Experimental Section[5]

4-Hydroxyphenylpyruvic Acid Hydrazone Hydrazine Salt.—A solution of 5.0 g (0.027 mole) of 4-hydroxyphenylpyruvic acid, 5.1 g (0.11 mole) of 99% hydrazine hydrate, and 700 ml of methanol was stirred at 60° for 1.5 hr. Concentration of the reaction mixture to about 70 ml under reduced pressure resulted in the crystallization of 5.2 g (84%) of product, mp 186–187° dec. White crystals, mp 186–187° dec, were obtained from methanol: infrared, 2.93 and 2.99 (NH), 3.1 (bonded OH), 3–4 region characteristic of an amine salt of a carboxylic acid, 6.1 (C=N), and 6.42 μ (carboxylate).

Anal. Calcd for $C_9H_{14}N_4O_3$: C, 47.78; H, 6.24; N, 24.77. Found: C, 47.70; H, 6.38; N, 24.48.

DL-2-Hydrazino-3-(4-hydroxyphenyl)propionic Acid.—A solution of 4.0 g (0.018 mole) of the above hydrazone and 50 ml of water was stirred at room temperature for 2 days with 120 g of 2.3% NaHg. The aqueous solution was separated from the amalgam and made acidic to congo red with HCl. The product, which crystallized as white needles, was collected, washed with a small amount of water, and air dried. Recrystallization from water (Nuchar) gave 1.2 g (41%) of white acid: mp 280–282° dec; infrared, broad absorption band with a series of peaks from 3.0 to 4.5, and carboxylate absorption at 6.32 μ; ultraviolet (90% methanol), λ 207, 226, and 279 mμ (ϵ_{max} 17,800, 26,400, 3860); chromatography, Whatman No. 1, decending, 1-propanol–water (70:30); detection, ninhydrin, showed single spot, R_f 0.77.

Anal. Calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.17; N, 14.28; O, 24.26. Found: C, 55.16; H, 6.21; N, 13.96; O, 24.63.

The inhibitory activity of DL-2-hydrazino-3-(4-hydroxyphenyl)-propionic acid on aromatic amino acid decarboxylase was found to be much lower than that of DL-2-hydrazino-2-(3,4-dihydroxybenzyl)propionic acid (hydrazino analog of methyldopa) both *in vivo* and *in vitro*. When compared with DL-2-hydrazino-3-phenylpropionic acid (hydrazino analog of phenylalanine) the compound showed equivalent activity *in vivo* and greater activity *in vitro*.[6]

(5) Melting points were taken on a Hoover Uni-Melt capillary apparatus and are corrected. Infrared spectra were taken in KBr disks using a Perkin-Elmer Infracord 137. The ultraviolet spectrum was determined on a Perkin-Elmer spectrophotometer Model 202. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

(6) *In vivo* studies were carried out by C. R. Creveling, J. W. Daly, and B. Witkop, *J. Med. Chem.*, **9**, 284 (1966); *in vitro* studies were carried out by J. W. Daly and B. Witkop, in press. We wish to thank the above for making these results available to us.

2-Methyl-3-phenoxycyclopropylamine

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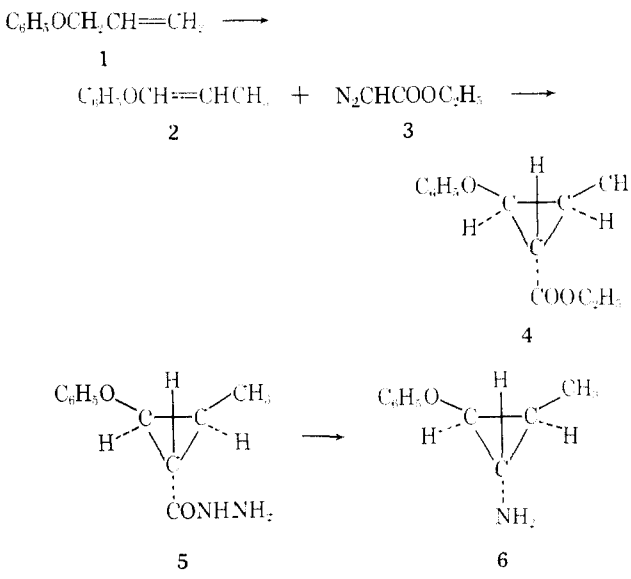
Since 2-phenoxycyclopropylamine[1] is a potent MAO inhibitor, we prepared 2-methyl-3-phenoxycyclopropylamine (**6**) in order to study the effect of such a structural change on the biological activity. Although the new compound was found to be inactive, we wish to report its synthesis.

