169. *Studies in the Indole Series. Part I. Attempted Preparation of Tryptophan from Tricyclic Compounds.*

By J. Elks, D. F. Elliott, and B. A. Hems.

Attempts to synthesise tryptophan from derivatives of 1-keto-2 : 3-dihydropentindole are described. A 2-carbalkoxy-derivative could not be prepared either by Dieckmann cyclisation of ethyl β-2-carbethoxyindole-3-propionate or by elimination of carbon monoxide from ethyl or *iso*amyl 1-keto-2 : 3-dihydropentindole-2-glyoxylate, although the analogous 1-keto-2-carbethoxy-1 : 2 : 3 : 4-tetrahydrocarbazole was prepared easily from the corresponding 2-glyoxylic ester.

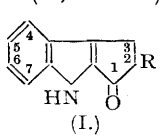
Bromination of 1-keto-1 : 2 : 3 : 4-tetrahydrocarbazole in neutral medium gave the same 6-bromo-derivative as bromination in acid medium.

Interest in the biological properties of individual amino-acids has led to the development of methods for their preparation in quantity. Most of them are readily accessible either by isolation from natural sources or by synthetic methods. Tryptophan is, however, an important exception; it is not abundantly present in any protein and its isolation from natural sources is troublesome. Until very recently four methods of synthesis had been reported, but none of these is convenient for preparing more than small quantities.

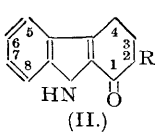
Ellinger and Flamand (*Z. physiol. Chem.*, 1908, **55**, 8; *Ber.*, 1907, **40**, 3029) synthesised tryptophan from indole-3-aldehyde by the azlactone method. Majima and Kotake (*Ber.*, 1922, **55**, 3859) prepared it from indolylidenehydantoin by reduction with sodium amalgam, followed by hydrolysis with baryta. A similar process was used by Boyd and Robson (*Biochem. J.*, 1935, **29**, 555, 2256), who developed a new method for the preparation of indolealdehyde, improved the yield of indolylidenehydantoin by using piperidine as a catalyst in the condensation, and converted the hydantoin into tryptophan in good yield by prolonged reductive hydrolysis with ammonium sulphide. Bauguess and Berg (*J. Biol. Chem.*, 1934, **104**, 679) prepared tryptophan by reduction of the oxime of indole-3-pyruvic acid, this acid being prepared by alkaline hydrolysis of the azlactone from the aldehyde (Ellinger and Matsuoka, *Z. physiol. Chem.*, 1920, **109**, 261).

After the completion of the work described in this and the following papers, another synthesis of tryptophan was described by Snyder and Smith (*J. Amer. Chem. Soc.*, 1944, **66**, 350) and Albertson, Archer, and Suter (*ibid.*, p. 500). Indole was condensed with formaldehyde and dimethylamine to give gramine, which was converted into the methiodide and thence, by condensation with ethyl acetamido- or benzamido-malonate, into ethyl acylamino(3-indolylmethyl)malonate. From this, tryptophan was prepared by hydrolysis to the malonic acid, decarboxylation and hydrolysis of the acyl group.

Attempts are reported in this and the following paper to find a new route to tryptophan which would avoid the troublesome preparation of indole and its 3-aldehyde. In this Part experiments involving the use of derivatives of 1-keto-2 : 3-dihydropentindole (I, R = H), and its homologue, 1-keto-1 : 2 : 3 : 4-tetrahydrocarbazole (II, R = H), are described.



(I.)



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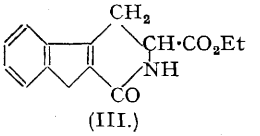

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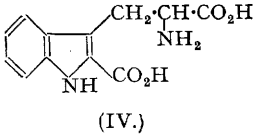

(IV.)

