verted to 4-fluoro-1,3-dimethylbenzene by Schiemann's method.[4] This was next oxidized to the acid with neutral permanganate which was subsequently converted to the acid chloride with thionyl chloride. The alkamine esters were obtained by the reaction of the acid chloride with the appropriate amino alcohol. The dihydrochloride salts of this series possessed no topical anesthetic activity, although the free bases did possess this property. The toxicities varied from one-half to one-eighth that of procaine hydrochloride. In general they followed the usual trend, the toxicity increasing with increase in length of the side chain.

Experimental

4-Fluoroisophthalic Acids.—To a 15-g. portion of 4-fluoro-*m*-xylene in a three-liter, three-neck flask fitted with mechanical stirrer and water condenser, on a heated steam-bath, a saturated solution containing 80 g. of potassium permanganate in water was added over a period of several hours. After oxidation was completed, the manganese dioxide was removed by filtration and the filtrate acidified with dilute hydrochloric acid. The 4-fluoroisophthalic acid precipitated as a white fluffy powder. This was dissolved in alkali and reprecipitated in order to purify it; yield, 70%. Neutralization equivalent: 92; theoretical, 92; melting point, 282–286°.

4-Fluoroisophthalyl Chloride.—A 10 g. portion of 4-fluoroisophthalic acid was treated with 60 cc. of thionyl chloride. The mixture was gently refluxed on a steam-bath until all of the acid went into solution. The excess thionyl chloride was removed by distillation. The acid chloride, a heavy colorless liquid, distilled at 100–103° at 2 mm. pressure; yield, 93%.

Anal. Calcd. for $C_8H_3O_2Cl_2F$: Cl, 32.09. Found: Cl, 31.92, 31.53.

(4) Schiemann and Balz, *Ber.*, **60B**, 1186 (1927).

TABLE I

DIHYDROCHLORIDES OF ESTERS OF 4-FLUOROISOPHTHALIC ACID (4)F—C_6H_3^{COOR(1)}_{COOR(3)}·2HCl

R	Yield, %	Melting point, °C.	Nitrogen, % Calcd.	Found
Bis-(β-diethylaminoethyl)	82	181	6.30	6.20
Bis-(β-dipropylaminoethyl)	88	195	5.60	5.48
Bis-(β-dibutylaminoethyl)	79	165	4.94	5.00
Bis-(γ-diethylaminopropyl)	70	155	5.78	5.68
Bis-(γ-dipropylaminopropyl)	63	110	5.17	5.05
Bis-(γ-dibutylaminopropyl)	70	193	4.69	4.55

Bis-(dialkylaminoalkyl)-4-fluoroisophthalates.—These compounds were prepared according to the method of Kamm,[5] wherein the acid chloride was allowed to react with the calculated amount of the appropriate amino alcohol, using anhydrous benzene as the solvent. In the case of the higher alkamine esters, it was necessary to reflux the mixture for about thirty minutes to complete the reaction, but the lower members reacted almost immediately. After refluxing, the mixtures were cooled and the dihydrochlorides of the esters separated. All of the esters crystallized nicely from the reaction mixture. They were purified by recrystallization from alcohol–ether mixtures.

The yields and analytical data are in the accompanying table.

Summary

4-Fluoroisophthalic acid, 4-fluoroisophthalyl chloride, and six dialkylaminoalkyl esters of 4-fluoroisophthalic acid were prepared and their properties investigated. The hydrochlorides of this series possess no topical anesthetic effect, but the free bases are topical anesthetics. These compounds are less toxic than procaine.

(5) Kamm, THIS JOURNAL, **42**, 1030 (1920).

CHICAGO, ILLINOIS RECEIVED SEPTEMBER 2, 1943

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

Cinchona Alkaloids in Pneumonia. XII. Derivatives of 6'-Aminoapocinchonidine

BY A. G. RENFREW, W. W. CARLSON AND L. H. CRETCHER

A new type of cinchona derivative, in which an alkylamino- group replaces the phenolic hydroxyl of apocupreine, has been prepared by the use of the Bucherer reaction.[1,2] This study of cinchona derivatives containing an additional basic component was undertaken in view of the recognized importance of the basic nucleus in compounds which show antimalarial action. Findlay[3] remarks that "any reduction in the basic character of cinchona alkaloids or other synthetic antimalarial drugs" is associated with a reduction or total disappearance of activity. Buttle, *et al.*,[4] make a similar statement after testing a number of modified cinchonas in bird malaria. In a somewhat different application Glen, *et al.*,[5] prepared a series of quinolyl-(acridyl)- ethenes and found that an amino group in position-6 in the quinoline ring seemed to confer trypanocidal power in tests against *T. brucei*.

