Ethylene glycol monobenzyl ether[2,5] b. p. 131° (13 mm.).

Propylene glycol monobenzyl ether, b. p. 128° (12 mm.).

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.3; H, 8.5. Found: C, 71.7; H, 8.5.

Trimethylene glycol monobenzyl ether, b. p. 142° (10 mm.).

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.3; H, 8.5. Found: C, 71.8; H, 8.3.

Glycerol α,γ-Dibenzyl Ether.—This compound was prepared by the method of Fairbourne, Gibson and Stephens[3] in 40% yield, b. p. 206° (3 mm.).

Benzyloxyalkyl *p*-Toluenesulfonates.—The esters were prepared in high yield by reaction of the desired hydroxyalkyl benzyl ethers with *p*-toluenesulfonyl chloride in the presence of pyridine in the usual way. The temperature was kept below 10° during reaction. The compounds were recrystallized from ether.

TABLE I

BENZYLOXYALKYL ESTERS OF *p*-TOLUENESULFONIC ACID

Ester	M. p., °C.	Formula	S Analyses, % Calcd.	Found
Benzyloxyethyl	45	$C_{16}H_{18}O_4S$	10.45	10.4
α-Methyl β-benzyloxyethyl	49	$C_{17}H_{20}O_4S$	10.0	10.1
γ-Benzyloxypropyl	37	$C_{17}H_{20}O_4S$	10.0	9.9
β-β′-Dibenzyloxyisopropyl	Amorphous	$C_{24}H_{26}O_6S$	7.5	6.6

(4) Stephan, *J. prakt. Chem.*, **60**, 248 (1899); Cox, Nelson and Cretcher, THIS JOURNAL, **49**, 1080 (1927).

(5) This substance recently has been made available by the Carbide and Carbon Chemicals Corporation.

Summary

The preparation of several hydroxyalkyl benzyl ethers and their *p*-toluenesulfonates is described.

PITTSBURGH, PENNA. RECEIVED APRIL 16, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY, MELLON INSTITUTE OF INDUSTRIAL RESEARCH]

Cinchona Alkaloids in Pneumonia. VI. A New Method for the Hydroxyalkylation of Phenolic Cinchona Alkaloids

BY C. L. BUTLER AND ALICE G. RENFREW

A convenient method for the preparation of hydroxyethyl ethers of phenolic cinchona alkaloids has been lacking up to the present, although much effort has been devoted at this Laboratory to the study of the problem. These compounds have interesting properties as antipneumococcic drugs.[1] Because of this and because investigation of other members of the hydroxyalkyl ether series is a part of our research program, the development of an efficient general method of preparation for this type of altered cinchona alkaloid was important.

During investigation of a wide variety of reagents, it was found that substances which might be expected to introduce the hydroxyethyl group directly, such as ethylene chlorohydrin or hydroxyethyl toluenesulfonate, did so only in very poor yield.[1] This result might be due, in part at least, to the high reactivity of these reagents in the alkaline medium used in the alkylation reactions. It was felt that the difficulty might be overcome by protecting the free hydroxyl group with a group which would be stable under the conditions used in alkylation. The complex ether obtained with such a reagent should be broken down readily to a hydroxyalkyl ether and both alkylation and partial hydrolysis should proceed with good yield if the plan were to be successful. The substances finally developed as being most suitable for the purpose were the benzyloxyalkyl arylsulfonates.[2] Alkylation of phenolic cinchona alkaloids such as hydrocupreine and apocupreine with these reagents proceeded in a normal way, to give good yields of benzyloxyalkyl ethers.

A different approach to this type of ether was also tried. β-Chloroethylapocupreine was prepared by alkylation of apocupreine with β-chloroethyl *p*-toluenesulfonate. This ether on digestion with sodium benzylate in benzyl alcohol solution gave benzyloxyethylapocupreine. The method was less satisfactory from the standpoint of yield and convenience than the one described above. It did, however, serve as a check on the structure of the product.

The benzyl ether group in these compounds was quite stable to dilute alkali, but in dilute mineral acid was considerably less stable than was the alkaloid ether group. Thus it was possible to accomplish a partial hydrolysis in hydrochloric acid solution, whereby the benzyl group was removed

(1) (a) Butler, Nelson, Renfrew and Cretcher, THIS JOURNAL, **57**, 575 (1935); (b) Butler, Renfrew, Cretcher and Souther, *ibid.*, **59**, 227 (1937).

(2) Butler, Renfrew and Clapp, *ibid.*, **60**, 1472 (1938).