#### **References and Notes**

- (1) H. Merz, A. Langbein, K. Stockhaus, G. Walther, and H. Wick, Adv. Biochem. Psychopharmacol., 8, 91 (1974)
- (2) N. B. Eddy and E. L. May in "Synthetic Analgesics. Part IIB. 6,7-Benzomorphans", D. H. R. Barton and W. von Doering, Ed., Pergamon Press, New York, N.Y., 1966, pp 126-128.
- (3)C. H. Boehringer Sohn (Ingelheim), H. Merz, A. Langbein, G. Walther, and K. Stockhaus, inventors, German Offen., P 2411382.4 (1975) and P 2437610.1 (1976).
- (4) A. F. Casy and A. P. Parulkar, J. Med. Chem., 12, 178 (1969). (5) J. Defaye, M. Naumberg, and T. Reyners, J. Heterocycl.
- Chem., 6, 229 (1969). (6) F. Haffner, Dtsch. Med. Wochenschr., 55, 731 (1929).
- G. Woolfe and A. D. MacDonald, J. Pharmacol. Exp. Ther., 80.300 (1944).
- (8) H. Blumberg, P. S. Wolf, and H. B. Dayton, Proc. Soc. Exp. Biol. Med., 118, 763 (1965).
- J. T. Litchfield, Jr., and F. Wilcoxon, J. Pharmacol. Exp. (9)Ther., 96, 99 (1949).
- (10) W. Straub, Dtsch. Med. Wochenschr., 37, 1462 (1911).
- (11) (a) Committee on Problems of Drug Dependence, Division of Medicinal Sciences, National Research Council, "Bulletin on Narcotics", Vol. XXV, no. 2, 1972, p 25; (b) J. E. Villarreal in "Recent Advances in the Pharmacology of Morphine-Like Drugs, Advances in Mental Sciences, Vol. II, Drug Dependence", R. T. Harris, W. McIsaak, and C. R. Schuster, Ed., University of Texas Press, Houston, Texas, 1970, pp 83-116.
- (12) H. H. Swain and M. H. Seevers, "Addendum to the 1974 Proceedings of the Committee on Problems of Drug Dependence", National Academy of Sciences, Washington, D.C.,

1974, p 1173.

- (13) (a) H. H. Swain and M. H. Seevers, "Addendum to the 1975 Proceedings of the Committee on Problems of Drug Dependence", National Academy of Sciences, Washington, D.C., 1975, in press; (b) H. H. Swain and M. H. Seevers, unpublished results (personal communication of Dr. E. L. May, National Institutes of Health, Bethesda, Md., April 1975.
- (14) H. W. Kosterlitz, University of Aberdeen, Scotland, U.K., personal communication, Nov 1974
- (15) L. Shuster, R. V. Hannam, and W. E. Boyle, J. Pharmacol. Exp. Ther., 140, 149 (1963)
- (16) I. Shemano and H. Wendel, Toxicol. Appl. Pharmacol., 6, 334 (1964).
- (17) P. S. Portoghese, J. Pharm. Sci., 55, 865 (1966).
- (18) A. F. Casy, Prog. Med. Chem., 7, 229 (1970).
- (19) Schering AG, NL Patent 7309-158 (1974).
- (20) E. M. Fry and E. L. May, J. Org. Chem., 24, 116 (1959).
- (21) B. F. Tullar, L. S. Harris, R. L. Perry, A. K. Pierson, A. E. Soria, W. F. Wetterau, and N. F. Albertson, J. Med. Chem., 10,383 (1966)
- (22) F. C. Hartman and R. Barker, J. Org. Chem., 29, 873 (1964).
  (23) L. H. Smith, in "Organic Syntheses", Collect. Vol. III, E. C. Horning et al., Ed., Wiley, New York, N.Y., 1955, p 793.
- (24) G. A. Deneau and M. H. Seevers, "Addendum to the 1962 Proceedings of the Committee on Drug Addiction and Narcotics", National Academy of Sciences, Washington, D.C., 1962, Table I, p 4.
- (25) J. E. Villarreal and M. H. Seevers, "Addendum to the 1972 Proceedings of the Committee on Problems of Drug Dependence", National Academy of Sciences, Washington, D.C., 1972, p 1045.

