of water and 2 ml. of ethanol was warmed with 0.6 g. of *p*-bromophenylhydrazine until the reagent dissolved, then placed in a vacuum desiccator over sulfuric acid and potassium hydroxide. After three days apparently colorless crystals which may have been the hydrazone were deposited. After an unsuccessful attempt to dissolve the crystals in warm ethanol the adhering gum was washed from them with liberal quantities of cold ethanol. The product which was now yellow melted at 224° after two recrystallizations from ethyl acetate. Votoček and Valentin[26] give 222–223° as the melting point of "*d*-rhamnose *p*-bromophenylosazone" and Freudenberg and Raschig[22] quote 225° for "*d*-chinovose *p*-bromophenylosazon."

Anal. Calcd. for $C_{18}H_{20}N_4O_3Br_2$ (500.21): N, 11.20. Found: N, 11.14, 11.22.

Acetylation of a small sample of the sugar with acetic anhydride in pyridine at 0° furnished only a water-insoluble oil which has so far not yielded crystalline material.

(26) Votoček and Valentin, *Compt. rend.*, **183**, 62 (1926).

We are indebted to Prof. Homer Adkins for providing facilities for the high pressure hydrogenation of the D-rhamnose.

Summary

The oxidation of D-rhamnitol by *Acetobacter suboxydans* was found to proceed normally to give crude D-fructomethylose sirup in 80% yield.

The behavior of the sugar with some standard carbohydrate reagents is described.

Recently reported physical constants of 6-desoxy-D-*arabo*-hexose phenylosotriazole are confirmed.

Methods are indicated by which purification of the crude sugar might be effected.

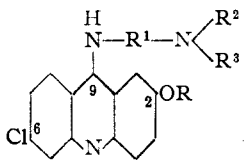
MADISON 6, WISCONSIN RECEIVED OCTOBER 6, 1947

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

The Hydroxyethyl Analog of Quinacrine

BY WARNER W. CARLSON AND LEONARD H. CRETCHER

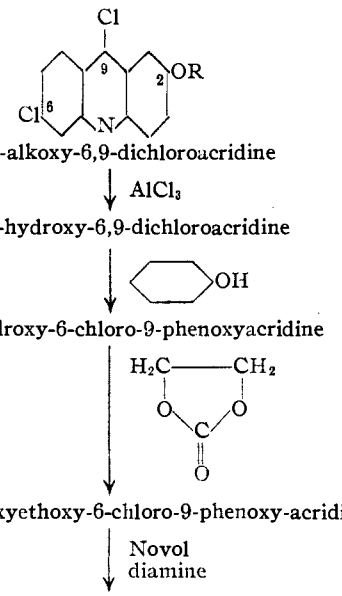
Modification of the host toxicity of quinacrine (I) was attempted by hydroxyalkylation at the



I. For quinacrine, R = CH_3—; $R^1{}_2$ = —$CH(CH_3)(CH_2)_3$—; R^2 = R^3 = C_2H_5—

2-position of the acridine ring. Literature reports were found of the introduction of the hydroxyl group into (a) the R_1 residue of the aliphatic side-chain,[1] (b) the terminal dialkylamino grouping,[2] and (c) one instance of hydroxylation of both R_1 and R_2 or R_3.[3] Introduction of a hydroxyl grouping into the R_1 residue was somewhat variable in effect, although generally there was a lowering of antimalarial activity unaccompanied by a compensating decrease in host toxicity.[1a,c] The presence of a hydroxyl group in the terminal dialkylamino grouping, either alone or in conjunction with another such radical in the R_1 residue, uniformly lowered antimalarial activity.[2b,3] No previous study was found of the effect of a hydroxyalkyl group at position 2.

The synthesis of the hydroxyethyl analog of quinacrine (VI) was accomplished as outlined in the accompanying diagram. The necessary intermediate II customarily is obtained by ring closure



II. 2-alkoxy-6,9-dichloroacridine

↓ $AlCl_3$

III. 2-hydroxy-6,9-dichloroacridine

↓ OH

IV. 2-hydroxy-6-chloro-9-phenoxyacridine

↓

V. 2-β-hydroxyethoxy-6-chloro-9-phenoxy-acridine

↓ Novol diamine

VI. 2-β-hydroxyethoxy-6-chloro-9-[(α-methyl-γ-diethylaminobutyl)-amino]-acridine

of an appropriately substituted diphenylamine carboxylic acid by means of phosphorus oxychloride,[4] this procedure precluding the presence of a hydroxyalkyl radical at this stage. Direct synthesis of the phenol III was unsatisfactory, while preparation of this compound by the action of various hydrolytic agents on II failed because of the lability of the 9-chloro substituent. Dealkylation of II by anhydrous aluminum chloride afforded the phenol III in good yield. Hydroxyethylation of III, or the 9-phenoxy derivative IV, was difficult because of the ease with which the 9-substituent split off to form an acridone

(1) (a) Cherntsov and Drozdov, *J. Gen. Chem. (U. S. S. R.)* **9**, 1435 (1939); (b) Magidson and Grigorovskii, *Ber.*, **69B**, 396 (1936); (c) Wiselogle, "Survey of Antimalarial Drugs," Vol. II, Part 2, J. W. Edwards, Ann Arbor, 1946, Compounds SN186, 5557, 5559, 5578 and 5545.

