collected). Fractions 3-8 contained 1.1 g (35%) of **13**: mp 46–48 °C; IR (film) 2690, 1700, 1470, 1298, 940, 710 cm^{-1}. Anal. ($C_{21}H_{40}O_2$) C, H.

1-Hydroxymethyl-3-pentadecylcyclopentane (14). $LiAlH_4$ (0.70 g, 0.018 mol) was added to 26.5 mL of dry ether in a 50-mL three-neck flask equipped with a reflux condenser, a gas inlet tube, and a rubber septum. A positive pressure of argon was maintained throughout the reaction. The $LiAlH_4$ solution was stirred magnetically at 25 °C and 1.97 g (0.006 mol) of **13** in 10 mL of ether was added dropwise over 10 min. After stirring overnight, 1.6 mL of ethyl acetate was added, followed by 1 mL of H_2O and then 25 mL of 10% H_2SO_4. The resulting clear solution was extracted with ether (3 × 40 mL). The combined extracts were washed with 10% NaOH, followed by H_2O, and dried (Na_2SO_4). Evaporation of the Et_2O gave 1.68 g (89%) of **14** as a low-melting solid: IR (film) 3350, 1460, 1020, 700 cm^{-1}. Anal. ($C_{21}H_{42}O$) C, H.

1-Hydroxymethyl-3-pentadecylcyclopentane Diphenyl Phosphate Ester (15). A solution of **14** (1.0 g, 0.003 mol) in 3 mL of dry pyridine was placed in a 25-mL flask. The flask contained a stirring bar and was stoppered with a rubber septum. The solution was cooled to 5 °C (ice bath) and 1.5 mL (0.007 mol) of freshly distilled diphenyl chlorophosphate in 3 mL of pyridine was added with a syringe. The resulting reaction mixture was stirred 15 min and kept at 5 °C overnight. Ice water (5 mL) was added and the solution stirred. After 30 min it was poured onto 60 g of ice and extracted with $CHCl_3$ (3 × 60 mL). The combined extracts were washed, first with dilute HCl and then with H_2O. The $CHCl_3$ solution was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was streaked on preparative TLC plates (20 × 20 cm × 1.5 mm, Al_2O_3) and developed with hexane. The bands remaining at the origin were removed with ether and streaked on additional alumina plates. These were developed with benzene to give a single band, R_f 0.5. Elution with ether gave 1.0 g (58%) of pure **15**: mp 34–35 °C; IR (film) 3080, 1600, 1480, 1470, 1280, 1185, 1030, 760, 680 cm^{-1}. Anal. ($C_{33}H_{51}PO_4$) C, H.

1-Hydroxymethyl-3-pentadecylcyclopentane Dihydrogen Phosphate (16). Diphenyl phosphate ester **15** (0.5 g, 0.0009 mol) was dissolved in 25 mL of absolute ethanol and reduced over 400 mg of PtO_2 at 55 psig for 60 h. Filtration and solvent evaporation left a quantitative yield of **16** as a low-melting wax: IR (film) 1465, 1170, 1010 cm^{-1}. Anal. ($C_{21}H_{43}PO_4$) C, H.

1-Hydroxymethyl-3-pentadecylcyclopentane Monosodium Phosphate (17). To a solution of **16** (0.36 g, 0.0009 mol) in 15 mL of H_2O was added freshly washed Dowex 50 W-X8 (3 mL, wet). The resulting mixture was stirred 1 h. Filtration and lyophilization gave a quantitative yield of the monosodium salt **17**: mp 57–61 °C. Anal. ($C_{21}H_{42}PO_4Na$) C, H.

Acknowledgment. This work was supported in part by NIH Training Grant GM-1341, by NIH Career Development Award GM-16007, and by the University of Kansas Research Fund. A.N.M. gratefully acknowledges receipt of an American Foundation for Pharmaceutical Education Fellowship. Thanks are also due to Dr. E. J. Walaszek for the biological data.

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Preparation and Biological Actions of Some Symmetrically N,N-Disubstituted Dopamines

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Received August 15, 1977

The title compounds have been synthesized and evaluated for emetic effects in the dog, actions on the cardioaccelerator nerve in the cat, pecking in pigeons, and for behavioral effects following both peripheral and direct intracerebral injection into the nucleus accumbens and caudate-putamen of the rat. Generally, in the series studied, the *N,N*-diethyl and *N,N*-di-*n*-propyl congeners of dopamine displayed notably high degrees of activity. However, the test compounds exerted differing effects on peripheral and central dopamine receptors and in the area postrema. Differentiations of the activities of the different homologues within the brain were also shown.

