Methyl 2-Oxa-3-oxo-5α-androstane-17β-carboxylate (40). A solution of the Δ^1-steroid **38** (1.0 g, 3.0 mmol) in a 2:1 mixture of $MeCl_2$–EtOAc (15 mL) was ozonized at −78 °C until blue color persisted for 2 min. The mixture was purged with N_2 as the temperature was allowed to rise to room temperature. The solution was evaporated and the residue treated with a solution prepared from 1.0 mL of 30% H_2O_2 in 10 mL of HOAc. After standing 3 h, the mixture was concentrated to a thick oil. The material was dissolved in Et_2O, washed with water, and extracted into 2.5 N NaOH solution. The aqueous layer was acidified and extracted with Et_2O. The organic layer was washed with water, dried, and concentrated to leave 958 mg of crude **17β-carbomethoxy-1-oxo-1,2-seco-A-nor-5α-androstan-2-oic acid (39).**

To a solution of the above aldehyde **39** (225 mg, 0.64 mmol) in a mixture of MeOH (17 mL) and water (5.6 mL) was added at room temperature a solution of $NaBH_4$ (100 mg, 2.6 mmol) in 9 mL of water. After 3 h, 2.5 N aqueous HCl solution was added and the solution concentrated one-half its volume. Water was added and the crude product separated. This material was chromatographed (1:1 EtOAc–C_6H_6) by TLC on 1000-μm silica gel plates. The major band was isolated and crystallized from Et_2O to give the 85 mg of the oxasteroid **40**, mp 202–204 °C.

Acknowledgment. We are indebted to Dr. Byron Arison and Herman Flynn for obtaining the 300-MHz NMR spectra and to Jack L. Smith for low-resolution and Deborah Zinc for high-resolution mass spectra. Microanalytical data were obtained by the Analytical Research Department of Merck Sharp Dohme Research Laboratories. We thank Dr. William F. Johns of G. D. Searle and Co. for a sample of the immediate precursor to compound **41**.

