(type 4A)] and evapd *in vacuo* at room temp. The residual oil was purified by glc. The major product was 1-isopropylamino-2-propanol (III) which had retention time 8.7 min on a column, 1.52 m × 0.63 cm of 10% Carbowax, 2 *M*, and 5% KOH on Chromosorb W (60–80 mesh), at 110° with flow rate 40 ml/min (N_2). It possessed the following nmr features[13] in $CDCl_3$: 8.94, d, J = 6 cps, 6 H; 8.85, d, J = 6 cps, 3 H; 7.7 q (A component of ABX system), J_{AB} cps, J_{AX} = 4.5 cps, 1 H; 7.3, q (B of ABX) J_{BX} = 2 cps, 1 H; 7.22, septet, J = 6 cps, 1 H; 6.26, m (X of $ABXY_3$), 1 H; 7.53, b, 2 H exchangeable; and had $[\alpha]^{20}D$ + 48° (*c* 6.0, $CDCl_3$).

(+)-1-Isopropylamino-2-propanol (III). Route B.—LAH (2 g) was added during 15 min to a stirred soln of (+)-1-chloro-3-isopropylaminopropan-2-ol (−)-di-*O,O*-*p*-toluoyltartrate (5.4 g) in dry THF at 5–10°. The mixt was refluxed for 3 hr and cooled and H_2O (2 ml), 2 *N* NaOH (2 ml), and H_2O (6 ml) were then added. The mixt was filtered and the THF was removed by distn at 1 atm; the residue consisted of an aq and an oily phase. The solid residue from the filtration was combined with the aq phase and the mixt was Et_2O extd continuously for 18 hr. The Et_2O ext was dried ($MgSO_4$) and evapd at 1 atm. The residual oil was purified by glc.

The major product had identical glc and nmr characteristics to those of the product of route A, and possessed $[\alpha]^{20}D$ + 46.4° (*c* 5.5, $CDCl_3$).

(+)-1-Chloro-3-isopropylamino-2-propanol (−)-Di-*O,O*-*p*-toluoyltartrate (IV).—A mixt of 2 *N* NaOH (15m l), 1-chloro-3-isopropylamino-2-propanol·HCl (27.36 g), H_2O (450 ml), and NaCl (150 g) was extd 4 times with 300 ml of Et_2O. The Et_2O exts were dried ($MgSO_4$) and added to a soln of (−)-di-*O,O*-*p*-toluoyltartaric acid (69.6 g) in Et_2O (200 ml). The mixt was filtd and the solid residue was crystd 5 times from *i*-PrOH, yield 6 g, mp softens 100°, decomp 140–144°. A sample was converted into the hydrochloride, mp 106°, $[\alpha]^{20}D$ + 25.9° (*c* 2.0, EtOH).

1-Chloro-3-isopropylamino-2-propanol·HCl.—A soln of *i*-PrNH$_2$ (85 ml) in MeOH (400 ml) was added slowly with stirring to epichlorohydrin (15.6 ml) at 25°. The mixt was stirred for 2 hr at ambient temp and then evapd under reduced pressure. The residue was distd; bp 72–76° (2.8 mm). The distillate was dissolved in Et_2O (100 ml) and acidified with ethereal HCl. The mixt was filtered and the solid residue was crystd twice from CPrOH–Et_2O (1:2); yield 3.65 g (10%), mp 93–94°. *Anal.* *i*-($C_6H_{14}ClNO$·HCl) C, H, N.

(+)-1-Isopropylamino-3-(1-naphthoxy)-2-propanol·HCl (V).—A mixt of 1-naphthol (0.7 g), EtOH (50 ml), (+)-1-chloro-3-isopropylamino-2-propanol (−)-di-*O,O*-*p*-toluoyltartrate (2.5 g), NaOH (0.6 g), and H_2O (5 ml) was heated under reflux for 3 hr. The mixt was filtered and the filtrate was evapd under reduced pressure. The residue was dissolved in Et_2O and acidified with ethereal HCl. The mixt was filtered and the solid residue crystd from Et_2O–EtOH: mp 190–192°; $[\alpha]^{20}D$ + 29.8° (*c* 0.44, EtOH).