Prior communications have described dopaminergic[1,2] and α-adrenergic effects[3] of *N,N*-dimethyldopamine (**1**). Ginos et al.[4] have demonstrated dopaminergic activities in a series of unsymmetrically N,N-disubstituted dopamines, but they found *N,N*-dimethyldopamine to be inert as a dopaminergic agonist in their assay systems. The dopaminergic activity of 2-amino-5,6-dihydroxytetralin and aporphine derivatives is modified qualitatively and quantitatively by N-alkylation, where ethyl or *n*-propyl substitution confers the maximal increase in activity.[5-8]

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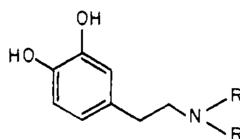
Table I. Various Biological Properties of Symmetrical N-Alkyl Homologues of Dopamine

Compd	Inhibition of cat cardioaccelerator nerve stimulation—rate		Emesis by dogs	Pecking by pigeons
	In vivo, ED_{50}, μmol/kg	In vitro, ED_{50}, μmol/L		
Apomorphine hydrochloride	0.10 (0.08-0.13)[a,b]	0.043 (0.007-0.073)	ED_{50} 0.14 μmol/kg (0.13-0.18)	e
1	0.024 (0.006-0.038)[c]	0.07 (0.04-0.15)	No emesis, no antagonism of apomorphine	Antagonizes apomorphine, ED_{50} 9.7 μmol/kg
2	0.041 (0.015-0.059)[b]	0.34 (0.23-0.57)	No emesis, no antagonism of apomorphine	No induced pecking, no antagonism of apomorphine
3	0.068 (0.011-0.104)[b]	0.42 (0.19-2.7)	ED_{50} ~1 mg/kg	Antagonizes apomorphine, ED_{50} 56 μmol/kg
4	No inhibn at 10 μmol/kg	No inhibn at 10 μmol/L	d	d

[a] 95% confidence intervals of ED_{50} values in parentheses. [b] Antagonized by haloperidol (0.2 mg/kg). [c] Antagonized by either phentolamine (2 mg/kg) or haloperidol (0.2 mg/kg). [d] Not tested. [e] 1.62 μmol/kg of apomorphine used to induce pecking.

While the primary amines within the 2-aminotetralin series and the secondary amine, norapomorphine, are behaviorally inactive or only weakly active on peripheral injection, due to their relative inability to cross the blood–brain barrier,[8,9] N-alkylation allows such agents to penetrate cerebral tissue and facilitates a more effective receptor interaction.[5,7] In the phenethylamine series, the primary amine dopamine is also behaviorally inactive on peripheral administration, due to its rapid peripheral metabolism and its failure to pass the blood–brain barrier. The possibility that symmetrical N,N-dialkylation with ethyl, n-propyl, and n-butyl groups might modify dopamine-like actions in the phenethylamine series has not been investigated. In the present study, we report the synthesis of a short series of symmetrically N,N-disubstituted dopamines (**2–4**) and assess their potential as



1, R = CH_3
2, R = C_2H_5
3, R = n-C_3H_7
4, R = n-C_4H_9

dopamine agonists for inducing emesis in dogs, pecking behavior in pigeons, cardioaccelerator nerve inhibition in cats, and in behavioral tests in the rat, using peripheral injection and administration into the nucleus accumbens and caudate-putamen using the intracerebral injection technique.

Compounds **2–4** were prepared by treatment of 2-(3,4-dimethoxyphenyl)ethylamine with a sodium borohydride–carboxylic acid (acetic, propionic, butyric) complex, according to a method of Marchini et al.[10] Spectral (IR, NMR, and MS) data on all intermediates and final compounds were consistent with the proposed structures.

Pharmacology. Activity for inhibition of the cardioaccelerator nerves following postganglionic nerve stimulation was determined in cats. Apomorphine and agents believed to activate dopaminergic receptors have been reported to induce pecking in pigeons, and this was used as an assay.[11] Also, the ability to induce emesis in dogs was evaluated, since dopamine itself as well as various cyclic analogues of dopamine are potent emetics. A summary of these biological activities is shown in Table I. The ability to inhibit stimulation of the cardioaccelerator nerve by an electrical current of 2-Hz frequency in cats decreased in potency with substitution of methyl through n-propyl. The compounds were not active when an electrical stimulation of 10-Hz frequency was used. The di-n-butyl compound **4** was inactive even with higher doses. The diethyl (**2**) and di-n-propyl (**3**) derivatives were antagonized by haloperidol (0.2 mg/kg) administered intravenously. In the cat, phentolamine (2 mg/kg) did not antagonize either the diethyl (**2**) or the di-n-propyl (**3**) derivatives. In the cat, N,N-dimethyldopamine (**1**) was partially antagonized by both phentolamine and haloperidol. In the dog, only phentolamine appeared to be an effective antagonist of the nerve terminal inhibiting property of this compound. As has been previously reported,[3] N,N-dimethyldopamine produced only a pressor response by activation of α receptors. Compounds **2** and **3** produced hypotensive responses of approximately the same duration as inhibition of the cardioaccelerator nerve terminal. Compound **4** did not alter the blood pressure in the doses tested. Haloperidol blocked the hypotensive effects of **2** and **3**. The only emetic in the series was **3**, and it was approximately $^1/_{15}$th as active as apomorphine. Compounds **1** and **2** did not induce emesis and they did not antagonize apomorphine. No observable changes were induced in any of the dogs with doses up to 2 mg/kg subcutaneously.