Our experiments were largely directed towards the preparation of 1-keto-2-carbethoxy-2 : 3-dihydropentindole, which might give rise, either by the action of hydrazoic acid (cf. Adamson, J., 1939, 1564) or by Beckmann rearrangment of its oxime, to the compound (III); from this, tryptophan should be obtainable by ring opening to (IV) and decarboxylation.

In the first series of experiments, attempts were made, under a variety of conditions, to prepare 1-keto-2-carbethoxy-2 : 3-dihydropentindole by Dieckmann cyclisation of ethyl β-2-carbethoxyindole-3-propionate (Kalb, Schweizer, and Schimpf, *Ber.*, 1926, **59**, 1858; Manske and Robinson, J., 1927, 240), but these were uniformly unsuccessful, much of the starting material being always recovered. Similar attempts to cyclise ethyl γ-2-carbethoxyindole-3-butyrate (Jackson and Manske, *J. Amer. Chem. Soc.*, 1930, **52**, 5029) also failed. Recently, Koelsch (*J. Org. Chem.*, 1943, **8**, 295) described a similar failure in attempts to cyclise ethyl β-2 : 6-dicarbethoxyindole-3-propionate.

Attention was next turned to the possibility of converting 1-keto-2 : 3-dihydropentindole (I, R = H) into the 2-carbethoxy-compound. Lions (*Proc. Roy. Soc. N.S.W.*, 1933, **66**, 516) prepared *cyclo*pentane-1 : 2-dione monophenylhydrazone by reaction between benzenediazonium chloride and ethyl *cyclo*pentanone-2-carboxylate (see also Dieckmann, *Annalen*, 1901, **317**, 63; Linstead and Wang, J., 1937, 807), and Manske (*Canadian J. Res.*, 1931, **4**, 595) has cyclised this compound to 1-keto-2 : 3-dihydropentindole by treatment with aqueous-alcoholic hydrogen chloride. We prepared the phenylhydrazone by the action of benzenediazonium chloride upon 2-formyl*cyclo*pentanone, and cyclised it by boiling with dilute sulphuric acid. The ketone differs considerably from 1-keto-1 : 2 : 3 : 4-tetrahydrocarbazole (Coffey, *Rec. Trav. chim.*, 1923, **42**, 528; Kent, J., 1935, 976; Lions, *loc. cit.*), having a much higher melting point and being much less soluble in the usual solvents.

These two keto-compounds reacted with ethyl oxalate in cold alcoholic sodium ethoxide to give *ethyl 1-keto-2 : 3-dihydropentindole-2-glyoxylate* (I, R = $CO{\cdot}CO_2Et$) and *ethyl 1-keto-1 : 2 : 3 : 4-tetrahydrocarbazole-2 glyoxylate* (II, R = $CO{\cdot}CO_2Et$), respectively. On heating, the latter lost carbon monoxide to give 1-*keto*-2-

carbethoxy-1 : 2 : 3 : 4-*tetrahydrocarbazole*, but the former could not be converted into the carbethoxy-compound, though many attempts were made to carry out the reaction, both at ordinary pressure and in a vacuum, and in presence and absence of catalysts. Since the high melting point of the glyoxylic ethyl ester may have been responsible for the failure to effect removal of carbon monoxide, the corresponding iso*amyl* ester (I, R = $CO{\cdot}CO_2C_5H_{11}$) was prepared in a similar manner in the hope that it might have a sufficiently low melting point to lose carbon monoxide on fusion, without undergoing extensive decomposition. The ester did, in fact, have a considerably lower melting point than the ethyl ester but, again, it was not possible to obtain the carboxylic acid ester from it.

The direct introduction of a carbethoxy-group into 1-keto-1 : 2 : 3 : 4-tetrahydrocarbazole by means of ethyl carbonate (Wallingford, Homeyer, and Jones, *J. Amer. Chem. Soc.*, 1941, **63**, 2252), and of a formyl group by means of ethyl formate, was not achieved.