# **Emetic Activity of N-Substituted Norapomorphines**

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Norapomorphine and ten of its N-substituted derivatives were prepared by modifications of procedures described earlier. In a dog emesis test the N-ethyl and N-n-propyl compounds had minimum effective doses of 0.00025 and 0.0005 mg/kg, respectively, when administered iv, sc, or im. In a modified Irwin mouse profile screen the minimum effective iv dose was 0.013 mg/kg for the N-ethyl and 0.0024 mg/kg for the N-n-propyl compound; percutaneous absorption was also observed in mice. All compounds examined caused the stereotyped apomorphine behavior syndrome but hypotensive effects were not serious.

During a study of compounds having both a high central nervous system (CNS) activity and a high therapeutic index, we decided to undertake a program to increase both the emetic potency and the therapeutic index of the wellknown emetic apomorphine. Our decision was supported by Cannon's subsequent description<sup>1</sup> of the chemistry and pharmacology of N-allylnorapomorphine, whose decreased toxicity in mice and superior emetic potency in dogs was also observed in our laboratories using a sample kindly provided by Professor Cannon. As a result of the high activity shown by some of the apomorphine homologs prepared by us and by Cannon, a total synthesis of these compounds was developed by Neumeyer.<sup>2</sup> More recently the pharmacokinetics of compounds 1, 2, and 4 (see Table I) in mice<sup>4</sup> and dopaminergic activity of certain aporphine ethers<sup>5</sup> have been described. The superior potency of 4 over 2 in producing stereotyped behavior has been confirmed in studies using rats.<sup>6</sup>

The purpose of the present communication is to record pharmacological activity in mice and dogs for the compounds in Table I, which were acquired as gifts<sup>1</sup> or by synthesis, and to describe improved synthesis procedures developed, subsequent to an earlier account of the work,<sup>7</sup> in connection with the preparation of large samples needed for preclinical pharmacology and toxicology studies. All of the compounds in Table I were derived from morphine and thus belong to the (6aR)-(-) series.<sup>8</sup> It is now known that (6aS)-(+)-apomorphine is a much less potent isomer and is not an antagonist for the (-) isomer,<sup>9</sup> an observation that has been confirmed by others.6

Chemistry. At the time of our work we prepared normorphine from heroin<sup>10</sup> by a von Braun demethylation procedure<sup>11</sup> in yields of 35%; more recently developed procedures<sup>12-15</sup> were then not available. N-Alkylnormorphine precursors for compounds 3, 4, 7, and 11 were prepared by reductive alkylation of normorphine by the appropriate aldehyde and NaBH<sub>4</sub> in yields of 50-80%; all were identical with materials prepared by alternative procedures.<sup>3,16-18</sup> The precursor of 5 was Merck's nalorphine; that of 8 was N-cyclopropylmethylnormorphine prepared by a literature procedure.19

