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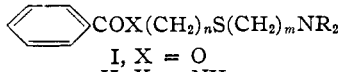
Sulfur-Containing Amines. VII.[1] Local Anesthetics. II

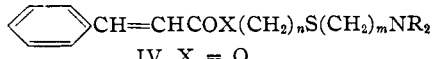
BY R. O. CLINTON, U. J. SALVADOR AND S. C. LASKOWSKI

A logical extension of local anesthetic type compounds derived from the 4-aminobenzoyl nucleus and sulfur-containing amines[2] is to analogous types containing other parent nuclei. Gilman, *et al.*,[3] have shown, in a correlation of therapeutic activity with aromaticity, that the dialkylaminoalkyl esters of cinnamic acid are more effective than the corresponding benzoate esters; this observation has been extended by McElvain[4] to a series of methylpiperidinoalkyl benzoates and cinnamates. In the latter series it was shown that activity was highest with the cinnamates; however, in general, toxicity was found to increase proportionally. It is also interesting to note in this connection that Gardner, *et al.*,[5] have succeeded in lowering toxicity with retention of activity in the cinnamate series, through the use of esters containing the terminal morpholine group.

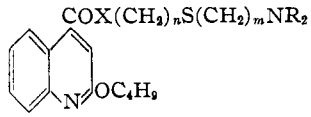
The present report describes a representative series of benzoates (I), benzamides (II–III), cinnamates (IV), cinnamamides (V, VI) and 2-butyloxycinchonyl derivatives (VII, VIII) derived from



I, X = O
II, X = NH
III, X = NC_2H_5



IV, X = O
V, X = NH
VI, X = NC_2H_5



VII, X = O
VIII, X = NH

certain of the sulfur-containing amines previously reported,[6] with the purpose of ascertaining whether the high therapeutic index associated with the related 4-aminobenzoyl types[2] could be extended to non-aminated nuclei. Compounds of types VII and VIII were of especial interest, since they contain the parent nucleus of the very active but very toxic substance, Dibucaine.

All of the above compounds were prepared by standard procedures with little difficulty. The pharmacological results will be reported upon by Dr. T. J. Becker and Dr. F. P. Luduena of these Laboratories at a later date. In general, it may be stated here that most of the compounds were of a low order of activity.

Experimental[7]

Esters and Amides, I–VI.—The esters were prepared from a slight excess of acid chloride and the appropriate alcohol[6] in cold dry benzene, and the amides from an excess of acid chloride and the amine[6] in chloroform–water mixture in the presence of sodium bicarbonate, with due precautions to avoid decomposition of the amines.[2] In general the bases were isolated in the usual manner and purified by washing with dilute sodium hydroxide solution. In certain cases distillation was necessary to provide bases suitable for conversion to salts. The yields varied from 80–95%.

1-(2-Dimethylaminoethylmercapto)-propyl-2 benzoate hydriodide, I, cottony white needles from isopropyl alcohol, m. p. 119.5–120.8°.

Anal. Calcd. for $C_{14}H_{22}INO_2S$: S, 8.11; HI, 32.36. Found: S, 8.25; HI, 32.70.

2-(3-(Piperidyl-1)-propylmercapto)-ethyl benzoate hydriodide, I, white needles from absolute alcohol, m. p. 116.0–117.5°.

Anal. Calcd. for $C_{17}H_{26}INO_2S$: S, 7.36; HI, 29.38. Found: S, 7.42; HI, 29.24.

3-(3-(Piperidyl-1)-propylmercapto)-propyl benzoate, I, pale yellow viscous oil, b. p. 147–148° at 0.05 mm.

Anal. Calcd. for $C_{18}H_{27}NO_2S$: N, 4.35; S, 9.97. Found: N, 4.35; S, 9.74.

The **citrate** formed rosettes of small white needles from absolute alcohol–acetone, m. p. 68.3–70.5°.

Anal. Calcd. for $C_{24}H_{35}NO_9S$: S, 6.24; N, 2.72. Found: S, 6.08; N, 2.85.

2-(3-(Piperidyl-1)-propylmercapto)-ethyl cinnamate hydrochloride, IV, small white needles from isopropyl alcohol, m. p. 131–134°.

