359. *The Synthesis of* r-α-*Methylamino-β-3-indolylpropionic Acid.**

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5-(3′-Indolylmethyl)-1-methylhydantoin can be readily obtained by condensing indole-3-aldehyde and 1-methylhydantoin in piperidine, suspending the product in pyridine, and reducing it with hydrogen sulphide. The reduced hydantoin is much more stable than tryptophan hydantoin towards boiling solutions of alkali. The method described, which dispenses with the usual precipitation involving mercuric sulphate, gives the pure amino-acid in good yield. An improved procedure for the preparation of 1-methylhydantoin from glycine is detailed.

For an investigation into the nature of certain colour reactions used for the detection of tryptophan (forthcoming paper), α-methylamino-β-3-indolylpropionic acid and a number of its derivatives were required. The mother compound has already been synthesised by Gordon and Jackson (*J. Biol. Chem.*, 1935, **110**, 151), but when their method is modified in accordance with procedures elaborated by Boyd and Robson (*Biochem. J.*, 1935, **29**, 542, 546, 555, 2256), considerable improvement in the results is effected. In carrying out the synthesis on these lines, we obtained certain data, recorded below, at variance with those in the literature.

The synthesis utilises indole-3-aldehyde and 1-methylhydantoin (cf. Gordon and Jackson, *loc. cit.*). These substances readily condense in the presence of piperidine and 5-(3′-*indolal*)-1-*methylhydantoin* can be isolated in excellent yield and purity. Reduction of this compound by means of hydrogen sulphide in pyridine followed. A variation in the procedure of Boyd and Robson had to be made in the final stage of hydrolysis, since it was found that 5-(3′-indolylmethyl)-1-methylhydantoin is much more stable towards the action of hot alkali than are the ordinary hydantoins. Gordon and Jackson (*loc. cit.*), on boiling this compound with a concentrated solution of barium hydroxide for seven hours, obtained a 59% yield of the amino-acid. When the period of hydrolysis is trebled (cf. Boon and Robson, *Biochem. J.*, 1935, **29**, 2684), the yield of amino-acid obtained approximates to the theoretical figure and in addition the use of the mercuric sulphate reagent for the purpose of purifying the product becomes unnecessary.

The 1-methylhydantoin was prepared in the usual way (Weitzner, *Annalen*, 1908, **362**, 125) from *N*-methylglycine, which was synthesised, but not isolated, according to an abbreviated method based on the findings of Cocker and Lapworth (J., 1931, 1894) and of Cocker (J., 1937, 1693).

Experimental.

N-Benzenesulphonylsarcosine.—To a warmed solution of glycine (19 g.) in 2N-sodium hydroxide (375 ml.; 3 mols.), benzenesulphonyl chloride (40 ml.; 1¼ mols.) was added with shaking. Solid sodium hydroxide (25 g.; 2·5 mols.) was then dissolved in the solution, the whole cooled, and methyl sulphate (48 ml.; 2 mols.) added in small portions. The solution, on acidification to Congo-red with concentrated hydrochloric acid, deposited *N*-benzenesulphonylsarcosine. This was collected after an hour, washed with a little cold water, and dried at 110°. The yield was 50 g. (87·5% of the theoretical). Recrystallisation was effected by dissolving the product in the minimum quantity of 50% alcohol, adding boiling water (500 ml.), and leaving the solution to cool overnight.

1-*Methylhydantoin.*—*N*-Benzenesulphonylsarcosine (40 g.) was refluxed with 50% sulphuric acid (95 ml.) for 4—5 hours, the solid dissolving after ½ hour. To the warm solution was added hydrated magnesium sulphate (38 g.; 1¾ mols.) in water (40 ml.); the mixture was agitated

* It is desirable that attention should be called to the possibility of confusion arising in connection with the nomenclature of this compound. Ghatak and Kaul (*J. Indian Chem. Soc.*, 1932, **9**, 383) isolated from the seeds of *Abrus precatorius* Linn. a compound, $C_{12}H_{14}O_2N_2$, which they named " abrine." Hoshino (*Annalen*, 1935, **520**, 31) showed this new compound to be *d*-α-methylamino-β-3-indolylpropionic acid and referred to it as " *N*-methyltryptophan," an obviously unsatisfactory name. Since the term " abrin " has for many years been applied to the mixture of two poisonous proteins, one a paraglobulin, the other a phytalbuminose, obtained from *Abrus precatorius* Linn., the name " abrine " as applied to the amino-acid should be discontinued.

and left in the ice-chest. The liquid was filtered, and the precipitated magnesium benzenesulphonate washed with a little saturated magnesium sulphate solution. The filtrate was diluted with an equal volume of water, and the p_H adjusted to 2 by the addition of a hot saturated solution of hydrated barium hydroxide (approximately 230 g.). The liquid was filtered, and the separated barium sulphate twice washed with boiling water. By the further addition of a hot solution of barium hydroxide (approximately 130 g.) to the combined filtrates, the p_H was adjusted to 12, *i.e.*, until the addition of barium hydroxide solution gave no further precipitate. The liquid was again filtered, and the solid washed with hot water. The solution was made neutral with 10% sulphuric acid and filtered, and the clear filtrate concentrated to a small bulk under reduced pressure. To the solution of *N*-methylglycine so obtained, a concentrated solution of potassium cyanate (14 g.; 1 mol.) was added. After ½ hour's heating on a boiling water-bath, the mixture was made acid to Congo-red with concentrated hydrochloric acid and heated for a further ½ hour. It was then evaporated to dryness under reduced pressure, and the residue extracted with three portions of absolute alcohol. The combined extracts were boiled with a little charcoal and concentrated. On cooling in the ice-chest, sheaves of colourless elongated plates were obtained (12·2 g.), m. p. 155—158°. By concentration of the mother-liquor a further crop (2·2 g.) of slightly less pure hydantoin was obtained. The total yield, calculated from the *N*-benzenesulphonylsarcosine used, was 72%. On recrystallisation from absolute alcohol, the 1-methylhydantoin was obtained in sheaves of elongated plates, m. p. 157—159°. Weitzner (*loc. cit.*) records 152—156°, and West (*J. Biol. Chem.*, 1918, **34**, 187), 155—156°.

