[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF WASHINGTON UNIVERSITY]

Some New Local Anesthetics Containing the Morpholine Ring. III. Esters of 2-Alkoxycinchoninic Acids

BY JOHN H. GARDNER AND WARREN M. HAMMEL

Extending the investigation of esters of morpholine alcohols as local anesthetics,[1] a series of esters of 2-alkoxycinchoninic acids has been prepared. These compounds are analogs of the series of alkamine esters prepared from diethylaminoethyl alcohol and 2-alkoxycinchoninic acids by Wojahn.[2]

In this investigation, β-4-morpholineethanol and γ-4-morpholinepropanol were prepared by the method of Gardner and Haenni.[1] 2-Chlorocinchoninic acid was prepared by the method of Camps[3] and this was converted into a series of 2-alkoxycinchoninic acids by reaction with solutions of sodium alcoholates in the corresponding alcohol.[3] From these, the acid chlorides, esters and finally the ester hydrochlorides were prepared.

These ester hydrochlorides have been found to show local anesthetic action when tested on the tongue, but no pharmacological measurements have been made.

Experimental

2-Alkoxycinchoninic Acids.—Methoxy, ethoxy, *n*-propoxy and *n*-butoxycinchoninic acids were prepared. To a solution of sodium in the alcohol, using 40 cc. of alcohol per gram of sodium there was added twice the weight of sodium of 2-chlorocinchoninic acid. The solution was boiled a half hour. The alcohol was evaporated and the residue dissolved in water. Dilute hydrochloric acid was added to the filtered solution to precipitate the 2-alkoxycinchoninic acid. This was filtered out, dried and crystallized from benzene. Yields and properties of the individual acids are given in Table I.

TABLE I

Cinchoninic acid	Yield, %	M. p.,[4] °C.	M. p. (Literature), °C.
2-Methoxy	77	177–178	178–179[a]
2-Ethoxy	82	142.2–143.8	145–146[b]
2-*n*-Propoxy	63	138–139.4	136[b]
2-*n*-Butoxy	60	96.6–97.6	111[b,c]

[a] Mulert, *Ber.*, **39**, 1901 (1906). [b] Ref. 2. [c] *Anal.* Calcd. for $C_{14}H_{15}O_3N$: C, 68.54; H, 6.17. Found: C, 68.35; H, 6.27.

2-Alkoxycinchoninyl Chlorides.—To solutions of the alkoxycinchoninic acids in benzene, using about 7 cc. of benzene per gram of the acid, there was added 4 to 5 g. of thionyl chloride per gram of the acid. The mixture was heated at 55–60° for ten minutes. After cooling, the benzene solution was filtered and the insoluble portion, which was largely 2-alkoxycinchoninic acid hydrochloride, washed well with benzene. The benzene solution was evaporated to dryness in a vacuum desiccator, the residue extracted with ligroin and the filtered ligroin solution evaporated to dryness in a vacuum desiccator. Yields, melting points and analyses of the individual acid chlorides are given in Table II.

TABLE II

Cinchoninyl chloride	Yield, %	M. p., °C.	Analyses, % Calcd. C	Calcd. H	Found C	Found H
2-Methoxy	43	45.6–6.5	59.59	3.64	59.79	3.65
2-Ethoxy	41	86–86.5	61.14	4.28	61.47	4.46
2-*n*-Propoxy	51	54–55	62.51	4.85	62.38	4.77
2-*n*-Butoxy	37	35.5–7.5	63.74	5.35	64.95	5.57[a]

[a] Probably not obtained entirely pure.

Morpholinealkyl 2-Alkoxycinchoninates.—To a solution of the alkoxycinchoninyl chloride in about eight times its weight of benzene there was added, with stirring, a slight excess of the morpholine alcohol dissolved in a small volume of benzene. The mixture was heated to 60° for one and a half hours, cooled and filtered. The benzene solution was extracted with dilute hydrochloric acid. The

TABLE III

Ester	M. p., °C.	Analyses, % Calcd. C	Calcd. H	Found C	Found H
β-4-Morpholineethyl ( )-cinchonate					
2-Methoxy	Oil	64.52	6.38	64.39	6.49
2-Ethoxy	44–6	65.42	6.72	65.69	6.93
2-*n*-Propoxy	Oil	66.24	7.03	66.26	7.11
2-*n*-Butoxy	Oil	67.00	7.32	66.91	7.30
γ-4-Morpholinepropyl ( )-cinchonate					
2-Methoxy	Oil	65.42	6.72	65.50	6.77
2-Ethoxy	57–8	66.24	7.03	66.85	7.08
2-*n*-Propoxy	Oil	67.00	7.32	66.72	7.27
2-*n*-Butoxy	Oil	67.70	7.58	67.73	7.53

TABLE IV

Hydrochloride	Yield, %	M. p., °C.	Cl Analyses, % Calcd.	Found
β-4-Morpholineethyl ( )-cinchoninate				
2-Methoxy	54	198–9	10.05	9.70
2-Ethoxy	27	147.0–6	9.67	10.35
2-*n*-Propoxy	54	150.6–1.2	9.31	9.19
2-*n*-Butoxy	45	150.5–1.4	8.98	9.25
γ-4-Morpholinepropyl ( )-cinchoninate				
2-Methoxy	81	155–60	9.67	9.91
2-Ethoxy	90	157	9.31	9.31
2-*n*-Propoxy	55	174.7–5.6	8.98	9.24
2-*n*-Butoxy	73	149.2–6	8.68	8.54

(1) Gardner and Haenni, THIS JOURNAL, **53**, 2763 (1931); Gardner, Clarke and Semb, *ibid.*, **55**, 2999 (1933).

