urethan group is more active than the *p*-aminobenzoate in causing anesthesia of mucous surfaces.

Summary

Improved procedures have been described for the preparation of 1,4-dihydronaphthalene and the corresponding chlorohydrin and oxide. Several amino alcohols have been synthesized from the two latter compounds and the benzoyl, *p*-nitrobenzoyl, *p*-aminobenzoyl, and phenylcarbamyl esters of these alkamines have been made. Several of these esters show local anesthetic activity and 2-diethylamino-1,2,3,4-tetrahydronaphthalene-3-phenylurethan is especially active.

NEW HAVEN, CONN. RECEIVED MAY 24, 1940

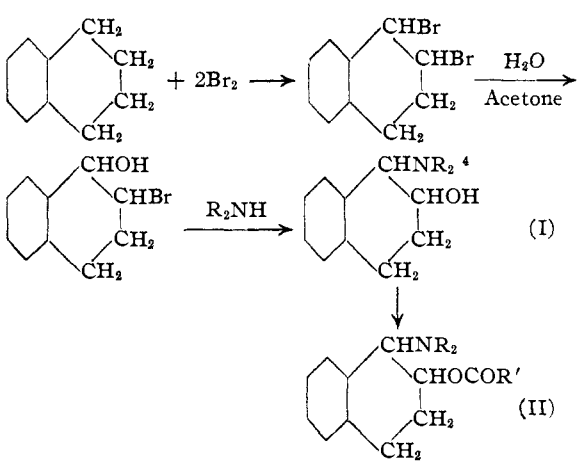
[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY OF YALE UNIVERSITY]

Local Anesthetics Derived from Tetrahydronaphthalene. II. Esters of 1-Dialkylamino-2-hydroxy-1,2,3,4-tetrahydronaphthalenes

BY ELTON S. COOK[1] AND ARTHUR J. HILL

In a previous paper[2] the authors described certain esters of 2-dialkylamino-3-hydroxy-1,2,3,4-tetrahydronaphthalenes. The local anesthetic properties of these compounds aroused interest in the isomeric 1-dialkylamino-2-hydroxy compounds and the present paper offers preliminary work in this series.

The following reactions, due essentially to von Braun and co-workers,[3] were employed in the synthesis of the alkamine esters:



Preliminary pharmacological tests on the benzoates and phenyl urethans show them to possess pronounced local anesthetic activity.

(1) Present address: Institutum Divi Thomae, Cincinnati, Ohio.

(2) Cook and Hill, THIS JOURNAL, **62**, 1995 (1940).

(3) (a) Von Braun and Kirschbaum, *Ber.*, **54**, 597 (1921); (b) v. Braun, Braunsdorf and Kirschbaum, *ibid.*, **55**, 3648 (1922); (c) Straus and Lemmel, *ibid.*, **46**, 232 (1913); and (d) Straus and Rohrbacher, *ibid.*, **54**, 40 (1921), have entered the series by preparing the dibromide from 1,2-dihydronaphthalene.

(4) Von Braun and Weissbach, *ibid.*, **63**, 3052 (1930), have shown that the 1-amino-2-hydroxy compound is formed, probably through the intermediate oxide.

Experimental Part

1,2-Dibromo-1,2,3,4-tetrahydronaphthalene and **1-hydroxy-2-bromo-1,2,3,4-tetrahydronaphthalene** were prepared from commercial tetralin according to the directions of v. Braun and Kirschbaum.[3a]

1-Dialkylamino-2-hydroxy-1,2,3,4-tetrahydronaphthalenes were prepared essentially according to Straus and Rohrbacher[3d] and our previous method.[2]

1-Diethylamino-2-hydroxy-1,2,3,4-tetrahydronaphthalene was obtained in 90% yield; b. p. 181° at 18 mm. (Straus and Rohrbacher[3d] give 166–167° at 12–13 mm.). *Anal.* Calcd. for $C_{14}H_{21}ON$: N, 6.39. Found: N, 6.25, 6.24.

1-Di-*n*-butylamino-2-hydroxy-1,2,3,4-tetrahydronaphthalene, b. p. 206–208° at 17 mm., was obtained in 65% yield. *Anal.* Calcd. for $C_{18}H_{29}ON$: N, 5.11. Found: N, 4.91, 4.96.

1-Piperidino-2-hydroxy-1,2,3,4-tetrahydronaphthalene was crystallized as needles from petroleum ether in a 90% yield; m. p. 74–75° (Straus and Rohrbacher[3d] give 73–74°). *Anal.* Calcd. for $C_{15}H_{21}ON$: N, 6.06. Found: N, 6.01, 5.98.

Benzoate Hydrochlorides.—The amino alcohol and two equivalents of benzoyl chloride were mixed, allowed to stand for forty-eight hours and heated on a steam-bath for three to five hours. The excess benzoyl chloride was removed with dry ether and the hydrochlorides were purified by adding dry ether to their solution in methyl alcohol or ethyl acetate.

1-Diethylamino-2-hydroxy-1,2,3,4-tetrahydronaphthalene benzoate hydrochloride was obtained in 86% yield as prismatic needles from ethyl acetate; m. p. 192–193°. *Anal.* Calcd. for $C_{21}H_{26}O_2NCl$: N, 3.89; Cl, 9.87. Found: N, 3.85, 3.90; Cl, 9.79, 9.90.

1-Piperidino-2-hydroxy-1,2,3,4-tetrahydronaphthalene benzoate hydrochloride was obtained in 90% yield as needles from methanol; m. p. 208–209°. Straus and Rohrbacher[3d] report a m. p. of 176.5–177.5°. *Anal.* Calcd. for $C_{22}H_{26}O_2NCl$: N, 3.76; Cl, 9.55. Found: N, 3.75, 3.67; Cl, 9.50, 9.45.

