Centrally Acting Emetic Agents IV: Synthesis and Chromatographic Methods for Certain Nornuciferine Derivatives

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Abstract □ *dl*-Nornuciferine has been synthesized by a literature procedure; alkyl groups were introduced on the nitrogen by direct alkylation, reductive alkylation, or by acylation followed by reduction to afford eight *N*-alkylnornuciferine derivatives. Selective cleavage of the ether function at Position 1 of the 1,2-dimethoxyaporphine systems was achieved by use of hydriodic acid in acetic anhydride. As a preliminary to metabolic studies on the products, thin-layer and gas chromatographic methods were devised for qualitative and quantitative analysis of them.

Keyphrases □ Emetic agents—centrally acting □ Nornuciferine derivatives—synthesis □ IR spectrophotometry—identity □ NMR spectroscopy—identity □ TLC—analysis □ GLC—analysis

In a continuing study of aporphine derivatives, which are potential emetic agents (1), a series of 1,2-dimethoxylated aporphine (nornuciferine) derivatives was investigated. Compounds I–XVI (Table I) were prepared for biological evaluation of their emetic effects and for initiation of a study of the metabolic fate of dioxygenated aporphine systems in mammals.

The literature reveals a paucity of information on metabolism or biological fate of aporphine systems in general; Compounds I–VIII have been selected for initial metabolic investigation. In considering possible biotransformations of *N*-substituted nornuciferines, *N*- and/or *O*-dealkylation seem to be plausible reactions (2). Thus, for Compounds II–VIII, three possible metabolite types are available for study: I, an *N*-dealkylated product; IX, an *N*- and *O*-dealkylated system; and X–XVI, *O*-dealkylated products of the parent compounds. Analytical systems were required for separation, identification, and quantitation of each of these substances as a prelude to the proposed metabolic studies.

TLC was envisioned as the qualitative method of choice. Solvents and techniques employed in the separation of closely related alkaloids (3) served as a reference point for the development of systems in this investigation. For quantitative analysis, gas chromatography was considered. Arndt *et al.* (4) chromatographed nornuciferine (I) and nuciferine (II) with an SE-30 column. Since the nuciferine analogs in the present study represent wider structural variation and were expected to possess poorer volatility, a similar but more thermally stable internal phase was sought. OV-17, a silicone polymer with 50% phenyl substitution and a temperature limit of approximately 350°, was used.

RESULTS AND DISCUSSION

dl-Nornuciferine (I), prepared by the method of Weisbach and Douglas (5), was *N*-alkylated directly with an alkyl halide or was *N*-acylated and then reduced with lithium aluminum hydride. *dl*-Nuciferine (II) was prepared by Eschweiler-Clarke methylation of I.

It is noteworthy that the Pschorr cyclization of 1-(2′-aminobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline to an aporphine system proceeded in approximately twice the percent yield reported for this step in the literature (5). Initial low recovery of products in the lithium aluminum hydride reductions increased significantly by use of a procedure (6, 7) in which the reduction mixture, after quenching with water, was stirred with an ammonium tartrate solution which presumably aids in breaking the aluminum complexes of the amino product.

Attempts were made to cleave the ether links of Compounds I–VII to form 1,2-dihydroxyaporphine systems; hydriodic acid in acetic anhydride (8) was selected as the most promising reagent. Elemental analysis of the ether-cleaved products of I–VIII indicated an incomplete cleavage and suggested that the products were monohydroxy- and monomethoxyaporphines. NMR spectra of all of the ether-cleaved materials demonstrated a singlet (3H) at 3.85–3.89 δ, while the parent dimethoxylated aporphines exhibited signals at 3.82–3.86 δ (3H) and at 3.60–3.62 δ (3H). The higher field shift has been assigned to the methoxyl group at Position 1 (9, 10), on the basis of steric interactions of the 1-methoxyl group with the *peri*-hydrogen at Position 11 and with the methoxyl group at Position 2. These interactions force the methyl portion of the Number 1 methoxyl out of the plane of the aromatic ring and make it more susceptible to the shielding effects of both aromatic rings. This assignment has been corroborated in the nuciferine system itself (11). Kametani and Noguchi (12) have prepared *dl*-*N*-methylcaaverine (1-hydroxy-2-methoxy-*N*-methylaporphine) by an unequivocal route. This compound, which is the free base form of Compound X (Table I), exhibited an NMR signal at 3.86 δ (3H) which was assigned to the protons of the 2-methoxy group. Therefore, the cleavage procedure employed in the present study was selective for the ether function at Position 1 of the 1,2-dimethoxyaporphines, giving a series of 1-hydroxy-2-methoxyaporphines (IX–XVI). There was no indication that isomeric 1-methoxy-2-hydroxyaporphines were formed in any of the cleavage reactions.