(13) Nmr data are recorded in order of chemical shift (TMS), multiplicity (d = doublet; q = quartet; m = multiplet; b = broad), coupling constant in cps, and integration.

Acknowledgment.—We are indebted to Dr. T. Leigh for supplying us with compounds **4**, **5**, **6**, **7**, and **8**; to Mr. B. Crooks for the purification of (+)-1-isopropylamino-2-propanol by gas phase chromatography; and to Mr. P. J. Taylor for providing, and helpfully commenting upon, the ir spectra.

Antihypertensive Agents. Substituted 3-Pyrrolemethylamines

CHARLES H. TILFORD,†

Chemistry Department, Emory University, Atlanta, Georgia 30322

W. J. HUDAK,* AND RICHARD E. LEWIS

Cardiovascular Section, Department of Pharmacology, The Wm. S. Merrell Company, Division of Richardson-Merrell Inc., Cincinnati, Ohio 45215

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1-Aryl-, aralkyl-, cycloalkyl-, and heterocyclic 2,5-dimethylpyrroles, prepared by reaction of primary amines with acetonylacetone, were formylated using $POCl_3$ and DMF. The resulting 1-substituted-2,5-dimethyl-3-pyrrolecarboxaldehydes were then converted into the desired 3-pyrrolemethylamines using a series of di- and triamines in the KBH_4-reductive alkylation procedure. In hypotensive tests, the most potent compound (**7**, Table I) caused a 75% drop in mean arterial blood pressure in dogs at 0.1 mg/kg iv that lasted over 1 hr.

A search for new types of compounds for lowering blood pressure led to the use of commercially available 2,5-dimethyl-1-phenyl-3-pyrrolecarboxaldehyde as a starting material. When activity was found in the first few amines prepared by reduction of Schiff's bases of this aldehyde, a series of diverse 3-pyrrolemethylamines was prepared to seek a product worthy of clinical testing. The compounds listed in Table I were prepared by the reaction sequence outlined in Scheme I.

As shown in Table I, A is an alkyl group substituted with a terminal basic function.

Herz and Settine[1] report the preparation of *tert*-3-pyrrolemethylamines from pyrroles of type I *via* the Mannich reaction, which might be considered an alternate method for preparing type IV compounds. However, the Mannich method could give appreciable 3,4-bisamine formation which might complicate isolation procedures beyond practicality.

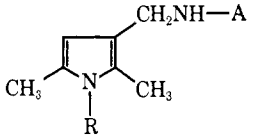
The method shown in Scheme I minimizes bisamine formation. The procedure of Rips and Buu-Hoï[2] was used for formylating 1-substituted-2,5-dimethylpyrroles (I) with DMF–$POCl_3$. As illustrated by the preparation of 2,5-dimethyl-1-phenyl-3-pyrrolecarboxaldehyde (73% yield),[2] their procedure gives good yields of 3-pyrrolecarboxaldehydes (II) which are readily separated from small amounts of the corresponding biscarboxaldehydes by fractional distillation. Thus, 3-pyrrolemethylamines IV obtained from aldehydes II prepared according to Rips and Buu-Hoï should not be contaminated with bisamines. As it was, decomposition problems were encountered when amines IV obtained by KBH_4 reduction of the Schiff's bases III were vacuum distilled. For example, in 3 successive experiments, attempts to distill crude base **8** (Table I)—actually the

† Present address: 2167 Greensward Drive, NE, Atlanta, Ga. 30345.

(1) W. Herz and R. L. Settine, *J. Org. Chem.*, **24**, 201 (1959).

(2) R. Rips and N. P. Buu-Hoï, *ibid.*, **24**, 372 (1959).