Registry No. **1a**, 58-22-0; **1c**, 57-83-0; **1f**, 40736-33-2; **1g**, 15959-00-9; **1h**, 6693-98-7; **1k**, 20817-72-5; **1l**, 63079-23-2; **1m**, 1865-62-9; **1n**, 92472-21-4; **1o**, 73671-97-3; **1t**, 302-97-6; **1w**, 2681-55-2; **1x**, 1452-33-1; **1y**, 92472-22-5; **1z**, 74352-90-2; **1aa**, 92472-20-3; **1bb**, 74352-89-9; **1ee**, 434-22-0; **2a**, 1759-35-9; **2c**, 3510-20-1; **2f**, 92472-25-8; **2g**, 92472-26-9; **2h**, 92472-27-0; **2k**, 92472-28-1; **2l**, 92472-29-2; **2m**, 92472-30-5; **2n**, 92472-31-6; **2o**, 73697-29-7; **2u**, 92472-32-7; **2w**, 92472-33-8; **2x**, 16870-58-9; **2y**, 92472-34-9; **2z**, 92472-35-0; **2aa**, 92472-23-6; **2bb**, 92472-24-7; **2ee**, 3762-52-5; **3a**, 82093-09-2; **3b**, 92472-37-2; **3c**, 20283-95-8; **3d**, 2102-23-0; **3f**, 92472-40-7; **3g**, 92472-41-8; **3h**, 92472-42-9; **3i**, 92472-43-0; **3j**, 92472-44-1; **3k**, 92472-45-2; **3l**, 92472-46-3; **3m**, 92472-47-4; **3n**, 92489-87-7; **3o**, 76763-13-8; **3p**, 73671-98-4; **3q**, 92472-48-5; **3r**, 92472-49-6; **3s**, 92472-50-9; **3u**, 92472-51-0; **3u** (methyl ester), 92524-41-9; **3w**, 92472-52-1; **3x**, 92472-53-2; **3y**, 92472-54-3; **3z**, 92472-55-4; **3aa**, 92472-36-1; **3bb**, 92472-38-3; **3ee**, 92472-39-4; **4a**, 76318-68-8; **4b**, 86284-02-8; **4c**, 73711-89-4; **4d**, 73671-90-6; **4e**, 7750-89-2; **4e** (4-*H* deriv.), 76318-67-7; **4f**, 92542-38-6; **4g**, 86283-91-2; **4h**, 73671-88-2; **4i**, 73671-89-3; **4j**, 86283-89-8; **4k**, 53874-94-5; **4l**, 92472-57-6; **4m**, 86307-05-3; **4n**, 92472-58-7; **4o**, 73671-87-1; **4p**, 73671-86-0; **4q**, 92472-59-8; **4r**, 92472-60-1; **4s**, 86283-86-5; **4t**, 76763-16-1; **4u**, 92472-61-2; **4v**, 86283-83-2; **4w**, 86283-81-0; **4x**, 86283-85-4; **4y**, 76763-19-4; **4z**, 73671-91-7; **4aa**, 86283-79-6; **4bb**, 89631-78-7; **4cc**, 92618-96-7; **4dd**, 86283-82-1; **4ee**, 92472-56-5; **5**, 92472-63-4; **6a**, 92472-64-5; **6b**, 92472-65-6; **6c**, 92472-66-7; **6d**, 92472-67-8; **6e**, 92472-68-9; **7aα**, 76763-12-7; **7aβ**, 76776-74-4; (2α(*R*)-**7b**, 92473-05-7; (2α(*S*))-**7b**, 92473-04-6; (2β(*R*))-**7b**, 92473-03-5; (2β(*S*))-**7b**, 92472-69-0; **8**, 76763-21-8; **9**, 92472-70-3; **10**, 92472-71-4; **11**, 92472-72-5; **12**(X = 0), 92472-73-6; **12**(X = 1), 92472-74-7; **13**, 92472-75-8; **14**, 92472-76-9; **15**, 92472-77-0; **16**, 2944-75-4; **17a**, 92472-78-1; **17b**, 92472-79-2; **18**, 92472-80-5; **19**, 92472-81-6; **20**, 92472-82-7; **21**, 92472-83-8; **22**, 86284-03-9; **23a**, 92472-84-9; **23b**, 92472-85-0; **23c**, 92472-86-1; **24**, 92472-87-2; **25a**, 86283-88-7; **25b**, 92472-88-3; **26**, 86283-87-6; **27**, 92472-89-4; **28a**, 92472-90-7; **28b**, 21522-08-7; **29a**, 92472-91-8; **29b**, 21522-14-5; **30a**, 92472-92-9; **30b**, 92472-93-0; **31**, 73671-93-9; **32**, 92472-94-1; **33**, 92472-95-2; **34**, 92472-96-3; **35**, 92472-97-4; **36**, 92472-98-5; **37**, 4139-88-2; **38**, 92472-99-6; **39**, 92473-00-2; **40**, 92473-01-3; **41**, 92473-02-4; **42**, 21813-68-3; **43**, 25709-34-6; **44**, 25744-31-4; **45a**, 7417-26-7; **45b**, 73672-01-2; CH_3NH_2, 74-89-5; NH_3, 7664-41-7; $C_2H_5NH_2$, 75-04-7; $C_6H_5NH_2$, 62-53-3; $HO(CH_2)_2NH_2$, 141-43-5; CH_3NHNH_2, 60-34-4; $(C_2H_5O)_2P(O)CO_2CH_3$, 1067-74-9; pregnenolone, 145-13-1; pregnenolone 21-pyridinium iodide, 73672-02-3; 17β-hydroxy-5α-androstan-4-one, 571-08-4; 5α-reductase, 9036-43-5.

Supplementary Material Available: A table listing additional analytical and spectral data for compounds described in this paper (22 pages). Ordering information is given on any current masthead page.

C(2)-Methylation Abolishes DA_1 Dopamine Agonist Activity of 2-Amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (6,7-ADTN): Steric Intolerance by the Receptor

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Received January 18, 1984

The synthesis of 2-amino-2-methyl-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene is reported. This compound did not produce vasodilation in the dog renal artery and was inactive as a DA_1-type dopamine agonist. This is in contrast to the 2-nonmethylated homologue 6,7-ADTN, which is a potent DA_1 agonist. High-field ^1H NMR studies of the *O,O*-dimethyl ethers for both compounds as their free bases in chloroform-*d* revealed that the 2-methyl homologue probably exists as a rapidly equilibrating mixture of conformers; it seems likely that it can adopt the active conformation proposed to be required by the dopamine receptor. The lack of activity is therefore attributed to the steric effect of the 2-methyl group, consistent with explanations offered by others that the dopamine receptor cannot tolerate alkylation at the α side-chain carbon.