It was realized that attempts to enhance pharmacological action by multiplication of the active groupings within a molecule frequently lead actually to less effective compounds. As will be observed from examination of the results of biological studies, the new 6'-hydroxyethylaminoapocinchonidine (II) showed relatively low mouse

(1) Woroshtzow and Kogan, *Ber.*, **65**, 142 (1932); Roger Adams, "Organic Reactions," J. Wiley and Sons, Inc., New York, N. Y.

(2) A similar application of this reaction has been reported by L. Ach in the preparation of 6'-aminohydrocinchonine and 6'-aminohydrocinchonidine; German Patent 720,160; *C. A.*, **37**, 2020 (1943).

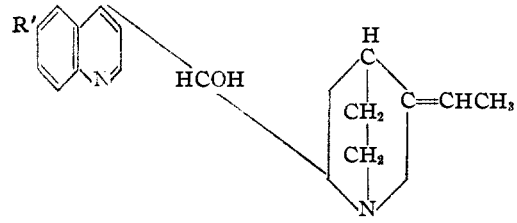
(3) Findlay, "Recent Advances in Chemotherapy," The Blakiston Co., Philadelphia, Pa., p. 115.

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

(5) Glen, Southerland and Wilson, *J. Chem. Soc.*, 654 (1938).

toxicity. However, the action against the pneumococcus was depressed.

The chemical procedure involving the replacement of the phenolic hydroxyl of apocupreine (I) was analogous to the studies of Woroshtzow and Kogan[1] with hydroxyquinoline. In the apocupreine series the loss of the 6′-hydroxyl group places the new compounds in the class of methoxyl-free levorotatory cinchonas; hence the new derivatives have been named as derivatives of apocinchonidine[6] and are related to the structural formula of apocupreine as shown below.



I. Apocupreine, R′ = HO
II. 6′-(β-Hydroxyethylamino)-apocinchonidine, R′ = $HOCH_2CH_2NH$
III. 6′-(β-Diethylaminoethylamino)-apocinchonidine, R′ = $(C_2H_5)_2NCH_2CH_2NH$—

The bacteriostatic action of the new compounds in tests *in vitro* against the pneumococcus and a report of the toxicity of these compounds for mice are presented in Table I. The antipneumococcal action of the 6′-alkylamino derivative was much less than the action of the corresponding oxygen ether, but it is interesting to note that the toxicity of β-hydroxyethylaminoapocinchonidine is of the same order as that of β-hydroxyethylapocupreine,[7,8] a lower toxicity than quinine itself.

TABLE I

BIOLOGICAL TESTING[a]

Compounds	Bacteriostasis against pneumococcus II, concn. of drug[b]	Intraperitoneal toxicity, approx. LD50[c]
β-Hydroxyethylapocupreine dihydrochloride	1:3 × 10^5	6–8 mg.[d]
6′-β-Hydroxyethylamino-apocinchonidine dihydrochloride (II)	1:0.5 × 10^5	6–7 mg.
6′-Diethylaminoethylamino-apocinchonidine acid *d*-tartrate (III)	Confluent growth at 1:0.5 × 10^5	2 mg.

[a] The biological testing was carried out by Drs. Bracken, Patrick, Maclachlan and Johnston of the Mercy Hospital, Pittsburgh, Pa. [b] This is the minimum concn. of drug effecting complete bacteriostasis *in vitro*. [c] Dose in milligrams for a 20 gram mouse. [d] LD_{50} for quinine is 5 mg.[8]