The literature contains numerous accounts of selective cleavage of polymethoxy aromatic ethers with sulfuric acid (13, 14) and with hydrohalic acids (15). Bruderer and Brossi's proposal (15) that selective ether cleavage in certain polymethoxylated heterocyclic systems is a function of differences in basicity of the ether oxygens due to electrostatic substituent effects has been rejected by Wilcox and Seager (16) following their kinetic study of similar systems, on the basis that this explanation requires postulating "unprecedently negative *ortho* σ (OCH_3) constants." These latter workers rationalized the greatly enhanced cleavage rates of the central methoxyl group of 1,2,3-trimethoxybenzene derivatives by hydrobromic acid in acetic acid as being due to steric acceleration factors; the greater basicity of the central methoxyl group is due to its being twisted out of the plane of the aromatic ring. In the present case of the apparently exclusive cleavage of the Number 1 methoxyl of 1,2-dimethoxyaporphines, the explanation of Wilcox and Seager (16) may be invoked as a reasonable one. The NMR data cited previously corroborated this type of steric disposition of the Number 1 methoxyl. Catalin models indicate serious nonbonded interactions of the Number 1 methoxyl with the Number 2 methoxyl and with the Number 11 hydrogen, when the Number 1 methoxyl is coplanar with the benzene ring to which it is attached.

X-ray crystallographic studies (17) indicate that the biphenyl portion of aporphine systems is appreciably strained, the angle of twist being 29.9°. This strain increases in aporphines bearing substituents at Positions 1 and/or 11. Based upon the premise that the release of steric strain in the course of a reaction can be a driving force, and upon the proposal (18) that the "packing strain" in di-