As part of our continued interest in structure–activity relationships of dopamine agonists, we have been studying the differences in the structural requirements of agonists at the two subtypes of the peripheral dopamine receptors. Of interest in this regard was the apparent lack of dopamine agonist activity for α-methyl-substituted dopamine derivatives. α-Methyldopamine (1) lacks agonist activity at the renal dopamine receptor[1] and its *N*-methyl, *N,N*-dimethyl, and other N-alkylated derivatives lack dopamine

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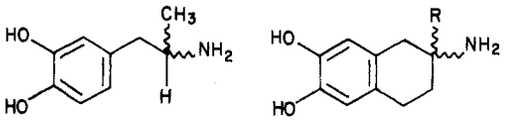

1 2, R = H 3, R = CH_3

activity in various other biological assays.[2,3]

Cannon et al.[2] have speculated that this lack of activity may be related to an inability of the side chain of 1 to adopt the requisite antiperiplanar conformation. This would be mainly attributed to the peri interaction between the α-methyl group and the hydrogen atoms on the aromatic ring ortho to the side chain. However, it seemed clear from other work in our laboratory with substituted phenylisopropylamine derivatives that the α-methyl does not prevent the side chain from adopting a trans, coplanar arrangement with the aromatic ring.[4] Rather, it was speculated that the dopamine receptor was intolerant of steric bulk attached to the α carbon. Erhardt has offered a similar explanation for the lack of dopaminergic activity for *trans*-2-(3,4-dihydroxyphenyl)cyclopropylamine, a semirigid congener of dopamine.[5] In that case, however, the argument is somewhat clouded by the lower pK_a of the cyclopropylamine and bond angles that give a conformation not likely to be adopted by dopamine itself.

As one possible approach to answering this question in a more definitive way, it was envisioned that a methyl group could be attached to the 2-position of 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (2, 6,7-ADTN) to give 3. The parent 2 possesses biological activity nearly comparable to that of dopamine itself.[6] However, the addition of the 2-methyl would provide steric bulk in the immediate environment of the amino group, which would project into a space that would seem to be more comparable to that occupied by the α-methyl of 1. Although technically 2 itself might be considered to be a rigid analogue of 1, a conformation for the latter where the α-methyl corresponds to C(3) in the tetralin 2 is not energetically favorable, due to the nonbonded interaction between the α-methyl and the hydrogens on the aromatic ring ortho to the side chain.[4] The α-methyl must be projected out of the plane of the ring when the ethylamine side chain is essentially coplanar and trans to the ring. Furthermore, the fact that 2 is active, while 1 is not, clearly indicates that 2 is not a good model for 1.

It should be noted that the addition of the methyl group to 2 will perturb the conformational equilibrium. In monosubstituted cyclohexanes, the conformational free-energy difference between the axial and equatorial orientation both for the methyl and amino is similar, 1.5–2 kcal/mol.[7] It was still anticipated, however, that 3 could assume an antiperiplanar conformation with respect to the dopamine fragment incorporated into the molecule.

In this paper we describe the preparation of 3 and its evaluation for DA_1 dopamine agonist activity in the canine renal artery. The relative conformational equilibria for 2 and 3 were studied by using 470-MHz ^1H spectrometry on the free bases of the *O,O*-dimethyl ethers of 2 and 3, 10, and 9, respectively. The conformational studies were carried out to ascertain that the addition of the 2-methyl in 3 had not "locked" the conformation of the reduced ring rather than to determine whether 2 and 3 had a similar preferred solution conformation.

Chemistry. The synthetic route leading to 3 is outlined in Scheme I. Commercially available (3,4-dimethoxyphenyl)acetone was allowed to condense with ethyl cyanoacetate following the method of Cope et al.[8] Conversion to the diacid 5 was effected following the procedure of Foucaud.[9] However, the diacid was very difficult to purify since it was contaminated by partial hydrolysis products. Therefore, the crude diacid was directly treated with acetic anhydride at reflux to afford, after isolation, the crystalline anhydride 6. Following treatment of this with polyphosphoric acid, the keto acid 7 was obtained in modest yield. Catalytic hydrogenolysis of 7 gave the reduced acid 8, which was subjected to conditions of the Curtius rearrangement to yield the isocyanate. This isocyanate proved to be very unreactive toward benzyl alcohol in attempts to prepare an *N*-carbobenzoxy derivative. Instead, the isocyanate was treated with methanolic KOH at reflux to yield the amine 9 directly, which was isolated as its HCl salt. This was converted to the desired catechol by treatment with 48% HBr at reflux and the HBr salt of 3 was isolated and used for biological testing.