5-(3′-*Indolal*)-1-*methylhydantoin*.—Indole-3-aldehyde (5 g.) (Boyd and Robson, *Biochem. J.*, 1935, **29**, 555), 1-methylhydantoin (5 g.; 1¼ mols.), and freshly distilled piperidine (10 ml.) were refluxed together; after 3—4 minutes the deep yellow solution began to deposit yellow crystals. After 1 hour, hot water (50 ml.) was added, and the mixture made acid to litmus with acetic acid. The yellow precipitate which separated was collected, washed with boiling water (100 ml.), and dried at 110° (yield, quantitative). Recrystallisation of the 5-(3′-*indolal*)-1-*methylhydantoin* was effected by dissolving it in the minimum quantity of hot pyridine and adding hot water until a slight permanent cloudiness appeared. The short rods obtained had m. p. 337—338° after softening at 328° (Found: N, 17·35. $C_{13}H_{11}O_2N_3$ requires N, 17·4%).

5-(3′-*Indolylmethyl*)-1-*methylhydantoin*.—To crude 5-(3-indolal)-1-methylhydantoin (2·5 g.) was added freshly distilled pyridine (60 ml.) and concentrated aqueous ammonia (1 ml.). The mixture was saturated at 0—5° with hydrogen sulphide and heated at 100—105° in a sealed vessel for 3 days: this procedure was repeated twice. After 9 days, the solution was evaporated to dryness under reduced pressure, and the solid extracted several times with boiling water (600 ml. in all). The extract was boiled with a little charcoal and filtered hot. On cooling, it deposited colourless or faintly yellow crystals of 5-(3′-indolylmethyl)-1-methylhydantoin. By concentrating the mother-liquor under reduced pressure a further quantity was obtained (total yield, 2 g.; 80%). The hydantoin, recrystallised from boiling water (solubility, approximately 1/200), formed octagonal-shaped plates, m. p. 211—212° (Gordon and Jackson, *loc. cit.*, give 213—214° after softening at 210°). It gave a positive glyoxylic test, an immediate deep pink colour on warming with Ehrlich's reagent, and no colour with bromine water (Found for a specimen dried over sulphuric acid for a week: N, 17·3. Calc. for $C_{13}H_{13}O_2N_3$: N, 17·3%).

α-*Methylamino*-β-3-*indolylpropionic Acid*.—Attempts to hydrolyse the above hydantoin by the methods of Boyd and Robson (*Biochem. J.*, 1935, **29**, 546, 2256) having proved tedious and unsatisfactory, the following technique was adopted. Crude 5-(3′-indolylmethyl)-1-methylhydantoin (2·5 g.) was refluxed with hydrated barium hydroxide (25 g.) in water (50 ml.) for 20 hours, carbon dioxide then passed into the boiling liquid (diluted with 300 ml. of water), and the precipitated barium carbonate washed twice with boiling water A few drops of dilute sulphuric acid were added to the filtrate to remove the remaining barium and the filtered solution was boiled with charcoal and concentrated to a small volume under reduced pressure. r-α-Methylamino-β-3-indolylpropionic acid, thrown out as fine needles, was washed with a little cold absolute alcohol and dried in the desiccator. Yield, 1·65 g. Concentration of the mother-liquor yielded a further crop (0·35 g.) (total yield, 90%). The amino-acid was sweet to the taste (cf. Ghatak and Kaul, *loc. cit.*). It gave with bromine water a pink colour, which was extracted by butyl alcohol; the extract changed to purple on standing. An intense purple colour was obtained with the glyoxylic test. Ehrlich's reagent gave a strong pink colour after 1 minute's boiling. The ninhydrin test was negative. After one recrystallisation from

water, the amino-acid had m. p. 245° (decomp.) after softening at 241° (Found : N, 12·8. Calc. for $C_{12}H_{14}O_2N_2$: N, 12·8%). Gordon and Jackson (*loc. cit.*) record decomp. at 297° after darkening at 280°. Ghatak and Kaul (*loc. cit.*) and Hoshino (*loc. cit.*) give m. p. 295° for the naturally occurring *d*-compound.

The picrate, prepared according to Ghatak (*Bull. Acad. Sci. U.P.*, 1934, **3**, 295), formed clusters of red stout needles, m. p. 185—186° (decomp.) (Gordon and Jackson, *loc. cit.*, give 186°).

On the addition of concentrated hydrochloric acid (0·2 ml.) to the amino-acid (0·1 g.) the latter dissolved to a colourless solution which rapidly solidified. The hydrochloride so formed was pressed between filter-papers, dried in a vacuum over soda-lime, and washed with dry ether to remove traces of free acid. It melted at 192—193° (for " abrine hydrochloride," Ghatak, *loc. cit.*, records 221·5°).

Formation of the hydantoin from the amino-acid by the usual method gave a product, m. p. 211—212° (after softening at 208°), not depressed by 5-(3′-indolylmethyl)-1-methylhydantoin.

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