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N-Allylnorapomorphine[1a]

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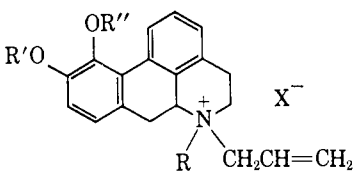
N-Allylnorapomorphine hydrochloride has been prepared by rearrangement of N-allylnormorphine using a modification of a procedure for the preparation of apomorphine hydrochloride; the structure of the product has been proved. Some derivatives of N-allylnorapomorphine have been prepared, and biological test data on N-allylnorapomorphine are reported.

As a part of a continuing study of structure–activity relationships of emetic substances, a sample of N-allylnorapomorphine (**1**) was required. A search of the literature revealed no reported preparation of this compound. Indeed, the only structural variations of the apomorphine molecule involving the nitrogen atom which were found in the literature were apomorphine methiodide,[2] a series of oxygen-acylated or -alkylated apomorphine methiodides,[3] N-aminoapomorphinium chloride,[4] and norapomorphine,[5] the composition and/or purity of the last-named compound being highly questionable.



1, R = R′ = R″ = H; X = Cl
2, R = R′ = R″ = CH_3; X = I
3, R = R″ = H; R′ = CH_3; X = Cl

Because of the inferior quality and the uncertain identity of the product, the reported norapomorphine synthesis was not considered suitable for N-allylnorapomorphine preparation. Attempts to demethylate dibenzoylapomorphine with nitrous acid, as reported by Speyer and Walther[6] for conversion of diacetylmorphine to normorphine yielded an intractable, red-brown gum. Treatment of apomorphine with cyanogen bromide under demethylating conditions has been reported to give a ring-scission product.[7] Rearrangement of N-allylnormorphine[8] under conditions of acid catalysis, using a variety of literature procedures,[9–11] led to low yields of extremely impure, deeply colored material, which could not be purified. Successful conversion of N-allylnormorphine to N-allylnorapomorphine was achieved by a modification of a method utilized by Oparina, *et al.*,[12] for the preparation of apomorphine. The identity of the rearrangement product was confirmed by converting it and a known sample of apomorphine to the same derivative, O,O′-dimethyl-N-allylapomorphinium iodide (**2**). Melting point and infrared data indicated that the difference in sequence of introducing the two different groups (allyl and methyl) onto the ring nitrogen did not produce N-epimeric quaternary salts as has been reported for certain tertiary amines of the tropane series, codeine, tetrahydroisoquinoline derivatives, and certain morphine derivatives.[13] Several attempts to convert N-allylnorapomorphine to N-allylnorapocodeine (**3**) by the method (and variations thereof) of Pschorr and co-workers[3] for the conversion of apomorphine to apocodeine were not successful; a noncrystalline material was isolated which contained no nitrogen.

Pharmacology. A. Preparations.—N-Allylnorapomorphine hydrochloride (**1**) and apomorphine hydrochloride were dissolved, in appropriate concentrations,

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(2) R. Pschorr, *Chem. Zentr.*, **76**, 702 (1905).

(3) R. Pschorr, B. Jaeckel, and H. Fecht, *Ber.*, **35**, 4377 (1902).

(4) B. Rudner, U. S. Patent 2,946,795 (July 26, 1960).

(5) J. von Braun, O. Kruber, and E. Aust, *Ber.*, **47**, 2327 (1914).

(6) E. Speyer and L. Walther, *ibid.*, **63**, 852 (1930).

(7) J. von Braun and E. Aust, *ibid.*, **50**, 43 (1917).

(8) The N-allylnormorphine hydrochloride used in this investigation was generously supplied by Merck and Co., Rahway, N. J., to whom the authors express their sincere thanks.

(9) A. Matthiessen and C. R. A. Wright, *Proc. Roy. Soc.* (London), **B17**, 455 (1869).

(10) C. R. A. Wright, *J. Chem. Soc.*, **25**, 652 (1872).

(11) K. W. Bentley, "The Chemistry of the Morphine Alkaloids," Oxford University Press, London, 1954, p. 302.

(12) M. P. Oparina, A. S. Karasina, and B. P. Smirnov, U.S.S.R. Patent 40,981 (Jan. 31, 1935); *Chem. Abstr.*, **30**, 7285 (1936).

(13) R. Bognar and S. Szabo, *Tetrahedron Letters*, 2867 (1964), and references listed therein.

in physiological saline or in distilled water. For those toxicity studies requiring high concentrations of drug, **1** was reduced to an impalpable powder and suspended in distilled water with vigorous shaking. No dispersing or suspending agents were employed.

