acetic acid with the diethylaminoethyl ester of this acid showed that the aralkylamino compound had a considerably reduced neurotropic activity. Other deviations are the length of the alkylene chain (here preferably more than three carbon atoms; in the substituted phenylacetic acid series preferably two or three carbon atoms) and the other acids which give high activity. The 3,4,5-trimethoxybenzoate of β-diethylaminoethanol is, for instance, much less active than the corresponding diphenylacetate ester.

The phenethylamine derivatives with a small substituent, *e.g.*, a hydrogen atom or a methyl group at the nitrogen atom (53, 54) possess considerable adrenolytic activity. Especially piperidine (10–12) and *p*-hydroxyphenylisopropylamine derivatives (18, 19, and 25) are fairly active.

Potent Decarboxylase Inhibitors. Analogs of Methyldopa [1]

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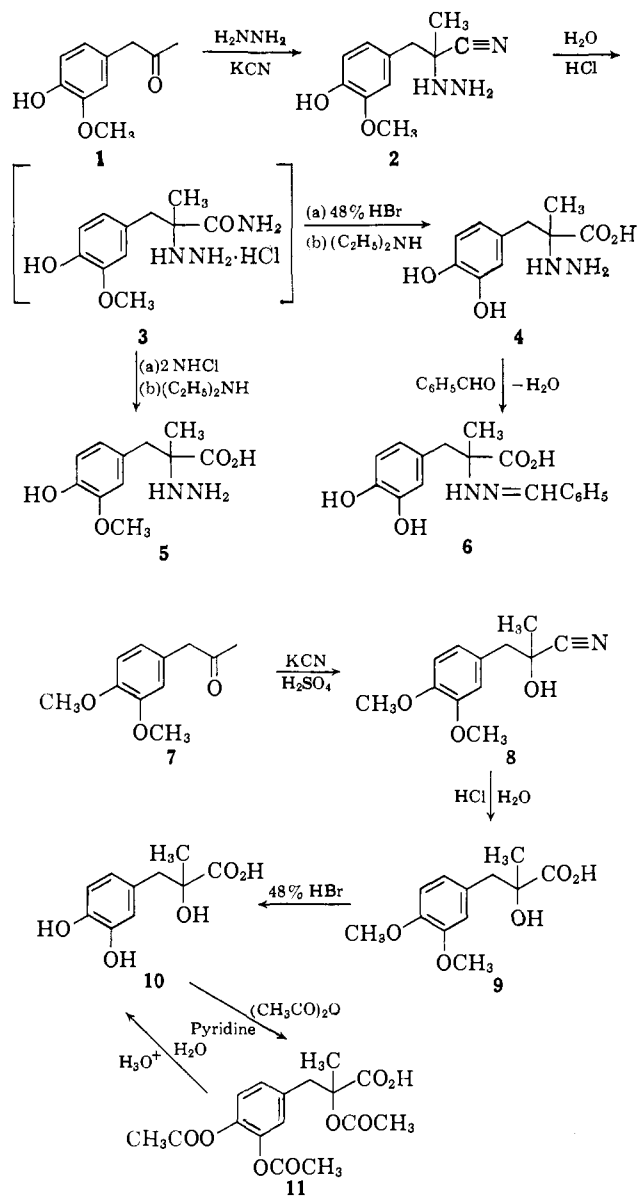
Two new classes of compounds analogous to L-α-methyl-3,4-dihydroxyphenylalanine, formed by replacing the α-amino group with α-hydroxy and α-hydrazino groups, have been prepared. Comparison with the parent compound in the ability to inhibit mammalian DOPA-decarboxylase shows that both new classes are potent inhibitors. Of the compounds prepared DL-α-hydrazino-α-(3,4-dihydroxybenzyl)propionic acid exhibits a potency *in vitro* approximately one thousand times that of the parent compound.

In a search for hypotensive compounds related to L-α-methyl-3,4-dihydroxyphenylalanine, two new classes of compounds were prepared. The new analogs can be pictured by substituting α-hydrazino or α-hydroxyl groups for the α-amino group of the parent compound. These compounds were used to test the hypothesis that hypotensive action is paralleled by ability to inhibit mammalian decarboxylase. The synthesis of the α-hydrazino analog began with a Strecker reaction in which 1-(4′-hydroxy-3′-methoxyphenyl)-2-propanone (**1**) was treated with aqueous hydrazine and potassium cyanide. This condensation, though reversible, succeeds because product (**2**) is sparingly soluble in the solvent. In hot chloroform the hydrazino nitrile (**2**) reverts to starting materials.