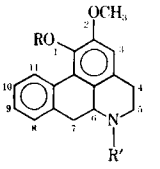

Table I—Nornuciferine Derivatives

No.	R	R′	Method	Yield, %	M.p., Recrystn. Solvent[a]	Molecular Formula	Anal., % Calcd.	Found
I	Me	H	C	88	263°, dec.[b] (M)	$C_{18}H_{20}NO_2Cl$[c]		
II	Me	Me	D	80	261°, dec. (EEt)	$C_{19}H_{22}No_2Cl$[c]	C, 68.78 H, 6.64 N, 4.22	C, 69.15 H, 6.84 N, 4.39
	Me	COMe	E	97	224–225° (M)	$C_{20}H_{21}NO_3$[d]	C, 74.30 H, 6.50 N, 4.33	C, 73.99 H, 6.35 N, 4.31
III	Me	Et	F	85	263°, dec. (E)	$C_{20}H_{24}NO_2Cl$[c,d]	C, 69.46 H, 6.95 N, 4.05	C, 69.71 H, 7.05 N, 4.04
	Me	COEt	E	73	210–211° (M)	$C_{21}H_{23}NO_3$	C, 74.78 H, 6.82 N, 4.15	C, 74.93 H, 6.93 N, 4.20
IV	Me	*n*-Pr	F	70	240°, dec. (E)	$C_{21}H_{26}NO_2Cl$[c]	C, 70.09 H, 7.20 N, 3.89	C, 69.93 H, 7.19 N, 4.01
	Me	CO—⟨	E	88	213–214° (M)	$C_{22}H_{23}NO_3$	C, 75.64 H, 6.59 N, 4.01	C, 75.50 H, 6.67 N, 4.09
V	Me	CH_2—⟨	F	89	244°, dec. (E)	$C_{22}H_{26}NO_2Cl$[c]	C, 71.06 H, 6.99 N, 3.77	C, 70.60 H, 6.93 N, 3.88
VI	Me	CH_2—CH=CH_2	G	61	270°, dec. (E)	$C_{21}H_{24}NO_2Cl$[c]	C, 70.49 H, 6.71 N, 3.92	C, 70.34 H, 6.73 N, 3.90
VII	Me	CH_2—C≡CH	G	86	240°, dec. (E)	$C_{21}H_{22}NO_2Cl$[c]	C, 70.89 H, 6.19 N, 3.94	C, 70.98 H, 6.25 N, 3.98
VIII	Me	CH_2—C_6H_5	H	39	259°, dec. (E)	$C_{25}H_{26}NO_2Cl$[c]	C, 73.62 H, 6.38 N, 3.44	C, 73.72 H, 6.66 N, 3.51
IX	H	H	I	55	248°, dec. (EEt)	$C_{17}H_{18}INO_2$[e]	C, 51.65 H, 4.56 N, 3.54	C, 51.45 H, 4.61 N, 3.59
X	H	Me	I	51	251°, dec. (W)	$C_{18}H_{20}INO_2$[e]	C, 52.85 H, 4.89 N, 3.42	C, 52.63 H, 4.93 N, 3.24
XI	H	Et	I	85	189–190° (EEt)	$C_{19}H_{22}INO_2$[e]	C, 53.89 H, 5.20 N, 3.29	C, 53.76 H, 5.53 N, 3.27
XII	H	*n*-Pr	I	89	184–185° (EWEt)	$C_{20}H_{24}INO_2$[e]	C, 54.69 H, 5.47 N, 3.20	C, 54.14 H, 5.55 N, 3.16
XIII	H	CH_2—⟨	I	72	245°, dec. (E)	$C_{21}H_{24}INO_2$[e]	C, 56.12 H, 5.35 N, 3.12	C, 56.20 H, 5.41 N, 3.51
XIV	H	CH_2—CH=CH_2	I	48	244°, dec. (EEt)	$C_{20}H_{22}INO_2$[e]	C, 55.17 H, 5.06 N, 3.22	C, 54.84 H, 4.97 N, 3.22
XV	H	CH_2—C≡CH	I	79	203°, dec. (EW)	$C_{20}H_{20}INO_2$[e]	C, 55.43 H, 4.62 N, 3.23	C, 55.20 H, 4.91 N, 3.09
XVI	H	CH_2—C_6H_5	I	58	207°, dec. (MEt)	$C_{24}H_{24}INO_2$[e]	C, 59.42 H, 4.95 N, 2.87	C, 59.30 H, 5.09 N, 2.94

[a] M = methanol; EEt = ethanol–ether; E = ethanol; W = water; EWEt = ethanol–water–ether; EW = ethanol–water; MEt = methanol–ether. [b] Weisbach and Douglas (5) give m.p. 262° (dec.). [c] Hydrochloride. [d] Baarschers *et al.* (11) give NMR data for this compound but do not otherwise characterize it or describe its preparation. [e] Hydroiodide.

tert-butyl ether accounts for its ease of cleavage under remarkably mild conditions, it seems reasonable that cleavage of the more strained ether function at Position 1 in the 1,2-dimethoxylated aporphine systems would relieve sufficient strain to account in part for the selectivity encountered. This proposal complements the hypothesis of steric inhibition of coplanarity of the Number 1 methoxyl.

No attempt was made to force the cleavage of the 1-hydroxy-2-methoxyaporphines to the diphenolic systems.

Thin-Layer Chromatography—Separation of the *N*-substituted nornuciferines (II–VIII) from their possible metabolites was attempted with 36 solvent systems; Table II lists the R_f values and detection characteristics of Compounds I–XVI in four solvent systems found suitable [*i.e.*, solvent systems yielding separation of each of the *N*-alkylated nornuciferines (II–VIII) from their *O*- and *N*-dealkylated congeners (I and IX–XVI)]. An advantage of the piperidine-containing systems (Systems 2–4) was that either the hydrohalide salts or free bases could be spotted and after development would reveal the same R_f values. Using Solvent System 1, comparable development without tailing was observed only with the free bases.