Allyl phenyl ether (**1**) was isomerized to phenyl propenyl ether (**2**),[2] probably the *cis* isomer as indicated by the infrared spectrum and vpc.[2,3] It was then treated with ethyl diazoacetate (**3**) to give a mixture of ethyl *cis–trans*-2-methyl-3-phenoxycyclopropanecarboxylate (**4**). Vpc showed the presence of the two isomers in a 7:1 ratio and, based upon our previous study,[1a] the major component is most likely *trans*. Since there appeared to be little difference between the *cis*- and *trans*-2-phenoxycyclopropylamines in MAO inhibition,[1a] we did not separate the isomers, but converted them into the corresponding hydrazides (**5**) which, *via* the Curtius rearrangement,[4] were transformed to an amine (**6**), presumably predominantly the *trans* isomer.



Experimental Section

The infrared spectra were determined on a Beckman IR5 double-beam spectrophotometer with NaCl optics. Gas chromatographic analyses were carried out on a Beckman GC 2A gas chromatograph, Thermotra C temperature programmer, and Sargent recorder Model SR. The melting points were determined on a Uni-Melt Thomas–Hoover capillary melting point apparatus and are corrected.

Allyl phenyl ether (**1**) was prepared as described by Kornblum and Lurie[5] in 86.6% yield; bp 74–75° (10 mm) [lit.[5] bp 74–76° (1 mm)]; $n^{20}D$ 1.5205 (lit.[5] $n^{20}D$ 1.5204); $\nu_{max}^{CHCl_3}$ 1656, 1242, 994, 928, and 692 cm^{-1}. The vpc showed a single band.

***cis*-Phenyl propenyl ether** (**2**) was prepared by the isomerization procedure of Price and Snyder;[2] bp 72° (13 mm); yield 78%; $\nu_{max}^{CHCl_3}$ 1670, 1253, and 726 cm^{-1}. Vpc showed a single band.

Ethyl *cis–trans*-2-Methyl-3-phenoxycyclopropanecarboxylate (**4**).—To a solution of 45 g of phenyl propenyl ether (**2**) in 100 ml of dry xylene with 1 g of copper powder and 1 g of powdered $CuSO_4$ stirred and heated at 110–120°, a solution of 54 g of ethyl diazoacetate[6] in 100 ml of dry xylene was added at a rate to maintain a steady, gentle evolution of nitrogen. Then the reaction was refluxed for 2 hr and filtered, and the filtrate was concentrated *in vacuo* and distilled. The liquid, bp 87–102° (1 mm), was collected and redistilled to obtain the product: bp 96–98° (1 mm); yield 45 g (74%); $\nu_{max}^{CHCl_3}$ 1704, 1244, 1025, and 688 cm^{-1}. Vapor phase chromatographic analysis gave two bands corresponding to 87.5 and 12.5% of the total area.

***cis–trans*-2-Methyl-3-phenoxycyclopropanecarboxhydrazide** (**5**).—A solution of 10 g of ester **4** was refluxed with 40 ml of 85% hydrazine hydrate in 30 ml of ethanol for 24 hr, and concentrated *in vacuo* to obtain the solid hydrazide. It was recrystallized from water, mp 130–131°, yield 7.5 g (82%).

Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.07; H, 6.79; N, 13.59. Found: C, 64.26; H, 6.58; N, 13.58.

***cis–trans*-2-Methyl-3-phenoxycyclopropylamine Hydrochloride** (**6**).—A solution of 22 g of hydrazide **5** in 160 ml of water and 18 ml of 6 *N* HCl was covered with 200 ml of ether and stirred at 0°.