NMR Studies. Calculation of the ^1H–^1H vicinal coupling constants between the aliphatic protons of the reduced rings of 2 and 3 would allow estimation of the preferred conformation of the rings. Due to the tendency for the catechols to oxidize, however, it was elected to carry out this study on the corresponding *O,O*-dimethyl ethers of 2 and 3, 10, and 9, respectively. It was felt that *O*-methylation would not have a significant effect on the conformational flexibility of the reduced rings. These studies were also carried out with use of the free bases in deuteriochloroform to obtain optimum resolution. It was recognized that in studies carried out with the amine salts in D_2O, solvation effects would tend to favor a pseudoequatorial conformation for the ammonium group, while we were more interested in examining the flexibility of 3. Coupling constants for all protons were refined by using an adaptation of LAOCN3 implemented in the Nicolet ITRCAL program.[11]

Pharmacology. Compound 3 was studied for DA_1 agonist and antagonist activity on renal blood flow in dogs. The testing procedure followed the method published by McNay and Goldberg.[12] The compound was also evaluated in the femoral artery for possible DA_2 dopamine agonist activity.[6]

Results and Discussion

Pharmacology. In six experiments, compound 3 was administered into the canine renal artery. Prior to phenoxybenzamine (POB), the compound produced vasoconstriction, initially evident at the 48-nmol dose. After POB

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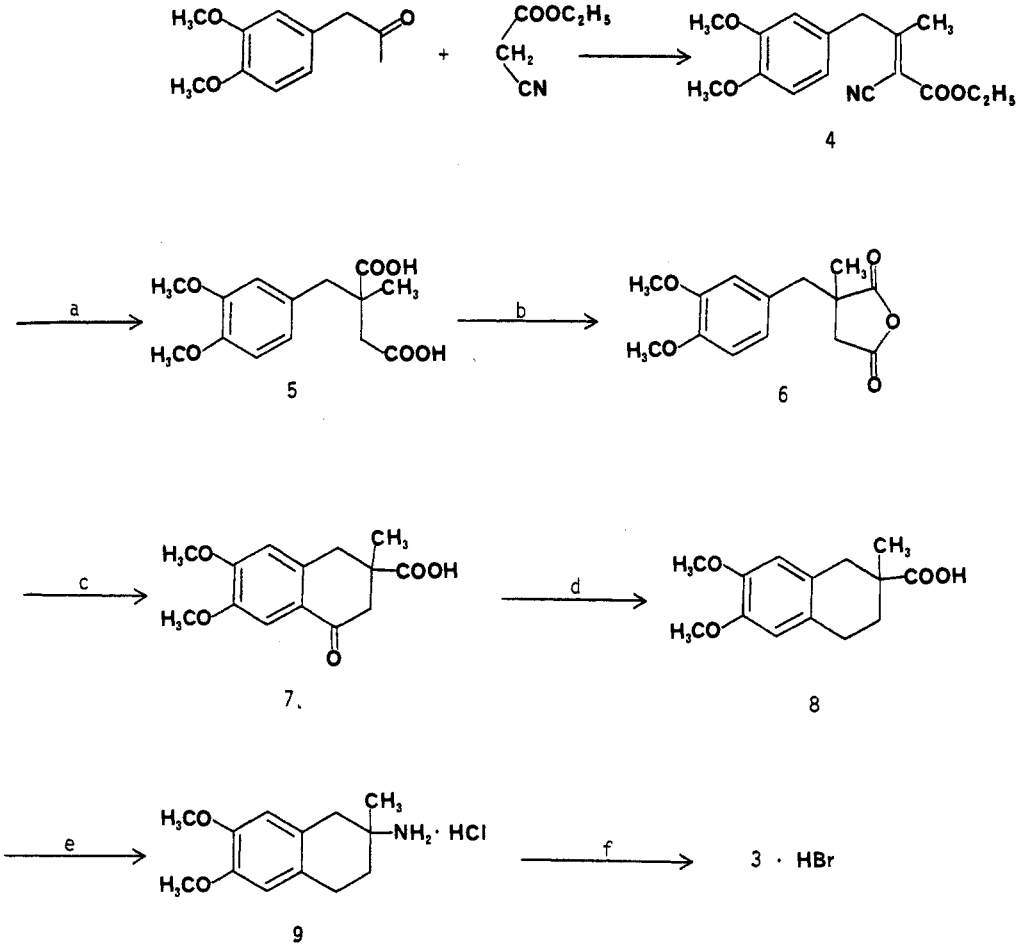
Scheme I[a]



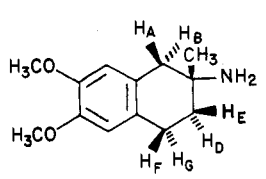
[a] (a) KCN, EtOH; NaOH, H_2O; H_2SO_4, (b) Ac_2O, reflux, (c) PPA, heat, (d) H_2, 10% Pd-C, $HClO_4$, (e) C_2H_5OCOCl, Et_3N, NaN_3; heat; KOH, MeOH, reflux, HCl, (f) 48% HBr, reflux.

pretreatment (5–10 mg/kg), while dopamine (48 nmol) produced an increase of 55 ± 6.5 mL/min in the renal blood flow (n = 6), **3** had no effect on renal blood flow until much higher doses (750 nmol) were given, which produced only vasoconstriction but no vasodilation. After similar pretreatment, **2** produces renal vasodilation with a potency comparable to dopamine.[6] In three experiments where **3** was administered (190 nmol) simultaneously with dopamine, no antagonism to the effect of dopamine was observed: dopamine alone produced a mean of 52 mL/min increase in renal blood flow, while dopamine combined with **3** produced a mean of 55 mL/min increase in renal blood flow.