(2) (a) Burckhalter, Jones, Holcomb, and Sweet, THIS JOURNAL, **65**, 2012 (1943); (b) ref. 1(c), Compounds SN189, 845, 856, and 9616.

(3) Ref. 1(c), Compound SN5588.

(4) Mietzsch and Mauss, *Angew. Chem.*, **47**, 633 (1934).

VII. However, alkylation of IV with ethylene carbonate[5] proceeded smoothly, and the hydroxy ethyl ether V was obtained in good yield. Condensation of V with 1-diethylamino-4-aminopentane then gave the hydroxyethyl analog of quinacrine VI.

The chronic toxicity to white mice of quinacrine and its hydroxyethyl analog was determined by the drug-diet method.[6] The results obtained are listed in Table I, from which it is estimated that the 2-hydroxyethoxy derivative is approximately one-third as toxic as the parent 2-methoxy compound. Determined in another laboratory, the chronic toxicity of VI to white mice has been estimated to be one-half that of quinacrine.[7] In regard to antimalarial activity, the hydroxyethyl derivative has been assigned a quinine equivalent of two[7]; in the same test (F-1), quinacrine was given a quinine equivalent of three.[8]

Experimental

2-Ethoxy-6,9-dichloroacridine (II), as well as the **2-methoxy** derivative, was prepared according to Magidson and Grigorovskii[1b]; over-all yield, 76%.

2-Hydroxy-6,9-dichloroacridine (III).—De-alkylation of II, the 2-ethoxy derivative being preferred, was accomplished by a modification of the method of Magidson, Grigorovskii and Gal'perin.[9] One hundred grams of anhydrous aluminum chloride and 20 g. of II were dissolved and suspended in 300 cc. of xylene in a flask equipped for reflux and stirring. The mixture was heated at 135° (oil-bath temperature) for three-quarters of an hour, cooled, and poured (two liquid layers) into 1.5 liters of ice water containing 60 cc. of concentrated hydrochloric acid, the hydrochloride salt of III precipitating. The product was filtered, washed with ice water, then ether, and dried; yield, 95%. The hydrochloride was ground in aqueous-alcoholic ammonia and crystallized from alcohol, giving the free base (III), m. p. 222°; Magidson, *et al.*,[9] give m. p. 220–222°.

2-Hydroxy-6-chloro-9-phenoxy-acridine (IV).—In a few cases III was hydroxyethylated, but in general better yields were obtained with the 9-phenoxy derivative IV. Conversion of III into IV was accomplished by two methods: (a) by heating III free base in excess phenol at 100° for one hour, adding ether and then precipitating IV hydrochloride; (b) by heating III hydrochloride in phenol containing one mole equivalent of potassium hydroxide, yielding IV free base. Method (a) gave yields of 70–80%, (b) of 85–93%. In a typical reaction (b), 12 g. of III hydrochloride was dissolved in 60 g. of hot phenol containing 3.9 g. of 85% potassium hydroxide. The mixture was heated for one hour at 100°, cooled slightly, 100 cc. of toluene added, and the solution extracted with 500 cc. of 10% sodium hydroxide. The aqueous layer was filtered and treated with carbon dioxide until neutral to phenolphthalein. The precipitated IV was dissolved in acetone, the solution filtered, the IV free base reprecipitated by addition of water: m. p. 219–20°, yield 92%.

Anal. Calcd. for $C_{19}H_{12}O_2NCl$: C, 70.90; H, 3.76; N, 4.36; Cl, 11.03. Found: C, 70.72; H, 3.80; N, 4.25; Cl, 10.94.

2-β-Hydroxyethoxy-6-chloro-9-phenoxyacridine (V).—Because of the sensitivity of the 9-substituent an excess of the hydroxyethylating agent was used as solvent.[5] In a typical experiment a mixture of 8 g. of IV, 10.3 g. of potassium carbonate and 44 g. of ethylene carbonate[5] was heated with stirring for one and one-half hours at 95°, cooled slightly and poured into 200 cc. of ice water containing 40 cc. of concentrated hydrochloric acid, V partly separating as a gum. The acid solution was decanted from the gum and poured into excess cold alkali, precipitating 2.9 g. of V; a trace of IV was recovered from the filtrate by treatment with carbon dioxide. The gummy product from above was taken up in 50% alcohol–acetone, the solution filtered, made alkaline to phenolphthalein and diluted with water, precipitating the hydroxyalkylated base V. The two crops of V were combined and crystallized from aqueous acetone, giving 8.4 g. of yellow needles, m. p. 153°, yield 89%.

