768. *The Synthesis of 5-Iodotryptophan and Some Derivatives.*

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The synthesis of 5-iodotryptophan through 5-iodogramine is described.

DURING an investigation of antagonists of serotonin (5-hydroxytryptamine) consideration was given to the synthesis of 5-substituted indole and tryptophan derivatives with special emphasis on halogens. Several of these compounds have been reported, and Rydon and Tweddle [1] have described the four *Bz*-chloro-indoles and -tryptophans.

It was decided initially to attempt the synthesis of 5-iodotryptophan, as it might be possible to incorparate iodine-131 in a synthesis of the amino-acid later.

Preliminary experiments on ethyl *p*-iodophenylpyruvate hydrazone were unsatisfactory so attention was directed to the Reissert synthesis of indoles. 5-Iodo-2-nitrotoluene was condensed with ethyl oxalate, and the resulting potassium 2-iodo-5-nitrophenylpyruvate was reduced and cyclised to 5-iodoindole-2-carboxylic acid with ammoniacal ferrous hydroxide. Decarboxylation was accomplished by first removing all traces of sulphate [1] and then heating with copper chromite in quinoline. Yields of 5-iodoindole were consistently good.

Condensation of the indole with dimethylamine and formaldehyde in acetic acid yielded 5-iodogramine; this was condensed with diethyl formamidomalonate,[2] and the condensate

[1] Rydon and Tweddle, *J.*, 1955, 3499.
[2] Galat, *J. Amer. Chem. Soc.*, 1947, **69**, 965.

smoothly hydrolysed and decarboxylated to the 5-iodotryptophan. Condensation with acetaldehyde gave the tetrahydro-β-carbolinecarboxylic acid, which gave a typical " carboline " blue with ferric chloride in concentrated sulphuric acid and was oxidised to 8-iodo-2-methyl-β-carboline by acidic dichromate.

Biological tests for possible anti-serotonin effects will be published elsewhere, but it is interesting to note that the iodo-amino-acid has no significant effect on the oxygen consumption or on body weight of guinea-pigs.

Experimental

All m. p.s are uncorrected.

5-Iodo-2-nitrotoluene.—This was prepared from 5-amino-2-nitrotoluene [3] by Artmann's method.[4]

5-Iodo-2-nitrophenylpyruvic Acid and 5-Iodoindole-2-carboxylic Acid.—Preliminary experiments indicated that the best procedure for the formation of the indole was to reduce the alkaline extract of the Reissert condensation without isolation of the 2-nitrophenylpyruvic acid.[5] Ethyl oxalate (30 g.) in benzene (100 ml.) was added (15 min.) below 15° to potassium ethoxide solution [from potassium (7·5 g.), dry ethanol (75 ml.) and benzene (350 ml.)], followed by 5-iodo-2-nitrotoluene (50 g.) in benzene (100 ml.). The solution was refluxed for 0·5 hr. and while still hot extracted with potassium hydroxide solution (5% w/v; 750 ml.) and with water (250 ml.). 5-Iodo-2-nitrotoluene (25 g.) was recovered from the benzene.

A part (100 ml.) of the alkaline extract was acidified to pH 1 (10N-hydrochloric acid at 0°) and extracted with ether (100 ml.). The ether was extracted with sodium hydroxide (5% w/v; 100 ml.), clarified (charcoal; 80°), cooled to 0°, and acidified as before. The *acid* formed sandy-yellow needles (2 g., 32% based on 5 g. of nitrotoluene), m. p. 134° (from benzene) (Found: C, 32·7; H, 1·9; N, 4·4. $C_9H_6O_5NI$ requires C, 32·2; H, 1·8; N, 4·1%).