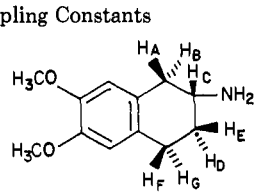
It is clear, therefore, that the addition of the 2-methyl group to **2** abolishes DA_1 agonist activity. In this respect **3** resembles **1**. The most obvious explanation for this is a simple steric effect of the methyl group.

Compound **3** was also examined for a DA_2 agonist effect in the femoral vascular bed, in five separate experiments. In four of five experiments, **3**, in doses of 3–190 nmols, produced vasodilation nearly equipotent to that elicited by *N,N*-dipropyldopamine.[13] It does not appear that this effect is mediated by a direct action at DA_2 receptors since in one experiment the vasodilation was blocked by the β antagonist propranolol, in one experiment the vasodilation was blocked by the DA_2 antagonist doperidone,[14] while in the other two experiments it was not blocked by either antagonist.

Table I. Chemical Shifts and Coupling Constants



9



10

no.	proton	chemical shift, ppm	coupling constants, Hz
9	A	2.54	J_{AB} = −15.97
	B	2.68	
	D	1.69	J_{DE} = 13.27, J_{DF} = 6.49, J_{DG} = 7.28
	E	1.65	J_{EF} = 6.40, J_{EG} = 7.42
	F	2.73	J_{FG} = −17.00
	G	2.82	
10	A	2.89	J_{AB} = −15.77, J_{AC} = 4.79
	B	2.47	J_{BC} = 9.24
	C	3.13	J_{CD} = 9.94, J_{CE} = 3.02
	D	1.55	J_{DE} = −12.74, J_{DF} = 9.90, J_{DG} = 5.94
	E	1.94	J_{EF} = 4.91, J_{EG} = 4.74
	F	2.76	J_{FG} = −15.72
	G	2.78	

Conformational Analysis. The magnitudes of the coupling constants for **10** (Table I) indicate two axial–axial and two axial–equatorial couplings for the $C_{(1)}$ and $C_{(3)}$ protons with the $C_{(2)}$ methine. Application of the Karplus equation[15] using the empirical parameters derived by

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Bothner-By[16] indicated that **10** exists as a slightly distorted chair. This result parallels that reported by De Jong et al.[17] for unsubstituted 2-amino-1,2,3,4-tetrahydronaphthalene hydrochloride in D_2O.

The 2-methyl compound **9**, on the other hand, has nearly identical vicinal coupling constants for the $C_{(3)}$ and $C_{(4)}$ protons. Since both the methyl and the amino group have similar *A* values in monosubstituted cyclohexanes,[7] it may be inferred that **9** exists as a rapidly equilibrating mixture of conformers. Using values for $J_{ax,ax}$ = 11 Hz, $J_{ax,eq}$ = 3 Hz, and $J_{eq,eq}$ = 3 Hz and the assumption that **9** is a 1:1 mixture of conformers (CH_3(ax), NH_2(eq) and CH_3(eq), NH_2(ax)) leads to calculated average vicinal coupling constants of 7 Hz for the $C_{(3)}$ and $C_{(4)}$ protons. Using this estimation in the ITRCAL program produced a spectral simulation nearly identical with that observed experimentally. As seen in Table I, the refined coupling constants for **9** are close to 7 Hz.

Although these studies were carried out on the *O,O*-dimethyl ethers of **2** and **3**, we assume that this will have no significant effect on the conformational mobility of the reduced ring when compared with the free catechols. It would therefore seem that **3** can adopt a conformation where the amino group is pseudoequatorial, although this is less favorable than in the nonmethylated **2**. These data, taken together with the lack of dopaminergic activity for cyclopropyl[6] and cyclobutyl[18] analogues of dopamine, seem consistent with the idea that it is the steric bulk of the 2-methyl group in **3**, and hence in **1**, per se that is responsible for the lack of activity. This further reinforces Erhardt's suggestion[5] that the vascular dopamine receptor cannot tolerate steric bulk attached to the α carbon of dopamine. This implies a receptor geometry that may either be a groove or slot into which the agonist fits or one where the receptor may fold in on the agonist during the process of receptor activation.

