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	$C_{24}H_{26}O_5S$	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.

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[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).

TABLE I

PHARMACOLOGICAL PROPERTIES OF APOCUPREINE ETHERS

Apocupreine ether dihydrochloride	*In Vitro*[3] Prevents growth of pneumococcus in conen. of	Toxicity (20 g. mice)[4] Deaths at dosages of 5 mg.	6 mg.	7 mg.	8 mg.	9 mg.	10 mg.	Eye damage (dogs)[4] Sub-lethal doses
n-Propyl	1:1,600,000	30/30	...	...	...	...	...	+
γ-Hydroxypropyl	1:800,000	1/30	7/30	23/30	10/10	..	...	+ but less marked than with *i*- or *n*-propyl
i-Propyl	1:1,600,000	30/30	15/15	...	...	..	...	+
α-Methyl β-hydroxyethyl	1:1,600,000	0/10	0/30	8/30	24/30	..	...	+ but less marked than with *i*- or *n*-propyl
β,β′-Dihydroxy isopropyl	1:300,000	...	...	...	..,	4/30	21/30	Not tested

as benzyl chloride and the rest of the molecule, a hydroxyalkyl ether, remained intact. Benzyloxyethylapocupreine, for example, on hydrolysis in boiling 11% hydrochloric acid gave a high yield of hydroxyethylapocupreine according to equation I.

$$(C_{19}H_{21}ON_2)OCH_2CH_2OCH_2C_6H_5 \xrightarrow{\text{dil. HCl}} (C_{19}H_{21}ON_2)OCH_2CH_2OH + C_7H_7Cl \quad (I)$$

The method has been applied successfully in the preparation of hydroxyethylhydrocupreine, hydroxyethylapocupreine, γ-hydroxypropylapocupreine, α-methyl-β-hydroxyethylapocupreine, and β,β′-dihydroxyisopropylapocupreine. The preparation of higher members of the hydroxyalkyl ether series is in progress.

The hydroxylated propylapocupreines, as shown in Table I, also have interesting possibilities as antipneumonic drugs. Toxicity as compared with the alkyl ethers was quite low, while pneumococcicidal activity was maintained at a very high level. This was especially true of the α-methyl-β-hydroxyethyl derivative. While hydroxylation of *n*-propylapocupreine in the γ-position reduced the antipneumococcic power by half, it appeared that isopropylapocupreine suffered no loss in this respect on monohydroxylation; dihydroxylation reduced the pneumococcicidal power considerably and brought about a further marked reduction in toxicity. The eye damage experienced by dogs when given doses close to the lethal was considerably less marked than was the case with the unaltered apocupreine alkyl ethers, and in most trials could not be detected in the living animal. Further work on the biological properties of the drugs is in progress.

Experimental

Benzyloxyethylapocupreine. (a) **Alkylation with Benzyloxyethyl *p*-Toluenesulfonate.**—Fifty grams of apocupreine and 10.6 g. of 85% potassium hydroxide were dissolved in 250 cc. of alcohol; 48 g. of benzyloxyethyl *p*-toluenesulfonate[2] was added and the mixture was warmed on a water-bath for two hours. After cooling 750 cc. of ether was added and potassium toluenesulfonate was filtered from the solution. The filtrate was concentrated to a sirup and to this was added 600 cc. of ether and 200 cc. of 12% sodium hydroxide. The mixture was agitated thoroughly, the aqueous layer drawn off in a separatory funnel, extracted twice more with ether and then discarded. The combined ether solution was washed with dilute alkali and water and dried over potassium carbonate. The crude gummy reaction product, obtained on evaporation of the ether, weighed 45 g. Pure benzyloxyethylapocupreine was obtained on crystallization of the crude material from dry acetone: $[\alpha]D$ −155°;[5] m. p. 115°.

Anal. Calcd. for $C_{28}H_{32}O_3N_2$: C, 75.7; H, 7.2; N, 6.3. Found: C, 75.7; H, 6.9; N (Dumas), 6.4.

(b) **Through β-Chloroethylapocupreine.**—One hundred and five grams of apocupreine was alkylated in the usual way in alcoholic solution with β-chloroethyl *p*-toluenesulfonate. The yield was 74 g. of crude base. The substance was purified by recrystallizing its dihydrochloride from alcohol, $[\alpha]D$ −205°.

