The systolic blood pressures and heart rates were compared to predose "control" values statistically using the Student's t test. Compounds having a level of significance $p = <0.05$ are regarded as active.

Antihypertensive DOCA Rat Assay. Sprague–Dawley male rate weighing 90–100 g were used in this assay. Deoxycorticosterone acetate (DOCA) was administered subcutaneously at a dose of 100 mg/rat per day for 5 days a week for 3 weeks. One percent saline was provided ad libitum for the 3-week period. Tap water was substituted for the 1% saline at the end of the treatment period.

Systolic blood pressure were determined by the tail cuff method, utilizing capacitance transducers for the detection of pressure, an aneroid manometer for measuring pressure, and an oscilloscope for visualizing the disappearance and/or appearance of the pressure pulse. Groups of five rats having systolic blood pressure of 170 mmHg or greater were chosen, and the test compound was administered at 100 mg/kg po as a solution or suspension in 0.25% methylcellulose (MC) at a volume of 5 mL/kg. One group served as the control and received the vehicle. Systolic blood pressures were recorded prior to dosing and again 4 h after drug. If a significant hypotensive effect was obtained at 4 h posttreatment, the pressure was again measured at 24 h posttreatment.

The 0- and 4-h postdose systolic blood pressures were compared statistically using the Student's t test. Compounds having a level of significance $p = <0.05$ were regarded as active.

Synthesis and Antihypertensive Activity of 5-Amino-2-pyridinecarboxylic Acid Derivatives

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The synthesis of various substituted 5-amino-2-pyridinecarboxylic acids and their derivatives is described by three general methods: (1) reductive alkylation of methyl 5-amino-2-pyridinecarboxylates (**2**) and subsequent hydrolysis; (2) alkylation of the urethane (**9**), followed by hydrolysis; and (3) selective $NaBH_4$ reduction of the appropriate amide of (**2**), followed by hydrolysis. A more specific process was used for the 5-(phenylamino) compound, i.e., nucleophilic displacement of nitrite from methyl 5-nitro-2-pyridinecarboxylate by sodioformanilide and subsequent hydrolysis. Many of these 2-pyridinecarboxylic acid derivatives were potent antihypertensive agents in the spontaneously hypertensive rat (SHR). Optimization of structural parameters for this activity yielded compounds **54**, **55**, **34**, **65**, and **22**, which were selected for further study in the renal hypertensive dog (RHD). Based on these studies, one compound, 5-[(4-fluorobenzyl)amino]-2-pyridinecarboxylic acid (**65**), was selected for preclinical toxicity evaluation. Based on the toxicological findings, it was decided not to pursue compound **65** clinically.

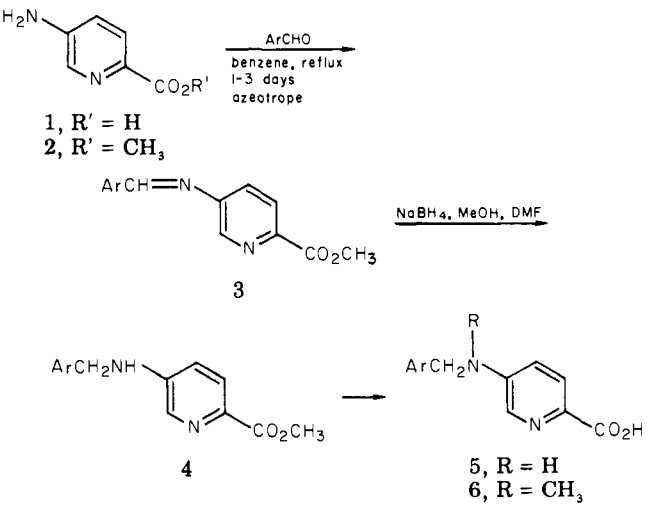
The reasons for our interest in vasodilators were described previously.[1] Fusaric acid, 5-butylpicolinic acid, is still actively studied as such, both preclinically[2] and clinically.[3] Synthesis of analogues in attempts to improve the profile continue.[4]

Our earlier efforts to improve on fusaric acid by studying 5-thio-2-pyridinecarboxylic acid derivatives were unsuccessful.[1] The more interesting compounds based on SHR (spontaneously hypertensive rat) data lacked sufficient efficacy in the RHD (renal hypertensive dog). We now describe compounds of the fusaric acid type, 5-amino-2-pyridinecarboxylic acids, which show good efficacy in both SHR and RHD models.

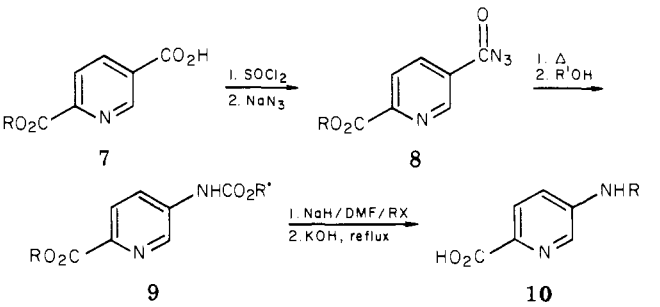
Chemistry. A very limited amount of work has been done with 5-amino-2-pyridinecarboxylic acids. Only the parent compound[5,6] and its 5-(dimethylamino)[5] and a few *N*-acyl derivatives have been described.[7]

We developed four methods to provide access to a broad range of substituted 5-amino-2-pyridinecarboxylic acids. For the most important structural types, i.e., substituted 5-(benzylamino)-2-pyridinecarboxylic acids, two of these methods were principally used. One is the reduction of the Schiff base from an aromatic aldehyde and methyl 5-amino-2-pyridinecarboxylate with sodium borohydride, followed by hydrolysis (Scheme I). The other method is the alkylation of the urethane derived from the Curtius reaction on ethyl 5-carboxy-2-pyridinecarboxylate, followed by hydrolysis (Scheme II). For other structural types,

