the synthesis of IIa. From 0.4–0.5 mole of acids Ib and Ic were obtained 80–85% yields of liquid esters IIb [bp 88–92° (12 mm)] and IIc [bp 101–112° (12 mm)], respectively. For analyses the crude esters were redistilled several times at reduced pressure and center constant-boiling fractions were collected; $n^{23}D$ 1.4295 for IIb, 1.4335 for IIc; infrared bands (neat) at 1775 ± 5 (strong, C=O) and 1666 ± 2 cm^{-1} (weak, C=N).

Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found for IIb: C, 55.55; H, 8.67; N, 7.82. Calcd for $C_{10}H_{19}NO_3$: C, 59.67; H, 9.52; N, 6.96. Found for IIc: C, 59.23; H, 9.46; N, 6.72.

2-(Isopropylideneaminooxy)-1-alkanols (III).—To an ice-cold solution of 22 g (0.127 mole) of ester IIb in 500 ml of anhydrous ether was added, in five portions and with stirring, 3.4 g (0.089 mole) of solid $LiAlH_4$. The reaction mixture was stirred 1 hr longer, allowed to stand at room temperature overnight, and then processed in the same fashion as used in the preparation of IIIa,[6] yield 14.3 g (78%) of IIIb, bp 83–86° (13 mm). After four more distillations an analytical sample was obtained; significant infrared bands (neat) at 3450 (OH) and 1640 cm^{-1} (C=N).

Anal. Calcd for $C_7H_{15}NO_2$: C, 57.90; H, 10.41; N, 9.65. Found: C, 57.97; H, 10.54; N, 9.34.

Likewise from 50 g (0.25 mole) of ester IIc and 6.4 g (0.17 mole) of $LiAlH_4$ was obtained 34.9 g (80%) of IIIc, bp 93–105° (21 mm). After three more distillations there resulted an analytical sample, bp 113–113.5° (13 mm), $n^{23}D$ 1.4455, significant infrared bands (neat) at 3390 (OH) and 1630 cm^{-1} (C=N).

Anal. Calcd for $C_9H_{19}NO_2$: C, 62.39; H, 11.05; N, 8.09. Found: C, 62.07; H, 10.90; N, 7.66.

2-(2,4,5,7-Tetranitro-9-fluorenylideneaminooxy)alkanoic Acids (IV).—The procedure followed that used by Newman and Lutz[3] for synthesis of IVa. A mixture of 23.1 g of 2,4,5,7-tetranitrofluorenone, 15.4 g of Ib, 2.5 g of *p*-toluenesulfonic acid, and 175 ml of glacial acetic acid was refluxed, cooled, and diluted with water. The precipitate was washed with dilute acetic acid, dissolved in 80 ml of propionic acid, and reprecipitated by addition of an equal volume of water to this hot solution; yield 24.8 g (84%) of IVb, mp 166–169°. For analysis, IVb was converted to the **IVb–benzene molecular compound** (by repeated recrystallization from benzene), obtained as pale yellow prisms or powder, mp 126–127°, stable to drying for 8 hr at 25° (0.1 mm).

Anal. Calcd for $C_{17}H_{11}N_5O_{11}\cdot C_6H_6$: C, 51.21; H, 3.18; N, 12.99. Found: C, 51.20; H, 3.11; N, 13.02.

Similarly Ic was converted to IVc (90% yield), mp 211.5–216°. Four recrystallizations from benzene gave yellow prisms of **IVc–benzene molecular compound**, mp 216–217.5°, stable to drying for 30 hr at 56° (0.05 mm).

Anal. Calcd for $C_{19}H_{15}N_5O_{11}\cdot C_6H_6$: C, 52.82; H, 3.72; N, 12.32. Found: C, 52.68; H, 3.93; N, 12.16.

Compounds Affecting the Central Nervous System. II. Substituted 1,2,3,4-Tetrahydropyrido[4,3-*b*]indoles

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The 1,2,3,4-tetrahydropyrido[4,3-*b*]indole (γ-carboline) ring system, in contrast to the β-carboline nucleus, has been little investigated as a source of biologically active compounds. N_2 quaternary salts of this ring system were investigated[2] as potential curarizing agents, some of them having a potency of about one-fifth that of *d*-tubocurarine. Hörlein[3] prepared 5-alkyl-, substituted alkyl-, arylalkyl-, and aryl-γ-carbolines, some of which were claimed to have antihistaminic activity. In particular 2-methyl-5-benzyl-1,2,3,4-tetrahydropyrido[4,3-*b*]indole (methyldrolin) was shown to have prolonged antihistaminic activity[4] with little sedative effect in man.[5]

No reports have appeared on the effect of γ-carbolines on the central nervous system, and, following our interest in the activity of 1-arylalkyl-4-piperidones,[6] the effect of replacing the oxygen function and 3-alkyl group in these compounds by an indole nucleus to give 1,2,3,4-tetrahydro-γ-carbolines was investigated.

