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Articles

N-Alkyl Derivatives of (±)-α-Methyldopamine

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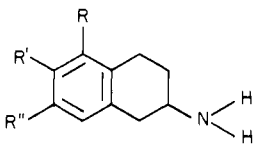
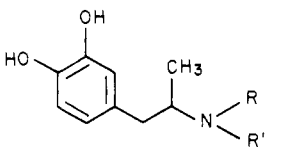
A series of N-alkylated α-methyldopamine derivatives has been prepared for comparison of their biological effects with those of semirigid dopamine congeners derived from 2-aminotetralin systems. All of the α-methyldopamine derivatives were inert as dopaminergic agonists in a variety of animal assays, both centrally and peripherally, although certain compounds produced powerful and prolonged locomotor hyperactivity on intra-accumbens injection in mice, by indirect mechanism(s). A rationalization, based upon conformational analysis, is presented for the lack of direct dopaminergic agonist activity of α-methyldopamine derivatives.

The pronounced dopaminergic agonist activity reported[1,2] for (±)-5,6-dihydroxy- (**1a**) and 6,7-di-



1a, R = R' = OH; R'' = H
1b, R = H; R' = R'' = 2-OH



2, R, R' = combinations of H, CH_3, C_2H_5, n-C_3H_7, 2-C_3H_7, n-C_4H_9

hydroxy-2-aminotetralins (**1b**) and their N-substituted derivatives prompted an investigation of central and peripheral effects in a variety of animal experimental models of an extended series of N-substituted congeners of (±)-α-methyldopamine **2** which, like the aminotetralins, bear the amino group on a secondary carbon, rather than on a primary carbon as in dopamine.

Accounts of biological testing of α-methyldopamine, a few N-alkylated derivatives, and some ether derivatives have indicated that some of these compounds exhibit "epinephrine-like" activity,[3] sympathomimetic effects,[4] β-adrenergic activity,[5] possible stimulation of release-inhibiting α-adrenoceptors in renal hypertensive rats,[6] weak positive inotropic effects,[7] and CNS stimulant effects (via an indirect mechanism).[8] However, the literature revealed only a few reports of investigation of dopamine-like effects of α-methyldopamine systems.[9-11] Noteworthy among these is the reported inability of both enantiomers of α-methyldopamine to produce vasodilatation of the renal artery[11] and the report[9] of a lack of consistent activity spectrum in (±)-α-methyldopamine and its *N*-methyl- and *N,N*-dimethyl homologues in oxotremorine antagonism, reserpine antagonism, and hypothermia assays.

Preparation of the compounds based on **2** involved reductive amination of 3,4-dimethoxyphenylacetone and, when appropriate, subsequent N-alkylation of the amine product. The Experimental Section describes representative types of alkylation procedures employed for the target compounds which are listed in Table I. Spectral (IR and NMR) data on all intermediates and final compounds were consistent with the proposed structures.

Pharmacology. Results. None of the compounds inhibited the positive inotropic or chronotropic response induced by field stimulation of cat atria. Compounds **8**, **15**, **9**, **12**, **2c**, and **2e** (Table I) increased heart rate and inotropic responses following field stimulation. The minimal effective dose for these compounds was 20 μg/L. Compounds **2f**, **2i**, and **2j** increased resting heart rate in doses of 50 μg/L. With these agents there was no increase in the inotropic responses. The very weak inotropic response reported by Tuttle and Mills[7] for *N*-isopropyl-α-methyldopamine (**2a**) was not observed here. The influence of the compounds on heart rate and blood pressure was evaluated in ten dogs anesthetized with sodium

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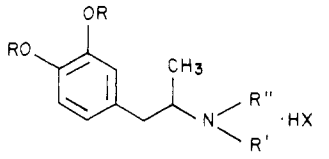
Table I. Derivatives of α-Methyldopamine



no.	R	R'	R''	free base bp, °C (kPa[l])	salt mp, °C[a]	meth of prepn	yield, %	formula	anal.
5	CH_3	H	H		148-151[b,c]		100		
6	CH_3	CH_3	H		117-121[d,e]	A	72		
7	CH_3	CH_3	CH_3		157-158[d,f]	B	58		
8	CH_3	C_2H_5	C_2H_5		174-175[d]	C	87	$C_{15}H_{26}ClNO_2$	C, H, N
13	CH_3	n-C_3H_7	n-C_3H_7		130-131[g]	C	54 (free base)	$C_{17}H_{30}ClNO_2$	C, H, N
14	CH_3	n-C_4H_9	n-C_4H_9		78-82[g]	C	87 (free base)	$C_{19}H_{34}ClNO_2$	C, H, N
15	CH_3	n-C_3H_7	H		143-146[d]	C[h]	38	$C_{14}H_{24}ClNO_2$	C, H, N
9	CH_3	n-C_4H_9	H		147-150[g]	D	89	$C_{15}H_{26}ClNO_2$	C, H, N
16	CH_3	C_2H_5	H	118-120 (0.026)	155-159[g]	D	56	$C_{13}H_{22}ClNO_2$	C, H, N
11	CH_3	2-C_3H_7	H	100 (0.0046)	153-157[g]	E	77	$C_{14}H_{24}ClNO_2$	C, H, N
12	CH_3	2-C_3H_7	CH_3	101 (0.04)	143-146[g]	F	82	$C_{15}H_{26}ClNO_2$	C, H, N
2a	H	2-C_3H_7	H		169-172[g,i]		73	$C_{12}H_{20}BrNO_2$	C, H, N
2b	H	C_2H_5	C_2H_5		169-172[g]		91	$C_{13}H_{22}BrNO_2$	C, H, N
2c	H	2-C_3H_7	CH_3		181-184[g]		63	$C_{13}H_{22}BrNO_2$	C, H, N
2d	H	n-C_4H_9	H		174-178 dec[g]		61	$C_{13}H_{22}BrNO_2$	C, H, N
2e	H	n-C_3H_7	n-C_3H_7		207-209[g]		86	$C_{15}H_{26}BrNO_2$	C, H, N
2f	H	n-C_3H_7	H		184-186[g,i]		78	$C_{12}H_{20}BrNO_2$	C, H, N
2g	H	n-C_4H_9	n-C_4H_9		153-156[g]		76	$C_{17}H_{30}BrNO_2$	C, H, N
2h	H	C_2H_5	H		126-129[g,i]		60	$C_{11}H_{18}BrNO_2$	C, H, N
2i	H	CH_3	CH_3		125-127[g,j]		55	$C_{11}H_{18}BrNO_2$	C, H, N
2j	H	H	H		179-182[g,k]		64	$C_9H_{14}BrNO_2$	