None of the compounds induced pecking in pigeons. Compound **2** did not antagonize apomorphine-induced pecking, but compounds **1** and **3** were effective antagonists of pecking induced by apomorphine. Compound **1** was approximately one-tenth as active as haloperidol in its ability to antagonize apomorphine in this preparation.

This study indicates that the N,N-dimethyl, -diethyl, and -di-n-propyl analogues of dopamine are capable of inhibiting the sympathetic nerve terminals innervating the heart. The dosage ranges are similar to those reported for dopamine. However, the presence of cocaine is required to produce inhibition by dopamine.[12] With these agents (**1–3**) the inhibitory action is manifested without the presence of cocaine. As evidenced by antagonism of the inhibitory action, the N,N-diethyl and N,N-di-n-propyl derivatives appear to be inducing inhibition by interacting with dopamine receptors on the nerve terminal. The N,N-dimethyl derivative appears to activate both α receptors and dopamine receptors to induce its inhibition. None of the compounds induced heart rate changes in the cat. In animals with intact sympathetic nerves, brady-

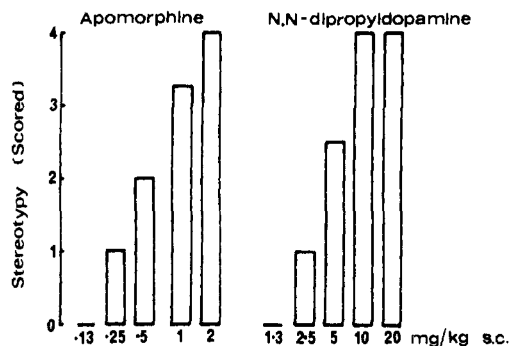


Figure 1. The dose-dependent nature of the stereotyped behavior induced by apomorphine and *N,N*-di-*n*-propyldopamine. Values represent the means of the maximum responses from 6 to 12 rats. Stereotyped behavior was assessed according to the scoring system described in the text.

cardia was produced by doses used in this study.

Though the mechanism by which apomorphine analogues induce emesis in dogs is controversial, the only agent with emetic activity was the di-*n*-propyl derivative **3** (see Table I).

All compounds appeared to be inactive in inducing pecking in pigeons. Consequently, *N,N*-di-*n*-propyldopamine appears to be an exception to the pattern usually found in the literature. The *N,N*-dimethyl and *N,N*-di-*n*-propyl derivatives antagonized apomorphine in this preparation, and they may be blocking dopamine receptors here.

Behavioral Effects. On subcutaneous injection, *N,N*-di-*n*-propyldopamine induced stereotyped behavior in the rat and, although less potent, produced fully as effective responses as apomorphine (Figure 1). While the onset of action of both agents was rapid (less than 5–10 min), the duration of stereotypy induced by *N,N*-di-*n*-propyldopamine was very brief (10–25 min) compared to apomorphine (20–90 min). In addition, animals receiving 40 mg/kg showed marked locomotor activity subsequent to the stereotypic phase. All behavioral effects were blocked by a 30-min pretreatment with haloperidol (0.4 mg/kg), whereas aceperone (5 mg/kg), propranolol (5 mg/kg), cyproheptadine (5 mg/kg), and an 18-h reserpine (5 mg/kg) plus 6-h α-methyl-*p*-tyrosine (250 mg/kg) pretreatment were ineffective. *N,N*-Dimethyl-, *N,N*-diethyl-, and *N,N*-di-*n*-butyldopamine (2.5–20.0 mg/kg) failed to induce either stereotypy or hyperactivity.

In the circling model, apomorphine and *N,N*-di-*n*-propyl- and *N,N*-diethyldopamine reversed the spontaneous ipsilateral circling behavior to a contralateral circling response (Figure 2). The onset of action for all agents was rapid (3–10 min), although the duration of circling due to *N,N*-di-*n*-propyl- and *N,N*-diethyldopamine (5–50 min) was less than that induced by apomorphine (40–80 min). Using the higher doses of apomorphine and *N,N*-di-*n*-propyldopamine, the development of stereotypy effectively reduced the circling response. The circling response induced by all agents was reduced by haloperidol (0.8 mg/kg); aceperone (5 mg/kg), propranolol (5 mg/kg), and cyproheptadine (5 mg/kg) were ineffective. *N,N*-Dimethyl- and *N,N*-di-*n*-butyldopamine (2.5–20.0 mg/kg) failed to induce circling.