1-Piperidino-2-hydroxy-1,2,3,4-tetrahydronaphthalene benzoate was prepared (because of the discrepancy between the melting points of the hydrochloride). It was

obtained from the hydrochloride by treating an aqueous solution with dilute sodium hydroxide. It formed elongated prisms from absolute methanol and melted at 81–82°, the melting point given by Straus and Rohrbacher for the free base. *Anal.* Calcd. for $C_{22}H_{25}O_2N$: N, 4.18. Found: N, 4.10, 4.11.

Phenyl Urethans.—These were prepared by refluxing equimolecular quantities of the amino alcohol and phenyl isocyanate in dry benzene. They were crystallized from 95% ethyl alcohol. The hydrochlorides were purified by crystallization from ether–ethyl alcohol or ether–acetone.

1 - Diethylamino - 2 - hydroxy - 1,2,3,4 - tetrahydronaphthalene phenyl urethan was obtained in 90% yield; m. p. 104–104.5°. *Anal.* Calcd. for $C_{21}H_{26}O_2N_2$: N, 8.28. Found: N, 8.31, 8.27.

Hydrochloride, m. p. 206–206.5°. *Anal.* Calcd. for $C_{21}H_{27}O_2N_2Cl$: Cl, 9.48. Found: Cl, 9.39, 9.41.

1 - Piperidino - 2 - hydroxy - 1,2,3,4 - tetrahydronaphthalene phenyl urethan was obtained in 90% yield; m. p. 145–146°. *Anal.* Calcd. for $C_{22}H_{26}O_2N_2$: N, 8.00. Found: N, 7.89, 7.93.

Hydrochloride, m. p. 203–204°. *Anal.* Calcd. for $C_{22}H_{27}O_2N_2Cl$: Cl, 9.18. Found: Cl, 9.07, 9.10.

1 - Piperidino - 2 - hydroxy - 1,2,3,4 - tetrahydronaphthalene - *p* - nitrobenzoate Hydrochloride.—Equimolecular quantities of the amino alcohol and *p*-nitrobenzoyl chloride were heated together on a steam-bath for two hours after which dry benzene was added and refluxed for six hours. After removal of the benzene the solid was crystallized from ethyl acetate, giving small brownish plates, m. p. 238.5–239.5° (mixed m. p. with *p*-nitrobenzoic acid, 160–170°). *Anal.* Calcd. for $C_{22}H_{25}O_4N_2Cl$: N, 6.72. Found: N, 6.56, 6.60.

Summary

Several esters of 1-dialkylamino-2-hydroxy-1,2,3,4-tetrahydronaphthalenes have been prepared. These compounds possess local anesthetic properties.

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[CONTRIBUTION FROM THE STAMFORD RESEARCH LABORATORIES OF THE AMERICAN CYANAMID COMPANY]

Chemotherapy. I. Substituted Sulfanilamidopyridines[1]

BY RICHARD O. ROBLIN, JR., AND PHILIP S. WINNEK

The successful application of sulfapyridine[2] as a chemotherapeutic agent for the treatment of pneumococcal and other bacterial infections has led us to the preparation of a number of substituted sulfanilamidopyridines.[3] The properties of these compounds are summarized in Table I. Several interesting and unexpected effects on chemotherapeutic activity were observed when the substituents on the pyridine ring were varied in this series of closely related sulfanilamide derivatives. Since the inception of this work, two of the compounds, namely, 3-sulfanilamidopyridine and 5-sulfanilamido-2-aminopyridine, have been reported by Winterbottom.[4] However, they are included along with sulfapyridine for purposes of comparison, and because their chemotherapeutic activity has not been reported previously.

It was felt that the solubilities[5] should be investigated in order to furnish a comparison with the blood level data. Accordingly, the water solubility of all the compounds was determined at 37°. These data were obtained by heating and stirring an excess of the compound in question with water on a steam-bath for one-half hour. The suspension was then agitated in a thermostat for twenty-four hours at 37°. A sample of the saturated solution was withdrawn through a sintered glass filter into a bottle held at the same temperature. An aliquot of the saturated solution was then diluted and analyzed by means of the Marshall[6] method. A General Electric recording spectrophotometer was used in comparing the colors developed with those of the standards. While separate standards for each compound were prepared, it was soon found that by taking into account the differences in molecular weights, any one compound could serve as a standard for all.

Blood level studies[7] were carried out on practically all of the compounds. We believe that this information is fundamental to any attempt to correlate chemotherapeutic activity with molecular structure. It is obviously impossible to declare a compound inactive on any theoretical

(1) Presented in part before the Division of Medicinal Chemistry, Cincinnati meeting of the American Chemical Society, April 11, 1940.

(2) Whitby, *Lancet*, **1**, 1210 (1938); Evans and Gaisford, *ibid.*, **2**, 14 (1938); Long and Bliss, "The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds," The Macmillan Company, N. Y., 1939, p. 228–239.

(3) Nomenclature according to Crossley, Northey and Hultquist, THIS JOURNAL, **60**, 2217 (1938).

(4) Winterbottom, *ibid.*, **62**, 160 (1940).

(5) Solubility determinations were carried out by Mr. H. E. Faith in these Laboratories.

(6) Bratton and Marshall, *J. Pharmacol.*, **66**, 4 (1939). The preliminary trichloroacetic acid treatment employed in this procedure was eliminated, since only aqueous solutions were being studied.

(7) The pharmacological and bacteriological investigations were made in these Laboratories under the direction of Dr. W. H. Feinstone.