B. Comparative Toxicities in Male Mice.—When administered by the intraperitoneal route, the median convulsive dose (± standard error) of apomorphine hydrochloride was estimated to be 118 ± 13 mg./kg., and the median lethal dose, 172 ± 21 mg./kg. The major symptoms of apomorphine toxicity in these animals includes behavioral excitation, tremors, and clonic convulsions. All symptoms are rapid in onset and death usually occurs within 10–15 min. of drug administration. N-Allylnorapomorphine hydrochloride, in doses exceeding 100 mg./kg. (intraperitoneally), produced mild ataxia, piloerection, and a locomotor depression not characteristic of apomorphine. No evidence of convulsive behavior was evident with doses up to 400 mg./kg., and no deaths occurred.

C. Gnawing Response in Male Mice.—In subconvulsive doses the most prominent response following apomorphine administration consists of vigorous and prolonged gnawing, chewing, or masticating movements. This symptom has been observed and described by a number of investigators in several rodent species.[14,15] The median gnawing dose of apomorphine hydrochloride was determined to be 2.65 ± 0.75 mg./kg., while that for **1** was 10.5 ± 1.8 mg./kg. Apomorphine appears to be about 3.9 times as potent (on a dose basis) as **1**. This gnawing activity represents the only major symptom elicited by both aporphines in mice.

D. Emesis in Dogs.—N-Allylnorapomorphine hydrochloride was administered subcutaneously to four untrained dogs (2 of each sex) in 0.2-mg./kg. doses. All animals vomited within 10 min. Eight days later the same animals received saline injections under identical conditions. After another 8-day period, **1** was readministered in 0.1-mg./kg. doses. All animals vomited within 10 min. Saline solution was again administered twice, at 5-day intervals. At the end of the third 5-day interval, 0.1 mg./kg. of apomorphine hydrochloride was administered. This protocol, involving alternating injection of drug and saline solutions at irregular intervals, was followed until the dose of both drugs was reduced to 0.025 mg./kg.

Saline solution consistently failed to evoke emesis or to produce any obvious pre-emetic symptoms, while apomorphine hydrochloride, 0.05–0.2 mg./kg., caused vomiting in all animals in 6–10 min. Apomorphine hydrochloride, 0.025 mg./kg., evoked emesis in one of four dogs. All dogs vomited in response to **1**, 0.1–0.2 mg./kg.; three of four vomited with a 0.05-mg./kg. dose; one of the four vomited with a 0.025-mg./kg. dose. The onset time, duration, and severity of **1**-induced emesis appear to differ in no significant manner from those of apomorphine hydrochloride.

Premedication of dogs with chlorpromazine (2 mg./kg., subcutaneously) prevented the emetic response to both apomorphine hydrochloride and **1** when these were administered in doses previously shown to be emetic.

(14) S. Morita, *Arch. exptl. Pathol. Pharmakol.*, **78**, 188 (1915).
(15) C. Amsler, *ibid.*, **97**, 1 (1923).

E. Pecking in Pigeons.—Preliminary observation revealed that, like apomorphine, the N-allyl derivative possessed the ability to trigger the pecking syndrome in pigeons. To assess the comparative potency of the two compounds with respect to this response, a cross-over assay was performed using a single group of 16 pigeons of mixed sex. The birds were not randomly selected from a general population, but rather were representative of a stock colony of birds whose high sensitivity to apomorphine at the 0.5-mg./kg. level had been established. Eight birds received apomorphine hydrochloride, 0.5 mg./kg. (intramuscularly), and the remaining eight received an equivalent dose of **1**. Cumulative pecking responses were determined for each bird according to a method previously described.[16] Seven days later, the experiment was repeated using the same birds, but with the drugs interchanged. Responses elicited by the two drugs were compared by computing a "t" statistic derived from a "paired comparison" design. Mean cumulative responses (pecks) for apomorphine hydrochloride and for **1** were 5896 and 2694, respectively. This difference in sample response was significant ($p < 0.01$). The potency of apomorphine, as a pecking syndrome stimulant, was approximately 2.2 times that of the N-allyl derivative.

F. Summary.—N-Allylnorapomorphine is less potent than apomorphine as a "gnawing" stimulant in mice; it is less effective than apomorphine as a pecking syndrome stimulant in pigeons; it is far less toxic than apomorphine in mice. Its emetic activity in dogs appears to be very similar, in terms of intensity of response and potency, to that of apomorphine. The emetic properties of both drugs could be abolished by prededication with chlorpromazine.

