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

Cinchona Alkaloids in Pneumonia. VII. Amyl and Hydroxyalkyl Apocupreine Ethers

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Recent work in the apocupreine ether series[3] has shown that on ascending in the series of alkyl ethers, a high pneumococcicidal activity is maintained through the C_4 derivatives. The situation is somewhat complicated by variations in the structure of the butyl group; however, isobutyl apocupreine dihydrochloride was shown to be as active *in vitro* as the very potent ethyl derivative. This is in marked contrast with the behavior of the corresponding hydrocupreine ethers.[4] It was also shown that hydroxyethylapocupreine,[5] which has found clinical application, has much stronger antipneumococcic activity than the corresponding hydrocupreine derivative. Further, hydroxypropyl ethers of apocupreine have very strong bacteriostatic action and much lower toxicity than the alkyl derivatives.[6] This higher activity in the apocupreine ether series is not surprising in view of the fact that apocupreine itself shows considerable activity, whereas hydrocupreine is quite low in bacteriostatic action.

The present work on β-hydroxypropyl, isomeric hydroxybutyl and isomeric amyl apocupreine ethers was undertaken in order to study further the influence of the size and structure of the ether group on antipneumococcic activity in this series. The amyl ethers were prepared readily by alkylation of apocupreine with the desired amyl *p*-toluenesulfonates. The preparation of the hydroxybutyl derivatives by alkylation with benzyloxybutyl *p*-toluenesulfonates and subsequent hydrolysis of the benzyl group offered no difficulty. Alkylations were also carried out with β-hydroxy-*n*-propyl and β-methyl-β-hydroxy-*n*-propyl *p*-toluenesulfonates. These reagents gave only very low yields of hydroxyalkyl ethers. The results are entirely in agreement with earlier data on the use of glycol monoesters in alkylations of basic phenolic substances.[5,7]

Some biological properties of the apocupreine ethers prepared in the course of the work are shown in Table I. A decided lowering in the toxicity of butyl apocupreine ethers was accomplished by introduction of the hydroxyl group into the butyl radical. This effect was accompanied by a decrease in the *in vitro* bacteriostatic activity, a decrease which was very marked in the β-methyl-β-hydroxy-*n*-propyl and the δ-hydroxy-*n*-butyl ethers. The suitability of the more active α-methylol *n*-propyl and α-methyl β-hydroxy-*n*-propyl ethers for trial in human pneumonia will

TABLE I[a]

BACTERIOSTATIC POWER AND TOXICITY OF APOCUPREINE ETHERS

Apocupreine ether dihydrochloride	*In vitro* prevents growth of pneumococcus in concn. of	Intraperitoneal—Toxicity (20 g. mice) deaths at mg. dosages of 2	3	4	5	6	7	8
β-Hydroxy-*n*-propyl	1:300,000				0/30	1/30	10/30	
β-Methyl-β-hydroxy-*n*-propyl	1:50,000				1/30	19/30		
δ-Hydroxy-*n*-butyl	1:50,000				7/30	25/30		
α-Methylol *n*-propyl	1:400,000				10/30	14/30		
α-Methyl-β-hydroxy-*n*-propyl	1:400,000				6/30	20/30	30/30	
n-Amyl	1:800,000	7/30	27/30		10/10			
i-Amyl[8]	1:300,000	6/30	20/30					
s-Butylcarbinyl	1:400,000	3/30	20/30		10/10			
α-Methyl-*n*-propylcarbinyl	1:400,000	2/30	12/30	29/30				
Diethylcarbinyl	1:400,000		4/30	28/30				

[a] The experimental testing of these alkaloids was carried out by Drs. Maclachlan, Bracken and Patrick of the Mercy Hospital, Pittsburgh, Penna.

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(3) Butler, Hostler and Cretcher, THIS JOURNAL, **59**, 2354 (1937).

(4) Morgenroth and Bumke, *Deut. Med. Wochschr.*, **40**, 539 (1914); **44**, 729 (1918); Morgenroth and Tugendreich, *Berlin. klin. Wochschr.*, **53**, 794 (1916); *Biochem. Z.*, **79**, 257 (1917).

(5) Maclachlan, Johnston, Bracken and Crum, *Am. J. Med. Sci.*, **197**, 31 (1939); Butler, Nelson, Renfrew and Cretcher, THIS JOURNAL, **57**, 575 (1935).

(6) Butler and Renfrew, THIS JOURNAL, **60**, 1473 (1938).

(7) Butler and Renfrew, *ibid.*, **60**, 1582 (1938).

(8) Miura and Okamoto, *Jap. J. Med. Sci.*, *V*, **1**, 1 (1930),

depend on the results (not yet available) of tests for visual disturbance.

Experimental[9]

Butylene Glycol Monobenzyl Ethers.—Isomeric monobenzyl ethers were prepared by a method which has already been described.[10]

TABLE II

Substance, ether	B. p. at 6 mm. °C.	Anal. ($H_{16}O_2$: Calcd. for C_{11} C, 73.3) C	(H, 8.9) H
1,2-Butylene glycol 1-monobenzyl	128–132	73.9	9.1
2,3-Butylene glycol monobenzyl	122–125	73.0	9.0
1,4-Butylene glycol monobenzyl	146–149	73.2	9.3

Various *p*-Toluenesulfonyl Esters.—Hydroxypropyl, hydroxybutyl, benzyloxybutyl and amyl *p*-toluenesulfonates were prepared in good yields from propylene glycol, isobutylene glycol, isomeric butylene glycol, monobenzyl ethers and isomeric amyl alcohols by methods described in previous papers in this series. Suitable alkylating reagents were obtained without extensive purification. Three of the esters were crystallized from ether.