2-Substituted 1,2,3,4-tetrahydro-γ-carbolines were prepared by condensation of the corresponding substituted 4-piperidone with phenylhydrazine hydrochloride in ethanolic hydrochloric acid.[3,7] When 1-substituted phenylhydrazines were used in this reaction the corresponding 2,5-disubstituted 1,2,3,4-tetrahydro-γ-carbolines were obtained. 5-Alkyl- and 5-dialkylaminoalkyl-1,2,3,4-tetrahydro-γ-carbolines were obtained by condensation of the appropriate 2-substituted 1,2,3,4-tetrahydro-γ-carboline with an alkyl halide in the presence of sodamide.[3] The parent compound, 1,2,3,4-tetrahydropyrido[4,3-*b*]indole, was prepared from 4-piperidone hydrochloride and phenylhydrazine hydrochloride, reaction with 2-diethylaminoethyl chloride giving 2-(2-diethylaminoethyl)-1,2,3,4-tetrahydropyrido[4,3-*b*]indole.

The spectra are, as would be expected, similar to the corresponding alkylindoles,[8–11] having a broad, partially resolved peak in the ultraviolet at 270–280 mμ (log ϵ_{max} 3.5–4.0) and a further peak at 225–230 mμ (log ϵ_{max} 4.5–4.8).

Biological Activity.—The pharmacological tests used to investigate the activity of these compounds on the central nervous system have been described in the preceding paper of this series.[6] 2-Methyl-1,2,3,4-tetrahydro[4,3-*b*]indole and its 8-bromo derivative blocked the conditioned avoidance response in rats (ED_{50} values 20 and 25 mg/kg, respectively). The LD_{50} values of the compounds were 430 and 370 mg/kg, respectively. The activity of chlorpromazine under similar experimental conditions was 10 and 200 mg/kg, respectively. These two compounds also had analgesic activity in the hot-plate test in mice (ED_{50} values 30 and 60 mg/kg, respectively). Replacement of the methyl group in the 2-position by ethyl, benzyl, phenethyl, and 2-diethylaminoethyl led to less active compounds. This contrasted with the parent piperidones where optimum activity was found with 1-arylalkyl-3-alkyl-4-piperidones.[6]

Substitution of the hydrogen atom on the indole nitrogen atom by alkyl, arylalkyl, aryl, or dialkylaminoalkyl gave compounds with no significant activity in the pharmacological tests employed in this study. Thus for activity in the conditioned avoidance response

(1) Allen and Hanburys Ltd., Ware, Hertfordshire, England.

(2) (a) V. Bocklehieda and C. Ainsworth, *J. Am. Chem. Soc.*, **72**, 2132 (1950); (b) V. Rosnatti and G. Palazo, *Gazz. Chim. Ital.*, **84**, 644 (1954); *Chem. Abstr.*, **49**, 13987 (1955).

(3) U. Hörlein, *Chem. Ber.*, **87**, 463 (1951); British Patents 752,688 (1954), 721,771 (1952), 733,123 (1953).

(4) U. Hörlein and G. Hecht, *Med. Chem., Abhandl. Med.-Chem. Forschungsstaetten Farbenfabriken Bayer*, **5**, 267 (1956); *Chem. Abstr.*, **55**, 10081 (1961).

(5) N. Jones, *Practitioner*, **185**, 334 (1960).

(6) C. R. Ganellin and R. G. W. Spickett, *J. Med. Chem.*, **8**, 619 (1965).

(7) A. H. Cook and K. J. Reed, *J. Chem. Soc.*, 399 (1945).

(8) N. J. Leonard and R. C. Elderfield, *J. Org. Chem.*, **7**, 556 (1942).

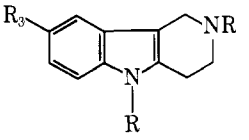
(9) T. Hoskins and K. Tamura, *J. Org. Chem.*, **500**, 42 (1933).

(10) M. M. Janot and R. Goutarel, *Bull. Soc. Chim. France*, [5] **18**, 588 (1957).

(11) F. G. Baker, *Helv. Chim. Acta*, **36**, 215 (1953).