Experimental[17]

N-Allylnorapomorphine Hydrochloride (1).—A suspension of 10 g. (0.03 mole) of N-allylnormorphine hydrochloride in 56 ml. of 85% H_3PO_4 was heated 1 hr. in an oil bath at 145–150° while passing anhydrous HCl through the mixture at a rapid rate. The hot reaction mixture was diluted with 190 ml. of cold water and allowed to stand 8 hr. The resulting clear brown solution was saturated with NaCl. A resin separated, a part of which floated on the surface of the liquid, while the remainder adhered to the sides of the vessel. The free-floating portion was collected on a filter paper and washed several times with small quantities of cold water. The combined resins (from the filter paper and from the sides of the vessel) were dissolved in a total of 250 ml. of warm (50–60°) water. The addition of sodium sulfite (10 g.), in small portions, yielded a finely divided, milky suspension. This mixture was cooled to room temperature, and shaken with 4 l. of ether in 10 portions. The combined ether extracts were divided equally between two 4-l. beakers, and 100 ml. of anhydrous ether saturated with anhydrous HCl was added to each beaker; white crystals formed within a few minutes. After 3 hr., each beaker was filled with anhydrous ether, covered, and left for 24 hr. The dull white solid which separated (4.4 g., 46%) was collected. There was no evidence of green discoloration of this material. However, when exposed to light and air for a few days it turned bluish green, grossly resembling oxidized apomorphine hydrochloride. The molybdic acid color test[18a] for N-allylnormorphine was positive (purple) for a sample

(16) A. M. Burkman, *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 558 (1960).
(17) Melting points were taken in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus. Analyses are by Huffman Microanalytical Laboratories, Wheatridge, Colo. Infrared spectra were recorded on a Beckman IR-5A spectrophotometer.
(18) (a) "The Pharmacopeia of the United States of America," 16th Revision, Mack Publishing Co., Easton, Pa., 1960: (a) p. 447; (b) p. 63.

of N-allylnormorphine hydrochloride, but was negative (green) for both apomorphine hydrochloride and for **1**. The nitric acid color test[18b] for apomorphine was negative (orange-red) for N-allylnormorphine hydrochloride but was positive (purple) for apomorphine hydrochloride and for **1**. N-Allylnormorphine hydrochloride melted at 265–266° with frothing, when placed in the melting point apparatus 5° below its melting point (lit. m.p. 260–263° [18a] and 269° dec.[19]). Compound 1 melted at 244–245° with frothing, and a mixture of the two compounds melted gradually, beginning at approximately 220°, under similar conditions. A Karl Fischer determination[20] indicated no physically or chemically bound water in 1; $\alpha^{30}D$ −64.0° (*c* 0.328, water).

Anal. Calcd. for $C_{19}H_{20}ClNO_2$: C, 69.10; H, 6.11; Cl, 10.74; N, 4.25. Found: C, 68.83; H, 5.89; Cl, 10.32; N, 4.22.

O,O′-Dimethylapomorphine methiodide was obtained in 68% yield by the method of Späth and Hromatka,[21] except that apomorphine base was not used. A suspension of apomorphine hydrochloride (S. B. Penick and Co.) in methanol was treated, under nitrogen, with an equimolecular amount of methanolic NaOH, and an ethereal solution of diazomethane was added to the resulting solution. The product was a light brown oil. Späth and Hromatka[21] reported a light yellow oil. No reliable physical data were found in the literature for this compound, and it was characterized as its methiodide salt. To a solution of 0.41 g. of the oil in 20 ml. of anhydrous ether was added 1 ml. of methyl iodide. The precipitate which separated was collected on a filter, washed several times with anhydrous ether, and the resulting product (0.06 g., 99%) was dissolved in hot anhydrous ethanol. It was recrystallized by addition of anhydrous ether; m.p. 188–190°, lit.[3] m.p. 195°.

O,O′-Dimethyl-N-allylnorapomorphine was obtained by a modification of the method of Späth and Hromatka[21] for the preparation of O,O′-dimethylapomorphine. Compound 1 (0.34 g.) was suspended in 5 ml. of anhydrous methanol in a flask immersed in an ice bath. Nitrogen was passed through the stirred suspension, and 0.04 g. of NaOH in 5 ml. of anhydrous methanol was added slowly. To this mixture was added an excess of ethereal CH_2N_2; the reaction flask was kept in the ice bath 1 hr. and at room temperature 11 hr. Half of the solvent was removed, and the concentrate was treated with an excess of ethereal diazomethane. It was left for 12 hr. Evaporation of the solvent (steam bath) yielded an oily residue which was dissolved in 15 ml. of cold 1 *N* HCl and transferred to a separatory funnel. Sufficient cold 50% NaOH was added to make the solution strongly alkaline, and it was shaken with 200 ml. of ether in divided portions. The combined ether extracts were washed once with 50% NaOH and once with water. The ether was removed, and the residue was stored in a desiccator under reduced pressure for several hours. The dried material was dissolved in anhydrous ether, the solution was filtered through sintered glass, and the ether was removed. The residue (0.223 g., 70%) was a light brown, viscous oil, $n^{24}D$ 1.6131.