[a] All dimethyl ethers isolated as HCl salts; all free catechols isolated as HBr salts. [b] From MeOH-Et_2O. [c] Lit.[9] mp 149-150 °C. [d] From EtOH-Et_2O. [e] Lit.[9] mp 123-124 °C. [f] Lit.[9] mp 155-157 °C. [g] From 2-PrOH-Et_2O. [h] Ratio of substrate/$NaBH_4$ = 1:2. [i] Reference 4 reported HCl salt. [j] Reference 9 reported HCl salt. [k] Lit.[9] mp 180-182 °C. [l] 1 kPa = 7.5 mmHg.

barbital (200 mg/kg). None of the compounds inhibited the dog cardioaccelerator nerve preparation. Compound **2a** in a dose of 30 μg/kg increased the heart rate an average of 23 beats/min and increased the blood pressure by 40%. At this dose, **2f** decreased the heart rate an average of 35 beats/min and increased the blood pressure by 35%. Compounds **2i** and **2j** at 50 μg/kg both increased the blood pressure by approximately 80% and increased heart rate approximately 50 beats/min. With the exception of **2g** and **2h**, which were not tested, the remaining compounds in doses up to 0.5 mg/kg produced no more than 1.3 kPa (10 mmHg) alteration in blood pressure. Likewise, the resting heart rate was not altered.

In tests in rats with unilateral denervation of the caudate nucleus, **2e**, **2f**, **2j**, **5–8**, 11, and **15** (the only compounds tested) were inactive following a 4 mg/kg dose administered subcutaneously. For comparison, significant rotational responses were obtained with *d*-amphetamine at 1 mg/kg and with apomorphine hydrochloride at 0.25 mg/kg.

None of the compounds induced emesis in dogs with subcutaneous doses as high as 2 mg/kg. Likewise, no antagonism to apomorphine-induced emesis was noted. None of the compounds produced pecking in pigeons. However, in this model, weak antagonistic action to apomorphine was seen with **7**, **8**, **13**, **12**, **2b**, **2c**, and **2j**.

Hyperactivity and Stereotyped Behavior Following Intracerebral Injection into the Nucleus Accumbens of the Rat. Of all of the compounds tested, **2f** caused the most marked hyperactivity response on bilateral injection into the nucleus accumbens in the absence of any pretreatment. Compound **2j** was also active in doses above 6.25 μg, although the response was generally delayed from onset to maximum. Compounds **2e**, **2b**, and **2h** caused significant increases in locomotor hyperactivity when injected into the nucleus accumbens, but only at doses of 50 μg. The intensity of the response to **2h** was the weakest and compared to the low intensity, but significant, response to intra-accumbens dopamine (Figure 1). The abilities of **2j** and **2f** to enhance locomotor activity on intra-accumbens injection were significantly reduced or abolished by pretreatments with α-methyl-*p*-tyrosine or haloperidol, although pretreatments with propranolol and aceperone failed to modify the activities of **2j** and **2f** (Figure 2). Compounds **2a**, **2c**, **2d**, **2g**, **2i**, **5**, and **15** in doses up to 50 μg, given bilaterally, each failed to cause a locomotor hyperactivity.

Scores 3 or 4 (biting, gnawing, or licking) for stereotypy were never recorded for any compound tested by intra-accumbens injection in the present study. Compound **2f** caused score 2 stereotypy at 50 μg, but the response was inconsistent at 12.5 μg. Compounds **2e**, **2j** (12.5–50 μg), **2h** (50 μg), and dopamine (200 μg) each caused a weak intensity sniffing behavior (never exceeding score 1). Compounds **2a–d**, **2g**, **2i**, **5**, and **15** all failed to induce any form of stereotyped behavior on intra-accumbens injection at doses up to 50 μg.

Climbing, Circling, and Stereotyped Behavior in the Mouse. Compounds **2a–j**, given subcutaneously in doses up to 20, 40, and 80 mg/kg, each failed to induce either climbing or circling behavior in the mouse, even though apomorphine was shown to be effective.[12] With the exception of **2b** which caused stereotyped head and limb movements at 40 and 80 mg/kg (intensity apparently unrelated to dose), all agents indicated above were also inactive in the production of stereotypies.