The remainder (900 ml.) of the alkaline extract was added with stirring to a suspension of alkaline ferrous hydroxide [heptahydrate (150 g.), water (750 ml.), and ammonia (*d* 0·88; 90 ml.)]. The mixture was boiled (10 min.) and filtered, and the filtrate boiled with dilute ammonia solution (5% v/v; 3 × 500 ml.). The combined filtrates were cooled and acidified to pH 1 (10N-hydrochloric acid), and the precipitate extracted with ether. The ether extracts were washed with water, barium chloride solution (0·5% w/v; 250 ml.), and again with water. On concentration the *indole* separated (15 g., 30% based on 45 g. of nitrotoluene); it formed hexagons, m. p. 248—250° (decomp.), from ethanol (Found: C, 37·5; H, 2·2; N, 5·2. $C_9H_6O_2NI$ requires C, 37·6; H, 2·1; N, 4·9%).

5-Iodoindole.—The crude, dry sulphate-free indole acid (20 g.) was ground with copper chromite [6] (2·0 g.), and the mixture in redistilled quinoline (50 ml.) gently refluxed for 2·0 hr. The mixture was poured into water, acidified (2N-hydrochloric acid), and extracted with ether. The ethereal extract was washed successively with 2N-hydrochloric acid, 2N-sodium hydrogen carbonate, and distilled water, dried (Na_2SO_4), and evaporated to give the crude indole (6·5 g., 64%) which was pure enough for preparation of the gramine. A portion twice recrystallized from aqueous methanol (charcoal) formed silvery plates, m. p. 99° (Found: C, 39·4; H, 2·5; N, 5·8. C_8H_6NI requires C, 39·5; H, 2·5; N, 5·8%).

3-Dimethylaminomethyl-5-iodoindole (*5-Iodogramine*).—Acetic acid (0·6 ml.) was added at 0—4° to a solution of dimethylamine (26% w/v; 0·7 ml.); this was followed by formaldehyde (36% w/v; 0·28 ml.), and the mixture poured on 5-iodoindole (1·22 g.). After 6 hr. at room temperature the solution was poured into sodium hydroxide (10 ml.; 2·5 N) and extracted with ether. The extract was washed with dilute alkali and then water, and extracted with 2N-hydrochloric acid. The acid was clarified (charcoal) and treated with a slight excess of dilute ammonia solution (10% v/v); *3-dimethylaminomethyl-5-iodoindole* was precipitated (0·72 g., 48%), and formed rectangles, m. p. 159°, from aqueous methanol (Found: C, 43·2; H, 4·4; N, 8·7. $C_{11}H_{13}N_2I$ requires C, 44·0; H, 4·3; N, 9·3%).

Diethyl α-Formamido-α-(5-iodo-3-indolylmethyl)malonate.—A mixture of 5-iodogramine

[3] Cohen and Dakin, *J.*, 1910, 321.
[4] Artmann, *Monatsh.*, 1905, **26**, 1091.
[5] Cf. Allen, Brunton, and Suschitzky, *J.*, 1955, 1283.
[6] Vogel, " Practical Organic Chemistry," Longmans, Green & Co., London, 2nd edn., 1951, p. 808.

(1·64 g.) and diethyl formamidomalonate (1·5 g.) was added to boiling toluene (5·0 ml.) containing sodium hydroxide (0·2 g.), and the mixture gently refluxed (0·5 hr.). The cooled mixture was treated with light petroleum (5 ml.; b. p. 40—60°), the solvents were decanted off, and ice-water (10 ml.) and ether (10 ml.) added to the residue. The ether extract was washed with water, dried (Na_2SO_4), and concentrated to yield *diethyl α-formamido-α-(5-iodo-3-indolylmethyl)malonate* (1·6 g., 64%), which formed stout rhombs, m. p. 156°, from aqueous methanol (Found: C, 45·4; H, 4·3; N, 6·2. $C_{17}H_{19}O_5N_2I$ requires C, 44·5; H, 4·1; N, 6·1%).

