tered to remove the RaNi which was washed with 3 × 10 ml of EtOH. The filtrate and washings were concd to 0.47 g of pale green crude product which was purified by sublimation [120° (100–200 μ)].

6-Chloro-1-indanone.[15] A mixt of 35 g of *p*-chlorohydrocinnamic acid[16] and 414 g of polyphosphoric acid was heated on a steam bath for 0.5 hr. Diln with 3 l. of H_2O gave a ppt which was dissolved in Et_2O. The Et_2O soln was washed with $NaHCO_3$, steam distd, and the steam-distd material recrystd from EtOH to give 9.5 g of material melting at 70–73° which was >95% pure by tlc.

6-Chloro-2-isonitroso-1-indanone. A soln of 5.7 g of 6-chloro-1-indanone in 60 ml of C_6H_6 was stirred and HCl gas was bubbled in as 4.8 g of *i*-AmONO was added dropwise over a period of 15 min. Addn of HCl was contd 20 min longer and the mixt was stirred 15 hr before 2.6 g of product was collected, mp 200–204° dec. Resubmission of the mother liquors gave 1.3 g of addnl product. *Anal.* ($C_9H_6ClNO_2$) C, H, N, Cl.

2-Amino-5-chloro-1-indanone·HCl. To a stirred mixt of 9.13 g of $SnCl_2 \cdot 2H_2O$ in 13 ml of concd HCl was added portionwise 3.6 g of 6-chloro-2-isonitroso-1-indanone over a period of 1.5 hr. The temp was kept <40° with intermittent cooling. After stirring 0.5 hr at room temp and 0.5 hr at 95°, the mixt was cooled and 500 ml of H_2O was added. The mixt was stirred and H_2S was bubbled in until no further ppt was obtained. Solids were removed by filtration and concn of the filtrate gave 1.5 g of crude product. Purification for analysis was achieved by recrystn from MeOH–Et_2O, mp 195–210° dec. *Anal.* ($C_9H_9Cl_2NO$) C, H, N, Cl.

5(7)-Chloro-2-mercapto-1,4(8)-dihydroindeno[1,2-*d*]imidazole. A mixt of 1.44 g of 2-amino-5-chloro-1-indanone·HCl and 0.675 g of KSCN were refluxed 15 min in 45 ml of glacial HOAc. After cooling, 0.60 g of crude product was collected on a filter and was used without further purification, mp >300°.

5(7)-Chloro-1,4(8)-dihydroindeno[1,2-*d*]imidazole (24). A 310-mg portion of crude 5(7)-chloro-2-mercapto-1,4(8)-dihydroindeno-[1,2-*d*]imidazole was treated with RaNi as in the prepn of **23** to give 106 mg of crude product which was purified by prep tlc (10% MeOH–$CHCl_3$ on silica gel G) followed by trituration with Et_2O. This gave 35 mg of product: mass spectrum (70 eV) *m/e* 190 (base peak).

2-Methylthioindeno[1,2-*d*]imidazole (25). To a slurry of 1.88 g of 2-mercaptoindeno[1,2-*d*]imidazole in 50 ml of THF was added 0.70 ml of MeI. After 16 hr of stirring the ppt was collected and stirred with excess 1 *N* NaOH. Collection of the ppt gave 1.11 g of product.

5(7)-Chloro-2-methylthio-1,4(8)-dihydroindeno[1,2-*d*]imidazole (26). A 0.31-g portion of crude product was heated with MeI as described in the prepn of **25** to yield 70 mg of crude product, mp 217–223°. This material was purified by sublimation at 150° (50 μ): mass spectrum (70 eV) *m/e* 236 (base peak).

§ Prepared in HOAc according to procedure of Norris and McKee.[14b]

2-(4-Trifluoromethylphenyl)-1,4(8)-dihydroindeno[1,2-*d*]imidazole (27). A mixt of 3.24 g of 2-bromo-1-indanone[17] in 30 ml of $CHCl_3$ and 3.30 g of 4-trifluoromethylbenzamidine·HCl in 10 ml of H_2O was stirred vigorously and 1.8 g of KOH in 10 ml of H_2O was added. The mixt was stirred and refluxed for 3 hr before the resultant ppt was collected and washed with H_2O and $CHCl_3$ to give 0.80 g of intermediate OH compd with a strong *m/e* of 340. A 0.70-g portion of this intermediate was refluxed 10 min in 7 ml of HOAc. The HOAc was removed *in vacuo* and the residue extd with 10 ml of Et_2O. The Et_2O ext was concd to 0.58 g of crude product which was recrystd 4 times from MeOH to give 0.27 g of pure product.