Detection was achieved with Dragendorff's reagent (3) and by fluorescence in 254-mμ radiation. With the latter immediately

Table II—Thin-Layer Chromatography

No.	R_f[a] in Solvent Systems[b] 1	2	3	4	Detection, Fluorescence[c]
I	0.16	0.46	0.31	0.45	Blue
II	0.49	0.57	0.54	0.57	Blue
III	0.53	0.62	0.61	0.64	Blue
IV	0.67	0.65	0.64	0.71	Blue
V	0.66	0.65	0.62	0.69	Blue
VI	0.74	0.65	0.63	0.70	Blue
VII	0.75	0.63	0.54	0.68	Yellow
VIII	0.81	0.69	0.64	0.77	Yellow
IX	0.08	0.32	0.17	0.35	Orange
X	0.34	0.47	0.29	0.48	Yellow
XI	0.36	0.51	0.35	0.52	Yellow
XII	0.51	0.53	0.38	0.53	Yellow
XIII	0.51	0.52	0.37	0.53	Yellow
XIV	0.66	0.52	0.33	0.53	Yellow
XV	0.74	0.48	0.31	0.50	Orange
XVI	0.75	0.52	0.38	0.52	Orange

[a] Average of 6 to 15 determinations; average of the percent standard deviation of R_f's of all compounds in Solvent Systems 1–4 = 4.4%. [b] With silica gel G plates, solvent systems employed were: 1, chloroform–methanol (93:7); 2, benzene–piperidine (9:1); 3, cyclohexane–chloroform–piperidine (8:1:1); 4, benzene–ethyl acetate–piperidine (6:3:1). [c] In 254-mμ radiation, after heating at 110° for 30 min.

after development, all compounds appeared as blue-fluorescing spots; with heating, characteristic and more intense orange, yellow, or blue spots were observed. Sensitivities using this technique were improved over Dragendorff's reagent, and the limit of detection was estimated to be less than 1 mcg. for most of the compounds.

Gas Chromatography (GC)—Initial GC attempts with nuciferine (II) utilizing copper columns revealed significant decomposition which was apparently metal-catalyzed and could be obviated by employing a glass column and glass-lined injection port. Good development of all compounds was attained, except for XV which appeared to decompose at all temperatures studied. Retention times, relative to nornuciferine (I), are indicated in Table III. Separation of all *N*-substituted nornuciferines (II–VIII) from their possible *N*- and *O*-dealkylated metabolites (I, IX–XIV, and XVI) was excellent, except in the *N*-ethyl series where *N*-ethylnornuciferine (III) could not be completely resolved from nornuciferine (I).

The satisfactory GC of the nornuciferine derivatives in general and the free phenolic systems (IX–XVI) in particular was somewhat unexpected, because these compounds readily decompose on heating. The successful GC of most of the phenolic aporphines may be due to intramolecular hydrogen bonding between the phenolic hydrogen and the oxygen of the vicinal methoxyl group (19, 20). Quantities analyzed were between 0.5 and 3.0 mcg., and curves of peak height *versus* amount chromatographed were linear for Compounds I–XIV and XVI.

EXPERIMENTAL[1]

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]*o*-nitrophenylacetamide**—*Method A*—This was a modification of the method of Gulland and Haworth (21). A mixture of *o*-nitrophenylacetic acid (100 g.), 400 ml. of thionyl chloride, and 600 ml. of chloroform was refluxed for 3 hr.; then volatile materials were removed under reduced pressure at room temperature. The resulting red oil was added dropwise to a well-stirred and chilled mixture of 50 g. of 3,4-dimethoxyphenethylamine in 200 ml. of ether and a solution of 70 g. of sodium hydroxide in 1 l. of water; the resulting mixture was stirred at room temperature for 1 hr. The solid which separated was collected on a filter and washed several times with water. It was then dissolved in chloroform; this solution was washed with saturated sodium chloride solution, dried over sodium sulfate, and filtered. Removal of solvent from the filtrate gave a brown solid which was taken up in hot chloroform, treated with charcoal, filtered, and concentrated to 250 ml. Upon cooling, 113 g. (79%) of buff-colored crystals was deposited, m.p. 112° [lit. (21) m.p. 109–111°]. An IR spectrum (10% in chloroform) showed a peak at 1665 cm.$^{-1}$ (amide).

