SYNTHESIS OF CARBOLINE BASES

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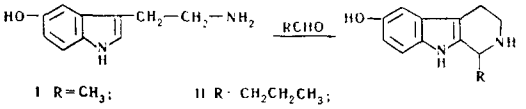
A study has been made of the condensation of serotonin with aldehydes to give the corresponding β-carboline derivatives. In most cases the reaction was run under biological conditions (pH 5.4, 36°). The following aldehydes were reacted: acetaldehyde, butyraldehyde, isobutyraldehyde, benzaldehyde, n-octaldehyde, and formaldehyde. The corresponding β-carboline derivatives are obtained from the first 5 of these. The reaction with formaldehyde leads to complete resinification.

The high physiological activity of indole alkaloids, as well as the recently established high anti-tumor activity of serotonin in experiments [1–3], prompted us to carry out work directed towards synthesizing carboline compounds from serotonin with the hydroxyl group in the latter remaining free. For this purpose a study was made of the reaction of serotonin with the following aldehydes: formaldehyde, acetaldehyde, butyraldehyde, isobutyraldehyde, benzaldehyde, and n-octaldehyde. The reaction did not proceed in the desired direction with formaldehyde; even using biological pH and temperatures [4] and methylal instead of the free aldehyde, there was complete resinification. This was obviously due to the free phenolic group. The next 4 aldehydes readily condensed with serotonin at pH 5.4 and 36°, to give good yields of the following compounds: 1-methyl-6-hydroxy-1,2,3,4,-tetrahydro-2-carboline (I); 1-propyl-6-hydroxy-1, 2,3,4-tetrahydro-2-carboline (II); 1-isoproply-6-hydroxy-1,2,3,4-tetrahydro-2-carboline (III); 1-phenyl-6-hydroxy-1,2,3,4-tetrahydro-2-carboline (IV). Of all of these compounds, which are carboline derivatives with a free phenolic group, the only one previously obtained [5] was 1-methyl-6-hydroxy-1,2, 3,4-tetrahydro-2-carboline, while the derivatives with methoxyl in place of the phenolic group were known [6].



I R=CH_3; II R=$CH_2CH_2CH_3$;

III R=$CH(CH_3)_2$; IV R=C_6H_5; V R=$(CH_2)_6CH_3$

It should be mentioned that the above pH and temperature give the best results; even small changes lead to large drops in yield. Regarding n-octaldehyde, reaction did not take place under the above conditions, and it was necessary to raise the temperature to obtain the corresponding carboline derivative, which was 1-n-hyptyl-6-hydroxy-1,2,3,4-tetrahydro-2-carboline (V), but even then the reaction did not proceed smoothly, and the yield did not exceed 15%. Compounds I, II, and V did not give crystalline free bases. Analyses and characterization had to be restricted to salts which crystallized well.

In tests of the compounds prepared, using intermeshed tumors, compounds II and III showed considerable activity (E. Ch. Pukhalskaya). A separate detailed publication will be made about this. All the microanalyses in this paper were carried out under the supervision of A. D. Chinaeva.

EXPERIMENTAL

1-Methyl-6-hydroxyl-1, 2, 3, 4-tetrahydro-2-carboline (I). 60 ml phosphate buffer solution (pH 5.4) and 1.75 acetaldehyde were added to a solution of 1 g serotonin hydrochloride in 60 ml water. The mixture was sealed in a tube and left for 10 days in a thermostat at 36°. Then to remove unreacted aldehyde the solution was extracted with a small amount of ether, made strongly alkaline with aqueous ammonia, and extracted with ether (2 00 ml). To remove the inconsiderably small amount of water, dried over Na_2SO_4, and the ether distilled off. The noncrystalline dry residue was dissolved in a very small quantity of dry ether, and ethanolic HCl was added dropwise until the mixture was slightly acid to Congo Red. A colorless crystalline precipitate of hydrochloride formed, yield 80% allowing for the serotonin recovered. Unreacted serotonin was extracted from the aqueous mother liquors with ether, the very unfavorable distribution coefficient making it best to extract in a Soxhlet. The picrate was prepared by mixing an alcohol solution of the base and an aqueous solution of picric acid.*