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Lowering of Serum Lipid Levels by "Masked" Nicotinic Acid Derivatives

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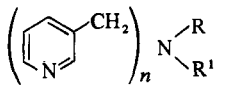
A series of "masked" nicotinic acid compounds (acyl derivatives of 3-pyridylmethylamines, nicotinic acid hydrazides, and nicotinohydroxamic acids) has been synthesized. These compounds have been evaluated with rats orally for their ability to reduce serum NEFA levels and parenterally to reduce serum cholesterol and triglyceride levels. The effective hypolipemic doses of the test compounds were roughly equivalent on a molar basis to those of the parent nicotinic acid. The peripheral vasodilating (flushing) or gastric secretion stimulating effects of these compounds appeared not to differ meaningfully from nicotinic acid.

Prophylactic and therapeutic efforts to control atherosclerosis in man have focused on the control of blood lipid levels. Nicotinic acid (NA), a clinically effective hypolipemic agent, decreases (1) nonesterified fatty acid (NEFA) release from the liver, (2) NEFA and glycerol levels in plasma, (3) liver uptake of circulating NEFA, and (4) hepatic triglyceride synthesis.[1] Its use, however, has been fraught with complications due to disturbances of liver function,[2,3] carbohydrate metabolism,[4–6] gastrointestinal distress,[7,8] and flushing.[9]

An interim report on a large-scale survey from the VA

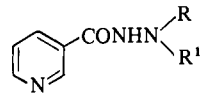
Table I. Serum NEFA Level Reducing Activities of NA and "Masked" NA Compounds[a]

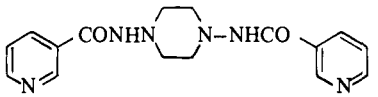
A. Amines and Acyl Amines



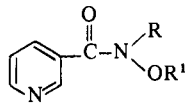
Compound	*n*	R	R¹	Salt	Mp or bp (torr), °C	I_{50},[b] mg/kg	I_{50},[b] μmole/kg[c]
Nicotinic acid[d]						5.5	45
3-Pyridylcarbinol[d]						23	210
1[d]	1	H	H			4	37
2[d]	2	H				3	20
3[e]	1	H	$COCH_3$	HCl	143–144.5	Inactive	
4	1	H	$CO(CH_2)_6CH_3$	HCl	143–146	35	130
5	1	H	$CO(CH_2)_7CH_3$	HCl	146–148	27	95
6	1	H	$CO(CH_2)_8CH_3$	HCl	148–149	29	97
7	1	H	$CO(CH_2)_{16}CH_3$		95–96	Inactive	
8	1	H	$COC_{17}H_{31}$[f]		231–235 (0.02)	34	92
9	1	H	$CO(CH_2)_{10}CONHCH_2C_5H_4N$[g]		160–161	Inactive	
10	2		$COCH_3$	2HCl	234–237	10	64
11	2		$CO(CH_2)_6CH_3$		199–201 (0.02)	7	43
12	2		$CO(CH_2)_7CH_3$		225–227 (0.05)	13	77
13	2		$CO(CH_2)_8CH_3$		178–182 (0.01)	17	96
14	2		$CO(CH_2)_{16}CH_3$		62.5–69.0	>50	>110

B. Hydrazides of Nicotinic Acid



Compound	R	R¹	Mp, °C	I_{50},[b] mg/kg	I_{50},[b] μmole/kg[c]
15	CH_3	CH_3	87–89	11	67
16	CH_3	C_6H_5	72–74	>50	>220
17	$(CH_2)_4$		126–128	12	63
18	$(CH_2)_5$		153–155	30	150
19	$(CH_2)_6$		114–115	45	210
20	$(CH_2)_2O(CH_2)_2$		181–183	Inactive	
21	$CH(CH_3)(CH_2)_3CH(CH_3)$		166–167	Inactive	
22	$(CH_2)_2N(CH_3)(CH_2)_2$		166–168	Inactive	
23			345 dec	Inactive	