Experimental Section

Melting points were determined in open glass capillaries with a Mel-Temp apparatus and are uncorrected. IR spectra were recorded on a Beckman IR-33 instrument. Routine NMR spectra were recorded on a Varian FT-80 spectrometer. The 470-MHz proton spectra for conformational studies were recorded on a Nicolet NTCFT 470-MHz superconducting FT NMR at the Purdue University Regional Biochemical Magnetic Resonance Laboratory. Chemical shifts are recorded in parts per million with Me_4Si as the internal reference, except when the solvent was D_2O; in these cases DSS was used. Elemental analysis was carried out by the Purdue Microanalytical Laboratory and determinations were within ±0.4% of the calculated values.

Ethyl 2-Cyano-3-methyl-4-(3,4-dimethoxyphenyl)-2-butenoate (4). Following the method of Cope et al.,[8] a mixture of 24.24 g (0.12 M) of 1-(3,4-dimethoxyphenyl)-2-propanone (Aldrich), 14.13 g (0.12 M) of ethyl cyanoacetate, 4.63 g of ammonium acetate, and 7.2 g of acetic acid were heated together at reflux in 65 mL of benzene for 21 h. Water was continuously removed by using a Dean–Stark trap. The reaction was cooled and the benzene solution was washed with 2 × 75 mL brine and 2 × 75 mL water and dried ($MgSO_4$). The solution was filtered and concentrated by rotary evaporation. The residue was vacuum distilled to yield 26 g (79%) of the product as a viscous yellow oil, which gradually solidified. An analytical sample was recrystallized from EtOAc–hexane: mp 70–71 °C; IR (neat) 2200 (CN), 1715 (C=O); NMR ($CDCl_3$) δ 6.85 (br s, 3, Ar H), 4.38 (d of q, 2, OCH_2), 3.90, 4.18 (2 s, 2, CH_2), 3.95 (s, 6, OCH_3), 2.23, 2.35 (2 s, 3, CH_3), 1.37 (t, 3, CH_3). Anal. ($C_{16}H_{19}NO_4$) C, H, N.

2-Methyl-2-(3,4-dimethoxybenzyl)succinic Anhydride (6). A solution of 28.9 g (0.1 M) of cyano ester **4** in 50 mL of EtOH was warmed to 60 °C and a solution of 11.25 g (0.17 M) of KCN in 20 mL of water was added. The solution was heated at reflux for 22 h.[9] To the reaction was then added 80 mL of 6 N NaOH and reflux was continued for 24 h. The cooled reaction mixture was then poured into 200 mL of ice–water containing 30 mL of concentrated H_2SO_4. The acidic mixture was extracted with 4 × 50 mL of ether, and the extracts were combined, washed with brine and then water, and dried ($MgSO_4$). Filtration and removal of solvent under reduced pressure yielded 20.8 g (74%) of the diacid **5** as a gummy product, which was very difficult to crystallize. The crude diacid was therefore treated with 500 mL of acetic anhydride and heated at reflux for 6 h. Concentration by rotary evaporation under vacuum gave a solid product which was recrystallized from ethyl acetate–hexane to yield 19.02 g (72%) of the anhydride **6**: mp 119–120 °C; IR (KBr) 1770, 1840 (C=O); NMR ($CDCl_3$) δ 6.75 (m, 3, Ar H), 3.87 (s, 6, OCH_3), 3.25 (d, 1, CH, J = 14 Hz), 3.05 (d, 1, CH, J = 19 Hz), 2.67 (d, 1, CH, J = 14 Hz), 2.56 (d, 1, CH, J = 19 Hz), 1.50 (s, 3, CH_3). Anal. ($C_{14}H_{16}O_5$) C, H.

2-Methyl-4-oxo-6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthoic Acid (7). A mixture of of 2 g (7.6 mmol) of anhydride **6** and 40 g of polyphosphoric acid was stirred on the steam bath for 45 min. The hot reaction mixture was poured over 500 g of ice and stirred to dissolve all of the syrupy reaction mixture. After the ice had melted, this was extracted with 3 × 100 mL of ether. The ether extracts were combined, washed with brine and water, and dried (Na_2SO_4). Filtration and solvent removal under reduced pressure yielded a viscous residue which was crystallized from ether–hexane to yield 1.1 g (55%) of product: mp 174–175 °C; IR (KBr) 1710 (C=O); NMR ($CDCl_3$) δ 9.20 (br s, 1, COOH), 7.45 (s, 1, Ar H), 6.62 (s, 1, Ar H), 3.90, 3.86 (2 s, 6, OCH_3), 3.28 (d, 1, CH, ^2J = 16.5 Hz), 3.02 (d, 1, CH, ^2J = 12.5 Hz), 2.82 (d, 1, CH, ^2J = 12.5 Hz), 2.44 (d, 1, CH, ^2J = 16.5 Hz), 1.36 (s, 3, CH_3). Anal. ($C_{14}H_{16}O_5$) C, H.