Originally<sup>7</sup> the rearrangement of normorphine and its

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Table

pduo	R	$Mp, \ ^{\circ}C^{a}$	Lit.mp, °Cª	Yield, $\%$	Formula	Analyses	MED," mg/kg iv, mouse (fiducial limits)	LD <sub>50</sub> , mg/kg iv, mouse (fiducial limits)	Dog emes min effec tive dose mg/kg i
T	Н	230-250 dec	280-282°	24	C <sub>16</sub> H <sub>15</sub> NO <sub>2</sub> +HCl		5.6	32.0	>0.05
8	CH <sub>3</sub>	Ч	h		C <sub>17</sub> H <sub>17</sub> NO <sub>2</sub> ·HC1		(1.8-18.0) 0.018	(10.0-100.0) 71.0	0.012
3	$C_2H_5$	287-289 dec	$278-280^{c}$	20	C <sub>18</sub> H <sub>19</sub> NO <sub>2</sub> •HC1	C, H, N; Cl <sup>∉</sup>	(0.011-0.030) 0.013	(56.0-89.0) 45.0	0.0002
4	n-C <sub>3</sub> H <sub>7</sub>	175-190 dec	$263-265^{c}$	47	C <sub>19</sub> H <sub>21</sub> NO <sub>2</sub> •HC1	C, H, Cl, N	(0.0055-0.032) 0.0024	(36.0-56.0) 79.0	0.0005
5	CH <sub>2</sub> =CHCH <sub>2</sub>	245-248 dec	$244-245^{e}$	23	C <sub>19</sub> H <sub>19</sub> NO <sub>2</sub> •HC1		(0.0013 - 0.0042) 0.13	(63.0-100.0)	0.006
9	HC≡CCH <sub>2</sub>		$245-250^{c}$		C <sub>19</sub> H <sub>17</sub> NO <sub>2</sub> ·HC1		(0.055-0.32) 3.2	100.0	10/
7	$n - C_4 H_9$	175-190 dec		23	C <sub>20</sub> H <sub>23</sub> NO <sub>2</sub> •HCI	C, H, CI, N	(1.0-10.0) 3.2	(32.0-320.0) 56.0	2.02
8	CH <sub>3</sub> CH <sub>2</sub> CHCICH <sub>2</sub>	170-175 dec		20	C <sub>20</sub> H <sub>22</sub> CINO <sub>2</sub> ·HCI	H, N; C, Cl <sup>f</sup>	(1.0-10.0) 0.18	(18.0-180.0) >10.0	0.012
6	$c-C_3H_5CH_2$		$260-263^{\circ}$		C <sub>20</sub> H <sub>21</sub> NO <sub>2</sub> ·HCI		(0.11-0.30) 0.075	56.0	0.002
0	$C_6H_5CH_2$		$262-264^{c}$		C <sub>23</sub> H <sub>21</sub> NO <sub>2</sub> ·HC1		(0.042-0.13) 18.0	(40.0-79.0) 56.0	0.02
Ξ	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub>	170-180 dec	259-262°	16	C <sub>24</sub> H <sub>23</sub> NO <sub>2</sub> ·HCl	H, Cl, N; C <sup>€</sup>	(5.6-56.0) 0.56 (0.34-0.94)	(18.0-180.0) >32.0	>0.1

N-substituted derivatives to compounds 1, 3–5, 7, 8, and 11 was carried out by Cannon's<sup>1</sup> modification of a literature procedure<sup>20</sup> in which dry HCl was passed through a hot  $H_3PO_4$  solution of the appropriate normorphine. Compound 8 was obtained presumably because the HCl opened the cyclopropyl ring. When it was reported<sup>3</sup> that N<sub>2</sub> was superior to HCl in the process, we then adopted its use; a typical rearrangement procedure is described in the Experimental Section.

In an effort to improve yields in the rearrangement reaction, reagents other than hot phosphoric acid were examined; the preparation of apomorphine (2) from morphine was used for convenience. Sulfonation accompanied rearrangement when concentrated  $H_2SO_4$  was used at  $40^{\circ}$ .<sup>21,22</sup> Rearrangement and monosulfonation were observed with 84.5%  $H_2SO_4$  after several days at room temperature. A solution of morphine in 50%  $H_2SO_4$  was refluxed for 7 hr and gave a 7% yield of apomorphine, isolated as its HCl salt after a standard work-up.

A solution of morphine in  $CH_3SO_3H$  developed a dark purple color after storage in the dark for 24 hr at room temperature; the 9% yield of apomorphine obtained was not improved by prolonged reaction times. No rearrangement occurred in 80%  $CH_3SO_3H$  at room temperature but after 5 hr of reflux apomorphine was obtained in 23% yield. Under the same conditions compound 4 was obtained in 26% yield from *N*-*n*-propylnormorphine. Prolonged refluxing in 50%  $CH_3SO_3H$  caused no rearrangement of morphine.

All of the alternative rearrangement techniques described above gave the same high yields of polymeric material as are obtained in the phosphoric acid process. These materials are not formed from apomorphine; a quantitative recovery was obtained from its purple solution in  $CH_3SO_3H$  after 7 days at room temperature.

Anhydrous HF and CF<sub>3</sub>COOH at reflux gave no significant yields of apomorphine.