(1) (a) J. Finkelstein, E. Chiang, and J. Lee, *J. Med. Chem.*, **8**, 432 (1965); (b) C. L. Zirkle, C. Kaiser, D. H. Tedeschi, R. E. Tedeschi, and A. Burger, *ibid.*, **5**, 1265 (1962).

(2) C. C. Price and W. H. Snyder, *J. Am. Chem. Soc.*, **83**, 1773 (1961).

(3) A. Schriesheim, J. E. Hofmann, and C. A. Rowe, Jr., *ibid.*, **83**, 3731 (1961).

(4) P. A. S. Smith, *Org. Reactions*, **3**, 337 (1946).

(5) N. Kornblum and A. P. Lurie, *J. Am. Chem. Soc.*, **81**, 2705 (1959).

(6) F. B. La Forge, W. A. Gersdorff, N. Green, and M. S. Schechter, *J. Org. Chem.*, **17**, 381 (1952).

A solution of 7.6 g of $NaNO_2$ in 20 ml of water was added dropwise and stirred 15 min, and the separated ether layer was dried. The filtered azide solution was added to 350 ml of dry toluene, heated on a steam bath to distil the ether, and the resultant solution was refluxed for 6 hr. The toluene was evaporated *in vacuo* (nitrogen). The liquid residue was redissolved in dry toluene, added to 30 ml of concentrated HCl, and warmed. After the gas evolution which took place at about 50° was complete, the solution was refluxed for 18 hr, made alkaline with 30% NaOH solution, and extracted with ether. The liquid remaining after evaporating the ether was distilled, bp 75–79° (1 mm). It was converted into its hydrochloride and recrystallized from ethanol–ethyl acetate mixture; mp 181–183°, yield 4 g (19%).

Anal. Calcd for $C_{10}H_{13}NO \cdot HCl$: C, 60.30; H, 7.03; N, 7.03. Found: C, 60.53; H, 7.05; N, 7.04.

Biological Results.—In comparison with several active compounds, 2-methyl-3-phenoxycyclopropylamine demonstrated no *in vitro* activity and very little *in vivo* activity against brain monoamine oxidase (rats) (Table I).

TABLE I[a]

Compd	MAO *in vitro* 50% inhib, *M*	Brain *in vivo* ED_{50} (rats), mg/kg
4-$(NC_5H_4)CONHNHCH(CH_3)_2$[b]	5.3×10^{-6}	25.0
$C_6H_5OCHCHNH_2$ (CHCH$_3$)	$>1 \times 10^{-3}$	50.0
trans-$C_6H_5OCHCHNH_2$[c] (CH_2)	1.6×10^{-7}	0.37
trans-$C_6H_{11}OCHCHNH_2$[d] (CH_2)	1.8×10^{-7}	0.35
trans-$C_6H_5CHCHNH_2$[e] (CH_2)	8×10^{-6}	0.25

[a] The pharmacological data were obtained under the direction of Dr. L. O. Randall, Director of the Pharmacological Laboratories. The methods are described in detail by L. O. Randall and R. E. Bagdon, *Ann. N. Y. Acad. Sci.*, **80**, 626 (1959). [b] Iproniazid, Hoffmann-La Roche, Inc. [c] Reference 1. [d] J. Finkelstein, E. Chiang, F. M. Vane, and J. Lee, in press. [e] Tranylcypromine, Smith Kline and French Laboratories, Inc.

Similarly, Zirkle and co-workers[1b] observed that although 2-phenylcyclopropylamine has potent MAO inhibitory activity, 2-methyl-3-phenylcyclopropylamine has relatively little activity.

