560. *A Convenient Alternative Synthesis of 5-Hydroxytryptamine.**

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A novel 7-stage synthesis of 5-hydroxytryptamine (I) from readily accessible starting materials, suitable for comparatively large-scale working, is described. *p*-Benzyloxybenzenediazonium chloride is condensed with ethyl α-acetyl-δ-phthalimidovalerate and the product is cyclised to ethyl 5-benzyloxy-3-2′-phthalimidoethylindole-2-carboxylate (II; R = O·CH_2Ph, R′ = CO_2Et). Relatively standard reactions lead from this ester to 5-hydroxytryptamine, which is isolated as its creatinine sulphate complex in 18·5% overall yield.

Several syntheses of 5-hydroxytryptamine (I) have been described.[1] In most of these the aminoethyl side chain is built up stepwise from a 5-hydroxyindole in which the hydroxy-group is protected and the 3-position unsubstituted. In such syntheses, particularly those of Hamlin and Fischer [1a] and Ash and Wragg,[1b] yields at the terminal stages are variable, so we sought a synthesis in which the side chain in a protected form was introduced at an early stage, and for which the starting materials required were readily available.

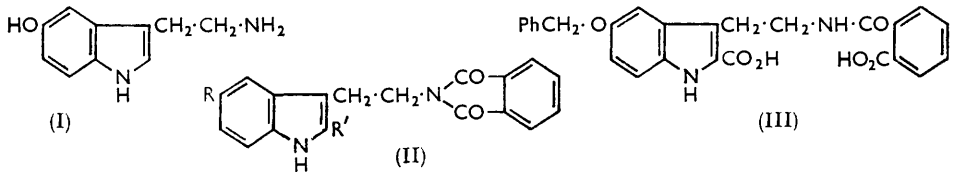
Apart from Harley-Mason and Jackson's synthesis,[1c] which is described on a scale giving only 0·63 g. of product, earlier syntheses [1d] along this line have involved relatively inaccessible intermediates or given poor yields. By adapting a synthesis [2] of ethyl 3-2′-phthalimidoethylindole-2-carboxylate (II; R = H, R′ = CO_2Et), we have obtained the 5-benzyloxy-analogue (II; R = O·CH_2Ph, R′ = CO_2Et) which proved a convenient intermediate, and could be made from readily accessible starting materials.

* Part of this work is the subject of B.P. Appl. 33,140/55.

[1] (*a*) Hamlin and Fischer, *J. Amer. Chem. Soc.*, 1951, **73**, 5007; (*b*) Ash and Wragg, *J.*, 1958, 3887, and the references cited therein; (*c*) Harley-Mason and Jackson, *J.*, 1954, 1165; (*d*) Bernini, *Ann. Chim.* (*Italy*), 1953, **43**, 559; Vejdelek and Tuma, *Cesk. Farm.*, 1955, **4**, 510; Abramovitch and Shapiro, *J.*, 1956, 4589; Sueros, Span.P., 227,606; *Chem. Abs.*, 1958, **52**, 2923; (*e*) Young, *J.*, 1958, 3493; Pietra. *Il Farmaco*, Ed. Sc., 1958, **13**, 75; Nenitzescu and Raileanu, *Chem. Ber.*, 1958, **91**, 1141.

[2] Keimatsu, Sugasawa, and Kasuya, *J. Pharm. Soc. Japan*, 1928, **48**, 762.

Ethyl α-acetyl-δ-phthalimidovalerate, obtained [2] in 96% yield from 3-phthalimidopropyl bromide and ethyl acetoacetate, coupled smoothly with *p*-benzyloxybenzenediazonium chloride [1b] in the presence of sodium acetate, and the resulting crude phenylhydrazone (>90% yield) was cyclised by saturating its boiling ethanolic solution with



hydrogen chloride (Method A) to give ethyl 5-benzyloxy-3-2′-phthalimidoethylindole-2-carboxylate (II; R = O·CH_2Ph, R′ = CO_2Et) in 51—58% overall yield on 0·75-mole scale. Alkaline hydrolysis of this ester gave a 98% yield of the diacid (III) which at 240—250° reproducibly underwent concomitant decarboxylation and dehydration to give 5-benzyloxy-3-2′-phthalimidoethylindole (II; R = O·CH_2Ph, R′ = H) in 84% yield on a 100-g. scale. Contrary to experience in an analogous preparation of 5-benzyloxyindole,[1b] the use of copper chromite in boiling quinoline for this decarboxylation was disadvantageous.