Experimental

6′-(β-Hydroxyethylamino)-apocinchonidine (II).—Preliminary studies were carried out in sealed glass tubes. A larger scale preparation, run in a steel cylinder, was handled in the following manner: 63 g. of apocupreine (0.2 mole) was stirred into a solution of 104 g. of sodium bisulfite (1 mole) in 600 cc. of water; 108 g. of ethanolamine (1.7 moles) was added. The cylinder was closed, adjusted for slow rocking and heated at 160° for fourteen hours. When cold, the product was obtained as a dense semicrystalline solid from which the aqueous solution was decanted. The solid was removed from the cylinder in alcoholic solution, recovered and freed from unchanged apocupreine by repeated solution in acid and precipitation in the presence of excess alkali. Finally the 6′-hydroxyethylaminoapocinchonidine was dissolved in 2 volumes of alcohol, ether was added to make a 1:1 alcohol–ether solution, and the solution was filtered from a small amount of a flocculent precipitate; 21 g. of base was recovered from the alcohol–ether solution: 30% of the theoretical yield. This product was again handled with acid, alkali and with alcohol-ether; 19 g. was recovered. The specific rotation in absolute alcohol was $[\alpha]_D$ −291°; α = −1.88°; c = 0.645; l = 1.

Anal. Calcd. for $C_{21}H_{27}O_2N_3$: N, 11.90. Found: N, 12.11.

The dihydrochloride, prepared in absolute alcohol, was an orange-colored salt, which crystallized from 1.5 volumes of absolute alcohol.

Anal. Calcd. for $C_{21}H_{27}O_2N_3 \cdot 2HCl$: N, 9.85; Cl, 16.66. Found: N, 9.5; Cl, 16.9.

Diethylaminoethylaminoapocinchonidine (III).—The preparation was carried out as above with the use of 93 g. of apocupreine (0.3 mole), 156 g. of sodium bisulfite in 800 cc. of water and 185 g. of diethylaminoethylamine (1.6 moles). The thick oily reaction product became granular when washed several times with ice-water. In chloroform solution the crude material was washed with alkali; then the alkaloidal base was recovered and purified as above. The yield was 43 g., or 37%. Ice was used in acidic solutions because the base seemed somewhat sensitive to mineral acids. The specific rotation in absolute alcohol was $[\alpha]_D$ −231°; α = −2.52°; c = 1.091; l = 1.

Anal. Calcd. for $C_{25}H_{36}ON_4$: N, 13.72. Found: N, 13.66.

Attempts to obtain a crystalline hydrochloride or sulfate were unsuccessful. The *d*-camphoric acid salt and the acid tartrate were isolated from alcoholic solutions of base and a molecular equivalent of the desired acid. The salts crystallized from concentrated alcoholic solutions. *Acid camphorate.* $[\alpha]_D$ −113°; α = −0.41°; c = 0.362; l = 1; aqueous solution.

Anal. Calcd. for $C_{25}H_{36}ON_4 \cdot C_{10}H_{16}O_4$: N, 9.2. Found: N, 9.5. *Acid tartrate.* $[\alpha]_D$ −150°; α = −0.70°; c = 0.464; l = 1; aqueous solution.

Anal. Calcd. for $C_{25}H_{36}ON_4 \cdot C_4H_6O_6$: N, 10.03. Tartaric acid, 26.8. Found: N, 10.08. Tartaric acid (by titration with NaOH), 26.6.

Summary

1. 6′-(β-Hydroxyethylamino)-apocinchonidine and 6′-diethylaminoethylaminoapocinchonidine have been prepared.

2. About the same mouse toxicity was observed for the β-hydroxyethyl group at the 6′-quinoline position of the cinchonas whether the linkage was through oxygen or through nitrogen. This toxicity is less than the toxicity of quinine itself.

3. In antipneumococcal value *in vitro* the 6′-β-hydroxyethylamino cinchona derivative was less effective than the corresponding oxygen derivative. 6′-Diethylaminoethylaminoapocinchonidine showed no action at the concentrations tested.

PITTSBURGH, PA. RECEIVED JUNE 29, 1943

(6) To prepare the alkylamino analogs of quinine or cupreine (*i. e.*, 6-alkylaminocinchonidines) by the present method, it would be necessary to apply the Bucherer reaction to naturally-occurring cupreine.

(7) Bracken, Johnston, Crum, Patrick, Permar and Maclachlan, *J. Pharmacol.*, **68**, 259 (1940).

(8) Renfrew and Cretcher, *Chem. Rev.*, **30**, 49 (1942).