Diethylcarbinyl-*p*-toluenesulfonate, m. p. 37°.[11] β-Hydroxy-*n*-propyl-*p*-toluenesulfonate, m. p. 46°. *Anal.* Calcd. for $C_{10}H_{14}O_4S$: S, 13.9. Found: S, 13.7. α-Methyl-β-benzyloxypropyl *p*-toluenesulfonate, m. p. 47°. *Anal.* Calcd. for $C_{18}H_{22}O_4S$: S, 9.7. Found: S, 10.1.

Alkylation of Apocupreine.—Alkylations according to the previously described methods proceeded smoothly and gave good yields of final products except, as noted above, when glycol monoesters were used as reagents. In these experiments, yields of 4–8% were obtained. δ-Benzyloxybutyl apocupreine was obtained in crystalline condition from ether; m. p. 104°; specific rotation −152°.[12] *Anal.* Calcd. for $C_{30}H_{36}O_3N_2$: N, 5.9. Found: N, δ-benzyloxybutylapocupreine, 5.7; α-benzyloxymethyl *n*-propylapocupreine, 5.9; α-methyl-β-benzyloxy-*n*-propylapocupreine, 5.9.

Hydrolysis of the benzyloxybutyl ethers in 1:1 hydrochloric acid proceeded smoothly[6] and good yields of the corresponding hydroxybutyl derivatives were obtained. Some physical properties and analyses of the various ethers which were prepared are shown in Table III.

TABLE III

Apocupreine ether	Bases: M. p., °C.	Sp. rot.	Formula	Nitrogen, % Calcd.	Found	Dihydrochlorides: Sp. rot.	Formula	Chlorine, % Calcd.	Found	Moisture Calcd.	Found
β-Hydroxy-*n*-propyl	170	−180°	$C_{22}H_{28}O_3N_2$	7.6	7.7	−216°	$C_{22}H_{28}O_3N_2 \cdot 2HCl$	16.1		...	...
β-Methyl-β-hydroxy-*n*-propyl	102	−169°	$C_{23}H_{30}O_3N_2$	7.3	7.3	−218°	$C_{23}H_{30}O_3N_2 \cdot 2HCl$	15.5	14.7	...	...
δ-Hydroxy-*n*-butyl	178	−179°	$C_{23}H_{30}O_3N_2$	7.3	7.2	−213°	$C_{23}H_{30}O_3N_2 \cdot 2HCl$	15.5	15.2	...	...
α-Methylol *n*-propyl	Amor-	−165°	$C_{23}H_{30}O_3N_2$	7.3	7.4	−202°	$C_{23}H_{30}O_3N_2 \cdot 2HCl$	15.5	13.8	...	...
α-Methyl-β-hydroxy-*n*-propyl	phous	−163°	$C_{23}H_{30}O_3N_2$	7.3	7.3	−212°	$C_{23}H_{30}O_3N_2 \cdot 2HCl$	15.5	14.0	...	...
n-Amyl[13]	146	−178°	$C_{24}H_{32}O_2N_2$	7.4	7.4	−230°	$C_{24}H_{32}O_2N_2 \cdot 2HCl \cdot 1.5$ aq.	15.2	15.8	5.8	5.2
i-Amyl	175	−181°	$C_{24}H_{32}O_2N_2$	7.4	7.3	−206°	$C_{24}H_{32}O_2N_2 \cdot 2HCl \cdot 2$aq.	14.9	14.8	7.3	7.1
s-Butylcarbinyl	169	−172°	$C_{24}H_{32}O_2N_2$	7.4	7.3	−225°	$C_{24}H_{32}O_2N_2 \cdot 2HCl \cdot$aq.	15.5	14.8	3.8	3.4
Methyl-*n*-propylcarbinyl	Amor-	−163°	$C_{24}H_{32}O_2N_2$	7.4	7.1	−212°	$C_{24}H_{32}O_2N_2 \cdot 2HCl \cdot 2$aq.	14.9	15.2	7.3	7.7
Diethylcarbinyl	phous	−150°	$C_{24}H_{32}O_2N_2$	7.4	6.7	−213°	$C_{24}H_{32}O_2B_2 \cdot 2H_2O \cdot 1.5$aq.	15.2	14.6	5.8	5.5

Summary

Hydroxypropyl, isomeric hydroxybutyl and isomeric amyl apocupreine ethers have been prepared. Some biological properties of these substances, of interest in the chemotherapeutic study of pneumonia, have been presented briefly.

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(9) The preparation of many of the reagents used in this work was carried out by Miss Mary Clapp.

(10) Butler, Renfrew and Clapp, THIS JOURNAL, **60**, 1472 (1938).

(11) Tabern and Volweiler, *ibid.*, **56**, 1141 (1934).

(12) Rotations of bases were measured in alcoholic solution; salts were measured in aqueous solution; $l = 1$, $c = 1$.

(13) Buttle, Henry, Solomon, Trevan and Gibbs, *Biochem. J.*, **32**, 47 (1938).