2-Methyl-6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthoic Acid (8). A mixture of 2.64 g (10 mM) of the keto acid **7** in 75 mL of acetic acid containing 1 mL of 70% $HClO_4$ and 0.7 g of 10% Pd–C was shaken on a Parr apparatus at an initial hydrogen pressure of 50 psig. The theoretical amount of hydrogen was absorbed after 3 h. The bottle was removed from the shaker and 1 g of potassium acetate was added, and the mixture was stirred for 5 min and then was filtered through Celite. The filtrate was concentrated by rotary evaporation and the residue was partitioned between water and ether. The ether was washed several times with brine and then H_2O to wash out traces of acetic acid. After drying (Na_2SO_4), the ether solution was filtered and concentrated. The solid residue was recrystallized from ethyl acetate–hexane to yield 2.1 g (84%) of reduced acid: mp 147–148 °C; NMR ($CDCl_3$) δ 9.5–9.0 (br, 1, COOH) 6.54 (s, 2, Ar H), 3.81 (s, 6, OCH_3), 3.13 (d, 1, CH, ^2J = 16.3 Hz), 2.75 (m, 2, CH_2), 2.53 (d, 1, CH, ^2J = 16.3 Hz), 2.04 (m, 1, CH), 1.79 (m, 1, CH), 1.30 (s, 3, CH_3). Anal. ($C_{14}H_{18}O_4$) C, H.

2-Amino-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene Hydrochloride (9). A solution containing 1.0 g (4 mmol) of the acid **8**, 0.43 g (4.24 mmol) of triethylamine, 0.8 mL of H_2O, and 4 mL of acetone was stirred at 0–5 °C (ice bath). To this was added, over 10 min, a solution of 0.512 g (4.72 mmol) of ethyl chloroformate in 3 mL of acetone. This was stirred for 10 min after addition was complete and then a solution of 0.328 g (5.04 mmol) of NaN_3 in 1.5 mL of H_2O was added. The reaction was allowed to stir for 30 min in the ice bath, the bath was removed, and the reaction was stirred for an additional 45 min. The mixture was diluted with 75 mL of H_2O and was extracted with 3 × 50 mL of toluene. The toluene was washed with brine and dried ($MgSO_4$). This solution was filtered and heated on the steam bath for 1 h, at which time the IR showed the absence of the starting acyl azide (2140 cm^{-1}) and a strong absorption of isocyanate (2260 cm^{-1}). The toluene was removed under reduced pressure and the resulting residue was taken up into 20 mL of 4 N KOH/MeOH and heated at reflux under N_2 for 24 h. The reaction was concentrated under reduced pressure and the residue was partitioned between water and ether. The ether layer was separated and the aqueous phase was extracted several times with

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ether. The combined ether extract was washed with brine and then water. The ether solution was then extracted with 3 × 20 mL of 2 N HCl. The acidic aqueous extracts were combined and reduced to dryness several times from absolute EtOH. The residue was recrystallized from EtOH–ether to yield 0.818 g (79%) of white crystals: mp 259–260 °C; NMR (free base, $CDCl_3$, 470 MHz) δ 6.58 (s, 1, Ar H), 6.50 (s, 1, Ar H), 3.81 (s, 3, OCH_3), 3.81 (s, 3, OCH_3), 2.82 (d of t, 1, CH), 2.73 (d of t, 1, CH), 2.68 (d, 1, CH), 2.54 (d, 1, CH), 1.69 (d of d, 1, CH), 1.65 (d of d, 1, CH), 1.58 (br s, 2, NH_2), 1.18 (s, 3, CH_3). Anal. ($C_{13}H_{20}ClNO_2$) C, H, N.

2-Amino-2-methyl-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene Hydrobromide (3). The hydrochloride salt **9** (103 mg, 0.4 mmol) was added to 5 mL of 48% HBr and heated at reflux for 1 h under N_2. The reaction was concentrated to dryness by rotary evaporation under reduced pressure. The solid was dissolved in 10 mL EtOH and again concentrated to dryness. This process was repeated two more times to remove traces of water. The resulting tan solid was recrystallized from EtOH–EtOAc and dried under high vacuum to yield 80.0 mg (73%) as off-white crystals: mp 248–250 °C; NMR (Me_2SO-d_6) δ 8.20 (br, 5 H, OH, NH_3^+), 6.48 (s, 1 H, Ar H), 6.44 (s, 1 H, Ar H), 2.69 (br s, 4 H, Ar CH_2), 1.81 (t, 2 H, CH_2), 1.25 (s, 3 H, CH_3). Anal. ($C_{11}H_{16}BrNO_2$) C, H, N.