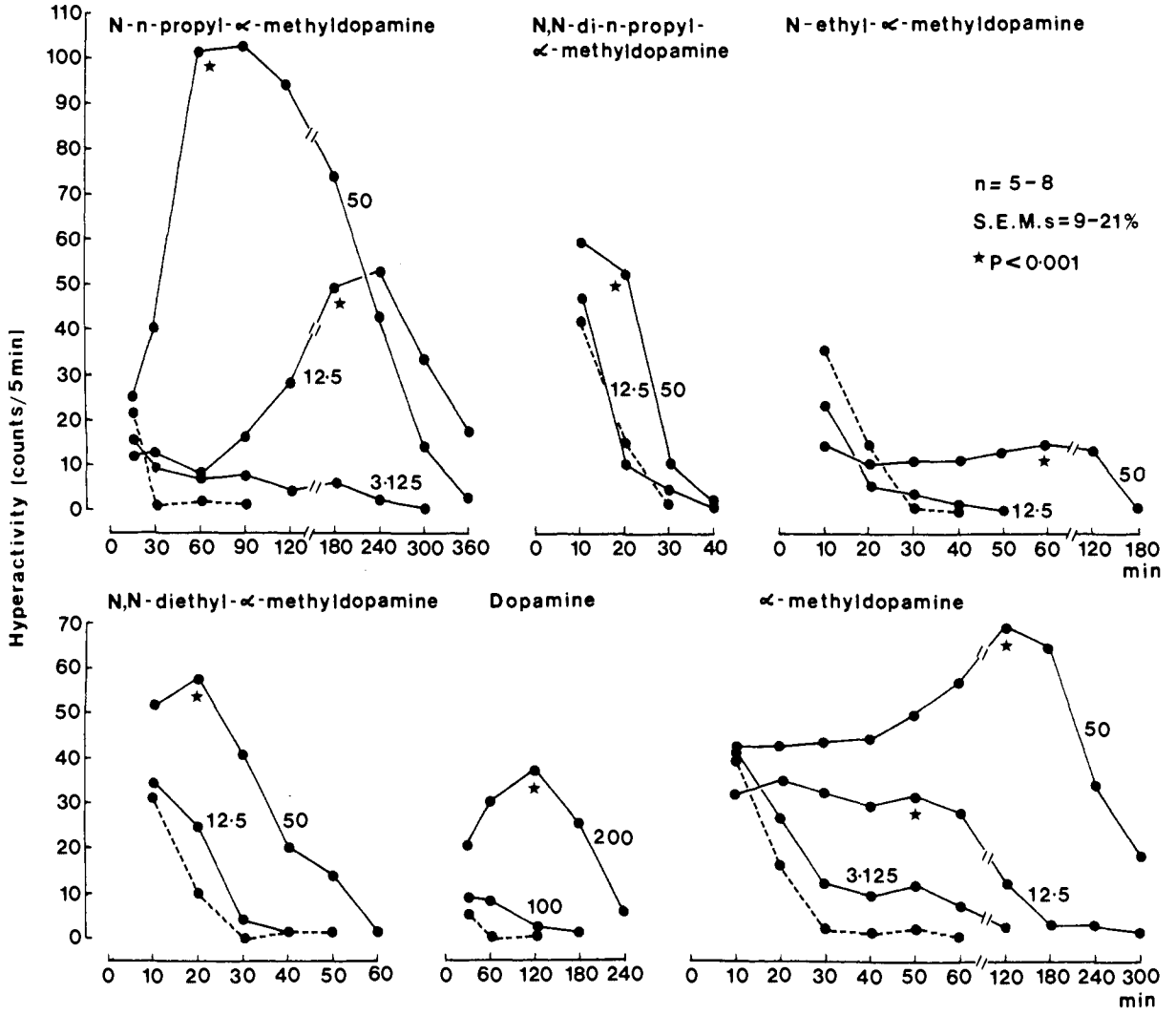


Figure 1. Hyperactivity induced by the intra-accumbens injection of dopamine, α-methyldopamine, and derivatives of α-methyldopamine. Doses are indicated in micrograms. Broken lines indicate the response of animals to intra-accumbens solvent.

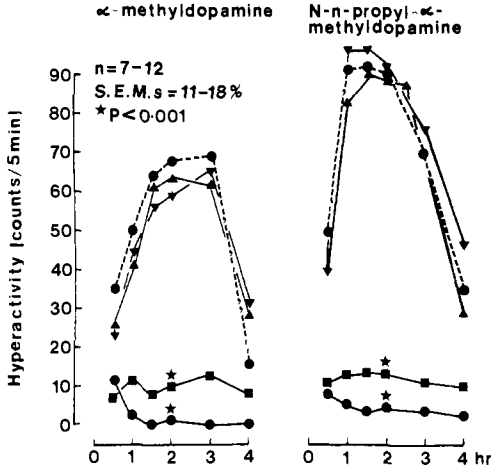


Figure 2. The induction of hyperactivity by 50 μg of **2j** or 50 μg of **2f** injected bilaterally into the nucleus accumbens 6 h after 250 mg/kg ip of α-methyl-*p*-tyrosine (■–■), 30 min after 0.1 mg/kg ip of haloperidol (●–●), 30 min after 5 mg/kg ip of propranolol (▲–▲), or 30 min after 2.5 mg/kg ip of aceperone (▼–▼). The responses of control (solvent treated) animals are indicated by ●--●.

Discussion

When peripherally administered, this series of α-methyldopamine analogues failed to demonstrate biological properties similar to those of dopamine in cat atria, in a dog cardioaccelerator nerve preparation, in rats with unilateral denervation of the caudate (turning response), in a pigeon-pecking assay, and as emetics in dogs. No evidence for inhibition of adrenergic nerve transmission was observed. Compounds **2i** and **2j** were quite potent in increasing heart rate and blood pressure in the dog; with these agents, there was no increase in chronotropic responses of isolated cat atria. The methyl ether derivatives (Table I, **5–12**) are relatively inactive on the cardiovascular system. This failure to induce increases in heart rate and blood pressure is in sharp contrast to the vasopressor responses reported for various hallucinogenic agents which are structural analogues.[8,13,14] At 3 μmol/kg, 2,5-dimethoxy-4-methylamphetamine (DOM) was an effective antagonist of apomorphine-induced pecking in pigeons. The analogues in the present study are much less active or inactive.