TABLE I
1-SUBSTITUTED-2,5-DIMETHYL-3-PYRROLEMETHYLAMINES



	R	A	Bp, °C (mm)	Formula (analysis)[a]	Salt[b]	Mp (corr), °C dec	% yield[c]	Hypotensive act.[d]
1	Ph	$(CH_2)_3NH_2$	155–156 (0.10)	$C_{16}H_{23}N_3$[e]	Citrate[f]	180–182	24	+++
2	Ph	$(CH_2)_3NEt_2$	155–157 (0.25)	$C_{20}H_{31}N_3$[g]	2HCl	196–197	42	+
3	Ph	$(CH_2)_3NH(CH_2)_2OH$	195 (0.10)	$C_{18}H_{27}N_3O$[h]	Citrate[i]	140	67	++
4	Ph	$(CH_2)_3NH$-cyclohexyl	190 (0.15)	$C_{22}H_{33}N_3$[j]	2HCl	209–210	35	+
5	Ph	$(CH_2)_2NH(CH_2)_2NEt_2$	172–175 (0.08)	$C_{21}H_{34}N_4$[k]	*l*		47	++
6	Ph	CH_2-4-piperidyl	178–180 (0.10)	$C_{19}H_{27}N_3$	Citrate[f]	185–187	63	++++
7	Ph	$(CH_2)_2$-4-piperidyl	182–184 (0.07)	$C_{20}H_{29}N_3$[m]	Citrate	188–189	64	++++
8	Ph	$(CH_2)_2$-1-piperazyl	189–192 (0.06)	$C_{19}H_{28}N_4$	Sulfate[i]	238–239	61	++++
9	Ph	$(CH_2)_3$-1-piperazyl	202–204 (0.10)	$C_{20}H_{30}N_4$	Citrate[f]	201–202	71	++
10	Ph	$(CH_2)_3$(4-Me-1-piperazyl)	*n*	$C_{21}H_{32}N_4$	3HCl[i]	235–238	43	++
11	Ph	$(CH_2)_2$-pyrrolidino	173–176 (0.10)	$C_{19}H_{27}N_3$[o]	2HCl[i]	180–181	73	±
12	Ph	$(CH_2)_2$(1-Me-2-pyrrolidyl)	173–176 (0.08)	$C_{20}H_{29}N_3$	Citrate[f]	65	68	+
13	Ph	$(CH_2)_2$-morpholino	182–185 (0.15)	$C_{20}H_{29}N_3O$	2HCl	246–247	58	++
14	Ph	CH_2CH(Me)-4-pyridyl	*n*	$C_{21}H_{25}N_3$	2HCl[i]	178–179	55	++
15	Ph	(1-Et-3-piperidyl)	173–175 (0.10)	$C_{20}H_{29}N_3$	Citrate	91–95	68	±
16	Ph	$(CH_2)_2N$(Et)-*m*-tolyl	*p*	$C_{24}H_{31}N_3$	2HCl	189–190	39	+++
17	2,6-Me_2Ph	CH_2-4-piperidyl	163–165 (0.05)	$C_{21}H_{31}N_3$[q]	Citrate	198–199	75	++
18	2,6-Me_2Ph	$(CH_2)_2$-4-piperidyl	183–185 (0.05)	$C_{22}H_{33}N_3$	Citrate[f]	175–177	77	++++
19	2,6-Me_2Ph	$(CH_2)_3NH_2$	155–157 (0.05)	$C_{18}H_{27}N_3$	Citrate	187–189	62	+
20	2,5-$(MeO)_2$Ph	CH_2-4-piperidyl	*r*	$C_{21}H_{31}N_3O_2$	2HCl[f]	264–266	27	+++
21	2,6-Cl_2Ph	CH_2-4-piperidyl	190–193 (0.05)	$C_{19}H_{25}N_3Cl_2$	*l*		67	+++
22	PhCH(Me)	CH_2-4-piperidyl	192–193 (0.07)	$C_{21}H_{31}N_3$	*l*		81	+++
23	$Ph(CH_2)_2$	CH_2-4-piperidyl	188–189 (0.08)	$C_{21}H_{31}N_3$[s]	2HCl[f]	214–216	75	+++
24	4-Me_2NPh	CH_2-4-piperidyl	214 (0.05)	$C_{21}H_{32}N_4$	Citrate[f]	190–192	47	+++
25	Cyclohexyl	CH_2-4-piperidyl	178–181 (0.05)	$C_{19}H_{33}N_3$[t]	2HCl[f]	259–262	60	++++
26	2-Pyridyl	CH_2-4-piperidyl	181–183 (0.05)	$C_{18}H_{26}N_4$[u]	*l*		50	+++
27	3-Pyridyl	CH_2-4-piperidyl	189–190 (0.05)	$C_{18}H_{26}N_4$[o]	Citrate[i]	139–140	60	+++
28	6-Me-2-pyridyl	$(CH_2)_2$-1-piperazyl	204–206 (0.05)	$C_{19}H_{29}N_5$[o]	Citrate[i]	152–153	64	+++
29	8-Quinolyl	CH_2-4-piperidyl	225–227 (0.05)	$C_{22}H_{28}N_4$[o]	Citrate[i]	200–202	36	+++
30	Catapress (Geigy)							++++