Conformational Analysis. ^1H–^1H vicinal coupling constants were determined between nonaromatic protons of the free bases of the *O,O*-dimethyl ethers **10** and **9**. Samples were run in $CDCl_3$. Chemical shifts are reported for high-resolution spectra relative to the $CHCl_3$ resonance at 7.25 ppm. Decoupling experiments were used to initially determine coupling constants. Subsequent refinements were carried out with use of the modification of LAOCN3[10] implemented in the Nicolet ITRCAL program.[11] Final chemical shifts and coupling constants were checked by generation of spectral simulations and comparison with experimentally obtained spectra.

Pharmacology. Following the method of McNay and Goldberg,[12] male mongrel dogs (20–25 kg) were anesthetized with sodium pentobarbital (30 mg/kg, iv). A tracheotomy was performed, and respiration was maintained with room air via a Harvard respirator.

The right renal artery was exposed by using a flank incision and retroperitoneal dissection. An electromagnetic flow probe was placed on the artery for measurement of blood flow, and a 25-gauge needle, bent at an 80° angle, was proximally inserted into the artery for drug administration. After infusion of phenoxybenzamine, 5 mg/kg ia, a dose–response curve to dopamine (12, 48, and 190 nmol) was obtained. Increasing doses of the test agonist were administered, up to 3000 nmol (0.82 mg of **3**). All dosages were injected in a fixed volume of 0.2 mL.

For measurement of femoral artery vasodilation and vasoconstriction, sciatic and femoral nerves were left intact and the paw circulation was occluded in all experiments. Initially, dose–response curves of dipropyl DA were generated in each experiment by injecting ia 4-fold increasing doses ranging from 3 to 190 nmol. Test compounds were injected to a maximum of 3000 nmol. Compounds causing vasodilation were also studied after administration of propranolol and domperidone. Propranolol was administered ia in a dose of 2.5 mg/kg and β adrenergic blockade was verified by elimination of isoproterenol-induced vasodilation. Domperidone was administered in a dose of 5 μg/kg iv and DA_2 receptor blockade verified by antagonism of DPDA-induced vasodilation.

Acknowledgment. The 470-MHz spectra were run at PUBMRL, which is supported by NIH Grant RR01077 from the Division of Research Resources. This work was supported, in part, by PHS Grants HL-23609 and HL-31106 and NIH Grant GM22220. We also thank Lisa Shull for technical assistance.

N^2-(4-Substituted-2,6-dichlorophenyl)-N^1,N^1-dimethylformamidines as Antihypertensive and Diuretic Agents[1]

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Received March 15, 1984

The synthesis of a series of N^2-[4-[(arylmethyl)amino]-2,6-dichlorophenyl]-N^1,N^1-dimethylformamidines that caused marked blood pressure lowering and/or diuresis in spontaneously hypertensive rats (SHR) is reported. Diuretic activity was not always associated with acute antihypertensive activity. Central nervous system effects, most notably sedation, were observed. Compound **9d**, which lowered arterial blood pressure 37 mmHg in SHR when dosed at 100 mg/kg, was further evaluated in chronic hypertensive dogs because of apparent minimal CNS effects. A reduction in arterial blood pressure of 32 mmHg at 1.0 mg/kg during a 6-h postdosing interval was observed. This response was unrelated to α- or β-adrenergic blockade, angiotensin I antagonism, or neuronal or ganglionic blockade. CNS effects were also observed.

Hypertension, a state of elevated arterial blood pressure, has been determined to be a contributing factor in the development of cardiovascular disease.[2] As a result, the desirability of controlling hypertension has led to the development of antihypertensive drugs that lower blood pressure via a number of mechanisms, including those that act on the central nervous system.

The clinical success of clonidine (1, Catapres)[3] and the subsequent extensive structure–activity relationship studies that resulted[4] led to the development of structurally related drugs represented by guanachlor (**2**)[5] and guanabenz (**3**),[5] which are centrally acting antihypertensive agents.

In this report we describe the results of an investigation on a related series of *N*-[4-[(arylmethyl)amino]-2,6-dichlorophenyl]formamidines **4** synthesized in an attempt to produce a compound that controls blood pressure

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0022-2623/84/1827-1705$01.50/0