Hydrolysis of the hydrazino nitrile (**2**) is accomplished in two stages. The nitrile moiety is hydrolyzed to an amide by fortified hydrochloric acid at −10 to 0°. Efforts to crystallize the amide (**3**) as the hydrochloride salt or free base did not succeed. The amide (**3**) was converted to the desired hydrazino acid (**4**) by refluxing with constant boiling hydrobromic acid. Other methods of hydrolysis were tried but none proved to be as good. Substitution of dilute hydrochloric acid for constant boiling hydrobromic acid permitted isolation of the analogous 3-methoxylated acid (**5**). DL-α-Hydrazino-α-(3,4-dihydroxybenzyl)propionic acid (**4**) was characterized as its benzaldehyde derivative (**6**).

The synthesis of the second class of analogs proceeds from 1-(3′,4′-dimethoxyphenyl)-2-propanone (**7**) which by the method of Davies, *et al.*,[2] is converted to 2-(3′,4′-dimethoxybenzyl)lactonitrile (**8**). Hydrolysis of the cyanohydrin (**8**) to the α-hydroxy acid (**9**) with refluxing constant boiling hydrochloric acid at atmospheric pressure for 5 hours cleaved the methoxyl groups to some extent. The methoxyl group of 3-methoxytyramine is cleaved about 90% by hydrolysis



(1) ALDOMET®.

(2) A. G. Davies, F. M. Ebeid, and J. Kenyon, *J. Chem. Soc.*, 3154, (1957).

for 42 hours under these conditions. Some unpublished results from our laboratories show that the 4-methoxyl group is more readily cleaved than 3-methoxyl.

2-(3,4-Dimethoxybenzyl)lactic acid (**9**) was demethylated with constant boiling hydrobromic acid at reflux. The hydroxy acid (**10**) is purified as the 2,3′,4′-triacetate (**11**) and recovered by mild hydrolysis.

In Table I the compounds of this paper are compared with L-α-methyl-3,4-dihydroxyphenylalanine (methyldopa) in their ability to inhibit mammalian DOPA-decarboxylase[3-5] *in vitro*.

TABLE I

INHIBITION OF DOPA-DECARBOXYLASE

Compound	μmoles/flask[6]	% Inhibition of DOPA-decarboxylase
Methyldopa	10	82
	1.0	64
4	0.001	85
5	0.10	83
6	0.005	85
2	1.0	67
10	1.0	54
11	1.0	41

In vitro the hydrazino acid (**4**) is a potent DOPA-decarboxylase inhibitor and a histidine decarboxylase inhibitor, while *in vivo* it is a potent inhibitor in the formation of serotonin. Unlike substituted hydrazides and substituted hydrazines the hydrazino acid (**4**) is a much less potent trapper of pyridoxal. Unlike methyldopa it does not depress the blood pressure of hypertensive or normotensive rats. Decarboxylase inhibition is therefore not the only requisite for hypotensive activity.

Experimental[7]

DL-α-Hydrazino-α-(4-hydroxy-3-methoxybenzyl)propionitrile (2).—To 300.0 g. (1.665 moles) of 1-(4′-hydroxy-3′-methoxyphenyl)-2-propanone[8,9] (or 500.0 g., 1.665 moles of its potassium metabisulfite adduct) were added 910 ml. of water, 292 ml. (5.06 moles) of 85% hydrazine hydrate (sp. gr. 1.0211) and 119.5 g. (1.77 moles) of potassium cyanide. The mixture was stirred vigorously at room temperature for 18 hr. An oily phase disappeared in about 6 hr. leaving solid and aqueous phases. The product was separated by filtration and washed successively with three 260 ml. portions of water and three 230 ml. portions of ether. After drying at 25° in air and *in vacuo* the yield of hydrazino nitrile, m.p. 106–107° dec.; $\lambda_{max}^{CH_3OH}$ 282 mμ (ε = 2,860), amounted to 228.4 g. (62.2%).

Anal. Calcd. for $C_{11}H_{13}N_3O_2$: C, 59.71; H, 6.83; N, 18.99. Found: C, 59.89; H, 6.76; N, 18.92.

Titration of the hydrazino group by iodometry gave a value 93.3% of the theoretical amount. Another sample of hydrazino nitrile was dissolved in chloroform at room temperature and crystallized on standing at 0°, m.p. 103–105° dec.; $\lambda_{max}^{CH_3OH}$ 282 mμ (ε = 3,120) $\lambda\lambda_{max}^{Nujol}$ 3.01, 3.7–3.9, 4.58 (weak), 6.14, 6.23 and 6.56 μ. The n.m.r. spectrum was in accord with the assigned structure. Found: C, 59.93; H, 6.70; N, 18.92. The compound decomposed in hot chloroform.