5-Benzyloxy-3-2′-phthalimidoethylindole was converted smoothly into 5-benzyloxytryptamine (isolated as the neutral sulphate) in 68—73% yield by an excess of hydrazine hydrate in boiling ethanol. Reductive debenzylation of the sulphate in the presence of palladium–charcoal gave crude 5-hydroxytryptamine, isolated as its monohydrated complex (m. p. 217—219°) with creatinine sulphate [3] in over 90% yield. Recrystallisation from aqueous ethanol gave analytically pure material, m. p. 219—221° (decomp.), with the correct ultraviolet spectrum.[4]

Experimental

M. p.s determined in evacuated capillaries are designated m. p. (e.c.).

Ethyl 5-Benzyloxy-3-2′-phthalimidoethylindole-2-carboxylate.—Method A. *p*-Benzyloxyaniline (150 g., 0·75 mole), dissolved in boiling ethanol (300 ml.), was treated as rapidly as possible with a mixture of concentrated hydrochloric acid (300 ml.) and water (450 ml.) followed by ice (600 g.). To this stirred suspension was added sodium nitrite (68 g., 0·975 mole) in water (150 ml.) during about 20 min. and the suspension was stirred for a further 40 min. at 5—10° (cooling). The solution was then treated with charcoal and filtered.

Ethyl α-acetyl-δ-phthalimidovalerate (237 g., 0·75 mole) was dissolved in warm ethanol (1100 ml.), and to the cooled solution was added anhydrous sodium acetate (615 g.) and ice (500 g.). To this stirred mixture at 5° was added rapidly the filtered solution of diazotised *p*-benzyloxyaniline described above, and the whole was stirred while being allowed to attain room temperature. The red viscous oil which separated was extracted with benzene (3 × 450 ml.), and the extracts were dried (Na_2SO_4) and evaporated. A solution of the crude phenylhydrazone in dry ethanol (1600 ml.) was saturated at the b. p. with a rapid stream of hydrogen chloride, then cooled in ice. The solid was filtered off, washed with ice-cold ethanol (2 × 400 ml.) and with water (2 × 400 ml.), and dried at 80°, to give the required *ester* (178 g., 51%) as needles, m. p. 188—190° (Found: C, 72·0; H, 5·15; N, 6·0. $C_{28}H_{24}N_2O_5$ requires C, 71·9; H, 5·1; N, 6·0%).

Method B. To secure reproducible results on increasing the scale of this preparation to 5 moles, we used the technique [1b] found optimum for the preparation of the corresponding 3-unsubstituted 5-benzyloxyindole-2-carboxylic ester. This involved addition of ethanol (3 vol.), saturated with hydrogen chloride at 0°, to a cold ethanolic solution (1 vol.) of the crude hydrazone; an exothermic reaction then occurred. While this method gave a similar yield (54—58%) to method A, the ester prepared *via* method B had m. p. 186—188°; its infrared and ultraviolet spectra were nevertheless identical with those of the material (m. p. 188—190°) prepared by method A. However, the diacid (III) obtained by hydrolysis of the lower-melting ester gave a low yield (45—48%) of poor quality product on dehydration and decarboxylation

[3] Speeter, Heinzelmann, and Weisblat, *J. Amer. Chem. Soc.*, 1951, **73**, 5514.
[4] Rapport, *J. Biol. Chem.*, 1949, **180**, 961.

by the one-step procedure described below; this diacid could nevertheless be used satisfactorily by carrying out the dehydration [5] and decarboxylation separately as described in the two-step procedure below, provided that the decarboxylation was restricted to 20-g. batches.

5-Benzyloxy-3-(2-o-carboxybenzamidoethyl)indole-2-carboxylic Acid (III).—Ethyl 5-benzyloxy-3-2′-phthalimidoethylindole-2-carboxylate (135 g., 0·288 mole) was suspended in ethanol (500 ml.). Potassium hydroxide (158 g., 2·8 moles) in water (1·8 l.) was added, and the mixture was warmed on the steam-bath until dissolution was complete (15 min.) and then refluxed for 1·5 hr. Most of the ethanol was then distilled off. The residue was cooled at 10°, acidified with 4N-hydrochloric acid, and set aside. The solid which separated was filtered off and washed with water, to give the almost colourless acid (129 g., 98%), m. p. 230—235° (decomp.) after dehydration at about 200°. Satisfactory analytical figures could not be obtained for this compound.

5-Benzyloxy-3-2′-phthalimidoethylindole.—(a) *One-step procedure.* 5-Benzyloxy-3-(2-*o*-carboxybenzamidoethyl)indole-2-carboxylic acid (100 g., 0·218 mole) was melted and then stirred at 250°, the evolved carbon dioxide being removed by a stream of nitrogen. Decarboxylation was complete in about 1·5 hr. The residue, which on cooling solidified to a glass, was dissolved in hot ethyl methyl ketone (about 1 l.) and a small quantity of insoluble material was removed. The filtrate was concentrated to about 300 ml. and hot ethanol (900 ml.) was added. The solid which crystallised on cooling was filtered off and washed with cold ethanol (100 ml.). A second crop was obtained by concentration. The two crops were combined and suspended in cold N-sodium hydroxide; the solid was filtered off and washed with water and then with cold ethanol. The *phthalimido-compound* (73 g., 84%) was obtained as pale yellow prisms, m. p. 179—181° (Found: C, 75·9; H, 5·16; N, 7·0. $C_{25}H_{20}N_2O_3$ requires C, 75·8; H, 5·05; N, 7·05%).

