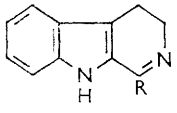
A Synthesis of 2-Alkyltryptamines and of 3,4-Dihydro-β-carboline

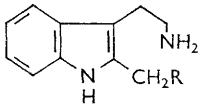
By Ian Fleming and John Harley-Mason

Wolff–Kishner reduction of 1-substituted 3,4-dihydro-β-carbolines gives 2-(substituted methyl)-tryptamines. 3,4-Dihydro-β-carboline itself is conveniently prepared by treatment of *N*(b)-thioformyltryptamine with acid.

We have developed a simple synthesis of 2-alkyltryptamines (II), a class of compound which is not well known. 3,4-Dihydro-β-carbolines (I; R = Me and Ph) are readily prepared [1] by the action of phosphorus pentoxide in xylene on the corresponding acyltryptamines. The dihydrocarbolines were reduced to the alkyltryptamines (II) by the Huang-Minlon [2] modification of the Wolff–Kishner reduction, a method previously used in the dihydroisoquinoline series.[3] The products were shown to be 2-alkyltryptamines by analysis, by the presence of the indole chromophore in the ultraviolet spectrum, and by the fact that (II; R = Me and Ph) were different from the other conceivable products, the known tetrahydrocarbolines. Finally, the picrate of 2-methyltryptamine (II; R = H), prepared from (I; R = H), was compared with an authentic sample prepared following the method of Young.[4]



(I)



(II)

In the preparation of the unsubstituted 3,4-dihydro-β-carboline (I; R = H) the conditions used by Späth and Lederer [1] are known to give very poor yields. Using phosphoric acid, better yields have been obtained,[5] and Gupta and Spenser noted the instability of this product. We have found that the best route to 3,4-dihydro-β-carboline is from *N*(b)-thioformyltryptamine [6] which, on brief boiling with acid, gave brownish but otherwise quite pure product. We were also able to recrystallise it from water, thereby obtaining the first analytically pure sample.

Experimental

Infrared spectra were measured for Nujol mulls and ultraviolet spectra for ethanol solutions.

2-Ethyltryptamine (II; R = Me).— 3,4-Dihydro-1-methyl-β-carboline [1] (I; R = Me) (0·35 g.) was refluxed in diethylene glycol (15 ml.) with hydrazine hydrate (0·5 ml.) and potassium hydroxide (1·0 g.) for 1 hr. under nitrogen; the ultraviolet spectrum of the mixture then showed an indole chromophore. The cooled mixture was shaken with ether (50 ml.) and water (50 ml.), and the ether layer was washed with water and dilute hydrochloric acid. The acid layer was made alkaline with sodium hydroxide solution, extracted with ethyl acetate, and the organic layer evaporated, giving 2-ethyltryptamine (330 mg., 92%) as a light brown oil. A portion was shaken with toluene-*p*-sulphonyl chloride in an ether–alkali mixture, to give *2-ethyl*-N(b)-*toluene*-p-*sulphonyltryptamine*, m. p. 157·5—158·5° (from ethanol) (Found: C, 66·4; H, 6·3. $C_{19}H_{22}N_2O_2S$ requires C, 66·6; H, 6·5%), $\nu_{max.}$ 3428m (indole N–H), 3280m (sulphonamide N–H), 1600 and 1568w (Ar), and 1312s and 1160s cm.$^{-1}$ (SO_2), $\lambda_{max.}$ 224, 284, and 291 mμ (ε 45,300, 7500, and 6770).

N-Toluene-p-sulphonyl Derivative of 1,2,3,4-Tetrahydro-1-methyl-β-carboline.— Sublimed 1,2,3,4-tetrahydro-1-methyl-β-carboline [7] (50 mg.) was shaken with ether (2 ml.), toluene-*p*-sulphonyl chloride (35 mg.), and aqueous sodium hydroxide (6 ml.; 10%) for 10 min.; crystals of *1,2,3,4-tetrahydro-1-methyl-2-toluene-p-sulphonyl-β-carboline* separated, m. p. 206—207° (from ethanol) (Found: C, 67·4; H, 6·0; N, 8·5. $C_{19}H_{20}N_2O_2S$ requires C, 67·1; H, 5·9; N, 8·2%), $\nu_{max.}$ 3390m (NH), and 1370 and 1155s cm.$^{-1}$ (SO_2).