DL-α-Hydrazino-α-(3,4-dihydroxybenzyl)propionic Acid (4).—Two liters of concd. hydrochloric acid at −10° was fortified with 339 g. of gaseous hydrogen chloride. To the stirred acid at −10° was added gradually over 15 min. 100 g. (0.451 mole) of DL-α-hydrazino-α-(3,4-dihydroxybenzyl)propionitrile. The mixture was allowed to stand overnight, during which time the temperature warmed to 0°. The mixture was filtered to remove 1.93 g. of hydrazine dihydrochloride, m.p. 201–203° dec., lit.[10] m.p. 198°, identical with authentic material by infrared spectrum, and the filtrate concentrated *in vacuo* at 50° to yield DL-α-hydrazino-(4-hydroxy-3-methoxybenzyl)propionamide hydrochloride (**3**) as a thick sludge which was not crystallized or characterized. To the resulting amide (**3**) was added 2 l. of 48% hydrobromic acid, the mixture placed under nitrogen and refluxed for 3 hr. It was concentrated to near dryness *in vacuo*. To the residue was added 250 ml. of *tert*-butyl alcohol and the mixture concentrated to near dryness *in vacuo*. After a repetition of the *tert*-butyl alcohol treatment, 850 ml. of absolute ethanol was added. The mixture was filtered to remove ammonium bromide and the filtrate brought to pH 6.4 by addition of about 45 ml. of diethylamine. Complete precipitation of the product was promoted by addition of 400 ml. of benzene and aging at 0° for 3 days. The crude hydrazino acid was collected on a filter, washed with methanol and dried. This material amounting to 60 g. was dissolved in 750 ml. of boiling water, treated with 10 g. of Nuchar C 1000 N and filtered through Super-Cel. The funnel was washed with three 100 ml. portions of hot water. The filtrate and washes were combined and allowed to stand overnight at room temperature. The mixture was cooled at 0° for 30 min., filtered and washed successively with two 50 ml. portions of methanol and two 50 ml. portions of ether. The product was dried 2 hr. *in vacuo* (0.5 mm) at 100°. The yield of white hydrazino acid was 46.58 g. (45.5%); m.p. 209–210° dec.; $\lambda_{max}^{CH_3OH}$ 282.5 mμ, (ε = 2,940), sh 223 mμ (ε = 5,430); $\lambda\lambda_{max}^{Nujol}$ 2.85, 3.05, 3.24, 6.10, 6.22 and 6.52 μ.

Anal. Calcd. for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.32; H, 5.94; N, 12.22.

The mother liquors were concentrated to dryness taken up in 153 ml. of boiling water, treated with 1 g. of Nuchar, filtered, washed and seeded. The product was obtained as before but dried at room temperature. The yield of tan fluffy crystals (monohydrate), m.p. 206–208° dec., amounted to 4.87 g. (4.4%).

Anal. Calcd. for $C_{10}H_{14}N_2O_4 \cdot H_2O$: C, 49.18; H, 6.60; N, 11.47; H_2O, 7.38. Found: C, 49.55; H, 6.19; N, 11.37; H_2O, 7.33 (Karl Fischer determination). The monohydrate is thus the stable form which crystallizes from water.

The hydrazino acid (**4**) was characterized as its benzal derivative (**6**), m.p. 200° dec.; $\lambda_{max}^{CH_3OH}$ 287.5 mμ, (ε = 18,600); $\lambda\lambda_{max}^{Nujol}$ 2.9–3.15, 5.93, 6.16 and 6.65 μ.

Anal. Calcd. for $C_{17}H_{18}N_2O_4$: C, 64.96; H, 5.77; N, 8.91. Found: C, 65.18; H, 5.78; N, 8.56.

