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Terpenoid *N*-Heterocyclics. II*

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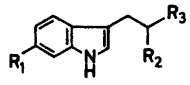
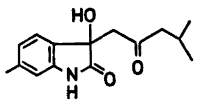
3-(4-Methyl-2-aminopentyl)-6-methylindole (*1a*) and some analogues have been prepared and their pharmacological properties studied. The OH-analogue of *1a* was prepared by LAH-reduction of a condensation product (*4*) from 6-methylisatin and methyl isobutyl ketone. Reductive cleavage to give 3,6-dimethylindole and 3-methylbutanol-1 was a by-reaction during the LAH-reduction.

Nitrogenous terpenoids are of potential pharmacological interest,[1] and the present study was undertaken, in order to prepare and to evaluate the pharmacological properties of the "sesquiterpene tryptamine", *1a*, and some closely related analogues, *e.g. 1b*.



1a	$R_1=CH_3$	$R_2=NH_2$	$R_3=CH_2CH(CH_3)_2$
b	$R_1=H$	$R_2=NH_2$	$R_3=CH_2CH(CH_3)_2$
c	$R_1=H$	$R_2=NH_2$	$R_3=CH(CH_3)_2$
2	$R_1=CH_3$	$R_2=NO_2$	$R_3=CH_2CH(CH_3)_2$
3a	$R_1=CH_3$	$R_2=OH$	$R_3=CH_2CH(CH_3)_2$
b	$R_1=H$	$R_2=OH$	$R_3=CH_2CH(CH_3)_2$
c	$R_1=H$	$R_2=OH$	$R_3=CH(CH_3)_2$



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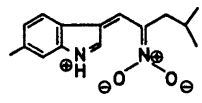

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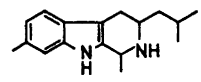

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* Part I. *Acta Chem. Scand.* **23** (1969) 2578.

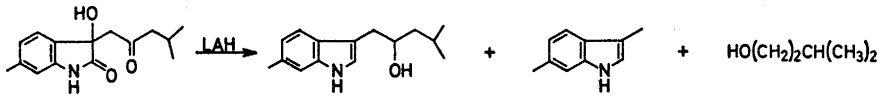
SYNTHETIC METHODS

Compound *1a* was prepared by condensation of 6-methylgramine and 3-methyl-1-nitrobutane and subsequent LAH-reduction of the nitrohexylindole (*2*) obtained.

The route *via* LAH-reduction of the oxime of *4* was inconvenient, owing to the low yield in this reduction. LAH-reductions of the nitronate (*5*) also gave unsatisfactory yields. The nitronate (*5*) was obtained by condensation of 6-methylindole-3-carboxaldehyde and 3-methyl-1-nitrobutane (*cf.* Refs. 2–4).

The tryptophol (*3a*) was obtained in fair yield by LAH-reduction of *4*. 3,6-Dimethylindole and 3-methylbutanol-1 was also formed in small amounts during this transformation.

Condensation of *1a* with acetaldehyde gave the 1,2,3,4-tetrahydro-β-carboline (*6*).



4 *3a*

PHARMACOLOGY

The compounds were tested in the general screening program of Astra Läkemedel AB, Södertälje. No interesting effects were found. The α-alkyltryptamines (*1*) and the 1,2,3,4-tetrahydro-β-carboline (*6*) showed LD_{50} values in the range 0.065–0.125 g/kg (i.p. on mice), convulsions being the most prevalent symptom.

EXPERIMENTAL

6-Methylgramine. 6-Methylindole (13.1 g, 0.1 mol) was added at 5° to a wellstirred solution of 40 % dimethyl amine in water (25 g), acetic acid (12 g) and 38 % formaldehyde (8 g). While this was being done the temperature rose to about 40°. After 5 h at 25° the reaction mixture was poured while stirring into 2 N sodium hydroxide (200 ml). The precipitate formed was washed with water, dried and recrystallized from ether (cooling to −20°). Yield: 15.5 g, 82 %. M.p. 123–124° (Lit.[5,6] 124–125°, 117°). NMR($CDCl_3$): τ=7.76 (s, 6H, NCH_3), τ=7.61 (s, 3H, 6-CH_3), τ=4.42 (s, 2H, CH_2), τ=0.9 (broad s, 1H, NH).

3-(4-Methyl-2-nitropentyl)-6-methylindole (2). Sodium (3.45 g) was dissolved in ethanol (250 ml). 3-Methyl-1-nitrobutane [7] (19.2 g) followed by 6-methylgramine (32.0 g) were then added. To this solution dimethyl sulfate (28.5 g) in ethanol (50 ml) was added during 0.5 h at 30–35°. The mixture was stirred for 3 h at 30–35° and then poured into Na_2SO_4, aq. (800 ml, 5 %). The solid formed was collected, washed with water, dried and recrystallized from cyclohexane. Yield: 26 g, 62 %. M.p. 89–91°. (Found: C 69.3; H 8.0; N 10.6. Calc. for $C_{15}H_{20}N_2O_2$: C 69.2; H 7.8; N 10.8.)