(2) Wojahn, *Arch. Pharm.*, **269**, 422 (1931).

(3) Camps, *ibid.*, **237**, 659 (1899).

(4) All melting points in this paper are corrected.

solid precipitate which had collected on the filter was dissolved in a small amount of water and this solution was added to the hydrochloric acid extract. The ester was precipitated by the addition of sodium carbonate. Melting points and analyses of the individual esters are given in Table III.

Morpholinealkyl 2-Alkoxycinchoninate Hydrochlorides.—Solutions of the esters in benzene were treated with the calculated quantity of a benzene solution of hydrogen chloride. The mixture was allowed to stand for several hours and the precipitated hydrochloride was filtered out, washed with benzene and dried in a desiccator. Yields, melting points and analyses of the individual compounds are given in Table IV.

Summary

1. Eight new morpholinealkyl esters of 2-alkoxycinchoninic acids and their hydrochlorides have been prepared.

2. The hydrochlorides are local anesthetics.

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

Chemical Studies of the Mechanism of the Narcosis Induced by Hypnotics. II. The Synthesis of Colored Derivatives of Phenobarbital[1]

BY ALAN E. PIERCE AND MARY M. RISING

The pharmacological and histological study of of a hypnotic which shows the property of selectively staining nerve cells may be found to give insight into the mechanism of hypnosis. With the synthesis of such a dye-hypnotic as an object, the work described in this paper consisted of the preparation of several colored derivatives of phenobarbital, or 5-phenyl-5-ethylbarbituric acid, $(C_6H_5)(C_2H_5)\underline{C}\underline{CONHCONHCO}$, which is itself a white compound. Several investigators[2] have attempted the preparation of physiologically active, colored derivatives of cocaine or procaine with varying degrees of success. It was hoped that phenobarbital would also be suitable for such a study.

In the first paper of this series,[3] the syntheses of four dye derivatives of phenobarbital by means of coupling diazotized 5-*m*-aminophenyl-5-ethylbarbituric acid with various phenolic compounds separately were described. Not one of these products, however, exhibited satisfactory hypnotic properties.

In the present investigation two colored derivatives of phenobarbital were prepared by the coupling of diazotized 5-*m*-aminophenyl-5-ethylbarbituric acid with *m*-phenylenediamine to form 5-*m*-(2,4-diaminophenylazo)-phenyl-5-ethylbarbituric acid, $(NH_2)_2C_6H_3N{=}NC_6H_4(C_2H_5)\underline{C}\underline{CONHCONHCO}$, and with 5-*m*-hydroxyphenyl-5-ethylbarbituric acid to form *x*-hydroxyazobenzene-*x*,3′-bis-(5-ethylbarbituric acid), $\underline{CONHCONHCOC}(C_2H_5)C_6H_4{-}N{=}N{-}(OH)C_6H_3(C_2H_5)\underline{C}\underline{CONHCONHCO}$. A third colored derivative is *m*-diazoamino-5-phenyl-5-ethylbarbituric acid, $\underline{CONHCONHCOC}(C_2H_5)C_6H_4{-}N{=}N{-}NHC_6H_4(C_2H_5)\underline{C}\underline{CONHCONHCO}$. In this synthesis it was hoped by means of linking two ureide nuclei to ensure the preservation of the physiological effect of phenobarbital.

In addition to 5-*m*-nitrophenyl-5-ethylbarbituric acid, obtained by the nitration of phenobarbital, the para nitro compound was isolated in small quantity and identified, but was not used in the syntheses.

For the pharmacological study of the compounds prepared in this work the writers are indebted to several investigators. The work was done in part by Dr. A. L. Tatum, Professor of Pharmacology, University of Wisconsin, and in part by Dr. H. A. Shonle and Mr. E. E. Swanson of the Eli Lilly Company, Indianapolis. Intraperitoneal administration of the sodium salts of the various compounds to rabbits and white mice produced no sedative action without undesirable effects. Neither the three colored compounds nor 5-*m*-hydroxyphenyl-5-ethylbarbituric acid were effective in sub-lethal doses. The 5-*p*-nitrophenyl-5-ethylbarbituric acid was not tested, since the meta isomer has been found to be physiologically inert.[4]

Experimental

5-*m*-Nitrophenyl-5-ethylbarbituric Acid.—The method of Bousquet and Adams[4] was followed in the nitration of

(1) This article is abstracted from the dissertation presented by Alan E. Pierce in partial fulfilment of the requirements for the degree of Doctor of Philosophy at the University of Chicago.

(2) (a) Ehrlich and Einhorn, *Ber.*, **27**, 1872 (1894); (b) Fulton, *Am. J. Physiol.*, **57**, 158 (1921); (c) Gardner and Joseph, THIS JOURNAL, **57**, 901 (1935).

(3) Rising, Shroyer and Stieglitz, *ibid.*, **55**, 2818 (1933).

(4) Bousquet and Adams, *ibid.*, **52**, 224 (1930).