DL-α-Hydrazino-α-(4-hydroxy-3-methoxybenzyl)propionic Acid (5).—From 25.0 g. (0.113 mole) of DL-α-hydrazino-α-(4-hydroxy-3-methoxybenzyl)propionitrile (**2**) the amide (**3**) was isolated as described in the previous section. The amide under nitrogen was refluxed for 5 hr. with 500 ml. of 2 *N* hydrochloric acid. The mixture was concentrated to dryness at 50° *in vacuo*, taken up in 200 ml. of absolute ethanol, filtered and the filtrate adjusted to pH 6.4 with diethylamine. Precipitation began in 15 min. and was completed overnight in the refrigerator. The yield of crude tan product, m.p. 204–205° dec., amounted to 12.8 g. This product was washed with 25 ml. of methanol, then dissolved in 50 ml. of hot water, treated with 0.7 g. of Nuchar C 1000 N and filtered. The golden filtrate was cooled slowly to room temperature then aged 1 hr. at 0°. The white crystalline product after filtering, washing and drying, had m.p. 204–205° dec.; $\lambda_{max}^{CH_3OH}$ 230 mμ, (ε = 7,230), 281 mμ, (ε = 3,000), sh 283 mμ, (ε = 2,860); $\lambda\lambda_{max}^{Nujol}$ 2.88, 3.00, 3.1–3.2, 6.21 and 6.59 μ. The yield was 7.74 g. (28.5% of theory over-all).

Anal. Calcd. for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 54.89; H, 6.95; N, 11.56.

2-(3′,4′-Dimethoxybenzyl)lactonitrile (8).—By the method of Davies, Ebeid and Kenyon[9] 126 g. of 1-(3′,4′-dimethoxyphenyl)-2-propanone (**7**) yielded 80.9 g. (57%) of 2-(3′,4′-dimethoxybenzyl)-lactonitrile (**8**), m.p. 123–126°; $\lambda_{max}^{CH_3OH}$ 230 mμ, (ε = 7,650), 279 mμ, (ε = 2,780), sh 283 mμ, (ε = 2,280); $\lambda\lambda_{max}^{Nujol}$ 2.84, 6.16, 6.22 and 6.56 μ.

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(4) S. M. Hess, R. H. Connamacher, M. Ozaki, and S. Udenfriend, *J. Pharmacol. Exptl. Therap.*, **134**, 129 (1961).

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(6) Conventional 15-ml. double sidearm Warburg flask, 2.8 ml. reacting volume.

(7) Melting points were measured on samples in open capillaries with total immersion thermometers and are not corrected.

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(9) I. A. Pearl and D. L. Beyer, *J. Org. Chem.*, **16**, 221 (1951).

(10) T. Curtius and R. Jay, *J. prakt. Chem.*, [2] **39**, 37 (1889).

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.71; H, 6.68; N, 6.25.

2-(3′,4′-Dimethoxybenzyl)lactic Acid (9).—To 47.7 g. of 2-(3′,4′-dimethoxybenzyl)lactonitrile (**8**) was added 108 ml. of concd. hydrochloric acid. The mixture was refluxed for 5 hr., concentrated, 20 ml. of water added and the mixture again concentrated. The residue was cooled to room temperature and extracted with ethyl acetate. The extract was washed with water, slurried with 1 g. of decolorizing charcoal, filtered and concentrated *in vacuo* to a small liquid volume containing crystals. The mixture was diluted with 100 ml. of ether and allowed to stand for 16 hr. Filtration yielded 24.84 g. (49.5%) of product, m.p. 118–121°; $\lambda_{max}^{CH_3OH}$ 230 mμ, (ε = 8,150), 278 mμ, (ε = 2,690), sh 283 mμ, (ε = 2,450).

The analytical material was obtained by recrystallization from acetone–Skellysolve B, m.p. 114–116°; $\lambda_{max}^{CH_3OH}$ 229.5 mμ, (ε = 8,080) 277.5 mμ, (ε = 2,740), sh 283 mμ, (ε = 2,475); $\lambda\lambda_{max}^{Nujol}$ 2.90, 3.6–3.9, 5.79, 6.18, 6.25 and 6.56 μ.

Anal. Calcd. for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 59.88; H, 6.40.

2-Acetoxy-2-(3′,4′-diacetoxybenzyl)propionic Acid (11).—To 13.85 g. of 2-(3′,4′-dimethoxybenzyl)lactic acid (**9**) was added 78.5 ml. of 48% hydrobromic acid. The mixture was purged with nitrogen, refluxed for 2 hr. and concentrated *in vacuo*. The residue was dissolved in *tert*-butyl alcohol and the mixture concentrated to dryness *in vacuo*. This procedure was repeated. The dark residue of crude 2-(3′,4′-dihydroxybenzyl)lactic acid (**10**) was dissolved in 65 ml. of pyridine and, while the flask was immersed in a cooling bath to maintain the temperature between 10 and 20°, 65 ml. of acetic anhydride was added. The mixture was allowed to stand for 16 hr. at room temperature and then concentrated *in vacuo* to an amber gum. This gum was dissolved in ethyl acetate and extracted successively with *N* hydrochloric acid, water and saturated salt solution. The ester phase was dried over anhydrous magnesium sulfate, concentrated *in vacuo* and the residue crystallized from a (1:1) benzene–hexane mixture. The crude product had m.p. 120–123°; $\lambda_{max}^{CH_3OH}$ 274 mμ, (ε = 6,050) sh 270 mμ, (ε = 5,380). The yield amounted to 18.28 g. Repeated recrystallizations from benzene yielded a product (**11**), m.p. 124–126°; $\lambda_{max}^{CH_3OH}$ 264 mμ, (ε = 5,380), sh 269 mμ, (ε = 4,970); $\lambda\lambda_{max}^{Nujol}$ 3.8–4.0, 5.70–5.75, 5.85, 6.25 and 6.61 μ.