C. Derivatives of Nicotinohydroxamic Acid



Compound	R	R¹	pK_a[h]	Mp, °C	I_{50},[b] mg/kg	I_{50},[b] μmole/kg[c]
24[i]	H	H	8.15	164–166 dec	46	330
25[j]	H	CH_3	7.75	66–69	13	86
26	H	$C_6H_5CH_2$	8.50	88–90	10	44
27	H	*p*-$ClC_6H_4CH_2$	8.35	142–144	25	96
28	H	$(C_6H_5)_2CH$	8.50	106–108	22	72
29	C_6H_5	H	7.75	197 dec	Inactive	
30	H	*p*-ClC_6H_4CO	5.60	122–124	Inactive	
31	H	*p*-$ClC_6H_4OC(CH_3)_2CO$	5.30	120–123	Inactive	

[a] Test materials were administered once by intubation to overnight fasted adult male rats (*ca.* 200 g each, 7 rats per group). Blood was taken 1 hr after administration of test compd. Serum NEFA levels were detd by forming the Cu soaps and estimating colorimetrically according to Duncombe.[17] [b] Graphically estimated amts of test materials required to reduce serum NEFA levels 50% based on 2 or more levels of test. [c] In "masked" NA equiv. [d] Aldrich Chemical Co. [e] Ref 18. [f] *N*-(3-Pyridylmethyl)linoleamide. [g] *N,N'*-Bis[3-pyridylmethyl]dodecanediamide. [h] 1:1 MeOH–H_2O. [i] See ref 19. [j] See ref 20.

Coronary Drug Project[10] revealed that one-third of the patients given aluminum nicotinate discontinued the medicament due to gastrointestinal discomfort and hepatic functional disturbances. Clinical trials with 3-pyridylcarbinol have demonstrated for this agent the effectiveness of lower doses than needed with niacin (NA), but similar side effects occurred.[11,12]

We have directed efforts toward the synthesis of compounds structurally related to NA. Acidic, neutral, and basic analogs have been examined for their ability to reduce

Table II. Effect of Test Compounds on Rat Serum Cholesterol and Serum and Liver Triglycerides Four Hours Post Administration

Test agent, ip	Dose (as NA), mg/kg	Serum cholesterol, mg/100 ml	Serum triglycerides, mg/100 ml	Liver triglycerides, mg/g
None	None	71.8 ± 3.1 (12)[a]	58.3 ± 5.6 (11)	4.47 ± 0.56
NA	250	50.4 ± 5.4 (12)	21.5 ± 2.5 (6)	2.52 ± 0.29 (8)
		P = <0.01	P = <0.001	P = <0.01
11	62[b]	87.0 ± 18.2 (6)	35.6 ± 2.5 (4)	
		ns	P = <0.01	
11	15.6	70.1 ± 5.3 (8)	44.8 ± 5.6 (7)	
		ns	ns	
15	250	55.0 ± 3.2 (12)	34.5 ± 2.9 (9)	2.02 ± 0.14 (7)
		P = <0.01	P = <0.01	P = <0.001
26	250	61.7 ± 3.1 (12)	32.6 ± 3.5 (12)	3.06 ± 0.42 (8)
		P = <0.05	P = <0.01	P = >0.8

[a]Number of rats in parentheses. [b]Toxic at 250 mg equiv of NA

the level of serum NEFA[13] in the rat. Additionally, representative compounds were compared with NA for their hypothermic effect in conscious guinea pigs[14] and for their effectiveness in stimulating gastric secretion in dogs and in rats.

Chemistry. The 3 classes of compounds examined were: (1) pyridylmethylamines and their acyl derivatives, (2) nicotinic acid hydrazides, and (3) nicotinohydroxamic acids.[15] The acyl derivatives of 3-aminomethylpyridine (**1**) and 3,3'-dipicolylamine (**2**) were prepared from the amine and acyl halide in pyridine. The nicotinic acid hydrazides and substituted nicotinohydroxamic acids were prepared from nicotinoyl chloride and the appropriate N,N-disubstituted hydrazines and substituted hydroxylamines, respectively. Most of the latter compounds were available *via* O-alkylation of acetone oxime followed by acid hydrolysis.

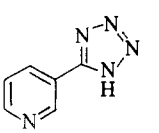
Results and Discussion

3-Pyridylcarbinol has been shown to be rapidly metabolized to nicotinic acid, accounting for its clinical effects.[16] A similar study apparently has not been done with 3-aminomethylpyridine (Table IA).

