2-Amino-5,6-dihydroxyindan-2-carboxylic Acid. A Potential Hypotensive Agent

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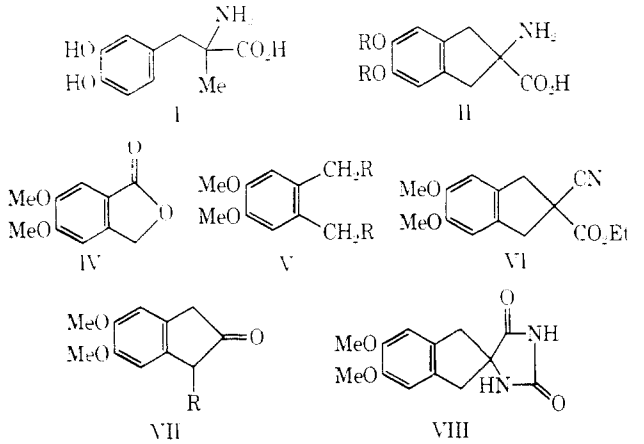
In view of the current interest in α-methyldopa (I, R = H),[1] the synthesis of 2-amino-5,6-dihydroxyindan-2-carboxylic acid (II), a cyclic analog with the α-Me group incorporated into the indan ring, was undertaken. It was hoped that this compound might possess a similar pharmacological profile to α-methyldopa, and be useful in treatment of hypertension.

Bromination of the diol[2] (V, R = OH), prepared by LAH reduction of *m*-meconine (IV),[3] using PBr_3 in C_6H_6 gave the dibromide (V, R = Br) in excellent yield. Cyclization of the dibromide with ethyl cyanoacetate using NaOEt as catalyst[4] gave the cyano ester VI in very low yield, so the proposed synthesis *via* Curtius rearrangement[5] of its derived hydrazide was abandoned. Instead the dibromide was converted into the dinitrile (V, R = CN) using NaCN in DMSO,[6] the optimum temperature for this reaction being 90°. Subsequent hydrolysis with ethanolic HCl gave the diester (V, R = CO_2Et) which was cyclized to the β-keto ester (VII, R = CO_2Et). Acid hydrolysis gave the dimethoxyindanone (VII, R = H) in good yield.



Structure III was deleted by the editor. Compounds were not renumbered.

The spiro hydantoin (VIII) was obtained in good yield by the method of Henze and Spear,[7] although subsequent hydrolysis with H_2SO_4 gave very low yields of the amino acid (II, R = Me). Hydrolysis with $Ba(OH)_2$ in refluxing H_2O,[8] however, gave the desired product in good yield. Demethylation of the amino acid, unsuccessful under a variety of conditions, was accomplished using BBr_3 in CH_2Cl_2,[9] the amino acid (II, R = H) being isolated as its HBr salt.

Both the amino acid (II, R = H) and its dimethyl ether (II, R = Me) were inactive *in vivo* when screened in nephrectomized rats with hypertension induced either by renal occlusion or DOCA–saline injections. The compounds were inactive in *in vitro* screens against dopa decarboxylase and related enzyme system. The rigidity and symmetry incorporated into this molecule compared with α-methyldopa may well be responsible for its lack of activity in the biological screens.

Experimental Section[10]

5,6-Dimethoxyphthalide (IV).—3,4-Dimethoxybenzoic acid (6 g), $(CH_2O)_3$ (16 g), and HCl (40 ml) were heated together at 60–70° for 6–7 hr. H_2O (30 ml) was added, and the mixture was neutralized with dil aq NH_3 with cooling. The solid material was collected and suspended in $CHCl_3$, and after separation of insoluble material the solution was dried and concentrated *in vacuo*. The product was recrystallized from EtOH to give 3.9 g (61%) of fine needles, mp 155–156°, lit.[3] mp 154–156°.

1,2-Bis(hydroxymethyl)-4,5-dimethoxybenzene (V, R = OH).—5,6-Dimethoxyphthalide (10 g) was added in portions to a gently heated, stirred suspension of LAH (3 g) in dry THF (200 ml). The mixture was boiled under reflux for 3 hr, and excess reagent decomposed by the addition of H_2O (6 ml) in THF (20 ml). The mixture was filtered and the filtrate dried and concentrated *in vacuo* to give 9.4 g (94% yield) of analytically pure product, mp 109–110°, lit.[2] mp 110°.

1,2-Bis(bromomethyl)-4,5-dimethoxybenzene (V, R = Br).—PBr_3 (12 ml) in dry C_6H_6 (50 ml) was added dropwise over 0.5 hr to a vigorously stirred suspension of the diol (V, R = OH) (18 g) in C_6H_6 (200 ml), the mixture heated at 50° for 1 hr, and stirred at room temp for a further 16 hr. The pH of the mixture was adjusted to 9 with aq Na_2CO_3, the organic layer washed with H_2O, dried, and concentrated *in vacuo*, and the product recrystallized from cyclohexane to give 27 g (92% yield) of analytically pure material, mp 107–109°. *Anal.* ($C_{10}H_{12}Br_2O_2$), C, H, Br.

