Synthesis of 3-(2-Acetylaminoethyl)-6-hydroxy-5-methoxyindole (6-Hydroxymelatonin)

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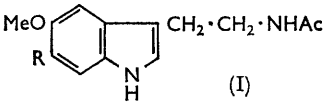
The title compound was prepared from vanillin by conventional methods *via* 6-benzyloxy-5-methoxyindole.

MELATONIN (I; R = H) is a hormone present in the pineal gland of certain mammals which assists in controlling the quantity and distribution of melanin in the skin.[1] It exerts a depressant (contracting) action on the melanocytes resulting in a lightening effect in tadpoles, frogs, fish, toads, and hens, although not on humans, by aggregation of the melanin granules. Two groups of workers [2,3] have shown that melatonin is rapidly metabolised to give the sulphate ester and the glucuronide of a hydroxymelatonin, and a third substance. The latter was not obtained in crystalline form but was shown to be



(I)

chromatographically identical with the hydrolysis product of the sulphate ester,[4] and its characterisation as the 6-hydroxy-derivative was based on colour tests, and on *in vitro* experiments with an enzyme known to hydroxylate indoles in the 6-position. The object of the present work was to synthesise 6-hydroxymelatonin for comparison with these metabolites.

6-Benzyloxy-5-methoxyindole (II) was first synthesised by the Nenitzescu method from vanillin and a very similar preparation has recently been described by Julia.[5]

Initial attempts to introduce the ethylamine side chain into the indole nucleus with oxalyl chloride, followed by ammonia [6] were unsuccessful owing to difficulties in effecting complete reduction of the glyoxylamide with lithium aluminium hydride. However, formylation followed by condensation with nitromethane [7] gave the 3-(2-nitrovinyl)indole (IV) in good yield, and the latter on reduction and acetylation afforded the acetyltryptamine (V).

Removal of the benzyl group was accomplished by hydrogenation over palladium charcoal to give the 6-hydroxymelatonin (I; R = OH) which was purified

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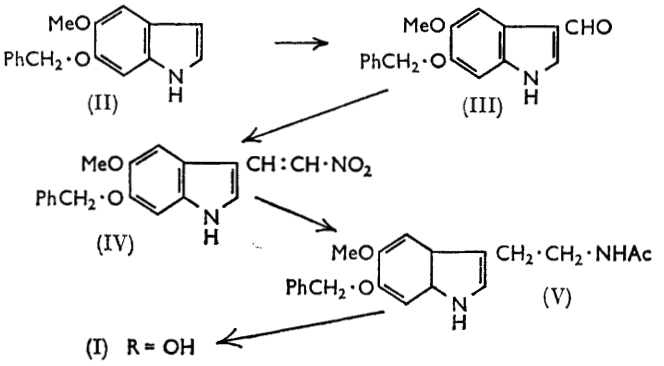
[1] A. B. Lerner, J. D. Case, Y. Takahashi, T. H. Lee, and W. Mori, *J. Amer. Chem. Soc.*, 1958, **80**, 2587; A. B. Lerner, J. D. Case, and Y. Takahashi, *J. Biol. Chem.*, 1960, **235**, 1192.
[2] I. J. Kopin, C. M. B. Pare, J. Axelrod, and H. Weisbach, *Biochim. Biophys. Acta*, 1960, **40**, 377; *J. Biol. Chem.*, 1961, **236**. 3072.
[3] S. Kveder and W. M. McIsaac, *J. Biol. Chem.*, 1961 **236**, 3214.
[4] J. Axelrod and H. Weisbach, *J. Biol. Chem.*, 1961, **236**, 211.
[5] M. Julia, P. Manoury, and C. Voillaume, *Bull. Soc. Chim.*, 1965, 1417.
[6] Cf. M. E. Speeter and W. C. Anthony, *J. Amer. Chem. Soc.*, 1954, **76**, 6209.
[7] Cf. E. H. P. Young, *J. Chem. Soc.*, 1958, 3493.

by sublimation. Its structure was confirmed by elemental analysis, and spectroscopic methods; the R_F value by paper chromatography agreed well with literature values.[2,8]

Since this work was completed, Taborsky *et al.*[8] have also described a synthesis of 6-hydroxymelatonin. Their



product was isolated and characterised as the picrate, and the crude free base liberated from the latter was shown to be chromatographically identical with the natural metabolite.

EXPERIMENTAL

Melting points are uncorrected. Nuclear magnetic resonance spectra were determined with a Varian A-60 spectrometer, and mass spectra with an A.E.I. MS 9 spectrometer.

6-*Benzyloxy*-3-*formyl*-5-*methoxyindole*.—Phosphorus oxychloride (5 ml.) was slowly added at 15—20° to dry dimethylformamide (17 ml.). and 6-benzyloxy-5-methoxyindole (10 g.) (m. p. 151°; lit.,[5] 146°) in dimethylformamide (10 ml.) was then added to this mixture at 20—30°. The dark red solution was heated at 35—40° for 45 min. and then poured into ice–water (100 ml.), and basified with 20% aqueous sodium hydroxide. After heating to reflux, and boiling for 3 min., the solution was cooled and the fawn precipitate filtered off and washed with water. Recrystallisation from alcohol gave the *formylindole* (8·6 g., 79%) as needles, m. p. 207° (Found: C, 72·5; H, 5·4; N, 4·6. $C_{17}H_{15}NO_3$ requires C, 72·6; H, 5·4; N, 5·0%).

