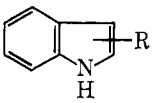
TABLE I

2- AND 3-SUBSTITUTED INDOLES



No.	R	Mp, °C	Formula	N, % Calcd	N, % Found	Infrared, μ NH	Infrared, μ C=O
I	3-COCONHNH$_2$[9]	223–225	$C_{10}H_9N_3O_2$			3.05	6.30
II	3-COCONHN(CH$_3$)$_2$	222–224	$C_{12}H_{13}N_3O_2$	18.10	18.02	3.03, 3.16	5.95, 6.25
III	3-COCONHNHCH(CH$_3$)$_2$	159–161	$C_{13}H_{15}N_3O_2$	17.13	17.21	3.09	6.28
IV	3-COCONNH$_2$ | CH(CH$_3$)$_2$	215–216	$C_{13}H_{17}N_3O_2$	17.13	17.23	2.99, 3.15	6.28
V	3-COCONHN[CH(CH$_3$)$_2$]$_2$	207–208	$C_{16}H_{21}N_3O_2$	14.62	14.21	3.12	5.95, 6.20
VI	3-COCOHNHCH(CH$_3$)$_2$ | CH(CH$_3$)$_2$	184–185	$C_{16}H_{21}N_3O_2$	14.62	14.48	3.02	6.20
VII	3-COCONHN⟨⟩	207–208	$C_{16}H_{19}N_3O_2$	14.73	14.17	3.10	5.99, 6.18
VIII	2-CONHNH$_2$	250–251 dec	$C_9H_9N_3O$	23.99	24.10	3.04	6.12
IX	2-CONHN(CH$_3$)$_2$	195–197	$C_{11}H_{13}N_3O$	20.67	20.30	2.94, 3.10	6.15
X	2-CONHNHCH$_2$C$_6$H$_5$	140–141	$C_{16}H_{15}N_3O$	15.84	15.23	3.00	6.10
XI	2-CONHN⟨⟩	182–183	$C_{15}H_{19}N_3O$	16.33	16.63	3.06	6.18

pletely inactive in this test at 300 mg. It is possible of course that on oral administration the absorption from the gastrointestinal tract influences the degree of the effect.

IX had some weak muscle relaxant activity at 300 mg/kg and also some analgetic activity at 150 mg/kg.

Experimental Section[12]

N-(3-Indolylglyoxylyl)-N′-isopropylhydrazide (III).—A solution of 2.85 g of indolylglyoxylylhydrazide was refluxed for 21 hr with 100 ml of acetone. The white precipitate was filtered and washed with some acetone. It melted at 255–256° after recrystallization from 2-pentanone. The yield was 3.0 g (85%). The hydrazone so obtained was hydrogenated in 240 ml of methanol containing 12 ml of glacial acetic acid, in the presence of Pt catalyst. It consumed the calculated amount of hydrogen in 2 hr and dissolved completely. On evaporation and recrystallization from methanol–water 90% of III was obtained.

Acetone isopropylhydrazone was prepared according to Lochte, *et al.*,[10] in 30% yield, boiling at 130–134° (760 mm). Warm vapors of the substance ignite spontaneously and burn quietly. Distillation and subsequent cooling of the apparatus had to be done under a nitrogen atmosphere.

N-Indolylglyoxylyl-N-isopropylhydrazide (IV).—Indolylglyoxylyl chloride (1.03 g) was dissolved in 10 ml of dioxane and added to 1.14 g of acetone isopropylhydrazone in 3 ml of dioxane. Kept at room temperature overnight, the red solution was diluted with 150 ml of water, and the precipitate recrystallized from ethanol–water; yield 0.58 g (46.5%), mp 215–216°.

Acknowledgment.—The financial support of Bristol Laboratories (Syracuse, N. Y.) is gratefully acknowledged. The pharmacological screening was performed by Dr. M. H. Pindell and his staff of Bristol Laboratories. Some of the compounds were prepared by Mr. T. W. Doyle to whom thanks are due.

(12) Melting points were taken in capillaries on a Gallenkamp electrically heated block and are corrected. Boiling points are uncorrected. Infrared spectra were taken on a Beckman IR-8 instrument in KBr disks. Analyses were performed by Dr. C. Daessle, Montreal.

DL-2-Hydrazino-3-(4-hydroxyphenyl)propionic Acid[1]

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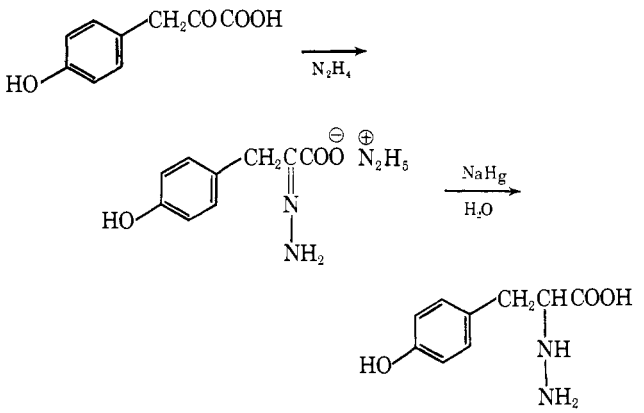
Received December 16, 1965

A number of hydrazino analogs of amino acids[2,3] have been used as inhibitors of dopa decarboxylase. The synthesis of the hydrazino analog of tyrosine has been reported;[4] however, the reference is not available. Therefore, we are reporting a convenient synthesis of this compound.



(1) This work supported by the Psychopharmacology Service Center of the National Institute of Mental Health under Contract No. SA-43-ph-3021.

(2) C. C. Porter, L. S. Watson, D. C. Titus, J. A. Totaro, and S. S. Byer, *Biochem. Pharmacol.*, **11**, 1067 (1962).

(3) S. Udenfriend and P. Zaltzman-Niremberg, *J. Pharmacol. Exptl. Therap.*, **138**, 194 (1962).

(4) V. Nickel, Thesis, University of Cologne, 1932; only title listed in *Chem. Abstr.*, **27**, 1357 (1933). This thesis was destroyed during World War II.

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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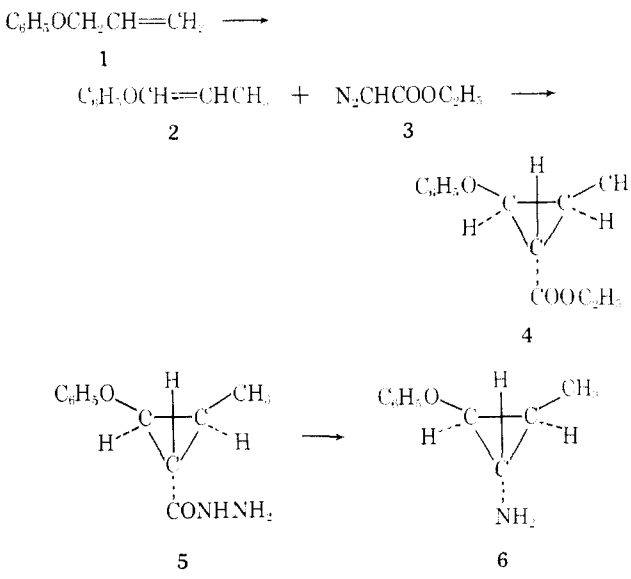
Received November 15, 1965

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).