It may be seen from Table IA that, for active compounds, the micromolar I_{50}'s remain relatively constant and in the range for NA itself. These data suggest that these compounds, too, may depend on metabolism to NA for their effect. If this is in fact true, the actual I_{50} levels may be somewhat lower, as no correction was made for fatty acids which would be released by breakdown of the test compounds. A similar correction[21] applied to data obtained by Linscheer, *et al.*,[22] indicated that the administration of octanoic acid to normal and cirrhotic volunteers actually reduced serum NEFA levels. A comparison of **7** and **8** reveals the effect of saturated *vs.* unsaturated higher fatty acid residues. A similar difference has been noted between the effect of *N*-cyclohexylstearamide and *N*-cyclohexyllinoleamide on lipid levels in cholesterol-fed rabbits.[23] In the latter study, the unsaturated isomer was effective in reducing serum cholesterol level, while the test group on the saturated amide did not significantly differ from controls until after the fourth week of medication. Another unsaturated derivative, *N*-(α-methylbenzyl)linoleamide[24] was found even more effective than the cyclohexyl analog.

The hydrazides **15**-**23** are capable of releasing NA by simple hydrolysis. It would appear, however, that the structure of the side chain plays a significant role, possibly related to steric (**21**) or electronic (**20**, **22**, and **23**) features. Again, the micromolar I_{50} doses do not differ significantly from NA.

Unlike the previous derivatives, the hydroxamic acids are themselves weak acids whose pK_a values are dependent on substituents. They are all weaker acids than NA (pK_a = 4.5). A relationship between pK_a of NA-like compounds and the decrease of NEFA levels has been suggested, and other acidic compounds such as the tetrazole A (pK_a = 4.1) have been shown to decrease NEFA levels effectively in animals.[25]



A

The present data demonstrate that acidity alone is insufficient to bring about reduction of NEFA levels.

In an effort to determine whether the test agents were releasing NA, a time study was conducted. Representative samples (**11**, **15**, and **26**) were administered by intubation, and serum NEFA levels were determined at 30, 60, and 90 min after test compound administration. Maximum effect for all compounds was reached at 30 min. At 60 and 90 min, NEFA levels in the test groups medicated with NA, **11** and **26** had rebounded above control levels,[26,27] while those in the groups medicated with **15** remained slightly depressed (Figure 1). A similar study with nicotinamide[28] demonstrated that the lipid-lowering effects of this drug paralleled blood levels of released NA. The longer serum half-life of nicotinamide (2.1 hr *vs.* 47 min for NA) provided extended lowering of NEFA levels without a rebound effect. It is possible therefore that the result with **15** is a consequence of a slower release of NA compared with **11** and **26**.

Dalton, *et al.*,[27] demonstrated that parenterally administered NA or 3-pyridylcarbinol lowers serum cholesterol and triglyceride levels in the fasted rat. Using this technique, a representative sample from each of the above chemical

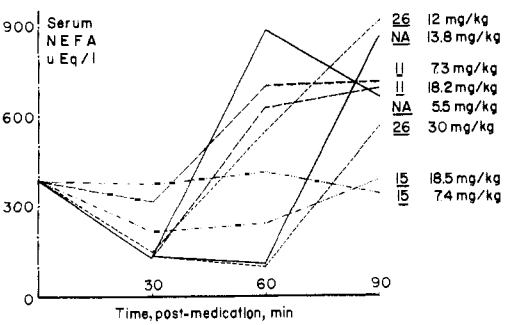


Figure 1. Serum NEFA time: course study; overnight fasted rats, 6 rats per point; medication route: ig.

Table III. Effect of 9 Daily ig or ip Administrations of NA or **26** on Rat Serum Cholesterol and Serum and Liver Triglycerides

Test agent	Dose (as NA), mg/kg	Weight, g		Serum cholesterol, mg/100 ml	Serum triglycerides, mg/100 ml	Liver triglycerides, mg/g
		Initial	Final			
None[a]	None	180	215 (11)[b]	66.2 ± 3.7 (11)	60.8 ± 3.9 (11)	2.89 ± 0.17 (11)
NA, ig	250	181	205 (11)	60.3 ± 3.6 (11)	34.1 ± 4.2 (11)	3.73 ± 0.62 (11)
			ns	ns	P = <0.001	ns
NA, ip	250	182	153 (3)	31.3 (3)	35.5 (3)	3.39 (3)
26, ig	250	180	211 (11)	52.3 ± 3.2 (11)	56.6 ± 8.5 (11)	3.55 ± 0.54 (9)
			ns	P = 0.01	P = >0.6	ns
26, ip	250	181	187 (9)	41.0 ± 4.3 (9)	39.6 ± 6.3 (9)	3.09 ± 0.88 (9)
			P = <0.001	P = 0.001	P = <0.02	ns

[a]Half the rats dosed with gum tragacanth orally, half parenterally. [b]Numbers of rats in parentheses.