6-*Benzyloxy*-5-*methoxy*-3-(2-*nitrovinyl*)*indole*.— The formylindole (2 g.), ammonium acetate (0·6 g.), and nitromethane (20 ml.) were boiled under reflux for 3·5 hr. The mixture was set aside overnight at 0°, and the orange precipitate which formed was filtered off, washed with water, and recrystallised from ethanol to give the *nitrovinylindole* (1·6 g., 69%) as vermilion needles, m. p. 191° (decomp.) (Found: C, 66·3; H, 4·95; N, 8·6. $C_{18}H_{16}N_2O_4$ requires C, 66·7; H, 5·0; N, 8·6%).

3-(N-*Acetylaminoethyl*)-6-*benzyloxy*-5-*methoxyindole* (6-*Benzyloxymelatonin*).—The nitrovinylindole (3·3 g.) in dry tetrahydrofuran was added slowly dropwise to a hot suspension of lithium aluminium hydride (2 g.) in dry tetrahydrofuran (50 ml.) and the mixture was then boiled under reflux for 4 hr. Unchanged lithium aluminium hydride was decomposed by the cautious addition of saturated sodium potassium tartrate to the cooled solution, and the product extracted with several portions of ether and dried (K_2CO_3). After evaporation of the ether the residual brown oily tryptamine was taken up in acetic anhydride (20 ml.) and pyridine (0·2 ml.) and kept overnight under nitrogen. The solution was then poured into water (100 ml.) sodium carbonate (20 g.) was added, and the mixture cooled to 0°. The yellow oily precipitate slowly solidified, and was filtered off, washed with water, dried, and crystallised from benzene to give 6-benzyloxymelatonin (2·2 g., 64%) as small prisms, m. p. 148° (lit.,[8] m. p. 151—152°) (Found: C, 71·0; H, 6·5; N, 8·3. Calc. for $C_{20}H_{22}N_2O_3$: C, 71·0; H, 6·55; N, 8·3%), n.m.r. spectrum (in $CDCl_3$): τ 1·7 (indole-N*H*), 2·55, 4·80 (6-$C_6H_5CH_2O$), 2·85 (7-*H*), 3·07 (2,4-*H*), 6·05 (5-CH_3O, 6·40m, 7·05m, 4·3, 8·08 ($CH_2CH_2NHCOCH_3$). Mass spectrum; *m/e* (%): 338 (M^+) (22), 279 (M — CH_3CONH_2) (4), 266 (M — $CH_2NHCOCH_3$) (5), 247 (M — $C_6H_5CH_2$) (100), 205 (M — $C_6H_5CH_2$–CH_2CO) (3), 188 (27), 176 (20), 160 (12), 146 (8), 91 (26).

3-(N-*Acetylaminoethyl*)-6-*hydroxy*-5-*methoxyindole* (6-*Hydroxymelatonin*).—The benzyloxymelatonin (0·30 g.) in methanol (100 ml.) and triethylamine (0·05 ml.) was hydrogenated at 1 atmos. and 20° over palladium–charcoal (150 mg., 10%). After removal of catalyst and solvent, the residual solid was sublimed at 170°/0·003 mm. to give 6-*hydroxymelatonin* (0·11 g., 55%) as needles, m. p. 175° (Found: C, 63·1; H, 6·8; N, 11·1. $C_{13}H_{16}N_2O_3$ requires C, 62·9; H, 6·5; N, 11·3%). Picrate, red needles, m. p. 146—147° (lit.,[8] m. p. 145—146°); n.m.r. spectrum (in NaOD): τ 2·95 (7-*H*), 3·15 (4-*H*), 3·30 (2-*H*), 6·17 (5-CH_3O), 6·65m, 7·15m, 8·10 ($CH_2CH_2NHCOCH_3$). R_F in n-butanol–acetic acid–water (4 : 1 : 1), 0·72 (lit.,[2,8] 0·67, 0·70) (blue colour with Ehrlichs reagent). Mass spectrum, *m/e* (%): 248 (M^+) (30); 205 (M — CH_3CO) (5); 189 (M — CH_3CONH_2) (100); 176 (M — $CH_2NHCOCH_3$) (100); 174 (36); 161 (66); 148 (6); 146 (10); 133 (17). *m**: 160 (189 ⟶ 174); 147 (176 ⟶ 161); 144 (248 ⟶ 189) 125 (248 ⟶ 176); 110 (161 ⟶ 133).

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[8] R. G. Taborsky, P. Delvigs, and I. H. Page, *J. Medicin. Chem.*, 1965, **8**, 855.