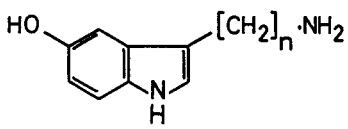
The influence of chain length upon the activity of 5-hydroxytryptamine

The molecular requirements for 5-hydroxytryptamine (5-HT)-like contractile activity in isolated tissue preparations such as the rat uterus or stomach fundus are specific. Structure-activity relations in the tryptamine series demonstrate that the 5-hydroxyl group and a primary amino function are essential for high activity (Barlow & Khan, 1959; Vane, 1959; Bertaccini & Zamboli, 1961), while replacement of the indolic imino moiety of 5-HT (I, n = 2) by bio-isosteric groups such as methylene or thio has a profound and deleterious effect on activity (Pinder, Green & Thompson, 1971). Relatively little information is available about the influence of chain length except in the homologous series of indole-3-alkylamines, where a marked peak of activity occurs with tryptamine itself (Vane, 1959). This trend is also confirmed with the more potent series of 5-methoxylated derivatives, in which 5-methoxytryptamine is respectively 5–10 and 500–1000 times more potent than the corresponding 3-(3-aminopropyl) and 3-(4-aminobutyl) compounds in producing contractions of the rat uterus (Arutyunyan, 1967). These studies, however, used compounds lacking the necessary 5-hydroxy group, and we now report the preparation and some pharmacology of three homologues of 5-HT, which contain one- (I, n = 1), three- (I, n = 3), or four-carbon (I, n = 4) alkylamine side-chains.



(I)

3-(5-Benzyloxyindol-3-yl)propionic acid (Justoni & Pessina, 1957) and 4-(5-benzyloxyindol-3-yl)butyric acid (Zenitz, 1966) were converted to their amides by treatment at 0° with phosphorus pentachloride followed by addition, also at 0°, to ammonium hydroxide. 3-(5-Benzyloxyindol-3-yl)propionamide, obtained in 65% yield, had m.p. 122–123° (benzene) (Found: C, 73·6; H, 6·4; N, 9·4; $C_{18}H_{18}N_2O_2$ requires C, 73·45; H, 6·2; N, 9·5%); 4-(5-benzyloxyindol-3-yl)butyramide, 59% yield, had m.p. 120–121° (benzene) (Found: C, 74·1; H, 6·6; N, 8·9; $C_{19}H_{20}N_2O_2$ requires C, 74·0; H, 6·5; N, 9·1%). Reduction with lithium aluminium hydride in ether afforded the respective amines; 3-(3-aminopropyl)-5-benzyloxyindole hydrochloride, yield 74%, m.p. 162–163° (ethanol–ether) (Found: C, 67·8; H, 6·7; N, 8·9; $C_{18}H_{20}N_2O{\cdot}HCl$ requires C, 68·2; H, 6·7; N, 8·8%); and 3-(4-aminobutyl)-5-benzyloxyindole hydrochloride, yield 67%, m.p. 202–203° (ethanol–ether) (Found: C, 68·9; H, 6·9; N, 8·5; $C_{19}H_{22}N_2O{\cdot}HCl$ requires C, 69·0; H, 7·0; N, 8·45%). Hydrogenolysis at room temperature and atmospheric pressure, with 10% palladized charcoal as catalyst, quantitatively gave 3-(3-aminopropyl)-5-hydroxyindole hydrochloride, m.p. 161–162° (propan-2-ol) (Found: C, 58·2; H, 6·5; N, 12·0; $C_{11}H_{14}N_2O{\cdot}HCl$ requires C, 58·3; H, 6·7; N, 12·4%); and 3-(4-aminobutyl)-5-hydroxyindole hydrochloride, m.p. 100–101° (propan-2-ol–ether) (Found: C, 59·6; H, 7·1; N, 11·4; $C_{12}H_{16}N_2O{\cdot}HCl$ requires C, 59·9; H, 7·1; N, 11·6%).

3-Aminomethyl-5-benzyloxyindole hydrochloride, m.p. 177–179° (ethanol–ether), was obtained in 46% yield by hydrogenation at 2·8 kg cm^{-2} of 5-benzyloxyindole-3-carbaldoxime (Young, 1958) in ethanol–hydrochloric acid, using 10% palladized charcoal as catalyst (Found: C, 66·6; H, 5·7; N, 9·4. $C_{16}H_{16}N_2O{\cdot}HCl$ requires C, 66·55; H, 5·9; N, 9·7%). Subsequent hydrogenolysis in neutral ethanol afforded a poor yield (<10%) of the easily oxidized 3-aminomethyl-5-hydroxyindole as its hydrogen oxalate, m.p. 150° (decomp.) (Found: C, 52·0; H, 4·8; N, 11·2. $C_9H_{10}N_2O$. $C_2H_2O_4$ requires C, 52·4; H, 4·8; N, 11·1%).

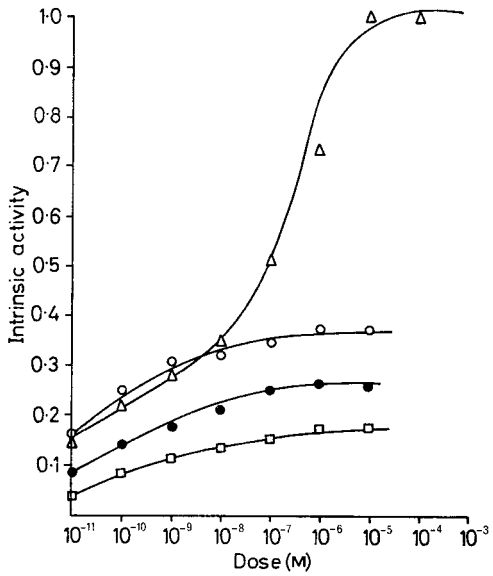


FIG. 1. Dose–response curves for the agonistic activity of 5-HT homologues in the rat stomach fundus strip. △, 5-HT; □, I(n=1); ●, I(n=3); ○, I(n=4). Range of s.e. for all points shown was 0·002–0·03.

5-HT-like activity was measured by contraction of rat fundus strips (Vane, 1959; Pinder & others, 1971), and is represented diagrammatically in Fig. 1. The intrinsic activities relative to 5-HT, ± standard error of the mean, for the homologues with alkylamine chain lengths of n = 1, n = 3, and n = 4 are respectively 0·176 ± 0·01; 0·263 ± 0·005, and 0·373 ± 0·009. These results demonstrate the strict molecular requirements of the 5-HT receptor in the rat stomach fundus, and confirm the results of Vane (1959) for the tryptamines without a 5-hydroxy substituent. Clearly, an ethylamine side-chain is a prerequisite for agonist activity on such receptors.

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