The peripheral administration of primary amino congeners based upon the tetralin ring (**1a, b**) does not induce behavioral effects which would indicate an enhanced central dopamine-like activity.[2] This was attributed to a failure of these agents to penetrate the blood–brain barrier, with rapid peripheral inactivation as a secondary consideration. The inactivity of peripherally administered α-methyldopamine (**2j**) in three behavioral models (stereotypy, climbing, and circling), designed to demonstrate increased cerebral dopamine activity in the mouse,[12,15] indicates that, while methyl substitution on the

α carbon may reduce metabolic inactivation by oxidase enzyme systems,[16] it is not sufficient to allow penetration of the molecule into the brain. van der Schoot et al.[10] earlier reported that intraperitoneally administered α-methyl dopamine (**2j**) did not elicit spontaneous motor activity in mice. Furthermore, while N-alkylation in dopamine itself and in other series of dopamine agonists (2-aminotetralins and octahydro benzo[*f*]quinolines) can facilitate passage into the brain,[2,17,18] the present study clearly indicates that this did not occur in the α-methyldopamine series.

In contrast to the general inactivity of the compounds on peripheral injection, the administration of α-methyldopamine and some derivatives directly into the nucleus accumbens of rat brain caused powerful locomotor responses. Such responses have been shown to be specific for dopamine and for dopamine agonists (having pre- and/or postsynaptic actions) and are very sensitive to neuroleptic inhibition.[19,20] Thus, the responses to α-methyldopamine (**2j**) and to *N*-*n*-propyl-α-methyldopamine (**2f**) were reduced by haloperidol but not by the α- and β-adrenoceptor blocking agents aceperone and propranolol. Although α-methyldopamine and its derivatives may possess varying degrees of α- and/or β-adrenergic stimulant activity, it appears unlikely that these properties per se are involved in the induction of the accumbens hyperactivity. It should be noted that both α-methyldopamine (**2j**) and *N*-*n*-propyl-α-methyldopamine (**2f**) were more active than dopamine itself in inducing hyperactivity from the nucleus accumbens, in the absence of pretreatment with a monoamine oxidase inhibitor. This may reflect the protection afforded against the enzyme by the α-methyl substitution.

Attempts have been made to assess the effects of N-alkylation on the ability to stimulate accumbens dopamine mechanisms, using a variety of dopamine agonists.[17,18,21] In the present study, using a variety of simple alkyl substituents on nitrogen, superficial similarities could be shown in the activity spectra of N-alkylated derivatives of α-methyldopamine and 2-aminotetralin compounds. Thus, *N*-methyl-, *n*-butyl-, dimethyl-, and di-*n*-butyl substitution abolished the potential of α-methyldopamine to cause hyperactivity, while this potential was retained, albeit in a modified form, by *N*-ethyl- and *n*-propyl substitutions. N,N-Dialkylation with these latter two groups produced compounds with very short durations of action. The same observations were made using *N*,*N*-diethyl- and di-*n*-propyl derivatives from the dopamine series. This may be related to the increased lipophilicity of these agents, which facilitates a rapid diffusion from the point of injection into the brain. *N*-*n*-Propyl-α-methyldopamine (**2f**) was found to be at least as effective as α-methyldopamine to induce hyperactivity, and this contrasted with the weak activity of the *N*-ethyl derivative **2h**. The optimal activity conferred by the *n*-propyl substitution is observed in other series of dopamine-like compounds.[17,18] Similarly, the importance of the free OH functions for optimal activity is demonstrated by the abolition of the hyperactivity potential in the dimethyl ethers of the α-methyldopamine series.

In previous intracerebral injection experiments using N-alkylated dopamine and 2-aminotetralin derivatives, we have hypothesized the optimal structures required to stimulate postsynaptic dopamine receptors.[2,17,21] This was considered to be reasonable, since the functional changes that were observed appeared to be independent of drug action on presynaptic dopamine mechanisms. However, in the present study, no such hypotheses are possible, nor

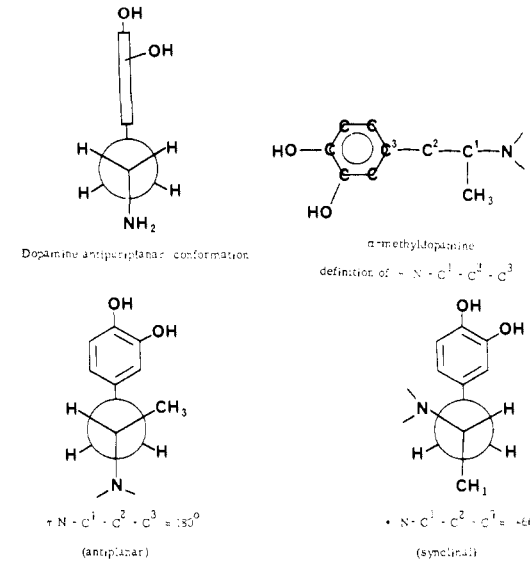


Figure 3. Conformations of dopamine and of α-methyldopamine.