3-(4-Methyl-2-aminopentyl)-6-methylindole. (1a). 3-(4-Methyl-2-nitropentyl)-6-methylindole (13 g) in ether (200 ml) was added dropwise, while stirring, to $LiAlH_4$ (5 g) in refluxing ether (500 ml). Heating was continued for 6 h. Excess $LiAlH_4$ was destroyed by careful addition of water. The mixture was filtered, dried ($MgSO_4$), and the solvent evaporated. The residue was crystallized from cyclohexane. This material contained cyclohexane, which was removed by heating under reduced pressure (55°, 10 mm) for 8 h. Yield: 9.2 g, 80 %. M.p. 98–99°. (Found: C 78.2; H 9.7; N 12.1. Calc. for $C_{15}H_{22}N_2$: C 78.2; H 9.6; N 12.2.)

3-(4-Methyl-2-oxopentyl)-3-hydroxy-6-methyloxindole (4). A mixture of 6-methylisatin [8,9] (24 g), methyl isobutyl ketone (45 ml) and diethylamine (3 ml) was shaken for 12 h. Ether (20 ml) was added, and the mixture was cooled (0°). The solid formed was recrystallized from ethanol/water (1:2) and then from benzene. Yield: 24 g, 62 %. M.p. 129–130°. (Found: C 69.1; H 7.4; N 5.3. Calc. for $C_{15}H_{19}NO_3$: C 68.9; H 7.3; N 5.4.)

3-(4-Methyl-2-hydroxypentyl)-6-methylindole (3a). 3-(4-Methyl-2-oxopentyl)-3-hydroxy-6-methyloxindole (6.5 g, 1/40 mol) was added in portions to a refluxing mixture of $LiAlH_4$ (3.8 g) in ether (500 ml). When this step was completed, the reflux was continued for 5 h. Excess of the hydride was decomposed by careful addition of water while stirring. The ether phase was evaporated and the residue crystallized from cyclohexane hexane (3:1). Yield: 2.5 g, 44 %. M.p. 76–77°. (Found: C 77.8; H 9.0; N 6.3. Calc. for $C_{15}H_{21}NO$: C 77.9; H 9.2; N 6.1.)

By-products from the mother liquor of 3a. The mother liquor previously obtained was fractionally distilled with steam and two main fractions were taken. Fraction "1" redistilled, when taking the fraction 130–132°/760 mm, gave 3-methyl-1-butanol (0.2 g, 10 %). The solid from fraction "2", when sublimed (5 mm), gave 3,6-dimethylindole (0.4 g, 10 %). M.p. 94–95° (Lit.[10] 94–95°).

The NMR signals recorded from *1a*, *2*, *3a*, and *4* were similar to those from their homologues.[11]

3-(Methyl-2-hydroxyiminopentyl)-3-hydroxy-6-methyloxindole. To 3-(4-methyl-2-oxopentyl)-3-hydroxy-6-methyloxindole (7.0 g) in hot ethanol (50 ml) was added hydroxylamine hydrochloride (2.4 g) in water (15 ml) followed by sodium acetate (4.2 g) in water (20 ml). The solution was kept at room temperature for 1 h, and then evaporated to a small volume under reduced pressure in a water bath. The solid was recrystallized from water/ethanol (1:1). Yield: 5.2 g, 71 %. M.p. 180–185° (dec. with red colouration). (Found: C 65.5; H 7.4; N 9.9. Calc. for $C_{15}H_{20}N_2O_3$: C 65.2; H 7.3; N 10.1.)

Reduction of 3-(4-methyl-2-hydroxyiminopentyl)-3-hydroxy-6-methyloxindole. The oxime was reduced by using the two methods of Franklin and White.[12] The yields were, however, meager (22 and 16 %, respectively). The base obtained was identical with *1a* (IR and mixed m.p.).

Nitronate (4). A solution of ammonium acetate (2.0 g), acetic anhydride (0.5 ml), and acetic acid (15 ml) was stirred for 20 min at 50°. 6-Methylindole-3-carboxaldehyde (3.2 g) and 3-methyl-1-nitrobutane [7] (5.0 g) were added. The mixture was refluxed for 4 h, cooled and poured into water. The solid formed was recrystallized twice from methanol. Yield: 2.3 g, 40 %. M.p. 172–174°. (Found: C 69.9; H 6.9; N 10.7. Calc. for $C_{15}H_{18}N_2O_2$: C 69.7; H 7.0; N 10.9.)

1,7-Dimethyl-3-isobutyl-1,2,3,4-tetrahydro-β-carboline (6). 3-(4-Methyl-2-aminopentyl)-6-methylindole (2.30 g, 0.010 mol) was dissolved in water (15 ml) containing H_2SO_4 (0.60 ml, 0.011 mol). A solution of 10 % acetaldehyde in water (30 ml) was added. The mixture was slowly heated to boiling for 1 h. Boiling was continued for 0.5 h. The mixture was allowed to cool, and then made alkaline. After stirring for 10 h the base was collected, dried and recrystallized from methylcyclohexane. Yield: 1.46 g, 57 %. M.p. 124–126°. (Found: C 79.6; H 9.4; N 10.8. Calc. for $C_{17}H_{14}N_2$: C 79.6; H 9.5; N 11.0.)

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