Scheme I



Scheme II



(1) N. Finch, T. R. Campbell, C. W. Gemenden, M. J. Antonaccio, and H. J. Povalski, *J. Med. Chem.*, **21**, 1269 (1978).
(2) L. Piesche, H. Hilse, and P. Oehme, *Pharmazie*, **34**, 332 (1979).
(3) M. Miyahara, H. Miyazake, H. Takayama, and Y. Minatogawa, *Jpn. Circ. J.*, **41**, 1161 (1977).
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(5) L. W. Deady, R. A. Shanks, A. D. Campbell, and S. Y. Chooi, *Aust. J. Chem.*, **24**, 385 (1971).
(6) J. Delarge, *Pharm. Acta Helv.*, **44**, 637 (1969).
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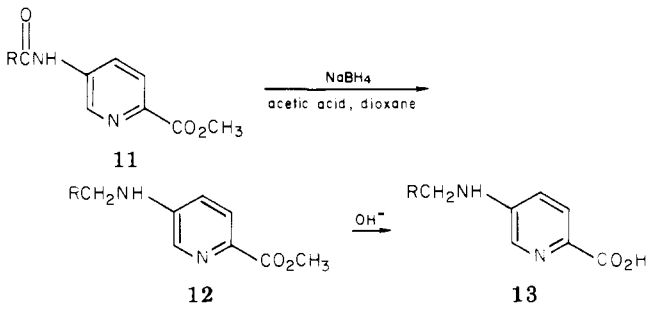
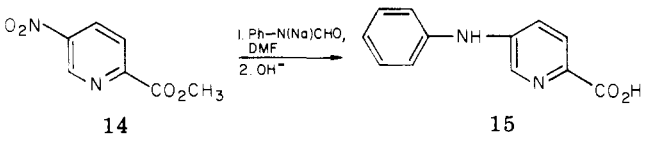
Scheme III



Scheme IV



selective reduction of methyl 5-amino-2-pyridinecarboxylates (Scheme III) or displacement of nitrite from methyl 5-nitro-2-pyridinecarboxylate (**14**) by sodioformanilide in DMF (Scheme IV) were employed. The parent 5-amino-2-pyridinecarboxylic acid (**1**) was prepared in quantitative yield by catalytic reduction of 5-nitro-2-pyridinecarboxylic acid, which was obtained as previously described.[1]

We were not able to obtain 5-amino-2-pyridinecarboxylic acid (**1**) in adequate yield via the Hofmann reaction on methyl 5-carbamoyl-2-pyridinecarboxylate as described by Delarge.[6]

The carboxylic acid derivatives in Table I, i.e., amides, esters, and hydrazides, were made by conventional procedures. The best procedure for the primary amides was according to Allred.[8] The carbinols, e.g., compound **59**, were available as byproducts from Scheme I (see Experimental Section). Other carboxylic acid functionalities were available from the carbinol by MnO_2 oxidation to the carboxaldehyde, which was converted sequentially to the oxime, nitrile, and tetrazole.

Pharmacology. The preliminary pharmacological data were obtained from the effects on the blood pressure and heart rate of the spontaneously hypertensive rat (SHR) (Table I). Methyl 5-(*n*-butylamino)-2-pyridinecarboxylate (**16**) is structurally the closest relative of fusaric acid, 5-*n*-butyl-2-pyridinecarboxylic acid. This compound proved to be only marginally antihypertensive at the screening dose (50 mg/kg po). Aliphatic carboxamides and all sulfonamides of 5-amino-2-pyridinecarboxylic acid, i.e., compounds **17–20**, were inactive. The benzamide (**21**) showed only a very modest antihypertensive effect in this model. The effects of terminal phenyl substitution were studied; i.e., 5-(phenylamino)- (**15**), 5-(benzylamino)- (**22**), 5-(phenethylamino)- (**23**), and 5-[(phenylpropyl)amino]-2-pyridinecarboxylic acids (**24**) were prepared. The activity was highest with one methylene group in the chain. The 5-(phenylamino) (**15**) derivative was essentially inactive, the 5-(benzylamino) (**22**) derivative was very active, and the 5-(phenethylamino) (**23**) and 5-[(phenylpropyl)amino] (**24**) derivatives were modestly active. The focus of further modification was, therefore, the 5-(benzylamino) type. The 5-[(cyclohexylmethyl)amino] compound (**25**) showed reduced activity and the compound was poorly tolerated. Substitution by methyl on the methylene group of the benzyl gave a compound (**26**) which was very active but less so than the parent. The product of N-methylation, compound **27**, also had reduced activity, but changes in profile were evident and it was clear that N-methylation should be explored with some other active analogues. Appropriate choices of substituents in the benzyl group were made by intuitive, rational (Topliss' tree[9]), and practical considerations, e.g., which aromatic aldehydes were conveniently accessible.

The most interesting compounds based on these screening results in the SHR, secondary evaluation in the SHR, and the dose–response relationships were the *m*-chlorobenzyl (**54**) and its *N*-methyl derivative (**55**), *m*-fluorobenzyl (**34**), *p*-fluorobenzyl (**65**), and the unsubstituted compounds (**22**). These compounds were evaluated further in the renal hypertensive dog (RHD) (Table II). The most interesting compound of these proved to be the *p*-fluorobenzyl compound (**65**). It was well tolerated in the RHD, whereas the other compounds sometimes caused emesis. It showed a good antihypertensive effect at 100 mg/kg po with some tachycardia. The 5-[*N*-(3-chlorobenzyl)-*N*-methylamino] compound (**55**) was also active in the RHD. This compound and the 5-[(*p*-fluorobenzyl)amino]-2-pyridinecarboxylic acid (**65**) were therefore the focus of final structural variations.

The analogues of the 5-[*N*-(3-chlorobenzyl)-*N*-methylamino] compound (**55**) studied involved variations of the carboxyl group, e.g., the methyl ester (**56**) which retained some activity, the amide (**57**) which was almost inactive, and the carbinol (**58**) which was quite active. Substitution of the pyridine ring at C_6 by a methyl group to give compound **62** reduced activity. Comparable variations of the NH group of compound **54** were also evaluated in the SHR, e.g., the carbinol (**59**), which was active, and the carboxaldehyde (**60**), which was less so. Substitution at C_6 by a methyl group, as in compound **61**, reduced activity. Since substitution on nitrogen affected the profile, two other N-substituted analogues were evaluated. The *N*-propionyl compound (**63**) was almost inactive, as for the simpler amides described previously. The bis(*m*-chlorobenzyl) compound (**64**) also had reduced activity.

The analogues of the *p*-fluorobenzyl compound (**65**) synthesized were evaluated as above in the SHR. Methyl subsitution of the benzylmethylene group, compound **66**, reduced activity. Pyridine *N*-oxide formation, compound **77**, likewise reduced the activity. Transformation of the carboxyl group to a nitrile (**67**) or *N*-ethylamide (**68**) essentially abolished the activity. Oddly, the unsubstituted amide (**69**) and the hydrazide (**70**) were quite active and the *N*,*N*-dimethylamide (**71**) was also active in the RHD. Functionalities biologically equivalent to carboxyl, i.e., the tetrazole (**73**) and methyl ester (72), showed good effects but were not superior to the parent compound. The carboxyaldehyde (**74**) and carbinol (**75**) also were very active but not superior. The aldoxime (**76**) was essentially inactive.