**Pharmacology.**<sup>†</sup> Compounds were evaluated for neuropharmacological effects in a modified<sup>23</sup> Irwin mouse profile screen.<sup>24</sup> For emetic potency in dogs two to four mongrel dogs of either sex (10–14 kg) were medicated iv for each dose at 0.3 log dose intervals; all the HCl salts described in Table I were adequately soluble in H<sub>2</sub>O. Animals were observed continuously for up to 60 min following medication and only the actual expulsion of gastric contents was scored as emesis.<sup>25</sup> For each compound the lowest tested dose able to elicit emesis in any of the dogs tested at that dose was recorded as the minimum effective dose, which was an observed value and not a statistically derived value. For potency comparisons, minimum effective dose values serve only to show the existence of large potency differences.

It is apparent that compounds 3 and 4 are by far the most potent emetics in this series and that there is no significant potency difference between them. Cannon<sup>3</sup> reported that 3 was the more potent emetic and also was more potent than 4 in eliciting the gnawing syndrome in mice. Because of the real superiority of 4 in the mouse profile we have selected 4 for continuing pharmacological evaluation.

It is well known that apomorphine causes emesis following either iv or po administration.<sup>26</sup> During the present work we have observed that 4 can be administered to dogs iv, sc, or im without significant change in the minimum effective dose. In a series of experiments in which dogs were forced to breathe an aerosol dispersion of 4 it was observed that, with a 5-min exposure duration, 4 induced emesis at a concentration of 0.010 mg/l. of air and was 40 times more potent than 2 used as a control. In the mouse profile work 4 was absorbed rapidly through the skin when administered in normal saline; in  $C_6H_5CH_2OH$  solution it was 11 times more potent. The minimum effective dose from  $C_6H_5CH_2OH$  was 30 times that for iv administration, however.

The stereotyped behavior syndrome (including a gnawing compulsion in animals) which is caused by all compounds in this series, and which has been ascribed to stimulation of dopaminergic neurons,<sup>27–29</sup> was observed in our mouse profile work. In monkeys, where the minimum dose of 4 needed to elicit overt behavior effects such as yawning and teeth grinding was 0.00075 mg/kg iv, doses of 10–20 mg/kg iv caused violent biting, behavior reminiscent of hallucinating activity in humans, and autocannibalism so severe that the animals had to be sacrificed. At such doses apomorphine did not produce these bizarre effects.

The hypotensive effect of apomorphine in the anesthetized cat, ascribed to stimulation of dopamine receptors in the CNS,<sup>30</sup> was observed with 4 also. A minimal but significant effect on blood pressure was observed at 0.075  $\mu$ g/kg iv, compared with a value of 1  $\mu$ g/kg for apomorphine. At 0.005 mg/kg iv mean arterial pressure decreased 39%. In unanesthetized dogs the minimum effective hypotensive dose of 4 was 0.005 mg/kg iv, ten times the minimum effective dose for emesis, and no greater hypotensive effect occurred at doses up to 0.02 mg/kg iv.

# **Experimental Section**

Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and by the late Dr. S. M. Nagy (Belmont, Mass.). Analyses indicated only by symbols of the elements were within 0.4% of the theoretical values. Satisfactory ir, uv, and NMR spectra were recorded for all compounds synthesized in this work.

A convenient sensitive qualitative color test<sup>31</sup> was used to detect the presence of all members of the apomorphine class during extractions and other work-up procedures. The test was not considered positive unless a purple color was extracted into  $Et_2O$ .

*N***-***n***-Propylnormorphine.** The following procedure, based on the reductive alkylation technique of Schellenberg,<sup>32</sup> was used for all *N*-alkylnormorphines. We were able to use Me<sub>2</sub>CO as a solvent because of its low reactivity with NaBH<sub>4</sub>.<sup>33</sup>

