bromination of the side chain. The acid, after two recrystallizations from benzene, was in the form of white prisms, m.p. 95.0–96.0°.

Anal. Calcd. for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.33; H, 6.27.

The infrared spectrum (10% chloroform) of *o*-methoxymethylbenzoic acid contains the typical, broad bands attributable to a carboxylic acid function (3525, 1693 cm.$^{-1}$), as well as a strong band at 1114 cm.$^{-1}$

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An Improved Synthesis of *N*-Phenethylnormorphine and Analogs

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N-Phenethylnormorphine (Ia) has been prepared[2] by direct phenylethylation of normorphine and exhibits six to ten times the analgesic potency[3] of morphine. We have had occasion to prepare this compound for addiction studies and wish to report an improved method of synthesis.

In this method normorphine was converted to the *N*-phenylacetyl derivative which, without purification, was reduced to the tertiary amine (Ia) with ethereal lithium aluminum hydride.[4] The isolation of Ia from the reduction mixture (in 90% yield based on normorphine) was rendered simple by reason of the low water solubility of its hydrobromide salt.[5] By a similar sequence, norcodeine and dihydrodesoxynorcodeine-D (the latter prepared by cyanogen bromide *N*-demethylation of dihydrodesoxycodeine-D) were transformed into the corresponding *N*-phenethyl derivatives Ib and IIb. There was no complication in isolation of the bases from the reduction mixture since the phenolic hydroxyl is protected in these instances. Hydrobromic acid demethylation of *N*-phenethyldihydrodesoxynorcodeine-D (IIb) gave the phenolic congener (IIa).

The analgesic potency of IIa is five times that of dihydrodesoxymorphine-D (desomorphine), while the effectiveness of Ib and *N*-phenethylnorheterocodeine is twice that of the parent compounds. The duration of action of Ia and the corresponding heterocodiene derivative is about the same as seen in the parent compounds, while Ib and IIb are analgesic twice as long as the *N*-methyl counterparts. In all cases testing was done in mice.

EXPERIMENTAL

Microanalyses and most of the rotations were performed by the Institutes service analytical laboratory, Dr. William C. Alford, director.

N-Phenethylnormorphine (Ia). Normorphine hydrochloride (5 g.),[6] 8 g. of K_2CO_3, 30 ml. of water, and 80 ml. of methanol were treated (stirring) with 6 ml. (2.8 molar equivalents) of phenylacetyl chloride during 0.4 hr. After stirring for an additional 3 hr., the mixture was diluted with water and extracted three times with ethyl acetate. The combined extracts were washed with a little dilute HCl, dried and evaporated to thorough dryness *in vacuo*. The residue and 50 ml. of dry ether were treated (stirring) with 100 ml. of 1.5*M* ethereal $LiAlH_4$ at such a rate as to cause gentle refluxing (10–15 min.). The mixture was refluxed for 15 hr. and treated gradually (vigorous stirring) with 75 ml. of 48% HBr in 130 ml. of water. All inorganic material gradually dissolved leaving a viscous, ball-like mass which, on cooling, crystallized and was easily pulverized. Filtration gave the gummy hydrobromide which, in warm methanol, was converted to the base (Ia) by addition of dilute NH_4OH; yield 5.5 g. (90%), m.p. 250–253° (dec.); thin prisms from absolute ethanol, $[\alpha]_D^{20}$ −117° (c 0.84 in 2:1 $CHCl_3$-MeOH).

Anal. Calcd. for $C_{24}H_{25}NO_3$: C, 76.76; H, 6.71. Found: C, 76.95; H, 6.54.

The tartrate,[1] prepared from the base in refluxing 95% ethanol, melted at 144–147° (froth) alone or in mixture with authentic material[7] and had $[\alpha]_D^{20}$ −68.9° (c 0.99 in 50% by vol. ethanol); reported[1] $[\alpha]_D^{20}$ −67° (solvent not specified).

