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

Cinchona Alkaloids in Pneumonia. VIII. Some Sulfur Derivatives of Apocupreicine Ethers and Aminoquinolines

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Reports of the experimental study and clinical use of hydroxyethylapocupreine in the treatment of pneumonia have been made by Maclachlan and Bracken.[1] Other new cinchona derivatives of high antipneumococcal action have been the subject of earlier papers in this series.[2]

Because of the bactericidal action of certain sulfanilamide derivatives, the sulfanilyl radical has been introduced on the piperidine nitrogen of quinicine and of hydroxyethylapocupreicine. Several quinolyl sulfanilamide derivatives also were prepared. Although none of the present compounds showed useful antipneumococcic power, the studies of toxicity and action *in vitro* are presented in relation to the correlation of chemical structure with physiological action in the cinchona series.

The optical rotations of the new apocupreicine ethers are significant because β-isoquinotoxine[3] is the only member of the apocupreicine series previously studied. As has been pointed out by Solomon[3] the optical rotation of the apocupreicine series is dependent on the steric configuration of carbon-4.[4] The asymmetry of C-3 has disappeared in the conversion of the vinyl to an ethylidene side-chain, and C-8 and C-9 are not asymmetric carbons in the cupreicine structure. The levorotations of the new ethyl and hydroxyethylapocupreicines are close to the value reported for methylapocupreicine (β-isoquinotoxine) and further substantiate the evidence for the levo contribution of this carbon in the naturally occurring alkaloids.

Experimental

Quinicine, ethylapocupreicine and hydroxyethylapocupreicine were prepared by the action of dilute acetic acid on quinine, ethylapocupreine and hydroxyethylapocupreine, respectively, according to the method of Heidelberger and Jacobs.[5] In each case the base was a viscous sirup which could be converted to a crystalline monohydrochloride by titration in alcoholic solution with one equivalent of hydrochloric acid.

TABLE I

	Compound[a]	M. p., °C.	Formula	Analyses, % Calcd. N	Calcd. S	Found N	Found S
1	N-*p*-Acetylaminobenzenesulfonylhydroxyethylapocupreicine	105	$C_{29}H_{33}O_6N_3S$	7.62		7.8	
2	N-*p*-Aminobenzenesulfonylhydroxyethylapocupreicine[b]	99	$C_{27}H_{31}O_5N_3S$	8.21	6.28	8.0	5.92
3	N-*p*-Acetylaminobenzenesulfonylquinicine		$C_{28}H_{31}O_5N_3S$	8.06		8.07	
4	N-*p*-Aminobenzenesulfonylquinicine		$C_{26}H_{29}O_4N_3S$	8.73	6.68	8.96	6.40
5	6-Amino 5-(*p*-sulfamidophenylazo)-quinoline[c]	240	$C_{15}H_{13}O_2N_5S$	21.4		21.27	
6	8-Amino 5-(*p*-sulfamidophenylazo)-quinoline[c]	245	$C_{15}H_{13}O_2N_5S$	21.4		21.66	
			$C_{15}H_{13}O_2N_5S \cdot HCl$	19.2		18.8	

[a] Solvent: 1 was precipitated from an acetone solution with ether. 2 was soluble in 40–50 volumes of alcohol and was recovered by concentrating under reduced pressure. 3 was precipitated from an alcoholic solution with ether. 4 was soluble in alcohol, acetone, dioxane or excess acid and was recovered by evaporating the organic solvent. 5 crystallized as red plates from alcohol. 6 was an orange powder sparingly soluble in alcohol. The monohydrochloride was purple. [b] The fact that an alcoholic solution of N-aminobenzenesulfonyl hydroxyethylapocupreicine was titrated to an end-point acid to methyl orange with one equivalent of HCl confirms the sulfonamide linkage. [c] The position of the azo-coupling with aminoquinolines has been investigated by Renshaw, *et al.*[8]

The N-1 substituted sulfanilamides[6] were prepared in benzene,[7] or chloroform solution, and hydrolysis of the N-4 acetyl group was accomplished by refluxing for an hour with 10% hydrochloric acid (sometimes with the addition of a little alcohol).

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(1) Bracken, Johnston, Crum, Patrick, Permar and Maclachlan, *J. Pharmacol.*, **68**, 259 (1940); Maclachlan, Johnston, Bracken and Crum, *Am. J. Med. Sci.*, **197**, 31 (1939); Maclachlan, Johnston and Bracken, in press.

(2) "Cinchona Alkaloids in Pneumonia. VII," Green, Renfrew and Butler, THIS JOURNAL, **61**, 1783 (1939).

(3) Solomon, *J. Chem. Soc.*, 6 (1938).

(4) Rabe and Riza, *Ann.*, **496**, 152 (1932).

(5) Heidelberger and Jacobs, THIS JOURNAL, **41**, 817 (1919).

(6) Northey, *Chem. Rev.*, **27**, 85 (1940).