Method B—An excess of an ethereal solution of diazomethane was added to a solution of 37 g. of *o*-nitrophenylacetic acid in 200 ml. of ether, and the resulting solution was stirred overnight at room temperature. Removal of the ether left a brown oil which was added to a solution of 73 g. of 3,4-dimethoxyphenethylamine in 300 ml. of benzene, and the resulting mixture was refluxed for 10 hr. The benzene was removed under reduced pressure, and the residual brown solid was recrystallized from methanol to yield 59 g. (78%) of product, m.p. 112°.

***dl*-Nornuciferine (I)**—*Method C*—This was prepared by the method of Weisbach and Douglas (5) and was recrystallized, m.p. 121–125° [lit. (21), (−)-nornuciferine, m.p. 124–125°]. A polymorphic form crystallized from 2-propanol, m.p. 165–166°.

***dl*-Nuciferine Hydrochloride (II)**—*Method D*—Conversion of I to *dl*-nuciferine hydrochloride was by application of the method of Icke and Wisegarver (22). A solution of 3 g. of I, 40 ml. of 88% formic acid, and 40 ml. of 37% aqueous formaldehyde solution was refluxed for 5 hr.; then volatile materials were removed under reduced pressure. The final residue was taken up in 250 ml. of 2% sulfuric acid, the solution was filtered, and the filtrate was treated with an excess of 14% ammonium hydroxide. The resulting mixture was extracted with ether; this extract was washed with saturated sodium chloride solution, dried with sodium sulfate, filtered, and treated with anhydrous hydrogen chloride. The white precipitate which separated was recrystallized (Table I). A portion of the hydrochloride salt of II was treated with sodium hydroxide solution, and the gummy solid resulting was extracted with ether. This extract was washed with saturated sodium chloride solution, dried with sodium sulfate, filtered, and concentrated to deposit large, slightly yellow prisms, m.p. 137–140° [lit. (21) m.p. 136–137°].

***N*-Acylated Nornuciferines**—*Method E*—A solution of a twofold excess of the appropriate acid chloride and 5 g. of nornuciferine (I) in 100 ml. of dry pyridine and 200 ml. of anhydrous benzene was refluxed and stirred for 2 hr. After cooling and filtering, the reaction solution was washed with 200 ml. of water; the water was extracted with benzene which was added to the original organic phase, and the combined organic solutions were washed with water, dried with sodium sulfate, and filtered. The solvent was removed from the filtrate under reduced pressure. The solid residue was recrystallized (Table I).

***N*-Alkylnornuciferines (III–V)**—*Method F*—A suspension of 15.5 mmoles of the appropriate *N*-acylnornuciferine in 250 ml. of purified tetrahydrofuran (distilled from lithium aluminum hydride) was added to a suspension of 5.2 g. of lithium aluminum hydride

Table III—Gas Chromatography

No.	Retention Time[a] Relative to Nornuciferine (I) at Operating Conditions[b] A[c]	B[d]
I	1.00	1.00
II	0.84	—
III	0.94	—
IV	1.11	—
V	1.90	—
VI	1.95	—
VII	2.18	—
VIII	—	4.92
IX	1.63	1.59
X	1.37	—
XI	1.53	—
XII	1.83	—
XIII	3.14	—
XIV	1.95	—
XV[e]	—	—
XVI	—	7.87

[a] Average of 4 to 15 determinations. [b] See *Experimental*. [c] Retention time of nornuciferine (I), 7.8 min. (22 determinations). [d] Retention time of nornuciferine (I), 3.0 min. (4 determinations). [e] Decomposes at all temperatures employed.