2-Carbethoxy-2-cyano-5,6-dimethoxyindan (VI).—To a solution of NaOEt (from 1.1 g of Na) in dry C_6H_6 (10 ml), solutions of ethyl cyanoacetate (5.5 g) in dry Et_2O (100 ml), and 7.8 g of V (R = Br) in dry C_6H_6 (30 ml) were rapidly added. The mixture was kept at room temp overnight, refluxed for 2 hr, cooled, and poured into H_2O. The solution was extracted (Et_2O) and the organic layer washed with H_2O, dried, and concentrated *in vacuo*. The solid was recrystallized from EtOH to give 600 mg (9% yield) of product, mp 105–106°. *Anal.* ($C_{15}H_{17}NO_4$), C, H, N.

1,2-Bis(cyanomethyl)-4,5-dimethoxybenzene (V, R = CN).—A solution of 1,2-bis(bromomethyl)-4,5-dimethoxybenzene (66 g) in dry DMSO (200 ml) was added to a stirred slurry of dry NaCN (22 g) in DMSO (200 ml) at 90°, and the mixture kept at this temperature for a further 3 hr. It was diluted with H_2O and extracted with $CHCl_3$ and the extracts were washed, dried, and concentrated *in vacuo*, to give 33 g (75% yield) of yellow product, mp 111–113°. Recrystallization from EtOH gave analytically pure material, mp 120–121°.[11]

1,2-Bis(carbethoxymethyl)-4,5-dimethoxybenzene (V, R = CO_2Et).—V (R = CN) (6.3 g) was refluxed in EtOH (100 ml) satd with HCl for 2 hr concentrated *in vacuo*, taken up in EtOAc, washed with H_2O, dried, and concentrated *in vacuo* to give 7.2 g (80%) of analytically pure product as a viscous gum. *Anal.* ($C_{16}H_{22}O_6$), C, H.

1-Carbethoxy-5,6-dimethoxyindan-2-one (VII, R = CO_2Et).—The diester (V, R = CO_2Et) in dry C_4H_4 (100 ml) was added dropwise to a stirred solution of NaOEt (from 5 g of Na) in C_6H_6 (200 ml) heated under reflux. The mixture was stirred for a fur-

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(10) Melting points (uncorrected) were determined on a Kofler micro hot-stage. Satisfactory ir, uv, and nmr spectra were recorded for all new compounds. Ir spectra were recorded on a Perkin-Elmer 257, uv on a Perkin-Elmer SP800, and nmr spectra on a Varian T60 spectrophotometer. Analyses were carried out by a Technicon autoanalyser.

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ther 1.5 hr, poured into H_2O, and extracted twice with Et_2O. The aq layer was acidified with aq HCl and the precipitated solid collected and dried. Recrystallization from H_2O–EtOH gave 21 g of the product (75%), mp 117–118°. *Anal.* ($C_{14}H_{16}O_5$) C, H.

5,6-Dimethoxyindan-2-one (VII, R = H).—VII (R = CO_2Et) (10 g) was heated at 100° with 20% H_2SO_4 (70 ml) for 2 hr. The solution was extracted with EtOAc and the organic phase washed with H_2O, dried, and concentrated *in vacuo*. The dark red residue was filtered through a Florisil column in C_6H_6, when removal of solvent and recrystallization from EtOH gave 6 g (83%) of product, mp 137–139°. *Anal.* ($C_{11}H_{12}O_3$) C, H.

Spiro(5,6-dimethoxyindan)-2,5′-hydantoin (VIII).—5,6-Dimethoxyindan-2-one (7 g), NaCN (3.6 g), and $(NH_4)_2CO_3$ (16.7 g) were heated in 40% EtOH (300 ml) for 3 hr at 60°. The temperature was maintained at 100° until unreacted $(NH_4)_2CO_3$ was removed, and allowed to cool when 4 g (42% yield) of the hydantoin, mp 298° dec was obtained. *Anal.* ($C_{13}H_{14}N_2O_4$) C, H, N.

2-Amino-5,6-dimethoxyindan-2-carboxylic Acid (II, R = Me).—A mixture of the hydantoin (VIII) (3.4 g) and $Ba(OH)_2$ (6 g) in H_2O (50 ml) was refluxed for 24 hr, the hot solution filtered, and the filtrate boiled with $(NH_4)_2CO_3$ (2 g). The filtrate was concentrated *in vacuo* until crystallization occurred, and MeOH (100 ml) was added, when 2.5 g (82% yield) of the product, mp 299–300° dec was obtained. *Anal.* ($C_{12}H_{15}NO_4$)C, H, N.