N-Phenethylnorcodeine hydrobromide (Ib). The reaction of phenylacetyl chloride (1.2 g.) with norcodeine hydrochloride (2 g.) was carried out as described for normorphine above. Reduction of the resultant amide (1.8 g.) with 20 ml. of 1.5*M* ethereal $LiAlH_4$ gave, after addition of 5–10 ml. of water and drying the ethereal filtrate, 1.5 g. of Ib. Acidification of an ether solution of this base with 33% HBr-AcOH yielded an amorphous hydrobromide which crystallized from acetone in prisms; yield 1.5 g., m.p. 273–275°. It was further purified by dissolving it in 225 ml. of boiling 95% ethanol, concentrating the solution to 50–75 ml. and cooling to 0°; m.p. 290–293° (dec.), $[\alpha]_D^{20}$ −97.0° (c 0.58 in MeOH-H_2O, 3:2).

Anal. Calcd. for $C_{25}H_{28}BrNO_3$: C, 63.83; H, 6.00. Found: C, 63.52, 63.46; H, 5.81, 5.95.

N-Phenethyldihydrodesoxynorcodeine-D hydrobromide (IIb). To 2.0 g. of cyanogen bromide (Eastman) in 13 ml. of dry chloroform was added (stirring) during 1 hr. 5.0 g. of dihydrodesoxycodeine-D[8] in 20 ml. of chloroform. The solution was refluxed for 3 hr. and evaporated to dryness *in vacuo*. The residue and 100 ml. of 6% HCl were refluxed overnight. Cooling and basification gave 4.5 g. of crude secondary base which was phenylacetylated as described for normorphine except that 2 molar equivalents of chloride was used. The amide in 50 ml. of dry ether was treated with 50 ml. of 1.5*M* ethereal $LiAlH_4$ during 10–15 min. and the mixture was refluxed overnight. After addition of 20 ml. of water (stirring)

(1) Deceased, June 1957.

(2) R. L. Clark, A. A. Pessolano, J. Weijlard, and K. Pfister, 3rd, *J. Am. Chem. Soc.*, **75**, 4963 (1953).

(3) C. A. Winter, P. D. Orahovats, and E. G. Lehman, *Arch. intern. pharmacodynamie*, **110**, 186 (1957); N. B. Eddy, unpublished.

(4) This procedure has been used successfully in preparing *N*-phenethyl analogs of synthetic analgesics, phenyl- and benzomorphans [E. L. May, *J. Org. Chem.*, **21**, 899 (1956); J. H. Ager and E. L. May, unpublished].

(5) In another set of experiments in which norheterocodeine was used, almost equally good yields of the *N*-phenethylnorheterocodeine could be obtained in the same fashion.

(6) Supplied by Merck & Co., Inc., *via* Dr. H. F. Fraser, PHS Hospital, Lexington, Ky.

(7) Supplied by Merck & Co., Inc. *via* Dr. Joseph Cochin of this Institute.

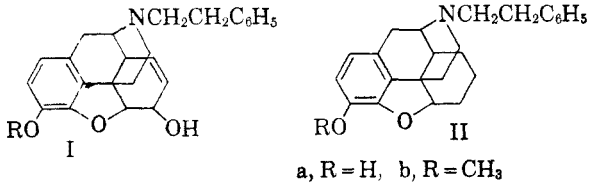
(8) L. F. Small and F. L. Cohen, *J. Am. Chem. Soc.*, **53**, 2227 (1931); H. Rapoport and R. M. Bonner, *J. Am. Chem. Soc.*, **73**, 2872 (1951).

the ether was filtered and dried. The base left from evaporation of the ether was acidified (in acetone) with about 3.0 ml. of 33% HBr-AcOH to give 3.0 g. of IIb hydrobromide, m.p. 243–245°; plates from acetone, m.p. 245–246°, $[\alpha]_D^{26}$ −77.2° (c 1.0 in MeOH).