Anal. Calcd. for $C_{19}H_{28}ClNO_2S$: S, 8.66; Cl, 9.58. Found: S, 8.68; Cl, 9.57.

N-(2-(2-Diethylaminoethylmercapto)-ethyl)-benzamide citrate, II, small white needles from absolute alcohol–ethyl acetate, m. p. 118–121°.

Anal. Calcd. for $C_{21}H_{32}N_2O_8S$: N, 5.93; S, 6.78. Found: N, 5.75; S, 6.80.

N-(2-(2-(Piperidyl-1)-ethylmercapto)-ethyl)-benzamide hydrochloride, II, needles from absolute alcohol–acetone, m. p. 118–120°.

Anal. Calcd. for $C_{16}H_{25}ClN_2OS$: S, 9.74; Cl, 10.78. Found: S, 9.78; Cl, 10.85.

N-(2-(2-Diethylaminoethylmercapto)-ethyl)-cinnamamide citrate, V, rosettes of white prisms from absolute alcohol–ethyl acetate, m. p. 82.5–85.0°.

Anal. Calcd. for $C_{23}H_{34}N_2O_8S$: N, 5.62; S, 6.43. Found: N, 5.45; S, 6.36.

N-Ethyl-N-(2-(2-Diethylaminoethylmercapto)-ethyl)-benzamide hydrochloride, III, white needles from ethyl acetate–Skellysolve B, m. p. 101.6–102.6°.

Anal. Calcd. for $C_{17}H_{29}ClN_2OS$: N, 8.07; S, 9.24. Found: N, 8.12; S, 9.40.

N-Ethyl-N-(2-(2-Diethylaminoethylmercapto)-ethyl)-cinnamide hydrochloride, VI, prisms from acetone–Skellysolve A, m. p. 105.2–107.6°.

(1) Paper VI: Fohlen, Huber, Laskowski and Clinton, THIS JOURNAL, **71**, 642 (1949).

(2) Clinton, Salvador, Laskowski and Suter, *ibid.*, **70**, 950 (1948).

(3) Gilman, *et al.*, *ibid.*, **47**, 245 (1925); **50**, 437 (1928).

(4) (a) McElvain, *ibid.*, **49**, 2835 (1927); (b) Bailey and McElvain, *ibid.*, **52**, 2007 (1930).

(5) Gardner, Clarke and Semb, *ibid.*, **55**, 2999 (1933).

(6) (a) Clinton, *et al.*, *ibid.*, **67**, 594 (1945); (b) Laskowski and Clinton, *ibid.*, **69**, 519 (1947).

(7) All melting points and boiling points are corrected. The authors are indebted to Mr. Morris E. Auerbach and staff for the analyses.

Anal. Calcd. for $C_{19}H_{31}ClN_2OS$: N, 7.51; Cl, 9.50. Found: N, 7.38; Cl, 9.64.

2-Butyloxyquinoline-4-carboxylic Acid Derivatives.—These compounds were readily prepared from 2-butyloxyquinoline-4-carbonyl chloride[8] and the amine or alcohol in dry benzene.

2-(2-Diethylaminoethylmercapto)-ethyl 2-butyloxyquinoline-4-carboxylate hydrochloride, VII, white leaflets from ethyl acetate, m. p. 125.8–127.0°.

Anal. Calcd. for $C_{22}H_{33}ClN_2O_3S$: N, 6.35; Cl, 8.04. Found: N, 6.20; Cl, 8.03.

2-(3-(Piperidyl-1)-propylmercapto)-ethyl 2-butyloxyquinoline-4-carboxylate hydrochloride, VII, waxy white needles from isopropyl alcohol, m. p. 118.4–120.4°.

Anal. Calcd. for $C_{24}H_{35}ClN_2O_3S$: N, 6.01; Cl, 7.61. Found: N, 6.01; Cl, 7.56.

N-(2-(2-Diethylaminoethylmercapto)-ethyl 2-butyloxyquinoline-4-carboxamide, VIII, long slender white needles from Skellysolve B, m. p. 63.5–64.5°.

Anal. Calcd. for $C_{22}H_{33}N_3O_2S$: N, 10.41; S, 7.94. Found: N, 10.31; S, 8.08.