is it valid to make unqualified comparisons between changes in structure and activity in the α-methyldopamine, dopamine, and 2-aminotetralin series, since the effects of α-methyldopamine and of *N*-*n*-propyl-α-methyldopamine were shown to be markedly reduced following disruption of catecholamine synthesis by α-methyl-*p*-tyrosine. This indicates that the actions of α-methyldopamine and of its *N*-*n*-propyl homologue involve a significant presynaptic component, and, although some post synaptic activity cannot be excluded, the evidence supports previous findings[8] that α-methyl dopamine derivatives probably enhance cerebral dopamine activity by indirect means, possibly by release of an endogenous transmitter and/or inhibition of reuptake processes. Since the relationships between drug structure and activity may differ for these processes, the present findings can only be interpreted to indicate a greater or lesser effect of α-methyldopamine and derivatives on unspecified dopamine mechanisms. An action via indirect mechanisms may explain the unexpectedly low activity of *N*,*N*-di-*n*-propyl derivative **2e** to induce hyperactivity only, the response characteristic of dopamine. In other series of compounds,[2,17] *N*,*N*-di-*n*-propyl substitution confers a potent stereotypic biting potential upon intra-accumbens injection, an effect mediated by postsynaptic receptors. It remains clear, however, that both α-methyldopamine and its *N*-*n*-propyl derivative, in the absence of any monoamine oxidase inhibitory pretreatment, can induce a powerful and prolonged locomotor hyperactivity on intra-accumbens injection. As such, these agents may prove useful in an examination of drug action on presynaptic dopamine mechanisms in the nucleus accumbens.

It seems reasonable that the absence of any postsynaptic dopamine agonist effects in the series of α-methyldopamine homologues is a reflection of the stereochemistry of the subject compounds. Evidence has been presented[2,18] supporting the proposal[22] that the conformation of dopamine required for direct agonist effects in the CNS as well as peripherally is a nitrogen–benzene ring antiperiplanar one (Figure 3), in which the benzene ring is coplanar with the side chain. Inspection of Dreiding models and of space-filling models suggests that the α-methyldopamine molecule can exist in a conformation with a torsion angle τ for N–C^1–C^2–C^3 (Figure 3) in the antiplanar range (180°), in which case the amino nitrogen and the benzene ring are anti, as illustrated. Neville et al.,[23] on the basis of high-resolution NMR studies in water solution, concluded

that the protonated amphetamine cation exists 50% in this nitrogen–benzene ring anti conformation, with the remainder of the molecular population existing in two nitrogen–benzene ring gauche conformations (Figure 3, τ for $N-C^1-C^2-C^3 = \pm 60°$, synclinal). As bulky substituents were placed on the nitrogen, the relative amount of the anti conformer increased. Ison et al.,[24] using solution NMR studies, and Bustard and Egan,[25] using MO calculations, concluded that in β-phenethylamine systems the presence of a 3,4-dihydroxy moiety on the benzene ring (as in dopamine) increases the relative amounts of nitrogen–benzene ring gauche rotamers ($\tau = \pm 60°$), due to inter- or intramolecular interaction between the amino group and OH on the benzene ring, involving a water bridge between these two entities.[25] However, Pullman and co-workers[26] have noted that energy barriers separating anti and gauche conformations in phenethylamines and in amphetamines are low and that external conditions will have an important influence on the shape(s) of these molecules, and it can be concluded that the dopamine molecule can adapt its conformation to accomodate in vivo receptors. While the literature has not revealed that conformational chemistry of α-methyldopamines has been investigated experimentally or with MO calculations, it appears that none of the studies on closely related systems provide data which would preclude the conclusion that α-methyldopamine can assume or approach the $N-C^1-C^2-C^3$ antiplanar torsion angle (Figure 3) necessary for the dopamine agonist effect.

However, inspection of space-filling models of α-methyldopamine systems reveals that if the molecule assumes the $\tau = 180°$ conformation and if the benzene ring is coplanar with the plane of the ethylamine side chain (Figure 3, $N-C^1-C^2$), as has been proposed to be essential for the dopamine agonist effect,[22] there exists some nonbonded interaction between the α-methyl group and the ortho hydrogen on the benzene ring. These interactions seem to be much less severe if the benzene ring is rotated 90° about the C^2-C^3 bond such that the plane of the ring is perpendicular to the plane of the side chain. Pullman et al.[26] have concluded, on the basis of MO calculations, that several β-phenethylamine-derived drugs, as well as ephedrine and amphetamine, exhibit an energy minimum corresponding to a conformer in which the plane of the side chain is approximately perpendicular to the plane of the benzene ring. It is therefore suggested that the α-methyldopamines described herein lack postsynaptic dopamine agonist activity due, among other possible steric factors, to an inability of the benzene ring easily to achieve coplanarity or approximate coplanarity with the side chain for optimal interaction with appropriate dopamine receptors. The high order of dopaminergic activity observed in 2-aminotetralin systems (**1a, b**) is a reflection of the high degree of conformational integrity imposed upon the dopamine moiety within the molecule by the partially saturated carbocyclic ring, which holds the dopamine moiety in the optimum antiperiplanar conformation for interaction with receptors.

Experimental Section

Melting points were determined in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus and are uncorrected. NMR spectra were recorded with a Varian Associates T-60 instrument using tetramethylsilane as the internal standard. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Where analyses are indicated by the symbols of the elements, analytical results were within ±0.4% of the theoretical values.

Pharmacology. Methods. Cat atria were isolated and placed in a Krebs bicarbonate medium. Field stimulation was used to induce positive chronotropic and inotropic responses. The test compounds were added in increasing doses (0.3 log unit) and field stimulation was reapplied. Also, changes in resting heart rate and force were noted.