2-Benzyltryptamine (II; R = Ph).— 3,4-Dihydro-1-phenyl-β-carboline (I; R = Ph) was prepared by the method of Späth and Lederer.[1] It was also prepared, though in lower yield, by converting *N*(b)-benzoyltryptamine into the thioamide with phosphorus pentasulphide and boiling this crude product with conc. hydrochloric acid. The dihydrocarboline (0·41 g.) was reduced under similar conditions to those used above, and the *product* formed needles, m. p. 160—161·5° (0·295 g., 71%) (from ethanol) (Found: C, 81·4; H, 7·2; N, 11·0. $C_{17}H_{18}N_2$ requires C, 81·6; H, 7·3; N, 11·2%), $\nu_{max.}$ 3320m and 3110s (NH), and 1580 and 1490s cm.$^{-1}$ (Ar), $\lambda_{max.}$ 224, 282, and 291 mμ (ε 41,500, 9900, and 8700), $\lambda_{infl.}$ 278 mμ (ε 9400). This compound was clearly different from a sample of the known 1,2,3,4-tetrahydro-1-phenyl-β-carboline.[8]

3,4-Dihydro-β-carboline (I; R = H).—*N*(b)-Thioformyltryptamine [6] (1·9 g.) was boiled with conc. hydrochloric acid (15 ml.) for 4 min. while hydrogen sulphide was evolved. The hot solution was poured into cold sodium hydroxide solution (120 ml.; 10%) and kept at 0° for 1 hr. 3,4-Dihydro-β-carboline separated as a brown solid (1·58 g., 99%). Recrystallisation from water caused losses but gave an analytical sample of cream needles, m. p. 187° with sintering at 175° (lit.,[1] 182—191° with sintering at 172°) (Found: C, 77·3; H, 6·1; N, 16·2. Calc. for $C_{11}H_{10}N_2$: C, 77·6; H, 5·9; N, 16·5%), $\lambda_{max.}$ 236, 242, and 318 mμ (ε 16,000, 16,000, and 14,500), (in 0·01N-ethanolic HCl) 246 and 359 mμ (ε 11,000 and 22,000).

2-Methyltryptamine (II; R = H).—Crude 3,4-dihydro-β-carboline (360 mg.) was reduced under conditions similar to those used above, to give an oil (360 mg., 99%), 120 mg. of which gave a picrate (220 mg., making the yield of 2-methyltryptamine at least 78%), m. p. 218—220° (decomp.) [lit.,[9] 218—219° (decomp.)], mixed m. p. 218—219° (decomp.). The infrared spectra of the picrates were identical.

University Chemical Laboratory,
Lensfield Road,
Cambridge.

[5/1079 *Received, October 11th*, 1965]

[1] E. Späth and E. Lederer, *Ber.*, 1930, **63**, 2102.
[2] Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487.
[3] J. Gardent, *Bull. Soc. chim. France*, 1960, 114.
[4] E. H. P. Young, *J. Chem. Soc.*, 1958, 3493.
[5] R. N. Gupta and I. D. Spenser, *Canad. J. Chem.*, 1962, **40**, 2049.
[6] A. R. Todd, F. Bergel, Karimullah, and R. Keller, *J. Chem. Soc.*, 1937, 361.
[7] S. Akabori and K. Saito, *Ber.*, 1930, **63**, 2245.
[8] T. Hoshino and Y. Kotake, *Annalen*, 1935, **516**, 76.
[9] W. E. Noland and R. F. Lange, *J. Amer. Chem. Soc.*, 1959, **81**, 1203.