In contrast to dopamine and *N,N*-diethyldopamine, *N,N*-di-*n*-propyldopamine failed to modify the motor function on intrastriatal injection. While *N,N*-diethyldopamine induced both hyperactivity and stereotypy, the most important effect of dopamine was to induce stereotypy (Figure 3). However, in the nucleus accumbens, the characteristic action of dopamine was to induce hyperactivity (the stereotypy which developed was never more intense than repetitive limb and head movements), while *N,N*-di-*n*-propyldopamine induced hyperactivity and all components of stereotypy. *N,N*-Diethyldopamine induced an intense hyperactivity response and an in-

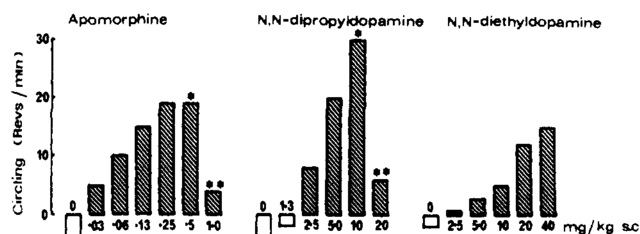


Figure 2. Circling behavior induced by apomorphine and *N,N*-diethyl- and *N,N*-di-*n*-propyldopamine after 6-hydroxydopamine lesion of the medial forebrain bundle in the lateral hypothalamus. Hatched columns = circling behaviors contralateral in direction to the side of the lesion; open columns = ipsilateral. Concomitant development of stereotyped head and limb movements (*) or stereotyped biting (**). Circling behavior is expressed as the maximum number of revolutions achieved in a 1-min period during the action of the drug. Animals were tested every 10 min throughout the duration of the drug effect. Standard errors are all less than 14% of the means.

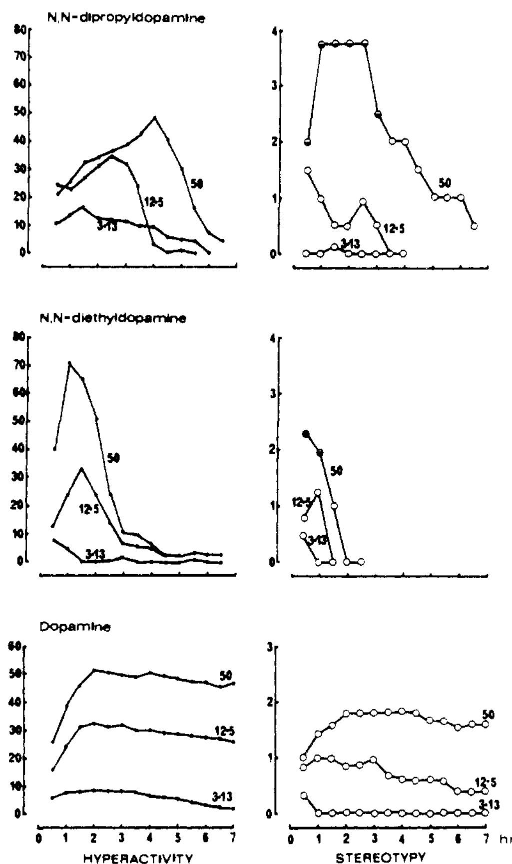


Figure 3. Hyperactivity and stereotyped behavior induced by dopamine and *N,N*-diethyl- and *N,N*-di-*n*-propyldopamine injected bilaterally into the nucleus accumbens. Doses indicate in micrograms the amount unilaterally administered in microliters to rats pretreated with nialamide (100 mg/kg ip, 2 h). Hyperactivity is expressed in counts/5 min and the results presented are considered to reflect "true" hyperactivity and not stereotyped movements. Stereotypy is scored according to the text. ○ represents sniffing behavior or repetitive head and limb movements; ● represents biting, gnawing, or licking; while ◒ indicates that some animals exhibited sniffing while others were biting. Hyperactivity and stereotyped behavior were recorded for 7 h as indicated. Six to eight animals were used at each dose level of drug and standard errors on the means are less than 15%.

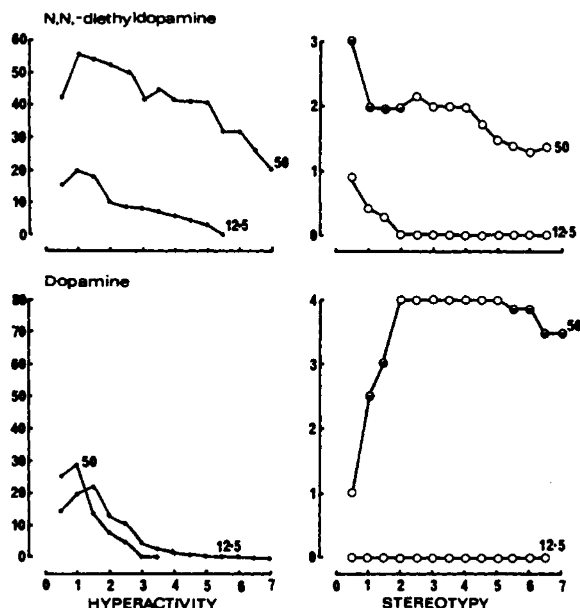


Figure 4. Hyperactivity and stereotyped behavior induced by dopamine and *N,N*-diethyldopamine injected bilaterally into the caudate-putamen. Doses indicate in micrograms the amount unilaterally administered to rats pretreated with nialamide (100 mg/kg ip, 2 h). Hyperactivity is expressed in counts/5 min and the results presented are considered to reflect "true" hyperactivity and not stereotyped movements. Stereotypy is scored according to the text. O represents sniffing behavior or repetitive head and limb movements; ● represents biting, gnawing, or licking; while ⊖ indicates that some animals exhibited sniffing while others were biting. Hyperactivity and stereotypy were recorded for 7 h as indicated. Six to eight animals were used at each dose level of drug and standard errors on the means were less than 18%.