The **citrate** formed tiny white prisms from absolute alcohol–ethyl acetate, m. p. 87.5–90.5° (dec.).

Anal. Calcd. for $C_{28}H_{41}N_3O_9S$: N, 7.05; S, 5.38. Found: N, 6.83; S, 5.22.

(8) Gardner and Hammel, THIS JOURNAL, **58**, 1360 (1936), report 37–51% yields of 2-alkoxycinchonyl chlorides, with accompanying by-products of the 2-alkoxycinchoninic acid hydrochloride. Modification of their procedure, by inclusion of a one hour reflux period of the acid–thionyl chloride–benzene mixture, increased the yields of acid chlorides to 95–97%, with no formation of 2-alkoxycinchoninic acid hydrochloride.

Summary

There has been described the preparation of a series of esters and amides derived from sulfur-containing amines.

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A Family of Long-Acting Depressors[1,2]

BY RICHARD BALTZLY, JOHANNES S. BUCK,[3] EDWIN J. DE BEER AND FREDERICK J. WEBB[4]

Some years ago Ide and Buck[5] prepared a number of N-methyltetrahydro*iso*quinolines by the cyclization of the appropriate N-methylphenethylamines with formalin and hydrochloric acid. A pharmacological study was performed by Fassett and Hjort,[6] who found all but one member of this group to be weak pressors or depressors with transient action, while 6-ethoxy-N-methyltetrahydro*iso*quinoline was an extremely potent depressor with a long period of action. While correlation of physiological action with chemical structure is on essentially an empirical basis at present, such correlation within classes of related compounds usually is fairly good. It was therefore felt that the physiological results cast grave doubt on the purity and identity of this sample of 6-ethoxy-N-methyltetrahydro*iso*quinoline.

An authentic specimen of 6-ethoxy-2-methyltetrahydro*iso*quinoline hydrochloride was prepared by an alternative route.[7] The new sample had none of the remarkable physiological activity of the older specimen. Further fractionation of material prepared according to the formalin procedure afforded a sample more nearly resembling the authentic (new) specimen. De-ethylation of the original material also yielded a sample of 6-hydroxy-N-methyl tetrahydro*iso*quinoline hydrochloride identical with an authentic specimen of this substance. It was thus evident that the Ide and Buck material was preponderantly 6-ethoxy-N-methyl tetrahydro*iso*quinoline hydrochloride contaminated by a small amount of a highly potent depressor substance whose physical properties and composition were not markedly different from those of the major component.

A number of formalin cyclizations of 3-ethoxyphenethylmethylamine followed by attempts to fractionate the reaction products gave rather irregular results. Usually such preparations, like the original one, produced strong, lasting depression of blood pressure when administered intravenously to anesthetized dogs in doses of 1 mg./kg. body weight. One specimen, a chloroform-insoluble hydrochloride obtained by successive precipitations from chloroform solution by ethyl acetate, was about four times as active.

Serious progress in elucidating the nature of the unknown depressor was not made until a change in the amine under study was effected. Cyclization of a phenethylamine to a tetrahydroisoquinoline by the formalin–hydrochloric acid procedure is effective only when there is an activating group para to the cyclization-point. Ortho and para methoxyphenethylmethylamines are not cyclized by this method. When these amines were treated by the usual procedure, however, the products were by far the most active depressors so far obtained. It was now possible to secure a fall in the blood-pressure of 100 mm. of mercury lasting for an hour or more with doses of the

(1) Presented before the Division of Medicinal Chemistry of the American Chemical Society, Washington Meeting, August, 1948.

(2) The work here reported is part of a project carried out in collaboration with a pharmacological group in these laboratories headed successively by A. M. Hjort and E. J. de Beer. The detailed pharmacological study will be published separately.

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(4) Present address: Firestone Rubber Co., Akron, Ohio.

(5) Ide and Buck, THIS JOURNAL, **59**, 726 (1937).

(6) Fassett and Hjort, *J. Pharmacol. Exptl. Therap.*, **63**, 253 (1938).

(7) Hjort, de Beer, Buck and Randall, *ibid.*, **76**, 64, 252 (1942).