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N-Cyclopropyltryptamines, Potent Monoamine Oxidase Inhibitors

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N-Cyclopropyltryptamine as well as the 5- and 7-methoxy derivatives is a potent monoamine oxidase inhibitor for both tyramine and tryptamine substrates.

The use of monoamine oxidase inhibitors as antidepressants has been largely replaced by the tricyclic antidepressants because of the hypotensive side effect of the MAO inhibitors. This field has been recently reviewed by Ho.[1] The most interesting recent developments have been the MAO inhibitors which have been reported to have selective action for tryptamine or serotonin over tyramine. Some examples are (phenoxyethyl)cyclopropylamine,[2] clorgyline,[3] and *N*-methyl-*N*-propargylamphetamine.[4] Certain tryptamines and certain cyclopropylamines have MAO inhibitory action,[1] but cyclopropyltryptamines have not yet been reported in the literature. In an attempt to get a MAO inhibitor specific for serotonin and tryptamine, we prepared three *N*-cyclopropyltryptamines (unsubstituted, 5-CH_3O, and 7-CH_3O) and *N*-cyclopropylmethyltryptamine. We synthesized the 7-CH_3O compound because of the work of Ho[5] on carbolines, in which substituents in the equivalent position enhance MAO inhibitory activity.

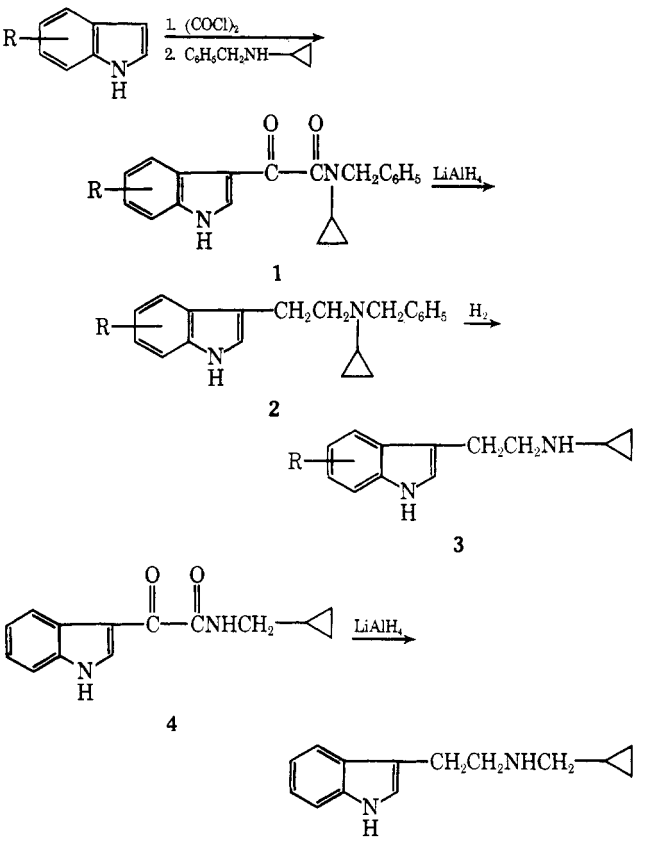
The compounds were prepared by a straightforward synthesis outlined in Scheme I. Attempted preparation of the 7-chloro analog of **3** failed when dechlorination accompanied debenzylation in the last step. A benzyl-protecting group is necessary because cyclopropylamides with free NH undergo ring opening on reduction with $LiAlH_4$.[10]

Pharmacology. Only structure **3** showed MAO inhibitory properties. The most potent was the unsubstituted compound **3a**, which was even more potent than pargyline. However, **3a** was equally potent with tyramine as a substrate as it was for tryptamine, so the hoped for selectivity was not present (Table I).

These compounds were tested for potentiation of the behavioral effects of 5-hydroxytryptophan (5-HTP) in mice. This test is similar to the Dopa potentiation test.[6] See Experimental Section for details. Compound **3a** showed marked potentiation of 5-HTP at 10, 25, and 100 mg/kg orally. Compound **3c** showed marked potentiation of 5-HTP at 10, 25, and 100 mg/kg and moderate potentiation at 5 mg/kg. However, **3b**, the compound which is the closest analog of serotonin, did not potentiate 5-HTP even at 100 mg/kg.