In a typical run 25 g (0.093 mol) of normorphine was dissolved in a mixture of 75 ml of HOAc, 400 ml of Me<sub>2</sub>CO, 160 ml of H<sub>2</sub>O, and 12 g of anhydrous NaOAc. Propionaldehyde (25 ml, 0.35 mol) was added and the mixture was cooled to  $-20^{\circ}$ . NaBH<sub>4</sub> (9 g, 0.24 mol) was added in portions to the stirred mixture at such a rate that the temperature remained at -3 to  $2^{\circ}$ ; the addition required at least 20 min and inferior yields invariably resulted when addition was hurried. Second batches of propionaldehyde and NaBH4 were then added in the same way and the mixture was stirred as it was allowed to warm to room temperature. The mixture was diluted with 250 ml of H<sub>2</sub>O and made strongly acidic with concentrated HCl. It was then allowed to evaporate at room temperature until most of the Me<sub>2</sub>CO escaped. Excess aldehyde was removed by extraction with Et<sub>2</sub>O. Concentrated NH<sub>4</sub>OH was added carefully until the mixture had pH 7 and dark-colored impurities were removed by filtration. Continued addition of NH4OH precipitated an almost colorless product at pH 8-9, but precipitation was often incomplete until after 20 min of stirring at that pH. Analytically pure material (mp 233-235°) could be obtained by recrystalllization from EtOH<sup>7</sup> but the 21 g (72%) originally obtained, mp 220-230°, gave satisfactory yields in the subsequent rearrangement reaction. In smaller scale runs yields were usually 80-90%.

**N-n-Propylnorapomorphine Hydrochloride (4).** The following modification of Cannon's preferred rearrangement procedure<sup>3</sup> was used for large-scale runs.

N-n-Propylnormorphine (36 g, 0.115 mol) was suspended in 216 ml of 85% H<sub>3</sub>PO<sub>4</sub> and dry N<sub>2</sub> was bubbled through the suspension while it was heated to 145–150° during 20 min. The dark homogeneous mixture was held at that temperature, with N<sub>2</sub> flowing, for 1 hr and then was allowed to cool. The mixture was poured on 500 g of ice and the resulting clear brown solution was stirred until it

<sup>&</sup>lt;sup>†</sup> In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals", as promulgated by the Committee on Revision of the "Guide for Laboratory Animals, Facilities and Care" of the Institute of Laboratory Animal Resources, National Research Council.

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warmed to room temperature. Solid NaCl was added with rapid stirring until the last portion no longer dissolved completely. The crude product HCl salts were sucked dry on the filter and were redissolved in about 2 l. of H<sub>2</sub>O at 60°; when they contained excess NaCl additional H<sub>2</sub>O was needed because they were much less soluble in the presence of excess chloride ion.

The warm solution of HCl salts was stirred while saturated aqueous  $Na_2SO_3$  was added in excess to precipitate the free organic bases. The precipitate was filtered without delay and handled in subdued light. The filter cake was transferred to an explosion-proof Waring blendor and extracted for 1 min each with three 750-ml portions of Et<sub>2</sub>O. In smaller scale runs the cake was extracted by shaking for 5 min in a stoppered flask. The Et<sub>2</sub>O extracts were separated from the insoluble paste of polymeric material by decantation.

The dry (MgSO<sub>4</sub>) extracts were combined and stirred vigorously while ethereal HCl was added carefully until precipitation was complete; excess HCl caused the formation of a sticky product. The colorless 4 was filtered and dried under vacuum at 60° to give 11.9 g (31%): mp 181-192°;  $[\alpha]^{23}D - 43°$  (c 1.5, H<sub>2</sub>O). The decomposition temperature was 260-265° (lit.<sup>3</sup> 263-265°). Recrystallization from dry EtOH containing a little HCl caused no significant change in physical properties or in purity as determined by quantitative uv spectroscopy.

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## **References and Notes**

- (1) J. H. Hensiak, J. G. Cannon, and A. M. Burkman, J. Med. Chem., 8, 557 (1965). Professor J. G. Cannon, University of Iowa, who was a consultant to our program, kindly provided samples of compounds 1, 5, 6, 9, and 10 (in Table I), whose syntheses were described in this reference and in ref 3. Syntheses of compounds 3, 4, and 11 were also described by Cannon<sup>3</sup> who prepared them in parallel independent work. A sample of his 4 gave dog emesis results (in our laboratories) identical with our own sample.
- (2) J. L. Neumeyer, B. R. Neustadt, K. H. Oh, K. K. Weinhardt, C. B. Boyce, F. J. Rosenberg, and D. G. Teiger, J. Med. Chem., 16, 1223 (1973).
- (3) M. V. Koch, J. G. Cannon, and A. M. Burkman, J. Med. Chem., 11, 977 (1968).
- (4) A. M. Burkman, R. E. Notari, and W. K. Van Tyle, J. Pharm. Pharmacol., 26, 493 (1974).
- (5) W. S. Saari, S. W. King, V. J. Lotti, and A. Scriabine, J. Med. Chem., 17, 1086 (1974).
- (6) R. I. Schoenfeld, J. L. Neumeyer, W. Dafeldecker, and S. Rof-

fler-Tarlov, Eur. J. Pharmacol., 30, 63 (1975).