Anal. Calcd. for $C_{21}H_{25}O_2N_2Cl \cdot 2HCl$: Cl, 23.9. Found: Cl, 23.4.

Sixty-five one-hundredth gram of sodium was dissolved in 30 cc. of benzyl alcohol and added to a solution of 9 g. of β-chloroethylapocupreine in 30 cc. of benzyl alcohol. The solution was kept at 92° for twenty-four hours. It was then cooled, filtered from practically a quantitative amount of sodium chloride and diluted with 250 cc. of ether. The base was extracted from the ether solution with several portions of normal sulfuric acid and the acid solution was in turn washed repeatedly with ether to remove all the benzyl alcohol. The base was precipitated from acid solution with alkali and extracted with ether. The yield of crude product on evaporation of the solvent was 9 g. Several recrystallizations from acetone yielded a product of $[\alpha]D$ −155°, melting at 115°. The melting point of a mixture of this material with benzyloxyethylapocupreine prepared by direct alkylation with benzyloxyethyl *p*-toluenesulfonate was not depressed.

Hydrolysis of Benzyloxyethylapocupreine.—Nine grams of benzyloxyethylapocupreine was dissolved in 60 cc. of an acid solution containing 16 cc. of concd. hydrochloric acid. The solution was concentrated three times at atmospheric

(3) Details will be published elsewhere by the medical staff connected with the problem. For the method, see Johnston, Burchell, Permar and Maclachlan, *J. Pharm. Exptl. Therap.*, **61**, 364 (1937).

(4) Dawson, Permar, Johnston and Maclachlan, *Am. J. Med. Sci.*, **193**, 543 (1937).

(5) The rotations of bases were measured in absolute alcoholic solution; salts were measured in aqueous solution: $l = 1$; $c = 1$.

pressure to a volume of 30 cc. and then steam distilled. The complex ether was thus hydrolyzed to hydroxyethylapocupreine and benzyl chloride, which was carried over into the distillate.

Hydroxyethylapocupreine was precipitated from the acid solution and worked up as dihydrochloride as has been described previously.[1] The yield of salt was 7.5 g. Several crystallizations from alcohol gave pure hydroxyethylapocupreine dihydrochloride of $[\alpha]D$ −228°.

Anal. Calcd. for $C_{21}H_{26}O_3N_2 \cdot 2HCl$: N, 6.6; Cl, 16.6. Found: N (Kjeldahl), 6.6; Cl, 16.0.

A sample of base, recovered from this salt, was converted to an amorphous diacetyl derivative by thorough acetylation with acetyl chloride.

Anal. Calcd. for $C_{25}H_{30}O_5N_2$: CH_3CO, 19.6. Found: CH_3CO, 19.5.

For a more direct preparation of hydroxyethylapocupreine it was found to be unnecessary to isolate the intermediate benzyloxyethyl derivative: 63 g. of apocupreine was alkylated as described above with 63 g. of benzyloxyethyl *p*-toluenesulfonate. After separating from potassium toluenesulfonate, the alcoholic solution of reaction product was concentrated to dryness and the residual gum[6] was taken up in 400 cc. of 11% hydrochloric acid. Hydrolysis was accomplished as described above.

The acid solution was diluted to about 500 cc., cooled and extracted with ether. After treatment with a little nuchar, the base was precipitated three times from cold dilute hydrochloric acid solution by addition of excess sodium hydroxide solution in order to ensure separation from alkali soluble material. The product was dissolved in 60 cc. of absolute alcohol and ether was added to a volume of 500–600 cc. to precipitate colored impurities. The solvent was removed from the ether–alcohol solution and the partially purified residue was converted to dihydrochloride. The salt was crystallized from alcohol in the usual way. The yield was 30 g. of a product which, on recrystallization, had a specific rotation of −228°.

A similar result was obtained using benzyloxyethyl benzenesulfonate.

Hydroxyethylhydrocupreine.[1]—Ninety grams of hydrocupreine on alkylation as described above with benzyloxyethyl *p*-toluenesulfonate, yielded 81 g. of crude benzyloxyethylhydrocupreine. Unsuccessful attempts were made to crystallize a small sample of this material. The rest of the crude gum (65 g.) was hydrolyzed in dilute hydrochloric acid as already described. The resulting crude hydroxyethylhydrocupreine was worked up as dihydrochloride: yield 35 g.; $[\alpha]D$ −181°.

Anal. Calcd. for $C_{21}H_{28}O_3N_2 \cdot 2HCl$: Cl, 16.5. Found: Cl, 16.0.