In a series of ten dogs, the right cardioaccelerator nerve was stimulated using bipolar electrodes at a frequency of 2 Hz and supramaximal voltage. The blood pressure was recorded from the right femoral artery and the heart rate was recorded using a Beckmann 7813 cardiotachometer. The influence of the experimental compounds on the positive chronotropic responses, resting heart rate, and blood pressure was evaluated following intravenous administration. The highest dose tested was 1.0 mg/kg.

A few selected compounds were evaluated in rats following unilateral injection of 6-hydroxydopamine into the substantia nigra. The rotations induced by the compounds were compared with those observed for apomorphine.

The ability to produce emesis or to antagonize apomorphine-induced emesis was evaluated in a series of unanesthetized dogs. The compounds were administered subcutaneously, and the dogs were observed for 45 min for emetic response. In other dogs, the compounds were administered subcutaneously, and apomorphine (100 μg/kg) was administered 15 min later.

The ability to induce pecking in pigeons was evaluated following intramuscular administration of the compounds in doses up to 4 mg/kg. The ability to antagonize pecking induced by apomorphine (1.62 μM/kg) was evaluated, and ED_{50} values were estimated.

Hyperactivity and Stereotyped Behavior Following Intracerebral Injection into the Nucleus Accumbens of the Rat. Rats (male, Sprague–Dawley, 250 ± 25 g) were prepared for bilateral drug injection into the nucleus accumbens using techniques described earlier.[27] Briefly, guide cannulae (0.65-mm diameter stainless steel) were stereotaxically implanted with their tips at anterior 9.0, vertical +2.5, lateral ±1.6[28] and were kept patent by stainless-steel stylets (0.3-mm diameter). Animals were used for intracerebral injection 10–14 days after surgery when the stylets were replaced by injection units which extended 2.5 mm below the guides to terminate at the center of the nucleus accumbens. Rats were manually restrained as the drug was delivered bilaterally in a volume of 1 μL (using Agla micrometer syringes) over a 60-s period. Rats were used once only. Guide cannulae locations were then determined histologically. All locations were found to be within the area of the nucleus accumbens and were indistinguishable from those previously reported.[27]

Hyperactivity was measured in cages (30 × 20 × 15 cm high), each fitted with one photocell placed off-center. The number of light-beam interruptions occurring within each 5-min period was recorded electromechanically and, at the same time, the animal's behavior was recorded from visual observation in order to eliminate counts due to behavior other than hyperactivity, for example, stereotyped behavior characterized by repetitive, restricted movements of the head or limbs. See ref 27 for further details.

Stereotyped behavior was assessed separately using a simple scoring system: 0 = no stereotyped behavior; 1 = periodic sniffing and/or repetitive head and limb movements; 2 = continuous sniffing and/or repetitive head and limb movements; 3 = periodic biting, gnawing, or licking; 4 = continuous biting, gnawing, or licking.

Climbing, Circling, and Stereotyped Behavior in the Mouse. Male albino B.K.W. mice were used (20–25 g for peripheral studies, 30–35 g at the time of surgery). Climbing behavior was measured in perspex cages (20 × 15 × 15 cm) lined with 1-cm^2 wire mesh (2-mm diameter wire). Animals were classed as climbing when they held the wire with all four paws. During a period of climbing a mouse moved constantly around the sides or top of the cage. Two different measures of climbing were determined: (1) the *climbing index*, which is a percentage of time spent climbing during the 30-min period following the first climb; and (2) the *maximum time*, which is the maximum time spent in a single climb throughout the duration of the drug effect (see also ref 12).

Circling behavior was assessed in mice with unilateral electrolesions of the caudate-putamen. An electrolesion was induced stereotaxically by placing a stainless-steel electrode (0.65-mm

diameter, insulated except at the tip) 1.0-mm anterior to Bregma, 2.3-mm lateral to the midline, and 3.5 mm from the skull surface and passing a current of 1.5 nA for 15 s. After 14 days, mice were tested for circling behavior using 1.0 μg/kg, subcutaneously, apomorphine. Only animals that circled 7+ revolutions/2 min, ipsilateral to the side of the lesion, were used in subsequent studies, after a further 7-day recovery period. Circling behavior was assessed visually as the number of complete revolutions, in one direction only, made by an animal housed in a perspex cage (20 × 15 × 15 cm). The correct location of the lesions was confirmed histologically on completion of the studies. The Atlas of Lehman[29] was used as a guide. The different components of stereotyped behavior in the mouse were simply noted as being present or absent.

Drugs. Dopamine, α-methyldopamine, and derivatives of α-methyldopamine were prepared for intracerebral and/or peripheral administration in nitrogen-bubbled distilled water containing 0.1% sodium metabisulfite. For peripheral administration, apomorphine hydrochloride (Macfarlan Smith) was dissolved in distilled water containing 0.1% sodium metabisulfite; haloperidol (Janssen), in 1% lactic acid; *dl*-propranolol hydrochloride (I.C.I.), in distilled water; aceperone (Janssen), in a minimum quantity of *N,N*-dimethylformamide; and *dl*-α-methyl-*p*-tyrosine (Sigma) was prepared as an aqueous suspension in 2% carboxymethylcellulose. Doses were calculated as the free bases. The peripheral injection volume was 1 mL/kg.