Diethyl α-Acetamido-α-(5-iodo-3-indolylmethyl)malonate.—Diethyl acetamidomalonate (0·7 g.) was added with shaking and cooling (ice) to sodium ethoxide [sodium (0·6 g.) and anhydrous ethanol (5·0 ml.)]. This was followed by 5-iodogramine (0·72 g.) and dimethyl sulphate (0·44 g.). The temperature was maintained at 40° for 6·0 hr. then at room temperature for 18 hr. Thereafter water (20 ml.) was added. *Diethyl α-acetamido-α-(5-iodo-3-indolylmethyl)malonate* crystallised (0·93 g., 82%), and formed cubes, m. p. 160°, from aqueous methanol (Found: C, 45·3; H, 4·3; N, 5·6. $C_{18}H_{21}O_5N_2I$ requires C, 45·7; H, 4·4; N, 5·9%).

5-Iodotryptophan.—Diethyl α-formamido-α-(5-iodo-2-indolylmethyl)malonate (1·0 g.), aqueous sodium hydroxide (2·5N; 8·0 ml.), and ethanol (2·0 ml.) were refluxed for 0·5 hr., the ethanol then distilled off, and refluxing continued for 5·0 hr. (charcoal). Acetic acid (1·0 ml.) was added and the solution refluxed for 1·0 hr. and then set aside overnight. 5-Iodotryptophan (0·55 g., 76%) formed rosettes from dilute ammonia solution or leaflets from glacial acetic acid that darkened at 250° and had m. p. 264° (Found: C, 38·8; H, 4·1; N, 7·6. $C_{11}H_{11}O_2N_2I,2H_2O$ requires C, 36·0; H, 4·1; N, 7·6%).

On mixing a dilute solution of the amino-acid with glyoxylic acid and underlayering it with concentrated sulphuric acid, an intense purple upper band and a blue-green lower band were formed. With dilute formaldehyde underlayered with sulphuric acid, an upper yellow orange band and a faint purple lower band were formed. A trace of ferric chloride made the bands almost black.

Attempted hydrolysis and decarboxylation of the acetamido-compound by refluxing it in 1·5N-hydrochloric acid were unsatisfactory and an increase in the strength of the acid caused marked decomposition.

2 : 3 : 4 : 5-Tetrahydro-8-iodo-2-methyl-β-carboline-4-carboxylic Acid.—5-Iodotryptophan (0·1 g.) in sulphuric acid (0·1N; 10 ml.) and aqueous acetaldehyde (10% w/v; 2·5 ml.) were maintained at 40° for 18 hr. The mixture was boiled, clarified (charcoal), and made alkaline (10% w/v ammonia). The *carbolinecarboxylic acid* (0·08 g., 75%) formed blunt, colourless rods, m. p. 277°, from dilute ammonia, and gave a typical " carboline blue " colour [7] with concentrated sulphuric acid and a trace of ferric chloride (Found: C, 40·7; H, 4·3; N, 7·3. $C_{13}H_{13}O_2N_2I,2H_2O$ requires C, 39·7; H, 4·3; N, 7·1%).

8-Iodo-2-methyl-β-carboline.—The clarified solution from the reaction of 5-iodotryptophan, acid, and acetaldehyde (previous experiment) was boiled with potassium dichromate (10 w/v; 5·0 ml.) and acetic acid (1·0 ml.) for 3 min. Aqueous sodium sulphite (saturated; 5·0 ml.) and aqueous sodium carbonate (saturated; 5·0 ml.) were added, and the mixture extracted with ether. The dried (Na_2SO_4) extract yielded pale brown crystals (40 mg.; 43%) that formed very pale brown tablets, m. p. 216°, from methanol (Found: C, 46·6; H, 2·9; N, 9·2%. $C_{12}H_9N_2I$ requires C, 46·7; H, 2·9; N, 9·1%).

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[7] Cf. Miller, Harvey, and Robson, *J.*, 1940, 153; Marchant and Harvey, *J.*, 1951, 1808.