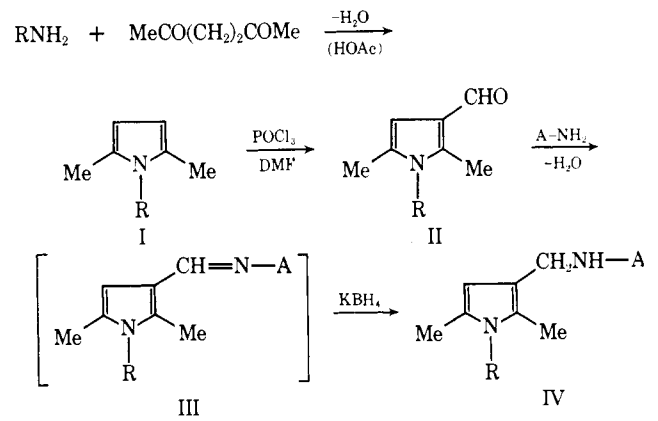
[a] C, H, N analyses are within 0.4% of calculated values unless given in this column. Midwest Microlab, Inc., Indianapolis, Indiana, carried out elemental analyses. [b] Citrate and sulfate salts have 1 mole of acid to each mole of base. [c] Values are for bases; usually the yields of salts from bases are 70–80%. [d] See Pharmacological Tests—Methods: ± = transient depressor in anesthetized dogs; + = prolonged (>20 min), strong (>20 mm) hypotension at 10 mg/kg *iv*; ++ at 3 mg/kg; +++ at 1 mg/kg; ++++ at <1 mg/kg. [e] C (base), calcd: 74.66; found: 73.72. [f] Hemihydrate. [g] Cl (salt), calcd: 18.35; found: 17.78. [h] C (base), calcd: 71.72; found: 71.19. [i] Hydrate. [j] C (base), calcd: 77.82; found: 77.39. [k] C (base), calcd: 73.65; found: 73.17. [l] One or more attempts to obtain pure salt failed. [m] N (base), calcd: 13.49; found: 13.01. [n] Crude undistilled base converted directly into pure salt. [o] Impure distilled base converted directly into salt. [p] Crude base was solid; one recrystallization from methanol gave impure base melting at 175–176°. [q] C (base), calcd: 77.49; found: 76.60. [r] Base could not be distilled without rapid decomposition. [s] C (base), calcd: 77.49; found: 76.98; C (salt), calcd: 61.91; found: 61.34. [t] C (base), calcd: 75.19; found: 74.74. [u] C (base), calcd: 72.45; found: 71.60.

second compound prepared in the series—caused rapid decomposition which made this method of purification impractical. An acid extraction of the reaction product prior to distillation eliminated most of this trouble, an exception being **20**, Table I.

Most of these polyaminopyrroles rapidly absorbed CO_2 from the air which resulted in low analytical C values. HCl salts were frequently deliquescent with darkening on storage. However, citrate and sulfate salts appeared stable although usually isolated as hydrates.

Most of the intermediate 3-pyrrolecarboxaldehydes II were purchased.[3] Known methods, illustrated in the reaction sequence of Scheme I, were used to prepare both the pyrroles I[4] and 3-pyrrolecarboxaldehydes[2]

SCHEME I



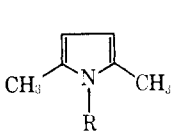
given in Table II. All of the polyamines (A-NH_2) used are commercially available.

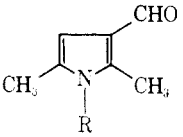
Pharmacological Tests. Methods.—Adult mongrel

(3) 2,5-Dimethyl-1-phenyl-3-pyrrolecarboxaldehyde is available from a number of sources; other aldehydes were specially prepared by the Organic Chemical Markets Department, Eastman Kodak Co., Rochester, N. Y.