1-(3,4-Dimethoxyphenyl)-2-(benzylamino)propane Hydrochloride (3). Freshly distilled benzylamine (7.28 g, 0.068 mol) in 20 mL of MeOH was treated with 5 N methanolic HCl to pH 7 (pH paper), then 13.2 g (0.068 mol) of 3,4-dimethoxyphenylacetone in 20 mL of MeOH was added, followed by 4.27 g (0.068 mol) of $NaCNBH_3$, and this mixture was stirred under N_2 at room temperature for 36 h. The reaction was quenched with excess concentrated HCl, and the volatiles were removed under reduced pressure. The residue was taken up in H_2O and washed with Et_2O. The aqueous phase was treated with excess KOH and extracted with $CHCl_3$. The extract was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The resulting light-yellow oil was converted to its HCl salt, which was recrystallized twice from MeOH–Et_2O to afford 17 g (78%) of white crystals, mp 175–178 °C. Anal. ($C_{19}H_{24}ClNO_2$) C, H, N.

1-(3,4-Dimethoxyphenyl)-2-aminopropane Hydrochloride (5). Compound **3** (6.0 g, 0.0186 mol) was hydrogenated over 1.2 g of 5% Pd/C in 80 mL of anhydrous MeOH at an initial pressure of 310 kPa (45 psig). When the calculated amount of H_2 was absorbed (18 h), the catalyst was removed by filtration and washed with $CHCl_3$. The combined filtrate and washings were evaporated under reduced pressure and the residue was recrystallized (see Table I).

1-(3,4-Dimethoxyphenyl)-2-aminopropane (4). Compound **5** was treated with excess 2 N NaOH, and the resulting mixture was extracted with $CHCl_3$. The solvent was removed and the free base was distilled through a "short-path" apparatus to afford a colorless, limpid liquid, bp 100 °C (0.053 kPa; 0.4 mmHg), lit.[9] bp 104 °C (0.039 kPa; 0.3 mmHg).

Method A. Reductive Amination of 3,4-Dimethoxyphenylacetone with $NaBH_4$. 1-(3,4-Dimethoxyphenyl)-2-(methylamino)propane Hydrochloride (6). A chilled (0–5 °C) solution of 3.75 g (0.019 mol) of 3,4-dimethoxyphenylacetone in 25 mL of MeOH was treated with 7.5 mL of a 36% aqueous solution of methylamine. Maintaining the temperature of this mixture at 0–10 °C, 0.75 g (0.019 mol) of $NaBH_4$ was added in small portions over 20 min and then the mixture was stirred at room temperature for 1 h. MeOH (10 mL) and 2.5 g of K_2CO_3 were added, and the mixture was evaporated under reduced pressure. H_2O (10 mL) was added to the residue, and this mixture was extracted with six 40-mL portions of Et_2O. The combined extracts were dried (K_2CO_3), and the solution was treated with ethereal HCl to yield a heavy gum, which upon washing with Et_2O yielded a white solid which was recrystallized (see Table I).

Method B. Reductive Amination of 3,4-Dimethoxyphenylacetone with $NaCNBH_3$. 1-(3,4-Dimethoxyphenyl)-2-(dimethylamino)propane Hydrochloride (7). A mixture of 5.82 g (0.03 mol) of 3,4-dimethoxyphenylacetone, 2.45 g (0.03 mol) of dimethylamine hydrochloride (previously dried by refluxing it for 3 h with toluene in a Dean–Stark apparatus), and 1.89 g (0.03 mol) of $NaCNBH_3$ in 75 mL of MeOH were stirred at room temperature for 72 h. The MeOH was removed under reduced pressure, the brown semisolid residue was taken up in 30 mL of 2 N HCl, and this solution was extracted three times with Et_2O. The H_2O layer was basified with KOH and the resulting mixture was extracted repeatedly with Et_2O. The combined extracts were dried (Na_2SO_4), and the volatiles were evaporated to leave a golden-yellow syrup, which was converted to its HCl salt with ethereal HCl (see Table I).

Method C. N-Alkylation of 1-(3,4-Dimethoxyphenyl)-2-aminopropane with $NaBH_4$–Carboxylic Acid Complex. 1-(3,4-Dimethoxyphenyl)-2-(diethylamino)propane Hydrochloride (8). Method "B" of Marchini et al.[30] was used. To 16.82 g (0.279 mol) of AcOH in 70 mL of benzene (distilled from Na) maintained at 10–15 °C under N_2 was added in small portions 3.17 g (0.084 mol) of $NaBH_4$. When evolution of H_2 ceased, 1.09 g (0.0056 mol) of **4** in 10 mL of dry benzene was added, and the resulting mixture was heated under reflux for 16 h. The reaction mixture was treated with excess 2 N NaOH and then was extracted repeatedly with Et_2O. The pooled extracts were dried (Na_2SO_4), and the volatiles were removed under reduced pressure to leave a yellow oil. This was treated with 3 mL of phenyl isocyanate and was permitted to stand at room temperature overnight. MeOH (25 mL) was added and the resulting solution was heated on a steam bath for 20 min; then volatiles were removed under reduced pressure. The residue was azeotroped with benzene, then fresh benzene was added, and the resulting solution was extracted repeatedly with 2.5 N HCl. The combined HCl extracts were extracted with Et_2O and the aqueous phase was treated with excess KOH. The resulting emulsion was extracted repeatedly with Et_2O. Evaporation of the pooled ethereal extracts left a light-yellow oil, which was treated with ethereal HCl (see Table I).

***N*-[1-(3,4-Dimethoxyphenyl)-2-propyl]acetamide (10).** A mixture of 2 g (0.01 mol) of **4** and 8 mL of Ac_2O was refluxed for 2 h. The resulting brown solution was treated with 80 mL of H_2O, and this mixture was extracted several times with benzene. The pooled extracts were washed with saturated $NaHCO_3$ and then with H_2O, dried ($MgSO_4$), and evaporated, to leave a yellow oil. This was chromatographed on 50 g of silica gel and eluted with EtOAc–MeOH (5:1). Evaporation of the eluate left a solid, which was crystallized from EtOH–petroleum ether to afford 1.52 g (63%) of white crystals, mp 89–91 °C. Anal. ($C_{13}H_{19}NO_3$) C, H, N.