Preclinical toxicity studies were therefore carried out with the 5-[(*p*-fluorobenzyl)amino]-2-pyridinecarboxylic acid (**65**) in mice, rats, dogs, and monkeys. While having a relatively low order of acute toxicity in dogs and monkeys, repeated administration of compound **65** to the monkey caused hepatic changes and renal dysfunction. Renal dysfunction was observed in rat and dog also at doses too close to the therapeutic dose to warrant further development of the compound for study in man.[10]

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(9) J. G. Topliss, *J. Med. Chem.*, **15**, 1006 (1972).

(10) V. M. Traina and R. M. Diener, Pharmaceuticals Division, CIBA-GEIGY, personal communication.

Experimental Section

Chemistry. IR spectral data were obtained as CH_2Cl_2 solutions or Nujol mulls on a Perkin-Elmer Model 21 or 521 spectrophotometer. NMR spectra were obtained in $CDCl_3$ and $(CD_3)_2SO$ on a Varian A-60, using Me_4Si as an internal standard. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Appropriate spectra were obtained on all isolated intermediates and final products. These spectra were compatible with the structural assignments.

5-[(3-Chlorobenzyl)amino]-2-pyridinecarboxylic Acid (54; Scheme I). Methyl 5-amino-2-pyridinecarboxylate (2; 30.44 g, 0.200 mol) and 3-chlorobenzaldehyde (30.9 g, 0.220 mol) were refluxed together in benzene (400 mL) with a Dean–Stark trap to collect the azeotroped water. After the solution was refluxed for 3 days, an appropriate amount of water had collected. The benzene was removed in vacuo, and a portion of the solid residue was recrystallized from benzene/ethyl acetate/ether to give methyl 5-[(3-chlorobenzylidene)amino]-2-pyridinecarboxylate, mp 139–142 °C. Anal. ($C_{14}H_{11}ClN_2O_2$) C, H, N. The bulk of the crude imine (3, Ar = 3-chlorophenyl; 60 g, 0.218 mol) was dissolved in DMF (180 mL) by warming. This solution was added rapidly to a well-cooled (below 0 °C) and stirred slurry of $NaBH_4$ (24 g) in methanol (1 L). The reaction temperature rose to 20 °C during the addition. The temperature was reduced to 0 °C, and the reaction mixture was stirred for 40 min. The reaction mixture was allowed to warm to room temperature. The methanol was removed in vacuo at 25–30 °C. The residue was cooled in an ice bath. Acetic acid (6 mL) was added. After the foaming had subsided, 12 N HCl and crushed ice/water were added to bring the pH to 5–6 and the reaction volume to about 1.5 L. The crude ester 4 (Ar = 3-chlorophenyl) separated as a white solid (49.91 g, 0.181 mol, 83%). It was collected, washed with water, and air-dried. A portion of the crude material, mp 109–113 °C, was recrystallized from ethyl acetate/ether to give the ester 4 (Ar = 3-chlorophenyl): mp 111–113 °C; IR (Nujol) ν_{max} 3350, 1721 cm^{-1}; UV (MeOH) λ_{max} 212 nm (ϵ 15 890), 291 (19 210), 307 (18 190); NMR ($CDCl_3$) δ 3.88 (s, 3), 4.40 (d, 2), 5.70 (t, 1), 6.67–7.00 (d of d, 1, J = 3 and 8 Hz), 7.13–7.42 (m, 4), 7.92 (d, 1, J = 8 Hz), 8.17 (d, 1, J = 3 Hz). Anal. ($C_{14}H_{13}ClN_2O_2$) C, H, N.

The bulk of the crude ester (30 g) was dissolved in 2-propanol (120 mL) and 2 N NaOH (60 mL) was added. The mixture was warmed on a steam bath for 3 min. 2-Propanol/ether (1:1) was added until there was evidence of precipitation. The mixture was cooled. Sodium 5-[(3-chlorobenzyl)amino]-2-pyridinecarboxylate (54) separated in quantitative yield: mp 250–255 °C; IR (Nujol) ν_{max} 3300, 1604 cm^{-1}; UV (MeOH) λ_{max} 278 nm (ϵ 18 130). Anal. ($C_{13}H_{10}ClN_2NaO_2$) C, H, N.

5-[*N*-(3-Chlorobenzyl)-*N*-methylamino]-2-pyridinecarboxylic Acid (55). The amino ester 4 (Ar = 3-chlorophenyl; 563 g, 2.03 mol) was dissolved in 97% formic acid (700 mL), 37% aqueous formaldehyde (700 mL) was added, and the mixture was heated on a steam bath for 18 h. The reaction mixture was then concentrated in vacuo. The residue was treated with 1:1 ethanol/toluene and reconcentrated in vacuo. The process was repeated twice more to remove water from the residue. Upon completion, a semisolid mass remained. NaOH, 50% (150 mL), was diluted with water to 3 L. This solution was added, and the mixture was heated on a steam bath until the solid dissolved. The solution was filtered. The filtrate was adjusted to pH 3.5 with 12 N HCl. After this solution was left standing at room temperature, the acid 55 crystallized. It was collected, dried, and recrystallized from 95% ethanol to give the acid 55, which was redissolved in base and precipitated by acid to give 55 (527 g, 93%): IR (Nujol) ν_{max} 1716, 1683 cm^{-1}; UV (MeOH) λ_{max} 282 nm (ϵ 17 350), 311 (9720); NMR ($CDCl_3$) δ 3.22 (s, 3), 4.67 (s, 2), 6.92–7.40 (m, 5), 8.05 (d, 1 J = 8 Hz), 8.20 (d, 1, J = 3 Hz). Anal. ($C_{14}H_{13}N_2O_2Cl$) C, H, N.

