1,2,3,4-Tetrahydropyrido[4,3-*b*]indole.—A mixture of 1-benzoyl-3-ethoxycarbonyl-4-piperidone[13] (68.5 g, 0.25 mole) and 6 *N* HCl (800 ml) was boiled under reflux for 8 hr. After cooling, the separated benzoic acid was filtered, and the filtrate was extracted several times with ether to remove dissolved benzoic acid; the aqueous layer was then evaporated to dryness. The residue was dissolved in ethanol (200 ml) and saturated with HCl at 0°; phenylhydrazine hydrochloride (36 g, 0.25 mole) was then added and the mixture was boiled under reflux for 1 hr. After cooling, the solid was filtered and dissolved in hot water, and the solution was neutralized with NH_3 to precipitate a light tan solid. Crystallization from ethanol gave 17.7 g (45%) of the base, mp 205–207°.

Anal. Calcd for $C_{11}H_{12}N$: C, 76.7; H, 7.02; N, 16.3. Found: C, 76.6; H, 7.23; N, 16.25.

2-(2-Diethylaminoethyl)-1,2,3,4-tetrahydropyrido[4,3-*b*]indole.—To a solution of 1,2,3,4-tetrahydropyrido[4,3-*b*]indole (1.72 g, 0.01 mole) in hot ethanol (20 ml) was added 2-diethylaminoethyl chloride hydrochloride (1.9 g, 0.011 mole) followed by KOH (0.67 g, 0.012 mole) dissolved in the minimum quantity of water. The mixture was boiled under reflux for several hours and cooled, and the precipitated KCl was filtered. The filtrate was evaporated to dryness and triturated with KOH solution, and the base was extracted into benzene. After drying ($MgSO_4$) the solvent was evaporated to leave a viscous oil (2.3 g). This was converted to its **dimaleate** salt which crystallized from isopropyl alcohol; mp 148–149°.

Anal. Calcd for $C_{17}H_{24}N_3 \cdot 2C_4H_4O_4$: C, 59.6; H, 6.61; N, 8.35. Found: C, 59.5; H, 6.76; N, 8.4.

2,3-Dimethyl-1,2,3,4-tetrahydropyrido[4,3-*b*]indole was prepared from 1,2-dimethyl-4-piperidone and phenylhydrazine hydrochloride and crystallized from ethyl alcohol in colorless needles, mp 205.5–207°.

Anal. Calcd for $C_{13}H_{16}N_2$: C, 78.0; H, 8.05; N, 14.0. Found: C, 77.7; H, 8.07; N, 3.7.

***1,1-Dimethyl-3-(4-chlorophenyl)*-1,2,3,4-tetrahydropyrido-[4,3-*b*]indole** was prepared from 2,2-dimethyl-6-*p*-chlorophenyl-4-piperidone and phenylhydrazine hydrochloride and crystallized from ethyl alcohol as pale yellow needles, mp 207.5–209.5°.

Anal. Calcd for $C_{19}H_{19}ClN_2$: C, 73.4; H, 6.16; N, 9.1. Found: C, 73.2; H, 5.99; N, 8.8.

Acknowledgments.—The author thanks Dr. D. K. Vallance and his colleagues of the Pharmacological Laboratories, Smith Kline and French Laboratories Ltd., for the pharmacological results and Mr. C. S. Whyatt for technical assistance.

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Indole Hydrazides as Potential Monoamine Oxidase Inhibitors

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The pharmacological activity of hydrazine derivatives is well known and made use of therapeutically. The antihypertensive hydrazinophthalazines,[1] analgetic and antipyretic pyrazolones, antiphlogistic dioxopyrazolidines, the tuberculostatic isonicotinoylhydrazines, and the various monoamine oxidase (MAO) inhibitory hydrazines and hydrazones are just a few examples.[2,3]

Since all these hydrazine derivatives influence the metabolism of serotonin as well as other amines, it seemed obvious to investigate hydrazine derivatives of indole structurally related to serotonin. Antimetabolic effects in addition to MAO inhibition should not be impossible among such compounds.

Very few reports on hydrazine derivatives of indoles can be found in the literature. Zeller, *et al.*,[4] report on the tryptophan isopropylhydrazide; a patent of Robinson[5] describes indolylethyl- and β-indolylpropylhydrazines; and other patents[6] deal with indole-3-carbohydrazides but give no pharmacological data. Elderfield and Wood[7] mentioned some N-mustard indolylhydrazides as cytostatics, and Teotino and Maffii[8] listed some indole-2-acetylhydrazides. Biological data are missing in all cases.

The simple indolylglyoxylylhydrazide (I) is mentioned by Heinzelman and Szmuszkovicz[9] as a fairly potent 5-hydroxytryptophan decarboxylase inhibitor (I_{50}, 10^{-4} *M*) (see Table I).

In connection with other investigations, we had the opportunity to synthesize a few indolylglyoxylylhydrazides and 2-indolylcarbohydrazides. In most cases no difficulty was encountered by using standard methods: reaction of indolylglyoxylyl chloride with an excess of the hydrazine derivative in aqueous suspension or dioxane solution. Since amide formation is much faster than the rate of hydrolysis, hydrazides are obtained in good yield even in aqueous media.

Since the isopropyl derivative III proved to be active, it was of interest to see if the other possible mono- and diisopropylhydrazide derivatives would show the same regularity in MAO inhibitory activity as the corresponding isonicotinoyl compounds described by Pletcher, *et al.*[3a] Therefore, IV was prepared from acetone–isopropylhydrazone[10] and the corresponding glyoxylyl chloride, with spontaneous hydrolysis of the isopropylidene group. Similarly, V and VI were prepared in the usual way from the substituted hydrazines. The indole-2-carbohydrazides VIII–XI were obtained from the acid chloride[11] by standard methods.

Pharmacology.—The isopropylhydrazide III was the only one with any reasonable MAO inhibitory activity following oral administration of 300 mg/kg in mice. The test is the reversal of reserpine-induced sedation. At lower doses, down to 38 mg, III antagonizes reserpine by non-MAO-related mechanisms.

Compounds IV and V exhibited evidence of MAO inhibition at 300 mg/kg, but none at 100 mg. Compound VI, which should have been more active than III in view of the report by Pletscher, *et al.*,[3a] was com-

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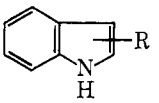
TABLE I

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°.

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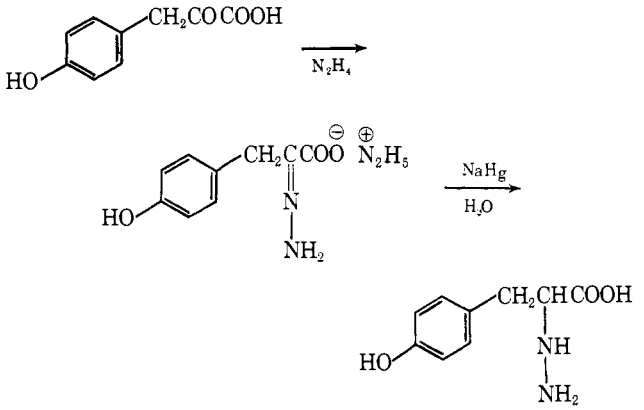
A number of hydrazino analogs of amino acids[2,3] have been used as inhibitors of dopa decarboxylase. The synthesis of the hydrazino analog of tyrosine has been reported;[4] however, the reference is not available. Therefore, we are reporting a convenient synthesis of this compound.



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