Table IV. Effect of Orally Administered Compound on Ear Skin Temperature of Unanesthetized Male Guinea Pigs

Compound	Dose (as NA), mg/kg	Peak time, min postmedication	Δ Temp, °C mean ± se
None	(7)		0.11 ± 0.18
NA	0.50 (7)	13	0.96 ± 0.67[b]
	1.25 (7)	15	3.59 ± 0.32
	3.2 (7)	12	2.34 ± 0.41
10	3.2 (5)	9	0.46 ± 0.12[b]
	12.5 (7)	16	0.99 ± 0.05
	50 (7)	20	2.50 ± 0.74
15	12.5 (7)	15	1.44 ± 0.22
	50 (10)	14	1.83 ± 0.20
26	3.2 (7)	16	4.05 ± 0.74
	50 (7)	12	2.17 ± 0.05
28	3.2 (7)	16	2.10 ± 0.61
	50 (7)	14	4.59 ± 0.69

[a]Number of guinea pigs in parentheses. [b]P not significant, all others P = <0.01 compared with control value.

classes was examined for its effects on serum and liver lipids (Table II).

Statistically significant reduction of serum cholesterol and serum triglyceride levels occurred following NA at 250 mg/kg and following molar equivalent amounts of **15** and **26**. Reduction of liver triglyceride levels was statistically significant for NA and **15** but not **26**. The ip toxicity of **11** prevented its being tested at NA equivalent levels. Using the same protocol in male gerbils, no lowering of serum cholesterol could be observed for NA or the test compounds. In a 9-day chronic study, equivalent doses of NA and **26** were compared orally and parenterally (Table III). Orally **26** had no adverse effect on body weight and significantly lowered serum cholesterol but not serum or liver triglyceride levels. Parenterally administered **26** significantly lowered serum cholesterol *and* triglyceride levels but adversely affected weight gain.

To assay the NA-like liabilities of vasodilation (flushing),[8] we examined the vascular effects of the drug in normal mice, hairless mice, and monkeys. No overt changes in the ears, snout, paws, or tail resulted from NA po in the mice at 500 mg/kg or in the monkeys at 100 mg/kg.[28,†] The procedure of Eriksson, *et al.*,[14] for detecting NA-like vascular effects in guinea pig ears was modified by utilizing conscious animals. The mean premedication ear temperature of 92 animals was 29.2° (26.8°-31.3°). As may be seen from Table IV, all of the test compounds elicted statistically significant temp increases suggesting that no diminution of vascular effects had been achieved.

That the gastrointestinal effects of NA might be associated with hyperacidity suggested the possibility of using gastric secretion assays as a means of determining whether test agents might be expected to produce this undesirable side effect. In dogs **26** produced less gastric secretion than NA but more than controls (Table V). In pyloric ligated rats, however, no change from controls was noted for **26** or NA.

Table V. Gastric Secretion Studies in Dogs[a]

Medication	Dose,[b] mg/kg	Average volume of gastric secretions collected during 2-hr period, ml
Control (1% GT)	(3)	4.7
NA	100 (6)	122.5
	75 (4)	34.8
26	185 (3)	60.2

[a]Gastric secretion was measured in overnight fasted beagle dogs which had been prepared with chronic gastric fistulas. The amounts secreted were based on the volume of gastric contents collected over a 2-hr period following oral administration of the test compound. [b]Number of dogs in parentheses.

Conclusions. The data suggest that the hypolipemic test compounds depend for their physiological effect on the release of nicotinic acid. The biological activity profiles of these compounds are qualitatively similar to nicotinic acid and indicate that this method of chemical modification would probably offer no clinical advantage over the parent drug.

Experimental Section‡

The following examples are illustrative of the methods used to prep the compds in Table I. Only single expts were performed, and no attempts were made to optimize yields.

A. Acyl Derivative. *N,N*-Bis(3-pyridylmethyl)octanamide (**11**). Octanoyl chloride (8.13 g, 0.05 mole) was added dropwise to a cooled (<30°) soln of 3,3′-dipicolylamine (9.96 g, 0.05 mole) in 50 ml of dry C_5H_5N. The mixt was stirred 16 hr at ambient temp and was then dild with H_2O and excess 10% NaOH. After extn with C_6H_6 and removal of the solvent, the residue was distd; bp 199–201° (0.02 Torr), 10.5 g (64.8% yield) $n^{25}D$ 1.5412.