5-[(3-(Trifluoromethyl)benzyl]amino]-2-pyridinecarboxylic Acid (43; Scheme II). Preparation of the Urethane (9). 6-(Carboethoxy)-3-pyridinecarboxylic acid (7;[11] 10 g, 0.051 mol) was refluxed in thionyl chloride (40 mL) for 2 h. The excess thionyl chloride was removed in vacuo. The residue was slurried in toluene, and the toluene was removed in vacuo. The solid residue, now free of traces of thionyl chloride, was dissolved in acetone (150 mL) and cooled to 10 °C in an ice bath. Sodium azide (4.2 g, 0.065 mol) in water (20 mL) was added dropwise. A solid separated during the addition. The mixture was stirred for a total of 2 h. Ice/water was added (150 mL). The solid was collected and air-dried (7.1 g): IR (CH_2Cl_2) ν_{max} 2185, 2143, 1740, 1680 cm^{-1}.

The crude azide 8 (R = Et; 10 g, 0.045 mol) was suspended in toluene (200 mL). The mixture was then refluxed for 2 h. Ethanol (50 mL) was added and the mixture refluxed for a further 2 h. The solvents were removed in vacuo. The residue (8.25 g) was a tan solid which was recrystallized from ethanol to give urethane 9 (R = R′ = Et) as white crystals: mp 177–178 °C (7.69 g, 62%); IR (Nujol) ν_{max} 3225, 3180, 1726 cm^{-1}; NMR (Me_2SO) δ 1.10–1.53 (overlapping pair of triplets, 6), 4.00–4.56 (quintet, 4), 8.05 (s, 2), 8.73 (s, 1), 10.2 (s, 1). Anal. ($C_{11}H_{14}N_2O_4$) C, H, N. For large-scale work the half propyl ester acid of isocinchomeronic acid (7; R = *n*-propyl) was used, as the azide 8 (R = *n*-propyl) proved to be more soluble in hot toluene. The resulting urethane (9; R = n-propyl; R^1 = CH_3) mp 149–151 °C, was obtained in comparable yield and could be recrystallized from methanol to give material: mp 150–152 °C; UV (MeOH) λ_{max} 255 nm (ϵ 17 550), 282 (14 680); IR (Nujol) ν_{max} 3180, 1735, 1718, 1610 cm^{-1}; NMR ($CDCl_3$) 1.05 (t, 3), 1.40–220 (m, 2), 3.88 (s, 3), 4.28 (t, 2), 8.00–8.50 (m, 2), 8.87 (s, 1), 10.45 (s, 1). Anal. ($C_{11}H_{14}N_2O_4$) C, H, N.

Alkylation and Hydrolysis of the Urethane (9). The urethane 9 (R = R^1 = Et; 5.94 g, 0.025 mol) was dissolved in DMF (60 mL) and NaH (1.58 g of 57% suspension in oil, i.e., 900 mg, 0.037 mol) was added at room temperature. The mixture was stirred at room temperature for 15 min. 3-(Trifluoromethyl)benzyl chloride (5.8 g, 0.037 mol) was added in DMF (10 mL). The mixture was heated at 60 °C for 18 h. The DMF was removed in vacuo. The residue was dissolved in CH_2Cl_2. It was washed with 2 N HCl, water, and dried ($MgSO_4$). The CH_2Cl_2 was removed. The crude benzyl urethane (11.18 g) was hydrolyzed without further purification.

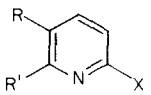
The crude benzyl compound (5.18 g, 1.31 mmol) was suspended in 20% KOH (25 mL) and heated to reflux. A small amount of ethanol (10–15 mL) was added to solubilize the urethane. The reaction mixture was refluxed for 28 h. Water was added and the mixture extracted with CH_2Cl_2. The aqueous part was cooled in ice and acidified (12 N HCl). A crystalline solid separated, which was dissolved in 10% $KHCO_3$, charcoaled, and reacidified (10 N HCl). The precipitate (3.20 g, 82%) was 5-[[3-(trifluoromethyl)benzyl]amino]-2-pyridinecarboxylic acid (43): mp 216–217 °C; NMR (Me_2SO) δ 4.62 (s, 2), 7.30, 7.45 (d of d, 1, J = 9 Hz), 7.50–8.17 (m, 9 almost half exchanges), 8.28 (d, 1, J = 3 Hz). Anal. ($C_{14}H_{11}F_3N_2O_2$) C, H, N.

Methyl 5-(Butylamino)-2-pyridinecarboxylate (16; Scheme III). Methyl 5-amino-2-pyridinecarboxylate (2) was converted into the butyrylamide 11 (R = $CH_3CH_2CH_2$), mp 186–190 °C (ex. MeOH), by warming in butyric anhydride/pyridine followed by a standard workup. The amide 11 (R = $CH_3CH_2CH_2$; 25.57 g, 0.115 mol) was dissolved in dioxane (385 mL). Sodium borohydride (21.8 g, 0.577 mol) was added with stirring. To the well-stirred and cooled reaction mixture, acetic acid (34.5 g, 0.576 mol) in dioxane (115 mL) was added during 10 min. After stirring for a further 20 min to complete gas evolution, the reaction mixture was heated on a steam bath for 30 min. After the reaction mixture cooled, additional acetic acid (11.5 mL) was added. The reaction mixture was poured into ice/water (500 mL) and extracted with CH_2Cl_2 (3×). The CH_2Cl_2 extracts were combined, washed with water, and dried ($MgSO_4$). The CH_2Cl_2 was removed in vacuo and the residue (16.4 g, 69%) crystallized. It was recrystallized from ethyl acetate/ether to give methyl 5-(butylamino)-2-pyridinecarboxylate (16), mp 79–82 °C (10.25 g, 43.1%). The homogeneity of this material was confirmed by TLC (silica gel GF; $CHCl_3$–EtOAc–MeOH 80:20:3): IR (Nujol) ν_{max} 3256, 1731 cm^{-1}; UV (MeOH) λ_{max} 294 m (ϵ 18 160), 307 (17 270); NMR ($CDCl_3$) δ 0.67–1.10 (t, 3), 1.10–1.90 (m, 4), 2.90–3.40 (m, 2), 3.90 (s, 3), 4.6 (br s, 1, exh), 6.73 (d, 1), 6.88 (d, 1), 8.06 (d, 1). Anal. ($C_{11}H_{16}N_2O_2$) C, H, N.

5-(Phenylamino)-2-pyridinecarboxylic Acid (15; Scheme IV). NaH, 50% in mineral oil (2.64 g, i.e., 0.055 mol of NaH), in a 500-mL flask was washed twice with dry hexane under N_2,

(11) P. I. Pollack and M. Windholz, *Heterocycl. Compd.*, 14 (Part 3), 257 (1974).