***N*-[1-(3,4-Dimethoxyphenyl)-2-propyl]butyramide (17).** A mixture of 1 g (0.0051 mol) of **4** and 7 mL of butyric anhydride was refluxed for 2 h. The resulting brown solution was treated with 40 mL of H_2O, and this mixture was extracted several times with benzene. The pooled extracts were washed with saturated $NaHCO_3$ and then with H_2O, dried ($MgSO_4$), and evaporated to leave a yellow oil, which was distilled through a "short path" apparatus, bp 175–177 °C (0.01 kPa; 0.1 mmHg), to afford 0.90 g (66%) of product. This was chromatographed on 50 g of silica gel and eluted with EtOAc–MeOH (5:1). Evaporation of the eluate left a crystalline solid, mp 80–83 °C. Anal. ($C_{15}H_{23}NO_3$) C, H, N.

Method D. Reduction of Amides with $LiAlH_4$. 1-(3,4-Dimethoxyphenyl)-2-(*n*-butylamino)propane Hydrochloride (9). To 0.429 g (0.01 mol) of $LiAlH_4$ in 50 mL of dry Et_2O was added dropwise under N_2 and with stirring 2.47 g (0.0093 mol) of the amide **10** in 20 mL of Na-dried benzene, and the reaction mixture was kept immersed in an ice bath. After addition of the amide, the reaction mixture was heated under reflux for 6 h. Excess $LiAlH_4$ was destroyed by the cautious addition of H_2O, and the reaction mixture was filtered. The filter cake was washed with benzene, and the filtrate and washings were evaporated under reduced pressure to afford 2.09 g of a yellow oil. This was treated with ethereal HCl, and the resulting salt was recrystallized (see Table I).

Method E. Reductive Alkylation of 1-(3,4-Dimethoxyphenyl)-2-aminopropane with Acetone and PtO_2. 1-(3,4-Dimethoxyphenyl)-2-(isopropylamino)propane Hydrochloride (11). Compound **4** (1.075 g, 0.0054 mol), 0.99 g (0.017 mol) of acetone, and 0.116 g of PtO_2 in 80 mL of EtOH were hydrogenated at room temperature at an initial pressure of 310 kPa (45 psig). When the calculated amount of H_2 was absorbed, the reduction mixture was filtered and the solvent was removed

from the filtrate under reduced pressure. The residue was distilled through a short-path apparatus, bp 100 °C (0.004 kPa; 0.03 mmHg), to yield 0.75 g (63%) of an oil. This was converted to its HCl salt with ethereal HCl and was recrystallized (see Table I).

Method F. Reductive Alkylation of a Secondary Amine with Formaldehyde and Pd/C. 1-(3,4-Dimethoxyphenyl)-2-(*N*-methyl-*N*-isopropylamino)propane Hydrochloride (12). The free base of 11 (1.47 g, 0.0062 mol) and 3 mL of 37% aqueous formaldehyde were hydrogenated in the presence of 0.2 g of 10% Pd/C in 80 mL of anhydrous EtOH at an initial pressure of 248 kPa (36 psig). After 1 h, the calculated amount of H_2 was absorbed; the reduction mixture was filtered and volatiles were removed from the filtrate under reduced pressure. The oily residue was treated with excess 5% KOH and this mixture was extracted with Et_2O. The volatiles were removed from this extract; the oily residue was taken up in 10% HCl and this solution was extracted with Et_2O, which was discarded. The aqueous phase was treated with excess KOH and was extracted with Et_2O. The extract was dried ($MgSO_4$) and the Et_2O was removed under reduced pressure to leave an oil: bp 101 °C (0.004 kPa; 0.03 mmHg); yield 1.40 g (90%); NMR ($CDCl_3$) δ 2.25 (s, 3 H, N-CH_3). This material was converted to its HCl salt with ethereal HCl, and the salt was recrystallized (see Table I).

Ether Cleavage Reactions. The amine or its HCl salt (0.001 mol) was heated under N_2 with 6 mL of 48% HBr at 110–120 °C for 3 h. Volatiles were removed under reduced pressure, and the residue was recrystallized (see Table I).

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Conformational Analogues of Dopamine. Synthesis and Pharmacological Activity of (*E*)- and (*Z*)-2-(3,4-Dihydroxyphenyl)cyclopropylamine Hydrochlorides

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(*E*)- and (*Z*)-(±)-2-(3,4-dihydroxyphenyl)cyclopropylamine hydrochlorides were synthesized as part of a program to assess the importance of conformational isomerism with respect to the various peripheral biological actions of dopamine. Although neither of the compounds possessed dopaminergic activity in the canine renal blood-flow model, both agents were weak α-adrenergic agonists and exhibited cardiostimulatory properties similar to dopamine. The *E* isomer was approximately 5 times more potent than the *Z* isomer in its α-adrenergic activity and approximately 15 times as potent in its cardiac effects. Possible reasons for the lack of renal dopaminergic activity exhibited by the *E* isomer are presented.

Dopamine is known to interact with a variety of peripheral receptors. In addition to its vasodilator activity in renal and mesenteric vascular beds, dopamine interacts with β_1- and α-adrenergic receptors[1] and induces release of norepinephrine from sympathetic nerves in the heart.[2] As part of a program to design a more specific dopaminergic agent[3] and to define the importance of certain molecular conformations of dopamine that might be

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