[1] Melting points are corrected. IR spectra were recorded on Beckman IR-5A and IR-10 instruments. NMR spectra were obtained with a Varian A-60 instrument; samples were prepared as 10% solutions in DMSO-d_6 using tetramethylsilane as internal standard. GC was performed with a Hewlett-Packard 5750B gas chromatograph equipped with dual-flame ionization detectors.

in 250 ml. of purified tetrahydrofuran, and the resulting mixture was refluxed for 6 hr. Water (10.4 ml.) was carefully added; then 200 ml. of saturated ammonium tartrate solution was added and the mixture was stirred for 1 hr. at room temperature. The layers were separated and the aqueous layer was extracted repeatedly with ether. The combined organic phases were washed with saturated sodium chloride solution, dried with sodium sulfate, and filtered; the filtrate was evaporated under reduced pressure. The residual brown oil was dissolved in dry ether, and this solution was treated with anhydrous hydrogen chloride to yield a white precipitate which was recrystallized (Table I).

***N*-Alkylnornuciferines (VI and VII)**—*Method G*—A mixture of 2 g. of nornuciferine (I), a 0.1 molar excess of the appropriate alkyl bromide, a 0.5 molar excess of sodium bicarbonate, and 25 ml. of anhydrous ethanol was refluxed for 10 hr. The resulting mixture was filtered while hot, and the filtrate was concentrated under reduced pressure to give a brown oil. Treatment of an anhydrous ether solution of this oil with anhydrous hydrogen chloride gave a white precipitate which was recrystallized (Table I).

***dl*-*N*-Benzylnornuciferine (VIII)**—*Method H*—This was prepared from *N*-[2-(3,4-dimethoxyphenyl)ethyl]*o*-nitrophenylacetamide by the method of Weisbach and Douglas (5) and was recrystallized, m.p. 98–99° [lit. (5) 98–99.5°].

Hydroiodides of 1-Hydroxy-2-methoxynoraporphine (IX) and *N*-Alkylated Derivatives (X–XVI)—*Method I*—These were prepared by a modification of the method of Howell and Robertson (24). Nitrogen was passed through a suspension of 3 mmoles of the appropriate 1,2-dimethoxyaporphine (I–VIII) in 7 ml. of acetic anhydride. To this suspension, 4.8 ml. of 57% hydriodic acid (stabilized with 1.4% hypophosphorous acid) was carefully added. The reaction mixture was refluxed in an oil bath of 150° under a stream of nitrogen for 0.5 hr.; then it was permitted to cool to room temperature in a stream of nitrogen. Excess volatile material was removed under reduced pressure, and the solid residue was recrystallized (Table I).

Thin-Layer Chromatography—Silica gel G plates (20 × 20 cm.) were prepared from a slurry containing 3 g. of silica gel G[2] and 7 ml. of water per plate. After air drying, plates were activated at 110° for 1 hr. and kept in a desiccator until used. Developing distance throughout was 10 cm. with the solvent systems listed in Table II. All solvents were reagent grade. Detection was accomplished with Dragendorff's reagent (Thies, Reuther, modified by Vagufalvi) (3) and by fluorescence under 254-mμ radiation, either immediately after development or following heating at 110° for 30 min.

Gas Chromatography—Glass columns [182.9 cm. (6 ft.) × 4 mm. i.d.] were packed with 3% OV-17 on diatomaceous earth,[3] 100/120 mesh. Operating temperatures were: (*a*) injection port, 260°; column, 260°; and detector, 300°; (*b*) injection port, 290°; column, 290°; and detector, 320°. Conditions held constant were: carrier gas (helium), 120 ml./min. (50 psig); hydrogen, 40 ml./min. (13 psig); air, 440 ml./min. (30 psig); attenuation, 8; and range, 10^2. For GC, aqueous solutions of hydrohalide salts were treated with equal volumes of pH 8.0 *tris*-hydrochloric acid buffer (0.2 *M*); free bases were extracted into 1% isoamyl alcohol in *n*-heptane. All compounds except IX could be recovered as the free base by this procedure; extraction of IX required 25% isoamyl alcohol in *n*-heptane. Quantities analyzed were between 0.5–3.0 mcg.; curves of peak height *versus* amount chromatographed were plotted.

[2] Brinkmann Instruments, Westbury, N. Y.
[3] Gas-Chrom Q, Applied Science Laboratories, State College, Pa.

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