(4) H. S. Broadbent, W. S. Burnham, R. K. Olsen, and R. M. Sheeley, *J. Heterocycl. Chem.*, **5**, 757 (1968).

TABLE II
1-SUBSTITUTED-2,5-DIMETHYLPYRROLES AND THEIR 3-CARBOXALDEHYDES





R	Mp (corr) or bp, °C (mm)	% yield	Formula[a]	Mp (corr) or bp, °C (mm)	% yield	Formula[a]
2-Pyridyl	98–100 (0.08)	73	$C_{11}H_{12}N_2$	155–156 (0.10)	14	$C_{12}H_{12}N_2O$[b]
6-Me-2-pyridyl	102–104 (0.10)	70	$C_{12}H_{14}N_2$	155–156 (0.10)	68	$C_{13}H_{14}N_2O$[c]
8-Quinolyl	145–149	52	$C_{15}H_{14}N_2$	119–122	60	$C_{16}H_{14}N_2O$[d]
4-Me_2NPh	91–93[e]	94	$C_{14}H_{18}N_2$	117–119	62	$C_{15}H_{18}N_2O$[f]

[a] C, H, N analyses are within 0.4% of calculated values except where indicated in this column. [b] *Anal.* Calcd: C, 71.98; N, 14.00; found: C, 71.25; N, 13.37. [c] *Anal.* Calcd: C, 72.87; found: C, 71.96. [d] *Anal.* Calcd: C, 76.78; found: C, 75.61. [e] Reported mp 95°; N. G. Buu-Hoi, *J. Chem. Soc.*, 2882 (1949). [f] *Anal.* Calcd: C, 74.35; found: C, 73.60.

dogs of either sex were anesthetized with sodium pentobarbital (35 mg/kg, iv). Blood pressure was obtained directly from the right femoral artery by standard manometric techniques. Respiration was recorded kymographically *via* a tracheal cannula and an inspirometer (Metro Industries). Lead II electrocardiograms were monitored continuously on a Grass oscillograph. The preparations were used to examine possible mechanism of hypotensive action through the utilization of the following test methods: bilateral carotid occlusion, stimulation of the centripetal and peripheral stump of the cut vagus nerve (15 V, 1 msec duration, 15/sec for 15 sec), bilateral vagotomy, and iv injections of norepinephrine and dimethylphenylpiperazinium bromide (DMPP). Atropine sulfate (1 mg/kg) was administered iv to block the parasympathetic system. Chemical sympathectomy was achieved by 3 consecutive doses of 3 mg/kg iv of hexamethonium bromide (C6) at 15-min intervals; and adrenergic blockade by 15 mg/kg iv of *N*,*N*-dibenzyl-β-chloroethylamine (Dibenamine). Test compounds were injected into a femoral vein.

Cats of 2–4 kg body weight and of either sex were anesthetized with Et_2O. Spinal cat preparations were set up as described by Burn.[5] Experimental neurogenic and renal hypertension were induced in registered beagles by the procedures of Grimson[6] and Grollman.[7] Indirect blood pressures were recorded from the front leg with a velcro-infant cuff with a built-in microphone and a Texas E & M Physiograph.

Pharmacological Results.—Table I shows the hypotensive activity produced by the various compounds in anesthetized dogs after iv administration. Compounds **6**, **7**, and **8** showed strong and prolonged hypotensive activity at doses of 1.0 mg/kg or less. Bradycardia accompanied the hypotensive responses produced by these compounds. Heart rate returned to predrug levels as the blood pressure returned.

Additional studies were conducted on these compounds in an attempt to characterize the possible mechanism of action. The pressor spikes produced by DMPP iv were inhibited to varying degrees by the compounds. The response to DMPP was blocked by ganglionic blocking agents; however, experiments conducted in spinal cats with these compounds indicated little if any ganglionic blockade. Acute pretreatment with atropine, Dibenamine, and hexamethonium did not modify the hypotensive responses produced by these compounds. The pressor responses produced by bilateral carotid occlusion were not significantly depressed. Bilateral vagotomy and carotid sinus denervation did not modify either the hypotensive responses or the bradycardia produced by these compounds. The results tend to indicate that the mechanism of hypotensive action produced by these compounds is not due to ganglionic or adrenergic blockade, a parasympathomimetic-like action, or mediated through reflex mechanisms, but possibly by a direct action on vascular smooth muscle or release of some humoral substance not antagonized by the agents previously mentioned.