consistent and transient stereotypy (Figure 4). The motor effects induced by dopamine and **2** and **3** when injected into either the caudate-putamen or nucleus accumbens were abolished by haloperidol (0.2–0.8 mg/kg) but not reduced by aceperone (5 mg/kg), propranolol (5 mg/kg), or cyproheptadine (5 mg/kg). *N,N*-Dimethyl- and *N,-N*-di-*n*-butyldopamine failed to modify the motor functions both on intrastriatal and intraaccumbens injection (3.13–50 μg).

As assessed in the 6-hydroxydopamine circling model, *N,N*-di-*n*-propyl- and *N,N*-diethyldopamine caused marked contralateral circling indistinguishable from that induced by apomorphine. If contralateral circling is taken as an index of striatal dopamine receptor stimulation,[13] with a locomotor component representing mesolimbic stimulation,[14] it is clear that, unlike dopamine, *N,N*-diethyl- and *N,N*-di-*n*-propyldopamine and other dopamine derivatives[4] have an ability to pass the blood–brain barrier and stimulate cerebral dopamine mechanisms. The antagonism of their effects by haloperidol and the ineffectiveness of α- and β-adrenergic and 5-hydroxytryptamine blocking agents, aceperone, propranolol, and cyproheptadine, further indicate an important dopaminergic involvement. Also, *N,N*-di-*n*-propyldopamine induced stereotyped behavior, which was antagonized by haloperidol but was resistant to aceperone, propranolol, cyproheptadine, and a combined reserpine plus α-methyl-*p*-tyrosine pretreatment. While *N,N*-diethyldopamine failed to induce stereotypy, this may simply reflect an insufficient dose relative to the dose of *N,N*-di-*n*-propyldopamine [cf. 2-(*N,N*-di-*n*-propylamino)- and 2-(*N,N*-diethylamino)-5,6-dihydroxytetralin[15]]. However, the *n*-butyl substitution in both the phenethylamine and the 2-aminotetralin series is clearly too large for an effective dopamine receptor interaction.

Considerable evidence now indicates that drug-induced stereotyped behavior is mediated via both extrapyramidal and mesolimbic dopamine systems.[16] Thus, whereas the nucleus accumbens is more sensitive to the stereotypic action of *N*-*n*-propylnorapomorphine and 2-(*N,N*-di-*n*-propylamino)-5,6-dihydroxytetralin,[5,7] the caudate-putamen is more sensitive to apomorphine and 2-(*N,N*-diethylamino)-5,6-dihydroxytetralin.[5,15] The apparent preferential action of dopamine agonists with *N*-*n*-propyl groups for the nucleus accumbens was further indicated by the consistent and prolonged stereotyped/hyperactive response induced by administration of **3** into the nucleus accumbens. At this site, compound **2** was far less effective as a stereotypic agent. Since the predominant effect of dopamine administered into the nucleus accumbens is to induce hyperactivity,[17] it is clear that *N,N*-di-*n*-propyl substitution within the phenethylamine series can modify a dopamine-like action to include a stereotypic component within the mesolimbic brain area. Although *N,N*-diethyl substitution failed to confer an effective stereotypic action, the hyperactivity potential was at least as great as that of dopamine itself. While the spectrum of hyperactivity/stereotypic action of N-alkylated phenethylamines administered into the nucleus accumbens generally reflects that of the N-alkylated 2-aminotetralin derivatives, N-alkylation within the two series does not necessarily confer the same dopamine-like properties for, in contrast to *N,N*-di-*n*-propyldopamine, 2-(*N,N*-di-*n*-propylamino)-5,6-dihydroxytetralin failed to induce hyperactivity.[7] Again, however, it is interesting that *N*-*n*-butyl derivatives from both series have no action.

Although injections of dopamine into the striatum can induce hyperactivity, a more consistent effect, particularly at higher doses, is the development of stereotyped biting.[18] *N,N*-Diethyldopamine induced both stereotyped and hyperactivity effects on intrastriatal injection, whereas *N,N*-di-*n*-propyldopamine had no consistent action. Thus, within both the phenethylamine and 2-aminotetralin series, it is apparent that *N,N*-diethyl substitution results in compounds that are more potent than *N,N*-di-*n*-propyl-substituted derivatives on intrastriatal injection. Similarly, *N*-*n*-butyl substitution fails to confer a dopamine-like action in both series.