Mouse symptomatology for these compounds showed tremors, decreased motor activity, ataxia, and dilation of blood vessels at 10 mg/kg oral dose for **3a** and **3b** (dilation of blood vessels occurs at 1.0 mg/kg for **3b**). Compound **3c** did not show tremors or decreased motor activity until 100 mg/kg (oral dose) with no dilation of blood vessels. This vasodilation was noted as a reddening of the ears of the mice.

Scheme I



1 2 3 4 5

a, R = H; **b**, R = 5-OCH_3; **c**, R = 7-OCH_3

The cyclopropylmethylaminotryptamine (**5**) showed little, if any, observable effects. Oral LD_{50}'s for **3a–c** and **5** respectively were 100, 100, 750, and 750 mg/kg (animals observed for 24 hr).

Experimental Section

All new compounds gave satisfactory elemental analyses (±0.4%). Nmr and ir spectra were in full accord with the assigned structure. Melting points were uncorrected. Concentrations *in vacuo* were done on a Büchi rotovac.

***N*-Benzyl-*N*-cyclopropylindole-3-glyoxalamide (1a).** Oxalyl chloride (25 g, 0.197 mol) in 80 ml of ether was added dropwise to 20.0 g (0.17 mol) of indole in 300 ml of ether at 0°. After stirring 20

Table I. Monoamine Oxidase Inhibitory Activity of Cyclopropyltryptamines (Tryptamine as a Substrate)

Compd	% inhibn at given concn, mol/l. 10^{-4}	10^{-5}	10^{-6}	10^{-7}
3a	100	93	81	67
3a[a]	100	93	74	56
3b	92	68	32	
3c	81			
5	5			
Pargyline	100	81	65	41

[a]Tyramine as the substrate. All bioassays were done at least twice. Values given are averages with no more than ±3% variation.

min at 0°, the yellow solid which formed was filtered and a suspension of this solid in 100 ml of CH_2Cl_2 was added to a cold solution of 30 g (0.202 mol) of *N*-benzylcyclopropylamine[7] and 18 g (0.18 mol) of Et_3N. After stirring 30 min at 25°, the solution was extracted with dilute HCl and then dilute Na_2CO_3 and concentrated to get 41.5 g (77%) of the amide **1a**, mp 158–160°. *Anal.* ($C_{20}H_{18}N_2O_2$) C, H, N.

By the same procedure 5-methoxyindole was converted into **1b**, mp 165–167°, in 78% yield. *Anal.* ($C_{21}H_{20}N_2O_3$) C, H, N.

7-Methoxyindole[8] was converted into **1c**, mp 150–152°, in 90% yield. *Anal.* ($C_{21}H_{20}N_2O_3$) C, H, N.

Indole and cyclopropylmethylamine[9] were converted into **4**, mp 186–187°, in 59% yield. *Anal.* ($C_{14}H_{14}N_2O_2$) C, H, N.

***N*-Benzyl-*N*-cyclopropyltryptamine Hydrochloride (2a).** Amide **1a** (8.0 g, 25.2 mmol) in 125 ml of tetrahydrofuran was treated with 7.0 g (0.184 mol) of $LiAlH_4$ and refluxed 4 hr. The excess $LiAlH_4$ was decomposed with EtOAc and the mixture worked up with 8 ml of H_2O and 15 ml of 15% NaOH solution. The base was acidified with HCl in *i*-PrOH to give **2a** · HCl salt: mp 200–201°; 6.20 g (76%). *Anal.* ($C_{20}H_{22}N_2$ · HCl) C, H, N.

Synthesized by the same procedure were **2b**, mp 190–192°, in 48% yield [*Anal.* ($C_{14}H_{18}N_2O$ · HCl) C, H, N]; **2c**, mp 203–205°, in 82% yield [*Anal.* ($C_{14}H_{18}N_2O$ · HCl) C, H, N]; and **4**, mp 177–178° (note: EtOAc not used in work-up), in 54% yield [*Anal.* ($C_{14}H_{18}N_2$ · HCl) C, H, N].