B. Hydrazides. Nicotinic Acid 2,2-Dimethylhydrazide (**15**). Nicotinoyl chloride HCl (36 g, 0.22 mole) was added in portions to a stirred, cooled (<40°) soln of 30 ml of Me_2NNH_2 in 150 ml of C_5H_5N. The mixt was stirred 10 min longer before it was concd on a rotary evaporator. The residue was treated with H_2O and excess 10% NaOH, and the product was extd into $CHCl_3$. Removal of the dried ($MgSO_4$) solvent and crystn of the residue from C_6H_6–hexane gave 21.8 g (60% yield) of pale yellow crystals, mp 87–89°.

C. Hydroxamic Acid Derivatives. *N*-(Benzyloxy)nicotinamide (**26**). A soln of *O*-benzylhydroxylamine§ (17.6 g, 0.14 mole) in 100 ml of dry C_5H_5N was stirred and cooled below 30° while nicotinoyl chloride HCl (25.4 g, 0.14 mole) was added in portions. After being stirred overnight, the reaction mixt was stripped free of solvent under reduced pressure, and the residue was dissolved in excess

†Similar results have been observed for normal mice, rats, rabbits, ground squirrels, sheep, and dogs.[29]

‡Mps were taken on a Mel-Temp app and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and Instranal Inc, Rensselaer, N. Y. Analytical results for C, H, and N for all new compds cited were within 0.4% of the theoretical values.

§Prepared according to ref 30.

10% NaOH. The aq soln was washed twice with Et_2O and was then neutralized with glacial HOAc. The soln was saturated with solid $NaHCO_3$, and the product was extd with several portions of C_6H_6. Evapn of the dried solvent left 17.7 g (55.5% crude yield) of product of mp 88–95°. Recrystn from 100 ml of *i*-PrOAc gave 13.5 g (42.3% yield) of crystals, mp 88–90°.

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Centrally Acting Emetics. 6. Derivatives of β-Naphthylamine and 2-Indanamine[1,†]

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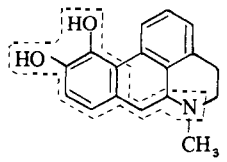
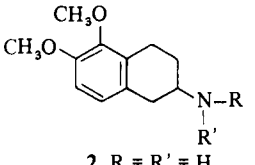
A series of dihydroxy aminotetralins and aminoindans has been prepared as analogs and congeners of fragments of the apomorphine molecule. The high emetic potency observed for certain of these compounds is consistent with current theories of the "dopaminergic" character of apomorphine. Marked differences in potency between the tetralin and the indan series are discussed.

Apomorphine (**1**), which has assumed considerable importance in efforts aimed at understanding the role of *l*-dopa and dopamine in the etiology and therapy of parkinsonism, has structural similarities (as indicated) to dopamine. Apomorphine probably directly activates "dopaminergic" receptors,[2] and McGeer[3] has stated that dopa may cause emesis by stimulation of the *chemoreceptor trigger zone* ("CTZ"), the receptor involved in the emetic action of apomorphine. Ernst and Smilek[4] have shown that dopamine, like apomorphine, is a potent elicitor of the gnawing response in rats.



1



2, R = R' = H
3, R = H; R' = Me
4, R = R' = Me

A prior communication from this laboratory[5] described preparation and emetic effects of a series of 5,6-dimethoxytetrahydronaphthylamines **2–4**. These compounds not only are congeners of a fragment of the apomorphine molecule, but they are also derivatives of a cyclic dopamine structure. Compounds **3** and **4**, while inert as emetics in the dog, were far more active in the pigeon than was apomorphine. Since it has been stated[1,6] that apomorphine must possess free, unetherified phenolic groups in order to exert central emetic effects, it was speculated that perhaps the emetic activity displayed by **3** and **4** in the pigeon reflects an ability of this species (as contrasted with the dog) efficiently to demethylate the phenolic ether systems, and to generate the biologically active catechol moiety. It was further speculated that if this were the case, the free phenol derivatives of **3** and **4** should elicit emesis in the dog as well as in the pigeon. Numerous attempts in this laboratory to cleave the ether links of **2–4** failed;[5] however, success has been realized utilizing a modification of a method of Thrift.[7]

Compounds **2–4** were prepared by the sequence of Sprenger *et al.*;[5] attempts to prepare **6** by the Sprenger method of Neber rearrangement of the oxime tosylate **5** with EtO^- in refluxing EtOH gave erratic results and frequently failed completely. Replacement of the EtOH solvent by benzene permitted consistently successful Neber reactions.

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