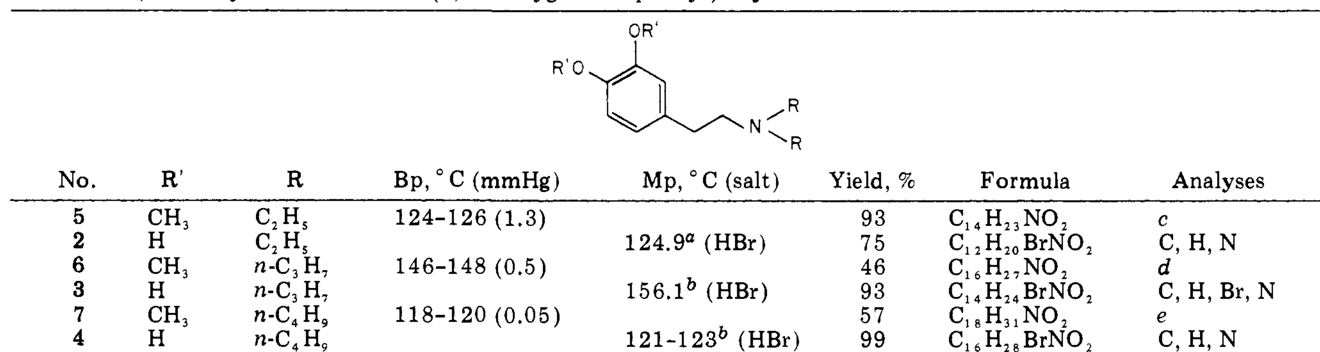
It is interesting to attempt some comparison between the actions of the symmetrically N,N-disubstituted homologues of dopamine on peripheral and central mechanisms. First, it is tentatively suggested that the requirements for peripheral and central dopamine receptor stimulation may differ; for example, the ability to inhibit stimulation of the cardioaccelerator nerve decreased from methyl to propyl, whereas behavioral effects characteristic of cerebral dopamine receptor stimulation induced by peripheral drug administration decreased from propyl to methyl. Second, the present data give the first indication that the dopamine receptors within the area postrema may differ from those within the periphery and other areas of the brain in their selectivity for only one homologue.

Experimental Section

Melting points were determined in open glass capillaries on a Mettler FP-5 automated melting point apparatus programmed for a 2 °C/min rise and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Where analyses are indicated by the symbols of the elements, the analytical results were within ±0.4% of the theoretical values.

Pharmacology. Methods. Cats were anesthetized with pentobarbital sodium (35 mg/kg), administered into the thorax. Tracheotomy was performed and ventilation was supported by a Harvard respiratory pump. The arterial blood pressure was

Table II. *N,N*-Dialkyl Derivatives of 2-(3,4-Dioxygenated phenyl)ethylamines



No.	R'	R	Bp, °C (mmHg)	Mp, °C (salt)	Yield, %	Formula	Analyses
5	CH_3	C_2H_5	124-126 (1.3)		93	$C_{14}H_{23}NO_2$	*c*
2	H	C_2H_5		124.9[a] (HBr)	75	$C_{12}H_{20}BrNO_2$	C, H, N
6	CH_3	*n*-C_3H_7	146-148 (0.5)		46	$C_{16}H_{27}NO_2$	*d*
3	H	*n*-C_3H_7		156.1[b] (HBr)	93	$C_{14}H_{24}BrNO_2$	C, H, Br, N
7	CH_3	*n*-C_4H_9	118-120 (0.05)		57	$C_{18}H_{31}NO_2$	*e*
4	H	*n*-C_4H_9		121-123[b] (HBr)	99	$C_{16}H_{28}BrNO_2$	C, H, N

[a] From *n*-BuOH-heptane. [b] From EtOH-Et_2O. [c] Mass spectrum *m/e* 237, corresponding to $C_{14}H_{23}NO_2$. [d] Mass spectrum *m/e* 265, corresponding to $C_{16}H_{27}NO_2$. [e] Mass spectrum *m/e* 293, corresponding to $C_{18}H_{31}NO_2$.

measured from the femoral artery using a Statham P-23AA transducer and was recorded using a Beckman RS dynograph. The heart rate was recorded using a cardiotachometer. All injections were made into the cannulated left femoral vein. The thorax was opened by a midline incision and the right cardioaccelerator nerves were exposed. Silver bipolar electrodes were placed on the postganglionic fibers. Increased heart rate was induced using a Grass Model 5 stimulator. The parameters of stimulation were a frequency of 2 or 10 Hz, pulse duration of 5 ms, stimulation for 15–30 s, and supramaximal voltage. After the positive chronotropic responses became consistent following stimulation, the experimental compounds were administered in increasing doses at 0.3 log intervals. Since the duration of action was relatively short, responses to nerve stimulation were allowed to return to control levels before additional doses were administered. Five animals were used to assay each compound. The dose required to produce 50% inhibition of the tachycardia induced by nerve stimulation was calculated from the regression line.