Compound **8** was administered orally to 2 unanesthetized, neurogenic, and renal hypertensive dogs. Ten mg/kg administered po, tid, for 3 days caused a decrease in arterial blood pressure of approximately 20%. On the 4th day, a single dose of 30 mg/kg lowered the blood pressure approximately 30%. These decreases in blood pressure occurred approximately 30–90 min after administration and persisted throughout the day; however, they were back to normal the following morning.

Structure–Activity Relationships.—In the series of substituted 3-pyrrolemethylamines studied (Table I), the effect of changing the R substituent is best illustrated in those compounds where A is 4-piperidylmethyl. In these examples, when R is changed from Ph (**6**) to substituted Ph (**17**, **20**, **21**, **24**), or aralkyl (**22**, **23**), or *N*-heterocyclic (**26**–**29**), the hypotensive potency is diminished. A comparison of **1** with **19** illustrates a similar decrease in potency when Ph is changed to substituted Ph.

Changes in the aminoalkyl group represented by A produced the most marked effects on hypotensive potency. Superior potency was observed for those compounds in which A is either 4-piperidyl or 1-piperazyl attached to either a CH_2 or $(CH_2)_2$ chain (for example, **6**, **7**, **8**). When the terminal basic functions of A are other N-heterocycles or primary, secondary, or tertiary amines, and the length of the alkylene chain is zero or greater than 2 C, hypotensive potency decreases (compare **6**, **7**, and **8** with **1**–**5** and **9**–**16**).

2-(4-Piperidyl)ethyl appears to be the most enhancing A substituent as shown by the increased potency of **18** over its next lower homolog (**17**). Also, **7** had a lower effective dose than either **6** or **8** in other more definitive studies.

(5) J. H. Burn, "Practical Pharmacology," Blackwell Scientific Publications, Oxford, England, 1952.
(6) K. S. Grimson, *Arch. Surg.*, **43**, 284 (1941).
(7) A. Grollman, *Proc. Soc. Exp. Biol. Med.*, **57**, 102 (1944).

Experimental Results

Substituted Pyrroles (I).—The procedure for preparing the pyrroles of Table II was that of Broadbent, *et al.*,[4] in which PhMe was used in place of C_6H_6 as given in their method F.

Substituted 3-Pyrrolecarboxaldehydes (II).—The intermediate aldehydes in Table II were prepared by the procedure of Rips and Buu-Hoï.[2] Others were purchased.[3]

1-Substituted-2,5-dimethyl-3-pyrrolemethylamines (IV).—As a general procedure 0.54 mole of polyamine[8] was rapidly added to a soln of 0.5 mole of pyrrolecarboxaldehyde in 700 ml of PhMe heated to about 90° with stirring. The mixt was refluxed until about the theoretical amt of H_2O (9 ml) collected in a Dean–Stark trap; this usually required about 2 hr. The solvent was removed in a rotary evaporator and the residue, dissolved in one-third its vol of EtOH, was added during 1.5 hr to a stirred mixt of 50 g of KBH_4 in 700 ml of MeOH at 5–10°. The mixt was stirred overnight at room temp, then evapd on the steam bath. The residue was stirred vigorously with a soln of 35 g of NaOH in 200 ml of H_2O and extd with PhMe, which in turn was extd with an excess of AcOH (70 ml of glacial AcOH in 200 ml of H_2O). The aq ext was treated with an excess of solid KOH with stirring, extd with PhMe, and fractionally distd.

All of the piperazine derivatives of Table I were water miscible and required care in the work-up. They also had an initial decompn period during distn before high vacuum could be obtained.

In the prepn of salts, an equiv of citric acid or H_2SO_4 dissolved in MeOH was added to a warm soln of the base in about 5 vol of MeOH. If the salt did not cryst readily when the soln was cooled overnight, crystn was induced by addition of Me_2CO. HCl salts were found less desirable in that they darkened on storage and often were very hygroscopic.