1-Propyl-6-hydroxy-1, 2, 3, 4-tetrahydro-2-carboline (II). 60 ml phosphate buffer solution (pH 5.4) and 0.6 g freshly distilled butyraldehyde in 60 ml EtOH were added to a solution of 1 g serotonin hydrochloride in 60 ml water. The reaction mixture was left in a thermostat at 36° for 14 days. Then the ETOH was vacuum distilled off, and the residue worked up as described for I. The free base II also did not crystallize. The hydrochloride and picrate were prepared. In the same isobutyraldehyde and serotonin gave 1-isopropyl-6-hydroxy-1, 2, 3, 4-carboline (III), while serotonin and benzaldehyde gave 1-phenyl-6-hydroxy-1, 2, 3, 4-tetrahydro-2-carboline (IV).

1-n-Heptyl-6-hydroxy-1, 2, 3, 4-tetrahydro-2-carboline (V). 60 ml phosphate buffer solution (pH 6.3) and a solution of 0.9 g freshly distilled n-octaldehyde in 60 ml EtOH were added to a solution of 1 g serotonin hydrochloride in 60 ml water. The whole was refluxed for 3 hr, then the EtOH distilled off under vacuum, and hydrochloric acid added to the solution until it was acid to Congo Red. The hydrochloride precipitated as fine needles which were very slightly soluble in water. The picrate was prepared by mixing an EtOH solution of the hydrochloride and an aqueous solution of picric acid.

*The table gives only the physical constants of picrates not previously described

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β-Carboline Derivatives

Compound	R	Mp, °C	UV spectrum in absolute EtOH (c × 10^{-4} M) λ_{max}, nm	lg ε	Formula	Found, % C	H	N	Cl	Calculated, % C	H	N	Cl	Yield, %
I	CH_3	Picrate 142–143 (ex water)			$C_{12}H_{14}N_2O \cdot C_6H_3N_3O_7$	49.83	4.14	16.07		50.11	3.94	16.24		
II	$CH_3—CH_2—CH_2$	Hydrochloride: 248–249 (ex absolute EtOH)			$C_{14}H_{18}N_2O \cdot HCl$	62.92	7.44	10.65		63.03	7.12	10.50		85
		Picrate: 209 (decomp., 30% EtOH)			$C_{14}H_{18}N_2O \cdot C_6H_3N_3O_7$	52.11	4.69	15.35		52.10	4.57	15.25		
III	$CH_3 \diagdown CH$ $CH_3 \diagup$	Base: 183–184 (decomp., ex benzene)	284	3.95	$C_{14}H_{18}N_2O$	72.82	7.77	12.48		73.04	7.82	12.17		75.0
		Picrate: 207 (decomp., ex water)			$C_{14}H_{18}N_2O \cdot C_6H_3N_3O_7$	52.15	4.49	15.59		52.10	4 57	15.25		
IV	C_6H_5	Base: 137–138	280	3.95	$C_{17}H_{16}N_2O$	77.57	6.22	10.57		77.27	6.06	10.60		60.6
		Hydrochloride: 254–255 (ex EtOH)			$C_{17}H_{16}N_2O \cdot HCl$	67.72	5.67	9.29		67.88	5.65	9.31		
		Picrate: 208–210 (decomp., ex 30% EtOH)			$C_{17}H_{16}N_2O \cdot C_6H_3N_3O_7 \cdot \cdot H_2O$	54.06	4.21	13.80		54.0	4.10	13.80		
V	$CH_3(CH_2)_6$	Hydrochloride: 205–207 (decomp., ex acetone–EtOH 1:2:5)	285	3.83	$C_{18}H_{26}N_2O \cdot HCl$	66.16	8.37	8.50	11.0	66.93	8.43	8.68	10.98	65.0
		Picrate: 179–180 (decomp., ex 30% EtOH)			$C_{18}H_{26}N_2O \cdot C_6H_3N_3O_7$	55.70	5.74	14.04		55.92	5.63	13.59		

*SF-4A instrument.
**Yield takes into account serotonin recovered.

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