The base was recovered from the dihydrochloride and crystallized from acetone, $[\alpha]D$ −131°.[1] A sample of base was converted to an amorphous diacetyl derivative; $[\alpha]D$ −30°.

Anal. Calcd. for $C_{25}H_{32}O_5N_2$: CH_3CO, 19.5. Found: CH_3CO, 17.9.

(6) In subsequent experiments the crude product was separated by simply diluting the alcoholic solution with a large volume of water and decanting the dilute alcoholic solution from the gummy reaction product.

γ-Hydroxypropylapocupreine.—Forty-six grams of apocupreine was similarly alkylated with 48 g. of γ-benzyloxypropyl *p*-toluenesulfonate,[2] giving 46 g. of crude benzyloxypropylapocupreine. The substance was obtained as a gum which could not be crystallized; 43 g. of the crude product was hydrolyzed in 11% hydrochloric acid and the resulting crude γ-hydroxypropylapocupreine was worked up as dihydrochloride from absolute alcoholic solution. The crystallized salt was obtained in a yield of 24 g., $[\alpha]D$ −225°.

Anal. Calcd. for $C_{22}H_{28}O_3N_2 \cdot 2HCl$: Cl, 16.1; N, 6.4. Found: Cl, 15.5; N, 6.4.

The base was liberated from the salt and crystallized from acetone: m. p. 140°; $[\alpha]D$ −181°. It was converted to an amorphous diacetyl derivative with acetyl chloride, $[\alpha]D$ −69°.

Anal. Base. Calcd. for $C_{22}H_{28}O_3N_2$: C, 71.7; H, 7.6. Found: C, 71.7; H, 7.5. Diacetyl derivative. Calcd. for $C_{26}H_{32}O_5N_2$: CH_3CO, 19.1. Found: CH_3CO, 18.8.

α-Methyl-β-hydroxyethylapocupreine.—This substance was prepared similarly, starting with 62 g. of apocupreine and 64 g. of α-methyl-β-benzyloxyethyl *p*-toluenesulfonate,[2] and purified through the dihydrochloride salt. The yield was 31 g., $[\alpha]D$ −224°.

Anal. Calcd. for $C_{22}H_{28}O_3N_2 \cdot 2HCl$: Cl, 16.1. Found: Cl, 16.0.

The base was recovered from the salt and crystallized from acetone: m. p. 105–108°; $[\alpha]D$ −180°. It yielded a gummy diacetyl derivative of $[\alpha]D$ −61°.

Anal. Base. Calcd. for $C_{22}H_{28}O_3N_2$: C, 71.7; H, 7.6; N, 7.6. Found: C, 71.9; H, 7.5; N, 7.4. Diacetyl derivative. Calcd. for $C_{26}H_{32}O_5N_2$: CH_3CO, 19.1. Found: CH_3CO, 18.6.

β,β′-Dihydroxyisopropylapocupreine.—Fifty-six grams of apocupreine on alkylation with 80 g. of β,β′-dibenzyloxy isopropyl *p*-toluenesulfonate,[2] yielded 85 g. of crude dibenzyloxyisopropylapocupreine; 81 g. of this product was hydrolyzed in 11% hydrochloric acid and the resulting β,β′-dihydroxyisopropylapocupreine was worked up and purified by crystallization of the dihydrochloride from absolute alcohol. The yield of salt was 29 g., $[\alpha]D$ −203°.

Anal. Calcd. for $C_{22}H_{28}O_4N_2 \cdot 2HCl$: Cl, 15.5; N, 6.1. Found: Cl, 15.0; N, 6.1.

The base, recovered from the dihydrochloride, could not be obtained in crystalline condition. After thorough drying under reduced pressure at 100°, it melted at 128°, $[\alpha]D$ −177°; amorphous triacetyl derivative, $[\alpha]D$ −46°.

Anal. Base. Calcd. for $C_{22}H_{28}O_4N_2$: C, 68.75; H, 7.3. Found: C, 67.9; H, 7.6. Triacetyl derivative. Calcd. for $C_{28}H_{34}O_7N_2$: CH_3CO, 25.8. Found: CH_3CO, 24.0.

Summary

A new method of hydroxyalkylation has been applied to the preparation of several hydroxyalkyl ethers of phenolic cinchona alkaloids. Some biological properties of these substances have been presented briefly.

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