(b) *Two-step procedure.* 5-Benzyloxy-3-(2-*o*-carboxybenzamidoethyl)indole-2-carboxylic acid (626 g.) was refluxed with acetic acid (6·5 l.) for 5 hr. and the hot mixture filtered from a little undissolved material. The product was filtered off at 20° and recrystallised from acetic acid (5·5 l.). The product was washed by resuspension in cold water (2 × 4 l.) and dried *in vacuo*, giving *5-benzyloxy-3-2′-phthalimidoethylindole-2-carboxylic acid* (423 g., 71%), m. p. 250—251° (decomp.) (Found: C, 70·8; H, 4·8; N, 6·4. $C_{26}H_{20}N_2O_5$ requires C, 70·9; H, 4·5; N, 6·4%).

5-Benzyloxy-3-2′-phthalimidoethylindole-2-carboxylic acid (20 g.) was decarboxylated at 260—270° under nitrogen during 45 min. The cold residual glass was dissolved in boiling ethyl methyl ketone (154 ml.), and the hot solution filtered, concentrated to *ca.* 60 ml., and treated with hot ethanol (192 ml.). The solid which separated was then treated as previously described, to give 17 g. (70%) of product, m. p. 181—182°.

5-Benzyloxytryptamine Sulphate.—5-Benzyloxy-3-2′-phthalimidoethylindole (32·5 g., 0·082 mole), 80% hydrazine hydrate (15·5 ml., 0·246 mole), and ethanol (850 ml.) were refluxed together for 2·5 hr. The solution was evaporated on a steam-bath, at reduced pressure in the final stages. 2N-Sodium hydroxide (250 ml.) was added to the warm residue, followed by ether (400 ml.), and the whole was cooled in ice until solid separated. After removal of this solid by filtration through " Hyflo," the ethereal layer was separated and washed with water until free from alkali. The base was extracted into N-acetic acid (150 ml.) and treated dropwise with an excess of concentrated sulphuric acid. The crude sulphate was washed with ice-water until free from acid and recrystallised (charcoal) from water. 5-Benzyloxytryptamine sulphate monohydrate (20 g., 73%) was obtained as almost colourless plates, m. p. (e.c.) 187—189° (Found: C, 61·3; H, 6·5; N, 8·3; S, 4·95. Calc. for $C_{17}H_{18}N_2O,0{\cdot}5H_2SO_4,H_2O$: C, 61·3; H, 6·3; N, 8·4; S, 4·8%).

5-Hydroxytryptamine (I).—Creatinine sulphate was prepared by dissolving ash-free creatinine (22·6 g.) in warm 2N-sulphuric acid (Analytical Reagent Grade, 100 ml.). The solution was clarified by filtration and poured into acetone (2 l.). The crude creatinine sulphate which separated was recrystallised (charcoal) from a mixture of ethanol (400 ml.) and water (160 ml.) to give ash-free creatinine sulphate hemihydrate (27·1 g., 80%) as prisms, m. p. (e.c.) 259—260° (decomp.) (Found: C, 28·25; H, 5·4; S, 9·2. Calc. for $C_4H_7N_3O,0{\cdot}5H_2SO_4,0{\cdot}5H_2O$: C, 28·05; H, 5·25; S, 9·4%). A suspension of 5-benzyloxytryptamine sulphate monohydrate (11·6 g., 0·035 mole) and palladised charcoal (from 0·42 g. of palladium chloride) in ethanol (180 ml.) and water (120 ml.) was hydrogenated at room temperature and 1 atm. (uptake 117%). The

[5] A. S. F. Ash, personal communication.

catalyst and charcoal were removed by filtration through "Hyflo" and the filtrate was evaporated to a thick syrup under reduced pressure in an atmosphere of nitrogen. The syrup was dissolved in a solution of ash-free creatinine sulphate hemihydrate (5·95 g., 0·035 mole) in hot water (35 ml.) and to this solution was added hot acetone (250 ml.). The solid which separated was filtered off, washed with acetone, and dried at 80°, to give crude 5-hydroxytryptamine creatinine sulphate (13 g., 93%), m. p. (e.c.) 217—219°. This material was combined with two similar batches (total 35·8 g.), and the whole recrystallised twice by dissolution in hot water (300 ml.), filtration (charcoal), and addition of ethanol (200 ml.). 5-Hydroxytryptamine creatinine sulphate monohydrate (25·5 g., 67%) crystallised as almost colourless prisms, m. p. (e.c.) 219—221° (decomp.) (Found: C, 41·5; H, 5·7; S, 8·2, 7·9; H_2O, 4·4, 4·8. Calc. for $C_{10}H_{12}N_2O,C_4H_7N_3O,H_2SO_4,H_2O$: C, 41·5; H, 5·7; S, 7·9; H_2O, 4·45%), $\lambda_{max.}$ 275 mμ (ε 5820) at pH 7 [lit., $\lambda_{max.}$ 275 mμ (ε 5800),[4] m. p. 214—216° (Kofler) [3]].

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