Table I



no.[c]	R	R′	X	salt	synth scheme	mp, °C	recrystn solvent	formula	dose, mg/kg po	antihypertensive effect in SH rat[d]	micro-anal.[e]
16	$CH_3(CH_2)_3NH$	H	CO_2CH_3		III	79-82	$EtOAc/Et_2O$	$C_{11}H_{16}N_2O_2$	50	+	C, H, N
17	CH_3CH_2CONH	H	CO_2H		*a*	215-219	EtOH	$C_9H_{10}N_2O_3$	100	inactive	C, H, N
18	$CH_3(CH_2)_3SO_2NH$	H	CO_2H		*a*	221-224	aq HOAc	$C_{10}H_{14}N_2O_4S$	100	inactive	C, H, N
19	$4\text{-}ClC_6H_4SO_2NH$	H	CO_2H		*a*	244-246	H_2O ph 9 → 4	$C_{12}H_9ClN_2O_4S$	100	inactive	C, H, N
20	CH_3CH_2OCONH	H	CO_2CH_3		*a*	166-169	EtOH	$C_{10}H_{12}N_2O_4$	100	inactive	C, H, N
21	C_6H_5CONH	H	CO_2H		*a*	215-220	aq MeOH	$C_{13}H_{10}N_2O_3$	100	+ +	C, H, N
15	C_6H_5NH	H	CO_2H		IV	180-183	aq MeOH	$C_{12}H_{10}N_2O_2$	50	inactive	C, H, N
22	$C_6H_5CH_2NH$	H	CO_2H		I	158-164	CH_3CN/ether	$C_{13}H_{12}N_2O_2$	50	+ + + + +	C, H, N
									25	+ + + +	
									10	+ + +	
23	$C_6H_5CH_2CH_2NH$	H	CO_2H		III	65-70	aq CH_3CN	$C_{14}H_{14}N_2O_2$	50	+ +	C, H, N
24	$C_6H_5(CH_2)_3NH$	H	CO_2H		I	167-169	MeOH	$C_{15}H_{16}N_2O_2$	100	+ + +	C, H, N
25	$C_6H_{11}CH_2NH$	H	CO_2H		I	139-141	CH_3CN/ether	$C_{13}H_{18}N_2O_2$	50	+ + (3/3 dead)	C, H, N
26	$C_6H_5CH(CH_3)NH$	H	CO_2H		II	213-215	aq MeOH	$C_{14}H_{14}N_2O_2$	50	+ + + + +	C, H, N
27	$C_6H_5CH_2NCH_3$	H	CO_2H		I	168-173	aq CH_3CN	$C_{14}H_{14}N_2O_2$	50	+ + +	C, H, N
28	$3\text{-}CH_3C_6H_4CH_2NH$	H	CO_2H		I	155-158	aq MeOH	$C_{14}H_{14}N_2O_2$	50	+ +	C, H, N
29	$3\text{-}CH_3C_6H_4CH_2NCH_3$	H	CO_2H		I	137-140	aq MeOH	$C_{15}H_{16}N_2O_2$	50	+ +	C, H, N
30	$3\text{-}CH_3OC_6H_4CH_2NH$	H	CO_2H		I	143-147	aq MeOH	$C_{14}H_{14}N_2O_3$	50	+ +	C, H, N
31	$3\text{-}CH_3OC_6H_4CH_2NCH_3$	H	CO_2H		I	130-134	benzene/hexane	$C_{15}H_{16}N_2O_3$	50	+ +	C, H, N
32	$3\text{-}C_6H_5OC_6H_4CH_2NH$	H	CO_2H		I	158-162	aq MeOH	$C_{19}H_{16}N_2O_3$	50	+ +	C, H, N
33	$3\text{-}C_6H_5OC_6H_4CH_2NCH_3$	H	CO_2H		I	121-123	H_2O, pH 9 → 4	$C_{20}H_{18}N_2O_3$	50	+ +	C, H, N
34	$3\text{-}FC_6H_4CH_2NH$	H	CO_2H		I	164-167	H_2O, pH 9 → 4	$C_{13}H_{11}FN_2O_2$	50	+ + + +	C, H, N
35	$3\text{-}FC_6H_4CH_2NCH_3$	H	CO_2H		I	151-156	CH_3CN	$C_{14}H_{13}FN_2O_2$	50	+ +	C, H, N
36	$3\text{-}BrC_6H_4CH_2NH$	H	CO_2H	Na	I	245-250	H_2O	$C_{13}H_{10}BrN_2NaO_2$	50	+ +	C, H, N
37	$3\text{-}BrC_6H_4CH_2NCH_3$	H	CO_2H		I	158-161	MeOH	$C_{14}H_{13}BrN_2O_2$		+ + +	C, H, N
38	$2\text{-}ClC_6H_4CH_2NH$	H	CO_2H	Na	I	245-250	H_2O	$C_{13}H_{10}ClN_2NaO_2$	100	+ + + +	C, H, N
39	$4\text{-}ClC_6H_4CH_2NH$	H	CO_2H	Na	I	293-296	aq 2-propanol	$C_{13}H_{10}ClN_2NaO_2$	100	+ + +	C, H, N
40	$4\text{-}ClC_6H_4CH_2NH$	H	CO_2CH_3		I	130-133	$EtOAc/Et_2O$	$C_{14}H_{13}ClN_2O_2$	100	+ + + +	C, H, N
41	$3,4\text{-}Cl_2C_6H_3CH_2NH$	H	CO_2H		I	218-223	aq HOAc	$C_{13}H_{10}Cl_2N_2O_2$	50	+	C, H, N
42	$3,4\text{-}Cl_2C_6H_3CH_2NCH_3$	H	CO_2H		I	193-197	HOAc/EtOH	$C_{14}H_{12}Cl_2N_2O_2$	50	+ + + +	C, H, N
43	$3\text{-}CF_3C_6H_4CH_2NH_3$	H	CO_2H		II	216-217	H_2O, pH 9 → 4	$C_{14}H_{11}F_3N_2O_2$	100	+ + + +	C, H, N
44	$4\text{-}H_2NCOC_6H_4CH_2NH$	H	CO_2H		I	258-261	HOAc/MeOH	$C_{14}H_{13}N_3O_3$	50	+	C, H, N
45	$4\text{-}(CH_3)_3CC_6H_4CH_2NH$	H	CO_2H		II	169-172	H_2O, pH 9 → 4	$C_{17}H_{20}N_2O_2$	50	+	C, H, N
46	$4\text{-}CF_3C_6H_4CH_2NH$	H	CO_2H		II	218-221	H_2O, pH 9 → 4	$C_{14}H_{11}F_3N_2O_2$	50	+ + +	C, H, N
47	$3\text{-}F\text{-}4\text{-}OCH_3C_6H_3CH_2NH$	H	CO_2H		I	213-216	HOAc/MeOH	$C_{14}H_{13}FN_2O_3$	50	+ +	C, H, N
48	$3,5\text{-}Cl_2C_6H_3CH_2NH$	H	CO_2H	Na	I	315-320	H_2O	$C_{13}H_9Cl_2N_2NaO_2$	50	+ + + +	C, H, N
49	$2\text{-}FC_6H_4CH_2NH$	H	CO_2H	Na	I	135 dec	aq CH_3CN	$C_{13}H_{10}FN_2NaO_2$	50	+ + +	C, H, N
50	$3,4,5\text{-}(OCH_3)_3C_6H_2CH_2NH$	H	CO_2H		I	224-227	aq CH_3CN	$C_{16}H_{18}N_2O_5$	50	+	C, H, N
51	3-pyridyl-CH_2NH	H	CO_2H		I	199-201	H_2O	$C_{12}H_{11}N_3O_2$	100	+	C, H, N
52	4-pyridyl-CH_2NH	H	CO_2H	Na	I	270-285 dec	H_2O	$C_{12}H_{10}N_3NaO_2$	50	+ +	C, H, N
53	2-pyridyl-CH_2NH	H	CO_2H	Ca	I	220-240 dec	H_2O	$C_{24}H_{20}CaN_6O_4$	50	+ +	C, H, N[f]
54	$3\text{-}ClC_6H_4CH_2NH$	H	CO_2H	Na	I	250-255	aq 2-propanol	$C_{13}H_{10}ClN_2NaO_2$	100	+ + + +	C, H, N
55	$3\text{-}ClC_6H_4CH_2NCH_3$	H	CO_2H		I	138-140	aq EtOH	$C_{14}H_{13}ClN_2O_2$	100	+ + + + +	C, H, N
									50	+ + + + +	
									25	+ + +	
56	$3\text{-}ClC_6H_4CH_2NCH_3$	H	CO_2CH_3		I	89-91	aq MeOH	$C_{15}H_{15}ClN_2O_2$	50	+ +	C, H, N
57	$3\text{-}ClC_6H_4CH_2NCH_3$	H	$CONH_2$		*a*	178-183	MeOH	$C_{14}H_{14}ClN_3O$	50	+	C, H, N