For the in vitro atrial experiments, cats were anesthetized as described above. The chest was opened by midsternal incision. The hearts were quickly removed and placed in Feigen's solution. Ventricular muscle, connective tissue, fat, blood vessels, and left atrium were excised from the right atrium. Preparations were appropriately dissected in oxygenated nutrient solution. The right atrium was placed horizontally in an isolated organ bath (15 mL) between a pair of platinum electrodes. The right atrium was suspended in Feigan's solution of the following composition (millimolar concentration): NaCl, 153.6; KCl, 5.6; $NaHCO_3$, 6.0; $CaCl_2$, 216; glucose, 11.1. The solution was gassed with 95% O_2–5% CO_2 and maintained at 36 °C. Resting tension was adjusted to 1 g. During the equilibration period (20 min), the bathing medium was replaced at intervals of 5 min with fresh solution. The atrial rate was measured by using a Statham strain gauge (G1OB) and a Beckman cardiotachometer. Stimuli were applied for 10 s at the following parameters: 5-ms duration, supramaximal voltage (60–80 V), and 2 Hz. The atrial rate was allowed to return to control values and 10 min was allowed before additional stimulations.

The ability to induce emesis was evaluated in dogs following subcutaneous administration. Possible interactions with apomorphine were evaluated by pretreating dogs with the compounds administered subcutaneously and 15 min later administering apomorphine hydrochloride at a dose of 100 μg/kg subcutaneously.

The ability to induce pecking in pigeons was evaluated following intramuscular administration. The ability to antagonize apomorphine was evaluated by administering the compounds intramuscularly and 15 min later administering apomorphine hydrochloride in a dose of 1.63 μmol/kg.

The studies of behavioral effects utilized male Sprague–Dawley rats weighing 250–300 g. For the intracerebral injection studies, bilateral stainless steel guide cannulae were stereotaxically implanted using the techniques of Costall et al.[5] to allow drug deposition into the nucleus accumbens (anterior 9.0, vertical 0.0, lateral ±1.6) and the caudate-putamen (anterior 8.0, lateral ±3.0, vertical ±1.5).[19] Drug solutions/vehicle were administered bilaterally in a volume of 1 μL over a 5-s period, with a further 55 s being allowed for drug deposition. Animals were used on one occasion only and were then sacrificed for histological examination. All cannulae locations were found to be correct for injections into the areas of the nucleus accumbens and caudate-putamen.

In the circling experiments, rats were subjected to unilateral denervation of the nigrostriatal projection (lateral hypothalamic injection of 8 μg of 6-hydroxydopamine[20]) and were used 14 days after surgery. Circling behavior was measured as the number of revolutions per minute performed by an animal after drug treatment during the 1-min period immediately following its placement in a circular cage 40 cm in diameter. The animals were observed for at least 1 h.

In the locomotor activity experiments, hyperactivity was measured by placing rats individually in perspex cages (30 × 20 × 10 cm high) fitted with photocells, and the number of light beam interruptions caused by the rat within each 5-min period was recorded for at least 7 h. During each 5-min period, the animals were also visually assessed for the presence or absence of locomotor activity and stereotyped behavior. Stereotypy was assessed on a simple scoring system where 0 = no stereotypy; 1 = periodic sniffing and/or repetitive head and limb movements; 2 = continuous sniffing and/or repetitive head and limb movements; 3 = periodic biting, licking, gnawing; 4 = continuous biting, licking, gnawing. Using this system, the presence of locomotor activity does not exclude the development of stereotypy. (The possibility that stereotypy may interfere with the recording of locomotor activity counts has been extensively discussed elsewhere.[18])

For peripheral administration, aceperone (Janssen) and reserpine (BDH) were prepared in the minimum quantity of glacial acetic acid and made up to volume with distilled water; propranolol hydrochloride (ICI), in distilled water, and cyproheptadine hydrochloride (MSD) were prepared in a minimum quantity of *N,N*-dimethylformamide and made up to volume with distilled water; α-methyl-*p*-tyrosine (Sigma) was prepared as a suspension in 2% carboxymethylcellulose; haloperidol (Janssen) was prepared in 1% lactic acid; and apomorphine hydrochloride (Macfarlan Smith) and *N,N*-diethyl-, *N,N*-di-*n*-propyl-, *N,N*-di-*n*-butyl-, and *N,N*-dimethyldopamine hydrobromide were prepared in a 0.1% solution of sodium metabisulfite. For intracerebral injection, dopamine hydrochloride (Aldrich), apomorphine hydrochloride, and *N,N*-dimethyl-, *N,N*-diethyl-, *N,N*-di-*n*-propyl-, and *N,N*-di-*n*-butyldopamine hydrobromide were freshly prepared in N_2-degassed distilled water.

