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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.

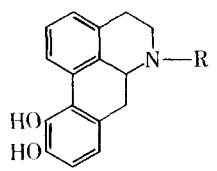
During a study of compounds having both a high central nervous system (CNS) activity and a high therapeutic index, we decided to undertake a program to increase both the emetic potency and the therapeutic index of the well-known emetic apomorphine. Our decision was supported by Cannon's subsequent description[1] 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.[2] More recently the pharmacokinetics of compounds **1**, **2**, and **4** (see Table I) in mice[4] and dopaminergic activity of certain aporphine ethers[5] have been described. The superior potency of **4** over **2** in producing stereotyped behavior has been confirmed in studies using rats.[6]

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[1] or by synthesis, and to describe improved synthesis procedures developed, subsequent to an earlier account of the work,[7] 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 (6a*R*)-(−) series.[8] It is now known that (6a*S*)-(+)-apomorphine is a much less potent isomer and is not an antagonist for the (−) isomer,[9] an observation that has been confirmed by others.[6]

Chemistry. At the time of our work we prepared normorphine from heroin[10] by a von Braun demethylation procedure[11] in yields of 35%; more recently developed procedures[12–15] 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 $NaBH_4$ in yields of 50–80%; all were identical with materials prepared by alternative procedures.[3,16–18] The precursor of **5** was Merck's nalorphine; that of **8** was *N*-cyclopropylmethylnormorphine prepared by a literature procedure.[19]

Originally[7] the rearrangement of normorphine and its

Table I. N-Substituted Norapomorphines (as Hydrochlorides)



Compd	R	Mp, °C[a]	Lit. mp, °C[a]	Yield, %	Formula	Analyses	MED,[b] mg/kg iv, mouse (fiducial limits)	LD_{50}, mg/kg iv, mouse (fiducial limits)	Dog emesis, min effective dose, mg/kg iv
1	H	230-250 dec	280-282[c]	24	$C_{16}H_{15}NO_2 \cdot HCl$		5.6 (1.8-18.0)	32.0 (10.0-100.0)	>0.05
2	CH_3	*h*	*h*		$C_{17}H_{17}NO_2 \cdot HCl$		0.018 (0.011-0.030)	71.0 (56.0-89.0)	0.012
3	C_2H_5	287-289 dec	278-280[c]	20	$C_{18}H_{19}NO_2 \cdot HCl$	C, H, N; Cl[d]	0.013 (0.0055-0.032)	45.0 (36.0-56.0)	0.00025
4	*n*-C_3H_7	175-190 dec	263-265[c]	47	$C_{19}H_{21}NO_2 \cdot HCl$	C, H, Cl, N	0.0024 (0.0013-0.0042)	79.0 (63.0-100.0)	0.0005
5	$CH_2{=}CHCH_2$	245-248 dec	244-245[e]	23	$C_{19}H_{19}NO_2 \cdot HCl$		0.13 (0.055-0.32)	>50.0	0.006
6	$HC{\equiv}CCH_2$		245-250[c]		$C_{19}H_{17}NO_2 \cdot HCl$		3.2 (1.0-10.0)	100.0 (32.0-320.0)	>0.1
7	*n*-C_4H_9	175-190 dec		23	$C_{20}H_{23}NO_2 \cdot HCl$	C, H, Cl, N	3.2 (1.0-10.0)	56.0 (18.0-180.0)	>0.2
8	$CH_3CH_2CHClCH_2$	170-175 dec		20	$C_{20}H_{22}ClNO_2 \cdot HCl$	H, N; C, Cl[f]	0.18 (0.11-0.30)	>10.0	0.012
9	c-$C_3H_5CH_2$		260-263[c]		$C_{20}H_{21}NO_2 \cdot HCl$		0.075 (0.042-0.13)	56.0 (40.0-79.0)	0.002
10	$C_6H_5CH_2$		262-264[c]		$C_{23}H_{21}NO_2 \cdot HCl$		18.0 (5.6-56.0)	56.0 (18.0-180.0)	0.02
11	$C_6H_5CH_2CH_2$	170-180 dec	259-262[c]	16	$C_{24}H_{23}NO_2 \cdot HCl$	H, Cl, N; C[g]	0.56 (0.34-0.94)	>32.0	>0.1

[a]Melting points were obtained in capillaries in a bath heated from room temperature at 5°/min and are uncorrected. Lit. melting points were decomposition temperatures, obtained by placing open capillaries in a bath 5° below the range cited (ref 1). [b]Minimum dose at which reactive signs were observed in half of the mice tested. [c]Reference 3. [d]Cl: calcd, 11.15; found, 10.50. [e]Reference 1. [f]C: calcd, 63.16; found, 62.55. Cl: calcd, 18.64; found, 17.55. [g]C: calcd, 73.16; found, 72.44. [h]S. B. Penick & Co., N.F.

N-substituted derivatives to compounds **1, 3–5, 7, 8,** and **11** was carried out by Cannon's[1] modification of a literature procedure[20] 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[3] that N_2 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°.[21,22] 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_3COOH at reflux gave no significant yields of apomorphine.

Pharmacology.† Compounds were evaluated for neuropharmacological effects in a modified[23] Irwin mouse profile screen.[24] 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_2O. Animals were observed continuously for up to 60 min following medication and only the actual expulsion of gastric contents was scored as emesis.[25] 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[3] 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.[26] 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,[27–29] 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,[30] was observed with **4** also. A minimal but significant effect on blood pressure was observed at 0.075 μg/kg iv, compared with a value of 1 μg/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[31] 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,[32] was used for all *N*-alkylnormorphines. We were able to use Me_2CO as a solvent because of its low reactivity with $NaBH_4$.[33]

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_2CO, 160 ml of H_2O, and 12 g of anhydrous NaOAc. Propionaldehyde (25 ml, 0.35 mol) was added and the mixture was cooled to −20°. $NaBH_4$ (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°; the addition required at least 20 min and inferior yields invariably resulted when addition was hurried. Second batches of propionaldehyde and $NaBH_4$ 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_2O and made strongly acidic with concentrated HCl. It was then allowed to evaporate at room temperature until most of the Me_2CO escaped. Excess aldehyde was removed by extraction with Et_2O. Concentrated NH_4OH was added carefully until the mixture had pH 7 and dark-colored impurities were removed by filtration. Continued addition of NH_4OH 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[7] 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[3] was used for large-scale runs.

N-*n*-Propylnormorphine (36 g, 0.115 mol) was suspended in 216 ml of 85% H_3PO_4 and dry N_2 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_2 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

† 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.

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_2O at 60°; when they contained excess NaCl additional H_2O 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_2O. In smaller scale runs the cake was extracted by shaking for 5 min in a stoppered flask. The Et_2O extracts were separated from the insoluble paste of polymeric material by decantation.

The dry ($MgSO_4$) 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_2O). The decomposition temperature was 260–265° (lit.[3] 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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