Anal. Calcd. for $C_{25}H_{30}BrNO_2$: C, 65.79; H, 6.63. Found: C, 65.93; H, 6.60.

N-Phenethyldihydrodesoxynormorphine-D hydrobromide (IIa). Refluxing 2.0 g. of IIb hydrobromide and 12 ml. of 48% HBr for 15 min., cooling and filtering gave a quantitative yield of the IIa hydrobromide, m.p. 285–290°. It crystallized from methanol in plates, m.p. 297–298° (dec.), $[\alpha]_D^{26}$ −74.2° (c 1.0 in MeOH), which analyzed for the hemihydrate; there was, however, no loss in weight of a sample dried for 5 hr. at 135° without vacuum.

Anal. Calcd. for $C_{24}H_{28}BrNO_2 + {}^1/_2\ H_2O$: C, 63.85; H, 6.48. Found: C, 63.92; H, 6.47.



a, R = H, b, R = CH_3

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2-Amino-6-substituted Benzothiazoles as Potential Anthelmintics

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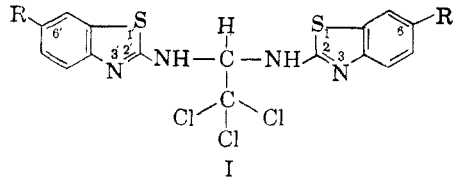
In an earlier communication Mackie, Stewart and Misra[2] reported the paralysant and lethal action of some benzothiazole compounds toward *Ascaris lumbricoides* and *Fasciola hepatica*. In view of the important physiological properties[3a,b,c] possessed by the 2-amino-6-substituted benzothiazoles, it appeared of interest to prepare the condensation products of these compounds with chloral, of the general structure (I), incorporating a lipoid-solubilizing group (trichloromethyl) which might assist the penetration of the compounds through the cuticle of *Ascaris lumbricoides* and thereby have a deleterious effect on the neuromuscular system of the intestinal nematodes and on other trematodes.



I

Condensation products of aromatic and heterocyclic amines with chloral had previously been reported by Sumerford and Dalton[4] and Nelson *et al.*[5] but no work in this respect seems to have been done with the 2-amino-6-substituted benzothiazoles.

The 1,1-bis(2-benzothiazolylamino)-2,2,2-trichloroethanes of the structure I were prepared by refluxing a benzene solution of the 2-aminobenzothiazole with an excess of freshly distilled chloral for 1.5 hr. on a water bath. The precipitate was filtered, washed with a small volume of dry benzene and recrystallized from a suitable solvent. Under the conditions of the experiment, the condensation did not take place with the 6-nitro, 6-carboxy or 6-carbethoxy-2-aminobenzothiazoles. In the case of 6-chloro-2-aminobenzothiazole, a small amount of its hydrochloride was obtained during reflux along with the unreacted base, while with 2-amino-4,5,6,7-tetrahydrobenzothiazole, the hydrochloride of the base was isolated in good yield. This was presumably due to the partial photochemical decomposition of chloral and the liberation of hydrochloric acid.[6]

The details of the *in vivo* biological activity of these compounds toward the dog hookworms and the ascarid infections in poultry and dogs will be reported later.

EXPERIMENTAL

The 2-aminobenzothiazole and its 6-substituted derivatives were prepared by the known methods.[7-11] The data concerning the new 1,1-bis(2-benzothiazolylamino)-2,2,2-trichloroethanes are listed in Table I. 2-Amino-4,5,6,7-tetrahydrobenzothiazole[12] gave its hydrochloride, which recrystallized in colorless rhomboids from benzene. Yield 50%, m.p. 236–237° (dec.).

Anal. Calcd. for $C_7H_{10}N_2S{\cdot}HCl$, C, 44.09%, H, 5.70%, N, 14.60%. Found C, 43.98%, H, 5.80%, N, 14.89%.

Sprague and Kissinger[13] gave the melting point of the hydrochloride, 249–250°.

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