***N*-Cyclopropyltryptamine (3a).** Compound **2a** (19.6 g, 62.5 mmol) was dissolved in 150 ml of H_2O, 150 ml of EtOH, and 500 ml of MeOH and hydrogenated with 4.0 g of 5% Pd/C catalyst. After uptake was complete, the catalyst was filtered, the solution concentrated, and the residue crystallized from *i*-PrOH to give 11.5 g (82% yield) of **3a**, mp 180–182°. *Anal.* ($C_{13}H_{16}N_2$ · HCl) C, H, N.

Synthesized by the same procedure were **3b**, mp 173–175°, in 82% yield [*Anal.* ($C_{14}H_{18}N_2O$ · HCl) C, H, N] and **3c**, mp 208–210°, in 90% yield [*Anal.* ($C_{14}H_{18}N_2O$ · HCl) C, H, N].

Pharmacology. MAO inhibitory activity was determined with MAO from mouse brains by the method of Wurtman and Axlerod.[11]

5-Hydroxytryptophan Potentiation. Three mice were first pretreated with pargyline (40 mg/kg ip), followed by the drug (oral), and then challenged with 5-HTP 4 hr later. Effects observed are tremors, head movements, abducted limbs, and irritability.

Acknowledgments. The microanalyses were done by Ms. J. Hood, nmr spectra under the direction of Dr. R. Egan, and ir spectra under Mr. W. Washburn. Pharmacological testing was done by Mr. F. Will and Ms. Fely Alix.

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Synthesis of 8-(3′-Deoxy-α-D-*threo*-pentofuranosyl)adenine and 9-(3′-Deoxy-α-D-*threo*-pentofuranosyl)adenine†

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Received December 6, 1974

3-Deoxy-2,5-di-*O*-*p*-nitrobenzoyl-α-D-*threo*-pentofuranosyl bromide (1) reacted with mercuric cyanide to give 2,5-anhydro-4-deoxy-D-*lyxo*-hexononitrile (2) which upon acid hydrolysis of the CN group gave acid 3. Saponification of the protecting groups gave 2,5-anhydro-4-deoxy-D-*lyxo*-hexonic acid (4) which reacted with 4,5,6-triaminopyrimidine forming an amide (5) that was pyrolized to give 8-(3′-deoxy-α-D-*threo*-pentofuranosyl)adenine (6). Reaction of bromide 1 with 6-(benzamido)chloromercuriopurine followed by saponification yielded 9-(3′-deoxy-α-D-*threo*-pentofuranosyl)adenine (8). 8-(β-D-Ribofuranosyl)adenine, 8-(β-D-arabinofuranosyl)adenine, and 8-(3′-deoxy-β-D-*erythro*-pentofuranosyl)adenine, as well as compound **6**, showed no antimalarial activity.

The antibiotic, cordycepin (3′-deoxyadenosine), which has shown some antiplasmodial activity, is deactivated by hydrolases and by adenosine deaminase.[1] In an attempt to overcome the deactivation by hydrolases, we synthesized 8-(3-deoxy-β-D-*erythro*-pentofuranosyl)adenine[2] and 8-(β-D-arabinofuranosyl)adenine,[3] as well as various 8-hydroxyalkyladenines[4] in which the hydrolyzable *N*-glycosidic bond was replaced by a more stable C–C bond.

In this paper we describe the synthesis of 8-(3′-deoxy-α-D-*threo*-pentofuranosyl)adenine (**6**) and 9-(3′-deoxy-α-D-*threo*-pentofuranosyl)adenine (**8**) and discuss some preliminary screening results of the antiplasmodial activity of various 8-substituted adenine C-nucleosides.

The starting material for the synthesis of 8-(3′-deoxy-α-D-*threo*-pentofuranosyl)adenine (**6**) and 9-(3′-deoxy-α-D-*threo*-pentofuranosyl)adenine (**8**) was 3-deoxy-2,5-di-*O*-*p*-nitrobenzoyl-α-D-*threo*-pentofuranosyl bromide (**1**)[5]

†This work was sponsored by the U.S. Army Medical Research and Development Command, Contract No. DADA 17-73-C-3053. This is Contribution No. 1330 from the Army Research Program on malaria.
‡Postdoctoral Fellow.