(7) Choudhury, Das-Gupta and Basu, *J. Ind. Chem. Soc.*, **14**, 733 (1937).

(8) Renshaw, Friedman and Gajewski, THIS JOURNAL, **61**, 3322 (1939).

TABLE II

BIOLOGICAL TESTING OF APOCUPREICINE AND QUINOLINE DERIVATIVES[a]

Substance	*In vitro* Bacteriostasis in broth at concn. of	Intraperitoneal toxicity Deaths at dosages in mg. per 20 g. mouse 2	3	4
Quinicine·HCl		0/30	11/30	30/30
Ethylapocupreicine·HCl	1:50,000	7/30	28/30	
Hydroxyethylapocupreicine·2HCl	1:50,000		5/30	28/30

Substance	Oral toxicity Deaths at dosages in mg. per 20 g. mouse 3	5	6	12	50	80	90	Mouse protection *vs.* Pnc. II.
N-*p*-Aminobenzenesulfonylhydroxyethylapocupreicine				0/10				neg.
6-N⁴-Acetylsulfanilamidoquinoline[b]					0/10		1/10	neg.
6-Sulfanilamidoquinoline[b,c]	1:100,000	7/30	13/30	21/30				neg.
6-Amino-5-(*p*-sulfamidophenylazo)-quinoline				0/30				neg.
8-Amino-5-(*p*-sulfamidophenylazo)-quinoline						6/10		neg.

[a] The experimental testing was carried out by Drs. Bracken, Patrick, Maclachlan and Johnston of the Mercy Hospital, Pittsburgh, Pa. For methods see ref. 1 and earlier papers. [b] Winterbottom, THIS JOURNAL, **62**, 160 (1940); Bobranski, *Arch. Pharm.*, **277**, 75 (1939); Ganapathi, *Indian J. Med. Research*, **27**, 971 (1940). [c] *In vitro* tests were made with the dihydrochloride.

Ethylapocupreicine Monohydrochloride.—Ethylapocupreicine was dissolved in alcohol and converted to the monohydrochloride. After repeated concentration of the alcoholic solution *in vacuo*, the salt crystallized from absolute alcohol: $[\alpha]_D$ −26.7°; c = 1 in water.

Anal. Calcd. for $C_{21}H_{26}O_2N_2 \cdot HCl$: N, 7.48; Cl, 9.36. Found: N, 7.59; Cl, 9.38.

Hydroxyethylapocupreicine.—The viscous hydroxyethylapocupreicine was very soluble in chloroform or alcohol and slightly soluble in ether or acetone. The dry monohydrochloride crystallized from absolute alcohol with one mole of alcohol of crystallization. This salt melted at 90° to a gum which would crystallize again if macerated with absolute alcohol. Because aqueous solutions of the salt clouded on dilution, the rotation was determined in normal sulfuric acid: $[\alpha]_D$ −29° for the crystalline salt (c = 1). A crystalline dihydrochloride was precipitated from alcohol solution with ether. This gave a clear but somewhat colored solution.

Anal. Calcd. for $C_{21}H_{26}O_3N_2$: N, 7.92. Found: N, 7.72. Calcd. for $C_{21}H_{26}O_3N_2 \cdot HCl \cdot C_2H_5OH$: C_2H_5OH, 10.5; Cl, 8.25. Found: C_2H_5OH, 9.0; Cl, 8.31.

Summary

Some new apocupreicine ethers are described. Substituted sulfonamide compounds containing quinicine, apocupreicine and aminoquinoline nuclei have been prepared and tested experimentally. None of these compounds showed useful antipneumococcic power.

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Oxidation Potentials of Ketones and an Aldehyde

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The relative strength as oxidizing agents of thirteen ketones was recently reported.[2] The values assigned to the various ketones were based upon the determinations with a polarograph of the concentrations at equilibrium of the ketones in systems of the type, $R_2CO + R_2'CHOH \underset{Al(OC_4H_9-t)_3}{\rightleftarrows} R_2CHOH + R_2'C{=}O$. The present paper describes the extension of this study so that it now includes twenty-three ketones, one aldehyde, and two anthraquinones. The inclusion of a quinone in the series makes it possible to assign to all the ketones and the aldehyde numerical values expressing in volts their oxidation potentials with respect to the hydrogen electrode, since the oxidation potentials of the quinones are known.[3]

Before describing the recent work it will be well to point out certain misconceptions expressed in the earlier paper. It was concluded that unsaturation was the most important structural factor bearing on the oxidation potential of a ketone.

(1) Assistant professor at the University of Kentucky and a fellow of the General Education Board at the University of Wisconsin during the year 1939–1940.

(2) Cox and Adkins, THIS JOURNAL, **61**, 3364 (1939).

(3) Conant and Fieser, *ibid.*, **46**, 1859 (1924); Fieser in Gilman's "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1938, pp. 105, 810.