***N,N*-Dimethyldopamine Hydrobromide (1).** This was prepared by the method of Borgman et al.:[21] mp 116–118 °C (lit.[21] mp 129–129.5 °C); NMR (CD_3OD) δ 2.89 (s, 6 H, NCH_3), 3.16 (center) (m, 4 H, aliphatic H), 6.73 (m, 3 H, aromatic H).

***N,N*-Dialkyl-2-(3,4-dimethoxyphenyl)ethylamines.** Solid $NaBH_4$ (7.13 g, 0.19 mol) was added in small amounts to a stirred solution of 0.62 mol of the appropriate carboxylic acid in 105 mL of Na-dried benzene, maintaining the temperature below 20 °C. Stirring was continued for 1.5 h; then 6.75 g (0.0375 mol) of 2-(3,4-dimethoxyphenyl)ethylamine in 15 mL of Na-dried benzene was added in one portion. This mixture was refluxed for 5 h and then was permitted to stand overnight at room temperature. It was then extracted with 1 L of 2 N NaOH in divided portions. The NaOH washings were extracted twice with benzene and the pooled organic phases were washed with water until the washings were nearly neutral to litmus. The organic phase was dried

(Na_2SO_4) and evaporated under reduced pressure to leave a light yellow mobile liquid. This was treated with 3 mL of phenyl isocyanate and was permitted to stand overnight at room temperature. Methanol (25 mL) was cautiously added and the resulting mixture was heated on a steam bath for 0.25 h; then it was evaporated under reduced pressure. The residue was taken up in benzene and this solution was extracted repeatedly with 2.5 N HCl. The pooled HCl extracts were washed with Et_2O, then excess 50% KOH was added, and the resulting mixture was extracted repeatedly with Et_2O. The pooled, dried (Na_2SO_4) ethereal extracts were evaporated under reduced pressure to afford an oily residue which was distilled. See Table II.

Ether Cleavage Reactions. The distilled amine (0.017 mol) was heated with 50 mL of 48% HBr under N_2 for 3 h. Volatiles were removed under reduced pressure, and the residue was recrystallized. See Table II.

Acknowledgment. This investigation was supported in part by Grant GM-22365, National Institute of General Medical Sciences, and in part by the Medical Research Council of the United Kingdom. Miss M. Y. Green gave excellent technical assistance throughout the behavioral studies.

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Acetylenics. 2. Synthesis and Pharmacology of Certain *N,N*-Dialkyl-3-phenylpropyn-2-amines. Some Analogues with Tryptamine-Like Behavioral Effects in Mice[1]

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Received March 3, 1977

A number of *N,N*-dialkyl-3-phenylpropyn-2-amines **7** have been prepared and tested for their biological action. Certain analogues show tryptamine-like behavioral effects in mice. The tryptamine-like activity of these compounds appears to be controlled by their lipophilicity. These compounds show only weak inhibition of rat liver monoamine oxidase. Although these compounds exhibit tryptamine-like action, experiments seem to indicate that there is no interaction with the tryptamine receptors.

Some time ago we reported the synthesis of some 3-phenylpropyn-2-amines.[2a] Preliminary pharmacological studies revealed that these compounds possessed some monoamine oxidase (MAO) inhibitory, anorexigenic, and blood lipid lowering activity.[2b] To study these compounds in greater detail, we undertook the synthesis of a number of their analogues. This paper reports the synthesis and pharmacology of certain *N,N*-dialkyl-3-phenylpropyn-2-amines **7**.

Compounds **7** were tested in vitro for their anti-MAO action and were subjected to a general pharmacological screening in mice. Tryptamine-like behavioral effects, not hitherto seen with these types of compounds,[3] were observed with some of the analogues.

Chemistry. Scheme I shows the synthetic routes used for the preparation of compounds **7**. Although all the compounds **7** (Table I) could be prepared by the Mannich reaction[4] (method A), the synthesis via the alcohol **5** (method B) was used to overcome the requirement of difficultly available substituted phenylacetylenes. In method B, the coupling of iodobenzenes with copper(I) acetylenides to prepare the alcohols **5** was according to the method of Atkinson et al.[5] The coupling reaction using the copper(I) acetylenide derived from the unprotected propargyl alcohol did not work and the unreacted acetylenide was recovered. This unreacted copper(I) acetylenide, probably because of long reflux in pyridine, was found to be highly explosive. Therefore the copper(I) acetylenide derived from the protected propargyl alcohol was used. In this way the coupling reaction proceeded smoothly giving a good yield of compound **4**.

Biological Testing and Results. In Vitro MAO Inhibition. All the final compounds (**7a–j**) were tested for their inhibitory action on rat liver MAO using kynuramine (10^{-4} M) as the substrate.[6] The MAO was solubilized[7] with Triton X-100. The activity was measured by following the increase in absorbance at 316 nm, due to the formation of 4-hydroxyquinoline, and not by following the decrease in absorbance, due to the disappearance of kynuramine, at 360 nm. It was found that, at a given

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