58	3-ClC$_6$H$_4$CH$_2$NCH$_3$	H	CH$_2$OH		*a*	101–105	CH$_3$CN/Et$_2$O	C$_{14}$H$_{15}$ClN$_2$O·C$_6$H$_{13}$NO$_3$S	50	+	+	+	+	+				C, H, N
59	3-ClC$_6$H$_4$CH$_2$NH	H	CH$_2$OH		*b*	85–88	EtOAc/Et$_2$O	C$_{13}$H$_{13}$ClN$_2$O	50	+	+	+	+	+				C, H, N
60	3-ClC$_6$H$_4$CH$_2$NH	H	CHO		*b*	102–105	EtOAc/Et$_2$O	C$_{13}$H$_{11}$ClN$_2$O	50	+	+	+	+	+	+			C, H, N
61	3-ClC$_6$H$_4$CH$_2$NH	CH$_3$	CO$_2$H	Na	I	240–245	aq 2-propanol	C$_{14}$H$_{12}$ClN$_2$NaO$_2$	50	+	+	+	+	+				C, H, N
62	3-ClC$_6$H$_4$CH$_2$NCH$_3$	CH$_3$	CO$_2$H		I	85–90	aq MeOH	C$_{15}$H$_{15}$ClN$_2$O$_2$	100	+	+	+	+	+				C, H, N
63	3-ClC$_6$H$_4$CH$_2$NCOCH$_2$CH$_3$	H	CO$_2$H		*a*	139–141	aq MeOH	C$_{16}$H$_{15}$ClN$_2$O$_3$	100	+	+	+	+	+				C, H, N
64	(3-ClC$_6$H$_4$CH$_2$)$_2$N	H	CO$_2$H		*a*	108–110	MeOH/Et$_2$O	C$_{20}$H$_{16}$Cl$_2$N$_2$O$_2$	100	+	+	+	+	+				C, H, N
65	4-FC$_6$H$_4$CH$_2$NH	H	CO$_2$H		I & II	197–200	H$_2$O, pH 9 → 4	C$_{13}$H$_{11}$FN$_2$O$_2$	50	+	+	+	+	+				C, H, N
									25	+	+	+	+	+				
66	4-FC$_6$H$_4$CH(CH$_3$)NH	H	CO$_2$H		II	214–217	EtOAc/CH$_3$CN	C$_{14}$H$_{13}$FN$_2$O$_2$	50	+	+	+	+	+				C, H, N
67	4-FC$_6$H$_4$CH$_2$NH	H	CN		*a*	88–90	EtOAc/Et$_2$O	C$_{13}$H$_{10}$FN$_3$	50	+	+	+	+	inactive				C, H, N
68	4-FC$_6$H$_4$CH$_2$NH	H	CONHEt		*a*	123–126	EtOAc	C$_{15}$H$_{16}$FN$_3$O	50	+	+	+	+	inactive				C, H, N
69	4-FC$_6$H$_4$CH$_2$NH	H	CONH$_2$		*b*	160–164	2-propanol	C$_{13}$H$_{12}$FN$_3$O	50	+	+	+	+	+	+			C, H, N
70	4-FC$_6$H$_4$CH$_2$NH	H	CONHNH$_2$		*a*	153–158	aq MeOH	C$_{13}$H$_{13}$FN$_4$O	50	+	+	+	+	+	+			C, H, N
71	4-FC$_6$H$_4$CH$_2$NH	H	CONMe$_2$		*a*	136–138	EtOAc	C$_{15}$H$_{16}$FN$_3$O	50	+	+	+	+	+	+			C, H, N
72	4-FC$_6$H$_4$CH$_2$NH	H	CO$_2$CH$_3$		I	107–109	aq MeOH	C$_{14}$H$_{13}$FN$_2$O$_2$	50	+	+	+	+	+	+			C, H, N
73	4-FC$_6$H$_4$CH$_2$NH	H	CHN$_4$		*a*	224–227	aq HOAc	C$_{13}$H$_{11}$FN$_6$	50	+	+	+	+	+	+			C, H, N
74	4-FC$_6$H$_4$CH$_2$NH	H	CHO		*a*	124–126	EtOAc/Et$_2$O	C$_{13}$H$_{11}$FN$_2$O	50	+	+	+	+	+	+	+		C, H, N
75	4-FC$_6$H$_4$CH$_2$NH	H	CH$_2$OH		*a*	127–133	EtOAc/Et$_2$O	C$_{13}$H$_{13}$FN$_2$O	50	+	+	+	+	+	+	+		C, H, N
76	4-FC$_6$H$_4$CH$_2$NH	H	CH=NOH		*a*	167–169	CH$_3$CN	C$_{13}$H$_{12}$FN$_3$O	50	+	+	+	+	+				C, H, N
77	4-FC$_6$H$_4$CH$_2$NH *N*-oxide	H	CO$_2$H	Na	*a*	206–209	aq EtOH	C$_{13}$H$_{10}$FN$_2$NaO$_3$	50	+	+	+	+	+				C, H, N
	(CH$_2$)$_3$CH$_3$-fusaric acid	H	CO$_2$H						100	+	+	+	+	+				C, H, N