2-Amino-5,6-dihydroxyindan-2-carboxylic Acid Hydrobromide (II, R = H).—The amino acid (II, R = Me) (1 g) in CH_2Cl_2 (30 ml) was treated at −70° with a solution of BBr_3 (0.5 g) in CH_2Cl_2 (10 ml) and cooled to −70°. The reaction mixture was allowed to reach room temp overnight, H_2O (1 ml) added, and the dark brown solid filtered off. Treatment of the solid with charcoal in hot EtOH gave on concentration *in vacuo*, 0.7 g (57% yield) of the product, mp 250–254°. An analytical sample was recrystallized from EtOH–Et_2O, mp 260° dec. *Anal.* ($C_{10}H_{12}BrNO_4$)C, H, N, Br.

Synthesis and Pharmacology of a Series of Substituted 2-Aminomethylpyrroles[1]

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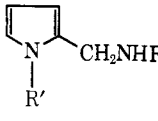
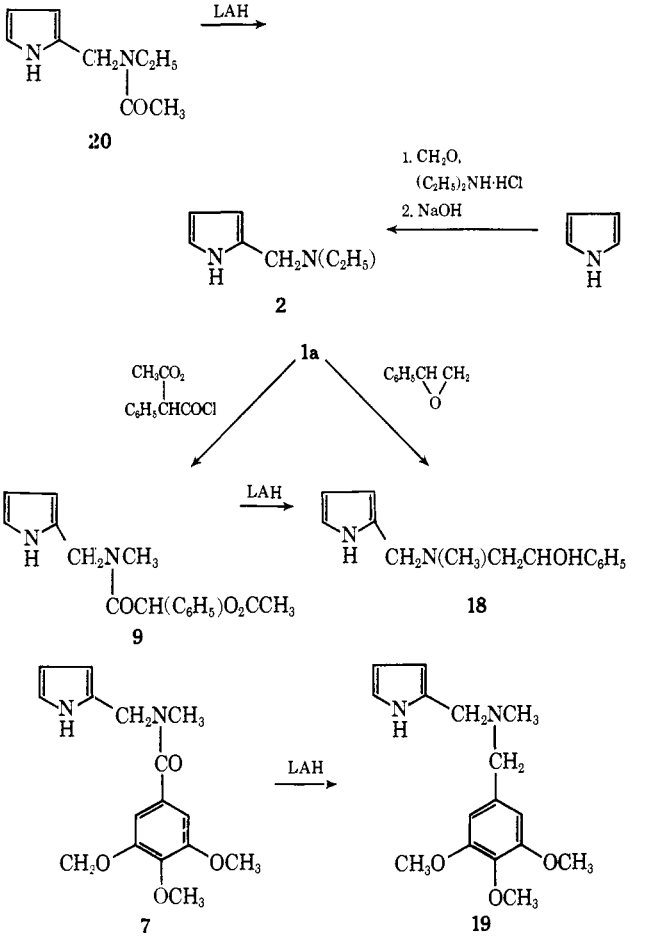
In a search for compounds which have an effect on the CNS, it was found that certain substituted 2-aminomethylpyrroles demonstrated a significant degree of depressant activity coupled with a relatively high LD_{50}. This note reports the compounds prepared in this area, in addition to their biological activity.

Chemistry.—The preparation of the necessary starting materials utilizing a Mannich reaction on pyrrole has been reported.[2] These substituted aminomethylpyrroles (**1a–d**) were treated with compounds having electrophilic groups (acid chlorides, acid anhydrides, isocyanates, isothiocyanates, etc.) giving in all cases the expected products (Table I).



	R′	R″
1a	H	CH_3
1b	H	C_2H_5
1c	H	$(CH_2)_2CH_3$
1d	CH_3	CH_3

The LAH reduction of **20** resulted in the formation of the known compound 2[3] confirming the assigned structure. The direction of ring opening of styrene oxide when combined with **1a** was established by a LAH reduction of **9**, while the amide **7** using the same reducing agent was converted into the tertiary amine **19**.



Pharmacology.—A number of compounds prepared demonstrated a significant degree of CNS depressant activity (see Table I) in dose range studies in mice. The MLD (2000 mg/kg, po) and the minimal symptomatic dose (31 mg/kg, po) were determined for **20**. Phenobarbital when employed in dose range studies was found to have a minimal symptomatic dose of 15 mg/kg po.

In addition, the compounds reported in this paper were administered orally and screened for antihypertensive activity in renal hypertensive rats,[4] antiinflammatory activity in the carrageenin abscess test in rats[5] and analgetic activity in the phenylquinone-induced writhing test in mice.[6] There was no significant activity noted in these areas.

Experimental Section

All compounds had ir spectra in agreement with their assigned structures and analyzed for C, H, and N within ±0.4 per cent of their theoretical values.

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