Anal. Calcd. for $C_{21}H_{16}O_3NCl$: C, 68.93; H, 4.41; N, 3.83; Cl, 9.70. Found: C, 68.74; H, 4.35; N, 3.71; Cl, 9.78.

2-β-Hydroxyethoxy-6-chloro-9-[(α-methyl-γ-diethylaminobutyl)-aminoacridine] (VI), SN3055.—In a typical preparation 3.65 g. (0.01 mole) of V was dissolved in 12 g. of hot phenol, 2.37 g. (0.015 mole) of 1-diethylamino-4-aminopentane was added, the solution was heated with stirring for two hours at 100°, then cooled to 40° and 10 cc. of ethanol added, followed by concentrated hydrochloric acid to congo red. Addition of 100 cc. of 50% acetone–ether precipitated a gum which was dissolved in alcohol; the solution was treated with acetone to turbidity and chilled, VI dihydrochloride separating as a light yellow powder, m. p. 250°; 3.8 g., 82%. From alcohol–ether it was obtained as clusters of pale yellow needles, m. p. 250°.

Anal. Calcd. for $C_{24}H_{34}O_2N_3Cl_3$: C, 57.30; H, 6.82; N, 8.36; Cl, 21.16. Found: C, 57.12; H, 6.75; N, 8.19; Cl, 20.98.

2-β-Hydroxyethoxy-6-chloro-9-acridone (VII).—This compound was obtained both as a by-product in the preparation of V and by the treatment of V for fifteen minutes with boiling 3 *N* alcoholic alkali, VII precipitating from solution upon dilution with water; crystallized from alcohol, m. p. >300°.

Anal. Calcd. for $C_{15}H_{12}NO_3Cl$: C, 62.16; H, 4.18; N, 4.83; Cl, 12.24. Found: C, 62.02; H, 4.15; N, 4.71; Cl, 12.29.

Toxicity of Atebrin and VI.—Estimation of the chronic toxicity to white mice of atebrin and its hydroxyethyl analog (VI) was carried out essentially as described by Bratton.[6b] The two drugs as dihydrochlorides were prepared in powdered Purina dog chow. The drug-diets were placed in the inner member of a double food cup; spilled food thus could be recovered. After being air-dried and sifted from extraneous material recovered diet was weighed and allowance accordingly made in estimating food intake. Male white mice in the weight range 15–20 g. were employed, and the experiment continued for

TABLE I

CHRONIC TOXICITY TO MICE OF QUINACRINE AND ITS HYDROXYETHYL ANALOG

No. mice	Drug in diet, %	Diet intake, g./kg./day	Drug intake, g./kg./day	Dead/total in two weeks	Average day of death	Weight change, %
			Atebrin			
10	0.15	153	0.230[a]	1/10	13	−20
10	.30	135	.405	5/10	11.6	−34
			Hydroxyethyl Analog			
10	0.30	163	0.489	0/10		−14
10	.45	151	.680[a]	1/10	9	−24
			Controls			
5		201		0/10		+18

[a] Maximum tolerated intake.

(5) Carlson and Cretcher, THIS JOURNAL, **69**, 1952 (1947).

(6) (a) Litchfield, White and Marshall, *J. Pharmacol.*, **67**, 441 (1939); (b) Bratton, *ibid.*, **85**, 111 (1945).

(7) Ref. 1(c), Compound SN3055.

(8) Ref. 1(c), Compound SN390.

(9) Magidson, Grigorovskii and Gal'perin, *J. Gen. Chem.* (*U. S. S. R.*), **8**, 56 (1938).

two weeks, the animals being weighed at frequent intervals. The results are given in Table I.

Summary

The 2-β-hydroxyethyl analog of quinacrine was synthesized and its chronic toxicity to white mice, as determined by the drug diet method, found to be one-third that of the parent drug.