Anal. Calcd. for $C_{16}H_{18}O_8$: C, 56.80; H, 5.36; acetyl, 38.2. Found: C, 56.72; H, 5.66; acetyl, 41.7.

DL-2-(3′,4′-Dihydroxybenzyl)lactic acid (10).—A mixture of 7.31 g. of 2-acetoxy-2-(3′,4′-diacetoxybenzyl)propionic acid (**11**), 86.3 ml. of 2.5 *N* hydrochloric acid and 30 ml. of water was purged with nitrogen and refluxed under a nitrogen atmosphere for 2 hr. The resulting mixture was concentrated *in vacuo*, and extracted with ether. The ethereal extract was washed with water and concentrated to an oil, which on drying *in vacuo* at 100° for 1 hr. yielded 4.45 g. (95.0%) of DL-2-(3′,4′-dihydroxybenzyl)lactic acid (**10**) as an amorphous solid, $\lambda_{max}^{CH_3OH}$ 282 mμ (ε = 5,980); $\lambda\lambda_{max}^{pyridine}$ 3.1–4.1 multiple absorption, 5.85, 6.59 μ. The infrared spectrum was the same as that of the acid before acetylation and unlike that of the 2,3′,4′-triacetate (**11**).

Anal. Calcd. for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.64; H, 5.97.

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Structure–Action Relations in N,N-Dimethyl-2-halogenophenethylamines

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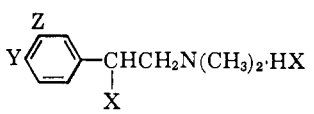
Antagonism to epinephrine, norepinephrine and histamine has been investigated in a series of compounds related to N,N-dimethyl-2-halogenophenethylamine. The relation between structure and antagonism is demonstrated and the implications for the intermediary chemical species responsible in aqueous reaction mixtures is discussed. Antagonism to stimulation of oxyntic cells and inhibition of rat uterus by histamine is noted.

Hunt[1] first reported the antiepinephrine activity of N,N-dimethyl-2-chlorophenethylamine (DMEA) and Ferguson and Wescoe[2] showed that this compound possessed in addition muscarine-like, nicotine-like and relaxant properties. Graham and James[3] confirmed these findings and examined some 60 analogs. Antagonism to epinephrine, norepinephrine, histamine, and 5-hydroxtryptamine was demonstrated. Three structural requirements were found to be necessary for antiepinephrine activity, *viz.*, (1) an aromatic ring structure, (2) a 2-halogenoethyl group, and (3) a secondary or a tertiary amino group. The ethanolamine derived from DMEA is not active against epinephrine, norepinephrine, histamine or 5-hydroxytryptamine but is a powerful local anaesthetic.

The present report is concerned with exploration of the substituent in the 2-position, on the phenolic ring, and on the 2-carbon. There are three groups of compounds in this series, with varying structures



Substituents on the ring: (1) *Monosubstituted compounds* where Z (*meta*) in the formula is H, the other substituent being Cl, Br, I, F, CH_3, or C_6H_5; compounds where Y (*para*) is H and Z is Cl, Br, or CH_3; in all cases but one (Table I, 13) X being Br. (2) *Disubstituted compounds* where X is Br or Cl and Y and Z are either dichloro, dibromo or dimethyl, or combinations of Cl, Br, CH_3, and F. (3) *Ethanolamines* where one hydrogen atom of the carbon in position 2 in the ethylamine side chain has been replaced by OH. The substituents on the phenolic ring are, respectively, dibromo, dichloro, dimethyl, and F–Br. These are the hydrolysis products of selected members of the disubstituted compounds. The structures are shown in Table I. Compound 29 has a structural resemblance to dichloroisoproterenol

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