[a] These compounds were prepared by conventional procedures from the appropriate precursor. [b] See Experimental Section. [c] All compounds have compatible UV, IR, and NMR spectra. [d] +, <20 mm; ++, >20 mm; +++, >40 mm; ++++, >60 mm; +++++, >80 mm (maximum blood pressure fall). [e] C, H, and N microanalyses conform to 0.4% of theory. [f] Anal. Calcd for $C_{24}H_{20}CaN_6O_4 \cdot 0.5H_2O$: C, 56.02; H, 4.30; N, 16.32. Found: C, 55.16; H, 4.33; N, 16.09.

the hexane wash being removed by decantation. The remaining NaH was covered by dry DMF (25 mL). Formanilide (7.26 g, 0.060 mol) was added in dry DMF (50 mL). Methyl 5-nitro-2-pyridinecarboxylate (9.1 g, 0.050 mol), dissolved in DMF (90 mL) by warming, was added with stirring. The mixture was heated on a steam bath for 30 min and then acetic acid (5 mL) was added. The reaction mixture was poured into ice/water (700 mL); the pH was approximately 6. A precipitate resulted (6.65 g), which was collected, washed, and dried. The material (5.85 g) obtained by $CHCl_3$ extraction of the filtrate was intractable. The precipitate was crude methyl 5-(phenylamino)pyridine-2-carboxylate. A portion (1 g) was recrystallized from acetonitrile to give methyl 5-(phenylamino)-2-pyridinecarboxylate (500 mg): mp 125–127 and 143–146 °C; IR (Nujol) 3340, 1698 cm^{-1}; UV (MeOH) λ_{max} 329 nm (ϵ 20 190); NMR (Me_2SO) δ 3.78 (s, 3), 6.82–7.68 (m, 6), 7.90 (d, 1, J = 9 Hz), 8.86 (d, 1, J = 3 Hz), 9.00 (s, 1). Anal. ($C_{13}H_{12}N_2O_2$) C, H, N.

The crude methyl 5-(phenylamino)-2-pyridincarboxylate (5.45 g, 0.024 mol) was dissolved in MeOH (100 mL) and excess 1 N aqueous NaOH. The reaction mixture was refluxed on a steam bath, allowing the methanol to boil off. Water was added, the pH was adjusted to 7 (acetic acid), and the resulting precipitate was removed. The filtrate was adjusted to pH 4 (concentrated HCl). The yellow precipitate was collected and air-dried. Recrystallization from aqueous MeOH gave analytically pure acid: mp 180–183 °C; IR (Nujol) ν_{max} 1667 cm^{-1}; UV (MeOH) 240 nm (ϵ 6230), 301 (17 690), 320 (16 680); NMR (Me_2SO) 5.80–7.10 (m, 6), 7.88 (d, 1, J = 9 Hz), 7.34 (d, 1, J = 3 Hz), 8.92 (s, 1). Anal. ($C_{12}H_{10}N_2O_2$) C, H, N.

5-[(4-Fluorobenzyl)amino]-2-pyridinecarboxamide (69). Sodium hydride (3.0 g of 56% in oil, 0.0625 mol) was washed free of oil by dry hexane under N_2. The hexane was removed by decantation and replaced by dry Me_2SO (50 mL). Formamide (4.5 g, 0.10 mol) was added, followed by methyl 5-[(4-fluorobenzyl)amino]-2-pyridinecarboxylate (**72**; 13.0 g, 0.050 mol) in dry Me_2SO (50 mL). The reaction mixture was heated on a steam bath under N_2 for a few minutes and then allowed to stand at room temperature for 1.5 h. Upon pouring into ice/water (700 mL), a precipitate developed, which crystallized on scratching. This material was collected and dried (10.9 g). It was recrystallized from 2-propanol to give the amide **69** (7.3 g, 60%): mp 160–164 °C; IR (Nujol) ν_{max} 3400, 3250, 1672, 1656 cm^{-1}; UV (MeOH) λ_{max} 287 nm (ϵ 18 920), 308 (15 350); NMR (Me_2SO) δ 4.40 (d, 2, J = 6 Hz), 6.84–7.66 (m, 5), 7.66–8.20 (m, 2). Anal. ($C_{13}H_{12}FN_3O$) C, H, N.

5-[(3-Chlorobenzyl)amino]-2-pyridinecarbinol (59). The aqueous filtrate from a large-scale $NaBH_4$ reduction of the imine (217.5 g, 0.79 mol) used to prepare methyl 5-[(3-chlorobenzyl)-amino]-2-pyridinecarboxylate (**4**; Ar = 3-chlorophenyl) by Scheme I was extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed (water), dried (MgSO4), and concentrated to dryness in vacuo. The residue was triturated with ether/hexane to give the crude carbinol, mp 75–85 °C (16.5 g, 8.4%), which was recrystllized from ether/ethyl acetate to give the carbinol **59** (9.75 g): mp 85–88 °C; IR (Nujol) ν_{max} 3300 cm^{-1}; UV (MeOH) λ_{max} 254 nm (ϵ 18 200), 314 (3930); NMR (Me_2SO) δ 4.20–4.50 (br t, 4), 5.00 (t, 1 exch), 6.30–7.50 (m, 7), 7.92 (br s, 1). Anal. ($C_{13}H_{13}ClN_2O$) C, H, N.