(8) All intermediate amines were obtained from chemical supply companies in the United States except 1-(3-aminopropyl)piperazine, which was kindly donated by Badische Anilin- & Soda-Fabrik AG, Ludwigschafen, West Germany. We are especially grateful to Dr. W. H. Rieger of Reilly Tar & Chemical Corp., Indianapolis, Ind., for a generous supply of 4-(2-aminoethyl)piperidine.

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5,8-Dihydroharman Derivatives. Their Preparation and Biological Activities

WILLIAM A. REMERS,* EUGENE N. GREENBLATT, LEON ELLENBOGEN, AND MARTIN J. WEISS

Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York 10965

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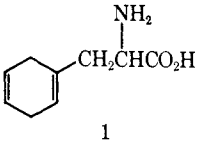
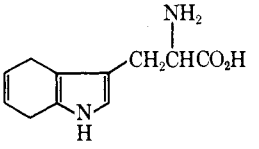
Li–NH_3 reductions of harmine, 6-methoxyharman, their 9-Me homologs, and 1,2,3,4-tetrahydroharmans afforded, among other products, the corresponding 5,8-dihydro derivatives. Imipramine was converted into its inactive 6,9-dihydro analog by the same technique. 5,8-Dihydro derivatives of harmine and 6-methoxyharman appeared to be at least as active as the parent compounds in inhibiting tetrabenazine-induced depression. Both harmine and 5,8-dihydroharmine reversed reserpine-induced hypothermia in mice. *In vitro* MAO inhibition assay and tetrabenazine assay data are given for a variety of harman congeners, and structure–activity relationships are discussed.

In a biologically active molecule, conversion of a benzene ring into its nonconjugated dihydro derivative represents a structure modification of considerable interest. However, this modification has received practically no attention.[1] Its potential significance lies in the expectation that whereas the size and shape of the molecule are altered only to a small extent and the polarity is not greatly different, its potential for biochemical reactivity might be significantly affected. Thus, it is conceivable that the nonconjugated diene system might approximate the benzene ring closely enough to allow interaction with important receptor sites, yet the molecule might not undergo metabolic processes such as aromatic hydroxylation. One example of a biologically active dihydroaromatic which appeared during the course of our investigation in this area[2] is 1,4-cyclohexadiene-L-alanine (**1**), a potent antagonist of the parent phenylalanine. The cyclohexadiene ring of **1** was shown to be planar by X-ray diffraction.[3] Another interesting dihydroaromatic is 4,7-dihydro-L-tryptophan.[4a,b] In the present article we describe the reduction of certain harmans and 1,2,3,4-tetrahydroharmans to the corresponding 5,8-dihydro derivatives and compare the biological activities of these derivatives with the parent compounds as well as related 3,4-dihydroharmans.



1



2

The pyrido[3,4-*b*]indole nucleus of harman and its derivatives presents a variety of possible sites for reduc-

* To whom correspondence should be addressed at the Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, Lafayette, Indiana.

(1) The reduction of 3-methoxyestratriene derivatives to the corresponding 1,4-dihydro derivatives is an important step in the preparation of 19-nor steroids, for example, see L. Miramontes, G. Rosenkranz, and C. Djerassi, *J. Amer. Chem. Soc.*, **73**, 3540 (1951). However, little has been reported about the biological activities of these dihydro intermediates.

(2) See M. J. Weiss, G. R. Allen, Jr., G. J. Gibs, J. F. Poletto, and W. A. Remers, First International Congress of Heterocyclic Chemistry, Albuquerque, New Mexico, 1967, Abstracts of the Meeting; "Topics in Heterocyclic Chemistry," R. C. Castle, Ed., Wiley-Interscience, New York, N. Y., 1969, for preliminary experiments in this area.

(3) B. A. Shoulders, R. M. Gipson, R. J. Jandacek, S. H. Simonsen, and W. Shive, *J. Amer. Chem. Soc.*, **90**, 2992 (1968).

(4) (a) O. Yonemitsu, P. Cerutti, and B. Witkop, *ibid.*, **88**, 3941 (1966); (b) see also J. E. Dolfini, H. E. Applegate, G. Bach, H. Basch, J. Bernstein, J. Schwartz, and F. L. Weisenborn, *J. Med. Chem.*, **14**, 117 (1971), for the synthesis of certain semisynthetic penicillins and cephalosporins derived from D-2-(1,4-cyclohexadienyl)glycine.