Anal. Calcd. for $C_{21}H_{23}NO_2$: C, 78.50; H, 7.17; N, 4.36. Found: C, 78.25; H, 7.18; N, 4.20.

O,O′-Dimethyl-N-allylapomorphinium Iodide (2). A. From O,O′-Dimethylapomorphine.—To 0.075 g. of O,O′-dimethylapomorphine in 20 ml. of anhydrous ether was added 1 ml. of allyl iodide (Eastman White Label) which had been distilled twice, protected from strong light, and stored in the dark. The solution was left in the dark for 3 hr. The solid which separated was collected on a filter and washed several times with anhydrous ether. The resulting product (0.11 g., 95%) was dissolved in hot anhydrous ethanol and recrystallized by addition of anhydrous ether; this procedure was repeated four times. The pale yellow microcrystalline product softened at approximately 154° and melted at 168–170° with frothing.

Anal. Calcd. for $C_{22}H_{26}INO_2$: C, 57.02; H, 5.62; I, 27.43; N, 3.02. Found: C, 57.00; H, 5.50; I, 27.59; N, 3.03.

B. From O,O′-Dimethyl-N-allylnorapomorphine.—O,O′-Dimethyl-N-allylnorapomorphine (0.015 g.) in 20 ml. of anhydrous ether was mixed with 1 ml. of methyl iodide and left for 3 hr. The solid which separated was collected on a filter and washed several times with anhydrous ether. The resulting product (0.02 g., 94%) was dissolved in hot anhydrous ethanol and recrystallized by addition of anhydrous ether; this procedure was repeated three times. The pale yellow microcrystalline product softened at approximately 150° and melted at 166–169° with frothing.

Anal. Calcd. for $C_{22}H_{26}INO_2$: C, 57.02; H, 5.62. Found: C, 57.30; H, 5.27.

A mixture melting point determination of the products of A and B showed no depression. The infrared spectra (Nujol) of A and B were superimposable.

(19) "The Merck Index," 7th Ed., Merck and Co., Inc., Rahway, N. J., 1960, p. 701.

(20) Performed by Huffman Microanalytical Laboratories, Wheatridge, Colo.

(21) E. Späth and O. Hromatka, *Ber.*, **62**, 325 (1929).

Constitution and Analgetic Activity of a New Product in the Benzomorphan Synthesis

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Cyclization of 3,4-diethyl-2-(*p*-hydroxybenzyl)-1-methyl-1,2,5,6-tetrahydropyridine (I) hydrochloride with aluminum bromide has given a mixture of α- and β-5,9-diethyl-2′-hydroxy-2-methyl-6,7-benzomorphans (II and III) and 1,5-dimethyl-4-ethyl-7-hydroxy-1,2,3,4,5,10,11,12-octahydrobenzo[*g*]quinoline (IV) in yields of 19, 14, and 27%, respectively. The structure of IV was proved by n.m.r. and mass spectrometry, and by degradation to 7-methoxy-1-methylnaphthalene. When I was cyclized with 85% phosphoric acid at 185°, II (50%) and III (25%) but no IV were obtained. The analgetic potency of IV is about half that of II, between morphine and codeine.

In the course of attempts to improve the yield of β-5,9-diethyl-2′-hydroxy-2-methyl-6,7-benzomorphan (III), a very potent analgetic with a favorable therapeutic ratio,[2] aluminum bromide cyclization of 3,4-diethyl-2-(*p*-hydroxybenzyl)-1-methyl-1,2,5,6-tetrahydropyridine (I) hydrochloride was found to yield a mixture of three[3] easily separable, well-defined products (see Scheme I). They are α- and β-5,9-diethyl-2′-hydroxy-2-methyl-6,7-benzomorphans (II, 19%, and III, 14%, respectively) and compound IV (27%) whose separation, constitutional proof, and analgetic activity are presented in this communication. De-

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(2) (a) J. H. Ager and E. L. May, *J. Org. Chem.*, **27**, 245 (1962); (b) J. H. Ager, S. E. Fullerton, and E. L. May, *J. Med. Chem.*, **6**, 322 (1963).

(3) J. H. Ager, S. E. Fullerton, E. M. Fry, and E. L. May, *J. Org. Chem.*, **28**, 2470 (1963), had reported that only two products, α- and β-benzomorphans were obtained in this cyclization.