5-[(3-Chlorobenzyl)amino]-2-pyridinecarboxaldehyde (60). The carbinol **59** (9.95 g, 0.040 mol) was dissolved in chloroform (400 mL) and activated MnO_2 (32 g) was added. The mixture was refluxed for 2 h, the MnO_2 was removed by filtration, the filtrate was concentrated to dryness in vacuo, and the residue (8.90 g, 89%) crystallized. It was recrystallized from ether/ethyl acetate to give the aldehyde **60**: mp 102–105 °C; IR (Nujol) ν_{max} 3280, 1674 cm^{-1}; NMR (Me_2SO) δ 4.45 (d, 2, J = 7 Hz), 6.91, 7.08 (d of d, 1, J = 10 and 3 Hz), 7.20–7.60 (m, 3), 7.72 (d, 1, J = 10 Hz), 8.22 (d, 1, J = 3 Hz), 9.73 (s, 1). Anal. ($C_{13}H_{11}ClN_2O$) C, H, N.

Pharmacology. Antihypertensive Assay in Spontaneous Hypertensive Rats. Male SHR approximately 16 weeks of age with systolic blood pressures greater than 150 mmHg were used for these studies. Animals were placed in individual Lucite restraint cages to restrict excess movement. The cages were placed in a large plastic chamber and the animals tails passed through an inflatable occlusive cuff. A pneumatic, rubber bulb pulse sensor was placed distal to the cuff (width 0.5 cm) and taped circumferentially about the tail. The connecting tubing from the pulse

Table II. Antihypertensive Activity of Compounds in Unanesthetized Renal Hypertensive Dogs (RHD)

compd	dose, mg/kg po		max Δ in BP[a] day 1	day 2	day 3	day 4
22	100	MBP:	−32 ± 10.8	−14 ± 16.2	−13 ± 16.1	−6 ± 13.6
		HR:	+74 ± 12.5*	+61 ± 13.2	+52 ± 13.6	+48 ± 28.6
34	100	MBP:	−30 ± 8.5	−46 ± 18.4	−56 ± 5.0*	−51 ± 5.2*
		HR:	+35 ± 12.7	+78 ± 17.2	+51 ± 13.5	+44 ± 10.1*
54	100	MBP:	−15 ± 6.8	−9 ± 1.7*	−4 ± 1.8	
		HR:	+16 ± 10.6	+11 ± 12.7	+11 ± 12.7	
55	100	MBP:	−21 ± 16.0	−25 ± 7.5		
		HR:	+1 ± 8.1	+39 ± 2.3		
65	100	MBP:	−69 ± 13.7*	−41 ± 0.3*	−49 ± 2.9*	−48 ± 9.0*
		HR:	+37 ± 10.7	+60 ± 13.1*	+52 ± 18.6	+41 ± 37.0
71	100	MBP:	+11 ± 6.1	−67 ± 5.2*	−40 ± 15.5	
		HR:	+20 ± 8.0	+112 ± 22.0*	+107 ± 8.1*	
fusaric acid	60	MBP:	−50 ± 7	−45 ± 12	−30 ± 7	
		HR:	+32 ± 18	+35 ± 17	+33 ± 5	

[a] Values are mean ± SE; an asterisk indicates $p < 0.05$. MBP = mean blood pressure (mm Hg); HR = heart rate (beats/min).

sensor was attached to a pneumatic pulse transducer (Narco Bio Systems), and a solenoid-controlled manifold connected to a blood pressure cuff pump (Narco Bio Systems) was calibrated to deliver a maximum air pressure of 250 mmHg. Upon completion of all connections, the chamber door was closed and a warm-air delivery system turned on. The system was electrically modified to heat upon demand of a thermistor probe within the chamber to maintain a temperature of 32.5 ± 0.5 °C. Air volume was such as to exchange three chamber volumes per minute. Animals were allowed to acclimate for 1 h to ensure adequate circulation in the tail. During this time, pressure calibration was checked and set on each of the electrophygmographs (Narco Bio Systems).

After 1 h of acclimation at least three systolic blood pressure readings were taken on each group of animals. Pressure in the occlusion cuff was raised to 250 mmHg, so that arterial pulse displacements were no longer apparent, and then gradually lowered. The systolic pressure was identified by th location of the point that the pulse reemerged. Heart rates were determined by counting the pressure pulses.

All drugs were administered at a standard dose of 50 mg/kg (in some cases also at 100 and 25 mg/kg) by gavage in a mixture containing 3% cornstarch, 5% PEG-400, and 1 drop of Tween 80 per milliliter.

Animals were dosed daily for either 2 or 4 consecutive days with four to six rats used for each drug studied. Blood pressures were recorded at 1, 2, 3 and 24 h after each drug administration. Reported antihypertensive activity represented peak falls in pressure.

Antihypertensive Assay in Renal Hypertensive Dogs. Male mongrel dogs were made hypertensive by unilateral nephrectomy and either renal artery constriction[12] or kidney encapsulation[13] on the contralateral side.

Four to six weeks were allowed to elapse after experimental surgery for convalescence and the establishment of elevated blood pressure. Animals were trained to lie quietly in a supine position while their blood pressure was measured by direct femoral artery puncture with a 22-gauge, 1-in. hypodermic needle connected by polyethylene tubing to a Statham 23AA pressure transducer and displayed on a Sanborn recorder. Heart rate was counted manually. Drugs were given orally once daily in solid form by gelatin capsule. Blood pressures were determined at 1.5, 3, 6, and 24 h after each drug administration with reported activity represented by maximum changes in blood pressure and heart rate over a daily monitored session.

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Synthesis and Antifertility Activity of 3,9-Dihydroxy-5,6,6aα,6bβ,11,12,12aβ,12bα-octahydrodibenzo[*a*,*g*]biphenylene, a Structural Relative of Diethylstilbestrol

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The title diphenol, **1a**, was synthesized from *p,p'*-dihydroxy-α-truxillic acid and shown to be active as an oral postcoital antifertility agent in rats: ED_{100} = 100 (μg/kg)/day. The oral uterotropic potency was estimated to be 16% of that of diethylstilbestrol (95% confidence limits of potency 8–35%). The structure of the diphenol, **1a**, was confirmed by single-crystal X-ray analysis of the dimethyl ether.

Despite the widespread use of antifertility drugs, some of the currently available ones exhibit undesired estrogenic side effects.[2] The apparent structural relationship of 3,9-dihydroxy-5,6,6aα,6bβ,11,12,12aβ,12bα-octahydrodi-

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