TABLE I

SUBSTITUTED 1,2,3,4-TETRAHYDROPYRIDO[4,3-*b*]INDOLES

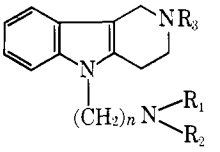


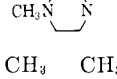
R_1	R_2	R_3	Recrystn solvent[a]	Mp, °C	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found
CH_3	H	H	3	169–171[b]	$C_{12}H_{14}N_2$	77.4	77.8	7.59	7.41	15.05	15.25
C_2H_5	H	H	2	125–126	$C_{13}H_{16}N_2$	78.0	78.0	8.05	7.92	14.0	14.1
$C_6H_5CH_2$	H	H	1	161	$C_{18}H_{18}N_2$	82.4	82.2	6.93	6.93	10.7	10.75
$C_6H_5CH_2CH_2$	H	H	1	166.5–168	$C_{19}H_{20}N_2$	82.6	82.7	7.29	7.60	10.1	10.0
$C_6H_5CH_2CH_2$	C_6H_5	H	1	124.5–125.5	$C_{25}H_{24}N_2$	85.2	85.2	6.86	6.88	8.0	8.0
$C_6H_5CH_2CH_2$	CH_3	H	2	65–66	$C_{20}H_{23}N_2$	82.7	82.8	7.64	7.56	9.7	9.8
$C_6H_5CH_2$	C_6H_5	H	2	92.5–94.5	$C_{24}H_{22}N_2$	85.2	85.3	6.55	6.71	8.3	8.4
$C_6H_5CH_2$	$C_6H_5CH_2$	H	3	154.5–155	$C_{25}H_{24}N_2$	85.2	85.1	6.86	6.98	7.95	8.0
$C_6H_5CH_2CH_2$	$C_6H_5CH_2$	H	1	86–88	$C_{26}H_{26}N_2$	85.2	84.9	7.15	6.93	7.7	8.0
CH_3	H	Br	1	165.5–167	$C_{12}H_{13}BrN_2$[c]	54.35	53.3	4.94	4.95	10.6	10.65
			4	264	$C_{12}H_{13}BrN_2 \cdot HCl \cdot 0.5H_2O$[d]	46.4	46.4	4.87	4.51	9.0	9.0
$C_6H_5CH_2$	n-C_4H_9	H	5	195–197	$C_{22}H_{27}N_2 \cdot HCl$[e]	74.4	74.3	7.67	7.95	7.9	7.9

[a] Solvents: 1, ethanol; 2, petroleum–ether (bp 40–60°); 3, benzene–petroleum ether; 4, water; 5, ethanol–ether. [b] A. H. Cook and K. J. Reed [*J. Chem. Soc.*, 399 (1945)] give mp 171–172°. [c] *Anal.* Calcd: Br, 30.1. Found: Br, 30.4. [d] *Anal.* Calcd: Cl, 11.4. Found: Cl, 11.5. [e] *Anal.* Calcd: Cl, 10.0. Found: Cl, 10.0.

TABLE II

1-SUBSTITUTED 5-DIALKYLAMINOALKYL-1,2,3,4-TETRAHYDROPYRIDO[4,3-*b*]INDOLES AND THEIR MALEATE SALTS



R_1	R_2	n	R_3	Recrystn solvent[a]	Mp or bp (mm), °C	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found
C_2H_5	C_2H_5	2	CH_3		140–144 (0.05)	$C_{18}H_{27}N_3$	75.8	75.7	9.47	9.54	14.6	14.7
				1	140.5–142	$C_{18}H_{27}N_3 \cdot 2C_4H_4O_4$	60.4	60.3	6.88	6.81	8.2	8.1
C_2H_5	C_2H_5	2	$C_6H_5CH_2$		192–196 (0.05)	$C_{24}H_{31}N_3$	80.0	79.7	8.60	8.64	11.51	11.6
				2	158–159	$C_{24}H_{31}N_3 \cdot 2C_4H_4O_4$	65.1	64.7	6.66	6.62	7.3	7.1
		2	CH_3		168–170 (0.1)	$C_{19}H_{27}N_3$	76.7	76.7	9.10	9.15	14.2	14.1
				2	151.5–152.5	$C_{19}H_{27}N_3 \cdot 2C_4H_4O_4$	61.35	61.2	6.64	6.66	8.0	8.0
C_2H_5	C_2H_5	2	$C_6H_5(CH_2)_2$		245–250 (0.1)	$C_{25}H_{33}N_3$	79.7	79.95	8.67	8.86	11.2	11.2
				2	162.5–164	$C_{25}H_{33}N_3 \cdot 2C_4H_4O_4$	65.1	65.2	6.76	6.80	7.0	6.9
		3	CH_3		207–210 (0.1)	$C_{20}H_{30}N_4$	73.5	73.6	9.03	9.26	17.25	17.2
				3	159–161	$C_{20}H_{30}N_4 \cdot 3C_4H_4O_4$	56.7	56.9	6.27	6.28	8.45	8.3
CH_3	CH_3	2	CH_3		154–159 (0.05)[b]	$C_{16}H_{23}N_3$	74.6	74.7	9.02	9.01	16.1	16.3
				2	169–170[c]	$C_{16}H_{23}N_3 \cdot 2C_4H_4O_4$	58.5	58.9	6.30	6.38	8.65	8.6
		2	CH_3		175–180 (0.5)	$C_{18}H_{25}N_3$	76.2	76.28	8.99	8.89	14.9	14.8
				2	136.5–137.5	$C_{18}H_{25}N_3 \cdot 2C_4H_4O_4$	60.7	60.6	6.34	6.45	8.2	8.15

