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Preliminary Communication

The Synthesis of β-Hydroxytryptamines

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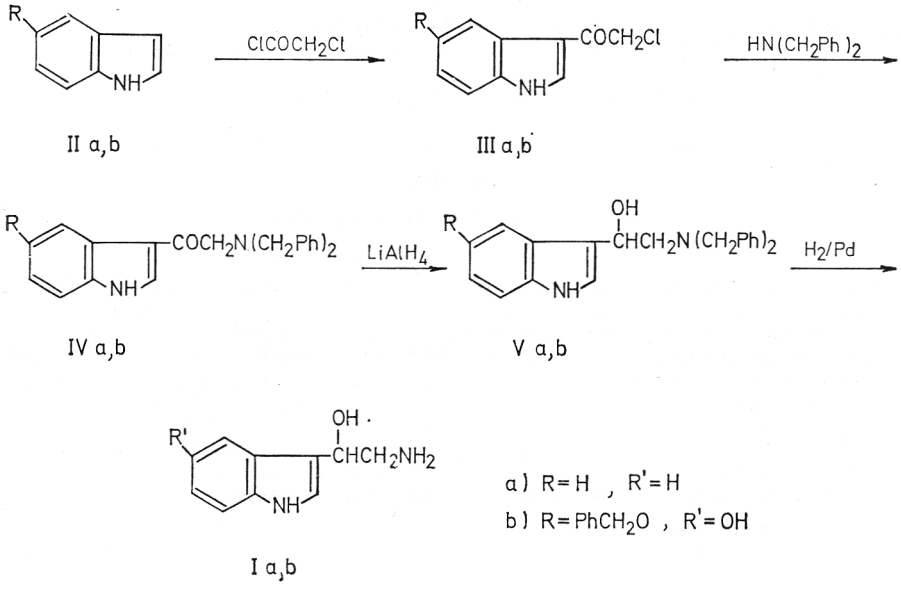
It might be expected that β-hydroxylation of the side chain of tryptamine, 5-hydroxytryptamine (serotonin) and 5-methoxytryptamine would be of biological importance as it is the case with phenylethylamine group of biogenic amines (*cf.* tyramine—octopamine, dopamine—noradrenaline).

So far only syntheses of β-hydroxytryptamine (Ia) have been reported[1–3], but in all cases the compound could be obtained only as the picrate salt — the form not adequate for further biological investigations. The synthesis of β-hydroxylated 5-hydroxytryptamine (Ib) was attempted[2], but only a gummy product was obtained which could not be purified. In this communication the syntheses of Ia and Ib, in form of stable, water soluble creatinine sulphate complexes, are reported.

The Grignard derivatives of indole (IIa) and 5-benzyloxyindole (IIb), respectively, reacted with chloroacetylchloride to give the corresponding chloromethyl 3-indolyl ketones (IIIa, b). By refluxing with dibenzylamine the halogen was replaced with the $-N(CH_2Ph)_2$ group, yielding IVa and IVb, respectively, which were then reduced with lithium aluminum hydride to 2-dibenzylamino-1-hydroxyethyl derivatives (Va, b). The removal of benzyl groups was achieved by catalytic hydrogenation, and after the addition of



creatinine and sulphuric acid to the reaction mixture, the creatinine sulphate complexes of Ia and Ib were isolated. M. p. (dec.) were above 200° C and TLC on silicagel G in water: methanol (4 : 1) gave R_f values of 0.53 and 0.46, resp. and violet spots with Ehrlich's reagent.

For all the compounds reported, except for Va and Vb, acceptable analyses, and IR and NMR spectra consistent with the structure, were obtained.

The position of the side chain was confirmed by NMR spectroscopy. The nitrogen ring proton of IIIa, b (methylsulphoxide-d_6) and of IVa, b (deuteroacetone) showed broad signals in the region from τ — 2 to τ 1.2, which disappeared after D_2O exchange. H-2 ring proton gave rise to doublets at τ 1.5 for IIIa, b and τ 2.1 for IVa, b, which collapsed to singlets upon deuteration. H-2 signal of IIIa and IIIb in deuteroacetone and methylsulphoxide-d_6 showed a difference in chemical shift of 0.2 ppm. Since it is known that the position of H-3 signal is not considerably influenced by the nature of solvents, as it is the case with the position of H-2 signal[4], the observed difference is a further indication for the substitution in the position 3 of the indole ring. The spectrum of the picrate complex of Ia in methylsulphoxide-d_6 showed the presence of **CH** (triplet at τ 5, J 6.5 Hz) and **CH_2**-group (doublet at τ 7, J 6.5 Hz).

The main difficulties in obtaining β-hydroxylated 5-hydroxytryptamine by the reported procedure were the poor yields in the Grignard step and in the recovery of the creatinine sulphate complex. Crystalline IIIa and IIIb were obtained in 20—30% yield, and IVa and IVb in 80% and 54% yields, resp. The crude oily hydroxy derivatives Va, b (96% and 86% yield), being unstable compounds, were subjected to hydrogenation step without further purification. The yields of crystalline creatinine sulphate complexes were 45% for Ia and 10% for Ib.

The work outlined here is being extended; further details will be reported elsewhere.

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IZVOD

Sinteza β-hidroksiliranih triptamina

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Sintetizirani su β-hidroksilirani triptamin (Ia) i β-hidroksilirani 5-hidroksitriptamin (Ib), supstance koje predvidivo imaju biološku aktivnost. Grignard-ovi derivati indola odnosno 5-benziloksiindola, reagirali su s kloroacetilkloridom dajući odgovarajuće klorometil 3-indolil ketone. Halogen je zamijenjen s dibenzilaminom a karbonil u postranom lancu reduciranjem u hidroksil s litium aluminium hidridom. Benzilne grupe uklonjene su katalitičkim hidriranjem, a Ia i Ib izolirani su kao kristalinični, u vodi topivi, kreatinin sulfatni kompleksi. Iskorištenja su zadovoljavajuća (45—96%) osim kod priprave klorometil 3-indolil ketona (20—30%) i kod izolacije kreatinin sulfatnog kompleksa hidroksiliranog 5-hidroksitriptamina (10%). Konstitucija spojeva istražena je NMR spektroskopijom.

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