- (7) S. Archer (to Sterling Drug, Inc.), U.S. Patent 3,717,643 (Feb 20, 1973; filed May 4, 1967).
- (8) (a) H. Corrodi and E. Hardegger, *Helv. Chim. Acta*, 38, 2038 (1955); (b) J. C. Craig and S. K. Roy, *Tetrahedron*, 21, 395 (1965); (c) M. Shamma in "The Alkaloids", Vol. 9, R. H. R. Manske, Ed., Academic Press, New York, N.Y., 1967, p 1.
- (9) W. S. Saari and S. W. King, J. Med. Chem., 16, 171 (1973).
- (10) Heroin used in this work was contributed by Dr. N. B. Eddy and by the Bureau of Narcotics.
- (11) H. Rapoport and M. Look (to U.S. Atomic Energy Commission), U.S. Patent 2,890,221 (1959).
- (12) A. Cave, C. Kan-fan, P. Potier, and L. LeMen, *Tetrahedron*, 23, 4681 (1967).
- (13) M. M. Abdel-Monem and P. S. Portoghese, J. Med. Chem., 15, 208 (1972).
- (14) M. P. Cava and M. Srinivisan, J. Org. Chem., 37, 330 (1972).
- (15) T. A. Montzka, J. P. Matiskella, and R. A. Partyka, Tetrahedron Lett., 1325 (1974).
- (16) R. L. Clark, A. A. Pessolano, J. Weijlard, and K. Pfister, J. Am. Chem. Soc., 75, 4963 (1953).
- (17) L. F. Small, N. B. Eddy, J. H. Ager, and E. L. May, J. Org. Chem., 23, 1387 (1958).
- (18) A. F. Green, G. K. Ruffell, and E. Walton, J. Pharm. Pharmacol., 6, 390 (1954).
- (19) M. Gates and T. A. Montzka, J. Med. Chem., 7, 127 (1964).
- (20) M. P. Oparina, A. S. Karasina, and B. P. Smirnov, USSR Patent 40,981 (1935); Chem. Abstr., 30, 7285 (1936).
- (21) C. C. Fulton, J. Lab. Clin. Med., 13, 750 (1928).
- (22) C. C. Fulton, J. Am. Pharm. Assoc., 26, 726 (1937)
- (23) W. J. Lennox, U.S. C. F. S. T. I., AD Rep., 852897 (1969).
- (24) S. Irwin, Psychopharmacologia, 13, 222 (1968).
- (25) H. L. Borison and S. C. Wang, *Pharmacol. Rev.*, 5, 193 (1953). The use of a dog emesis test involving 100 animals has been described by C. J. E. Niemegeers, *Pharmacology*, 6, 353 (1971).
- (26) R. A. Hatcher and C. Eggleston, J. Am. Med. Assoc., 63, 469 (1914).
- (27) M. Fekete, A. M. Kurti, and I. Pribusz, J. Pharm. Pharmacol., 22, 377 (1970).
- (28) J. Rotrosen and M. B. Wallach, Psychopharmacologia, 26, 185 (1972).
- (29) M. Nymark, Psychopharmacologia, 26, 361 (1972).
- (30) A. Barnett and J. W. Fiore, Eur. J. Pharmacol., 14, 206 (1971).
- (31) Identification Test A, "National Formulary XIII", American Pharmaceutical Association, Washington, D.C., 1970, p 61.
- (32) K. A. Schellenberg, J. Org. Chem., 28, 3259 (1963).
- (33) H. C. Brown and I. Ishikawa, J. Am. Chem. Soc., 83, 4372 (1961).