[a] Solvents: 1, methyl alcohol–ether; 2, ethyl alcohol–ether; 3, ethyl alcohol. [b] V. Hörlein [*Ber.*, **87**, 463 (1954)] gives bp 200–205° (2.5 mm). [c] Lit.[b] mp 164–165°.

test the 5-position of the nucleus should be unsubstituted. When this position was unsubstituted optimal activity resulted when the group in the 2-position was methyl.

Experimental Section[12]

Substituted 1,2,3,4-Tetrahydropyrido[4,3-*b*]indoles (Table I). **A.**—A mixture of the appropriately substituted 4-piperidone (0.1 mole), the appropriately substituted phenylhydrazine hydrochloride (14.6 g, 0.1 mole), and alcohol saturated with HCl at 0° (200 ml) was heated under reflux for 3 hr. The mixture was cooled overnight and filtered, and the solid was triturated with dilute NH_3 to give the required tetrahydro-γ-carboline. The alcoholic filtrate was concentrated and poured into dilute NH_3, when a further quantity of the tetrahydro-γ-carboline was obtained. The products were crystallized to constant melting point prior to analysis.

B.—To a stirred solution of a 2-substituted 1,2,3,4-tetrahydropyrido[4,3-*b*]indole (0.05 mole) in hot xylene (100 ml) was added finely powdered sodamide (2.3 g, 0.06 mole). When the evolution of NH_3 was complete, the appropriate halide (0.10 mole) was slowly added and the mixture boiled under reflux for 6 hr. Inorganic material was filtered, and the solvent was distilled *in vacuo*. The residual base was usually purified by distillation and then converted to the appropriate salt. The 5-dialkylaminoalkyl-2-substituted 1,2,3,4-tetrahydropyrido[4,3-*b*]indoles listed in Table II were also prepared by this procedure.

(12) Melting points were recorded using an electrothermal melting point apparatus comprising a gas heater block and a thermometer calibrated for exposed stem. Microanalyses are by Mr. M. Graham and spectra by Miss E. V. Egginton. The ultraviolet and infrared spectra of all the products was recorded.

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.

(13) G. Stork and S. McElvain, *J. Am. Chem. Soc.*, **68**, 1053 (1946).

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-

(1) E. Schlittler, J. Druey, and A. Marxer, *Progr. Drug Res.*, **4**, 319 (1962).

(2) E. Jucker, *Angew. Chem.*, **71**, 321 (1959).

(3) (a) A. Pletscher, K. F. Gey, and P. Zeller, *Progr. Drug Res.*, **2**, 417 (1960); (b) J. H. Biel in "Molecular Modifications of Drug Design," Advances in Chemistry Series, No. 45, American Chemical Society, Washington, D. C., 1964, p 114.

(4) P. Zeller, A. Pletscher, K. F. Gey, H. Gutman, B. Hegedus, and O. Straub, *Ann. N. Y. Acad. Sci.*, **80**, 558 (1959).

(5) R. A. Robinson (to Searle Inc.), U. S. Patent 2,947,758 (1960); *Chem. Abstr.*, **55**, 3615 (1961).

(6) (a) Laboratoires Français de Chimiotherapie, French M. 71 (1961); *Chem. Abstr.*, **58**, 1315 (1963); (b) Roussel-UCLAF, British Patent 933,566 (1963); *Chem. Abstr.*, **60**, 2899 (1964).

(7) R. C. Elderfield and J. R. Wood, *J. Org. Chem.*, **27**, 2463 (1962).

(8) U. M. Teotino and G. Maffii, U. S. Patent 3,005,827 (1960); *Chem. Abstr.*, **56**, 3460 (1962).

(9) R. V. Heinzelman and J. Szmuszkovicz, *Progr. Drug Res.*, **6**, 85 (1963).

(10) H. L. Lochte, W. A. Noyes, and J. R. Bailey, *J. Am. Chem. Soc.*, **44**, 2556 (1922).

(11) T. Nogrady, T. W. Doyle, and L. Morris, *J. Med. Chem.*, **8**, 656 (1965).