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Agents Affecting Lipid Metabolism. XXI. Miscellaneous Compounds Related to *trans*-1,4-Bis(2-chlorobenzylaminomethyl)cyclohexane[1]

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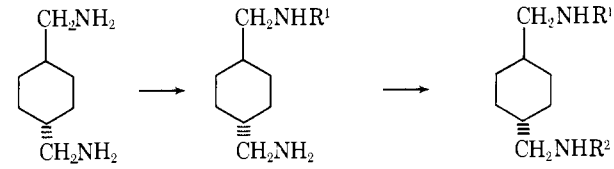
We have recently reported the synthesis[2–4] of many symmetrical compounds derived structurally from the potent cholesterol-lowering agent *trans*-1,4-bis(2-chlorobenzylaminomethyl)cyclohexane.[5] This report describes the synthesis of some miscellaneous related compounds. The biological activities of these and other compounds of this series[2–4] are reported separately.[1]

The first group of compounds consists of the unsymmetrically N,N′-disubstituted cyclohexanebis(methylamine) derivatives (IV–VI, Chart I). They were prepared from cyclohexane-*trans*-1,4-bis(methylamine) (I) by reducing the Schiff's base formed with 1 equiv of a carbonyl component, to yield the monosubstituted derivatives II and III, and then condensing these with a second carbonyl component to yield, after reduction, the unsymmetrical disubstituted compounds IV–VI. The properties of the final products and intermediates as their hydrochloride salts are presented in Table I.

CHART I

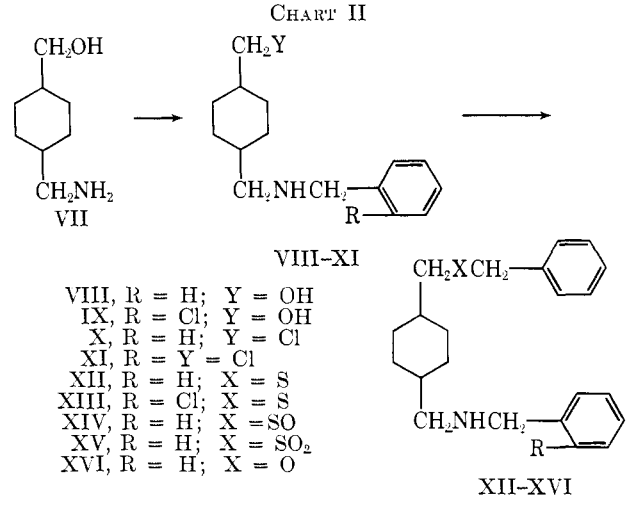


I II, R^1 = 2-$ClC_6H_4CH_2$ III, R^1 = cyclohexyl IV–VI

IV, R^1 = 2-$ClC_6H_4CH_2$; R^2 = cyclohexylmethyl
V, R^1 = 2-$ClC_6H_4CH_2$; R^2 = cyclohexyl
VI, R^1 = cyclohexyl; R^2 = cyclohexylmethyl

A second group of compounds, represented by the series shown in Chart II, are analogs of a 1,4-bis(benzylaminomethyl)cyclohexane in which one of the nitrogens is replaced by oxygen, sulfur, the sulfoxide, or the sulfonyl group. They were prepared from 1-hydroxymethyl-4-cyclohexanemethylamine (VII) as indicated in Chart II. The physical properties and analytical data are given in Table II.

CHART II



VII VIII–XI XII–XVI

VIII, R = H; Y = OH
IX, R = Cl; Y = OH
X, R = H; Y = Cl
XI, R = Y = Cl
XII, R = H; X = S
XIII, R = Cl; X = S
XIV, R = H; X = SO
XV, R = H; X = SO_2
XVI, R = H; X = O

The primary amino group of VII was substituted by either the benzyl or 2-chlorobenzyl group, by reducing the Schiff base formed with the appropriate aldehydes, to give VIII and IX, respectively, which were con-

(1) Part XX: L. G. Humber, C. I. Chappel, A. V. Marton, M. Kraml, and J. Dubuc, *J. Med. Chem.*, **9**, 329 (1966).
(2) L. G. Humber, *ibid.*, **7**, 826 (1964).
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(4) L. G. Humber, *J. Med. Chem.*, **8**, 401 (1965).
(5) C. I. Chappel, J. Dubuc, D. Dvornik, M. Givner, L. G. Humber, M. Kraml, K. Voith, and R. Gaudry, *Nature*, **201**, 497 (1964).