PITTSBURGH 13, PA. RECEIVED SEPTEMBER 22, 1947

[CONTRIBUTION FROM THE PURDUE RESEARCH FOUNDATION AND THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

Synthesis of Chromans from Phenols and from ortho-Hydroxy Aromatic Aldehydes[1,2]

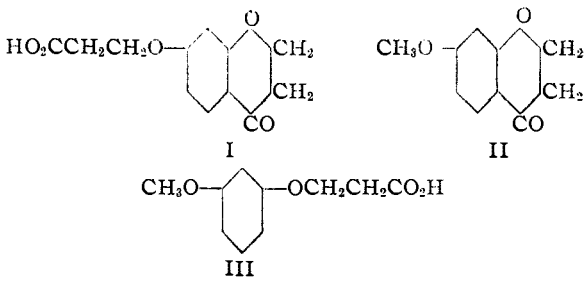
BY G. BRYANT BACHMAN AND HAROLD A. LEVINE[3]

The success of the recently developed synthesis of benzo[f]chromanones by cyclization of β-naphthoxypropionitriles obtained from addition of β-naphthols to acrylonitrile[4] suggested a study of the application of this method to other phenols, especially those in the benzene series. From phenol itself 3-phenoxypropionitrile[5] was obtained in good yield, but a series of cyclization experiments gave only traces of impure ketonic material or no reaction. *p*-Nitrophenol and methyl salicylate did not add, and *o*- and *p*-chlorophenols added only slowly to acrylonitrile. Apparently, electron-withdrawing groups on the benzene nucleus hinder the addition. Even 6-bromo-2-naphthol gave poor yields (10%) of 3-(6′-bromo-2′-naphthoxy)-propionitrile. This cyclized satisfactorily, however, in the presence of sulfuric acid to 8-bromo-1-benzo[f]chromone.

The presence of electron-supplying groups on the benzene ring apparently increases the ease of addition of phenolic hydroxyl groups to acrylonitrile but does not necessarily increase the ease of cyclization of the product because of an increased tendency of such compounds to sulfonate. Resorcinol gives a dinitrile[5] in 40% yields, but treatment with cyclizing agents gives poor yields of a monocyclized product, 7-(2′-carboxy-ethoxy)-chromanone (I). Resorcinol monomethyl ether gives a nitrile in 76% yield. With 85% sulfuric acid this cyclizes to the expected 7-methoxy-chromanone (II),[6] while with 85% phosphoric acid the uncyclized 3-(3′-methoxyphenoxy)-propionic acid (III)[6] is obtained.

In all of these reactions sulfonation and phosphorylation led to considerable amounts of water-soluble, ether-insoluble products which were not investigated. The desired products were obtained in poor yields.

An alternative preparation of derivatives of chroman based on the addition of the hydroxyl group of salicylaldehyde to acrylonitrile followed by an aldol cyclization was also investigated.



When salicylaldehyde was heated in an excess of acrylonitrile in the presence of dimethylbenzyl-cetyl-ammonium hydroxide (Triton B) as a catalyst, reaction proceeded to only a limited extent. Three crystalline products were isolated from the alkali-insoluble fraction of the reaction mixture in yields of 1–2%. These compounds were identified by qualitative tests and analytical data as 2-(β-cyanoethoxy)-benzaldehyde (IV), 3-cyano-4-chromanol (V), and 3-cyano-1,2-benzopyran (VI). Attempts to increase the yield of V by the use of other condensation catalysts were unsuccessful. When the condensation was carried out at 100° with Triton B as a catalyst, there was a marked increase in the amount of alkali-insoluble product, but pure V could not be isolated. 3-Aminomethyl-4-chromanol (VII) was prepared by reduction of V in acetic anhydride with platinum oxide catalyst,[7] followed by hydrolysis with methanolic sodium hydroxide.

A second synthesis of derivatives of chroman from salicylaldehyde was also developed. The base catalyzed addition of salicylaldehyde to an aliphatic primary nitroölefin followed by an aldol-type of cyclization gives both the nitroalcohol (VIII) and the nitroölefin (IX) of the expected structures. β-Chloronitroparaffins prepared according to the method of Riley[8] were used as sources of the nitroölefins. The two reactions may be accomplished in one step by condensing the chloronitroparaffin with the sodium salt of salicylaldehyde. Of the three chloronitroparaffins tried, 2-chloro-1-nitroethane, 1-chloro-2-nitropropane and 2-chloro-1-nitropropane, only the last gave the desired products. The others gave polymeric material. This result was not unexpected since the intermediate nitroölefins of the type

(1) From the Ph.D. thesis of H. A. Levine, Purdue University, February, 1947.

(2) The assistance of Mr. A. Karler in many of these experiments is gratefully acknowledged.

(3) Present address: Neurological Institute of New York, New York, N. Y.

(4) Bachman and Levine, THIS JOURNAL, **69**, 2341 (1947).

(5) Cook and Reed, *J. Chem. Soc.*, 920 (1945).

(6) Pfeiffer and Oberlin, *Ber.*, **57**, 208 (1924).

(7) Carothers and Jones, THIS JOURNAL, **47**, 3051 (1925).

(8) McBee and Riley, U. S. Patent 2,337,912 (Dec. 28, 1943).