Attempts to oxidise 1-keto-1 : 2 : 3 : 4-tetrahydrocarbazole to the 1 : 2-diketone *via* the *iso*nitroso-compound, or directly by means of selenium dioxide in alcohol, benzene, or acetic acid, also met with no success.

Bromination of 1-keto-1 : 2 : 3 : 4-tetrahydrocarbazole in acetic acid has been shown by Mears, Oakeshott, and Plant (J., 1934, 272) to lead to the 6-bromo-compound. We have found that the same compound is obtained when the reaction is maintained neutral by bromination in chloroform solution in the presence of calcium carbonate.

Experimental.

cyclo*Pentane*-1 : 2-*dione Monophenylhydrazone*.—A mixture of *cyclo*pentanone (21 g.) and ethyl formate (18·5 g.) was cooled to — 20° and added to a solution of sodium ethoxide, prepared from sodium (6 g.) and anhydrous ethyl alcohol (85 c.c.), also at — 20°. The mixture was kept at — 20° for 30 minutes and then at 0° overnight. Ice-water was added to dissolve the solid sodium salt of 2-hydroxymethylene*cyclo*pentanone, and the solution neutralised to Congo-red by addition of dilute acetic acid at 0°. This solution was added gradually, with stirring, to a solution of benzenediazonium hydroxide, prepared by diazotising aniline (18·5 g.) in 5N-hydrochloric acid (95 c.c.) with sodium nitrite (16 g. in 40 c.c. of water), neutralising it at 0°, and filtering. The resulting orange precipitate was filtered off after 2 hours (longer standing gave a darker product in smaller yield), washed with water, and recrystallised from ethyl alcohol. *cyclo*Pentane-1 : 2-dione monophenylhydrazone separated in orange-brown needles, m. p. 199—200° (Lions, *loc. cit.*, gives m. p. 203°) (yield 22 g.; 59%).

1-*Keto*-2 : 3-*dihydropentindole* (I, R = H).—The foregoing phenylhydrazone (6·3 g.) was boiled for a few minutes with a solution of concentrated sulphuric acid (7 c.c.) in water (70 c.c.), and the mixture then digested on the water-bath for 1 hour. The cooled mixture was filtered, and the residue crystallised from ethyl alcohol after treatment with charcoal. 1-Keto-2 : 3-dihydropentindole separated as yellowish leaflets (2·9 g.; 51%), m. p. 249—251° (decomp.) (Found : C, 77·0; H, 5·3; N, 8·2. Calc. for $C_{11}H_9ON$: C, 77·2; H, 5·3; N, 8·2%). Manske, *loc. cit.*, gives m. p. 248—249°.

On a larger scale it was necessary to boil the mixture for 1½ hours in order to ensure complete reaction. Owing to the sparing solubility of the product in ethyl alcohol, larger quantities were best purified by dissolving it in chloroform, adding a large quantity of alcohol, and distilling off the chloroform till crystallisation began. The overall yield of 1-keto-2 : 3-dihydropentindole from aniline could be increased to 40% by omitting the crystallisation of the phenylhydrazone.

Ethyl 1-*Keto*-2 : 3-*dihydropentindole*-2-*glyoxylate* (I, R = $CO{\cdot}CO_2Et$).—A mixture of 1-keto-2 : 3-dihydropentindole (20 g.) and ethyl oxalate (18 g.) was treated at 0° with a solution of sodium ethoxide, prepared from sodium (3·0 g.) and anhydrous alcohol (60 c.c.). The mixture was left at 0° for 2 days, and then acidified with dilute sulphuric acid. The orange-yellow solid was filtered off, and crystallised from ethyl alcohol or glacial acetic acid, *ethyl* 1-*keto*-2 : 3-*dihydropentindole*-2-*glyoxylate* being obtained as yellow crystals, m. p. 222—223° (decomp.) (Found : C, 66·4; H, 4·8; N, 5·6. $C_{15}H_{13}O_4N$ requires C, 66·4; H, 4·8; N, 5·2%); yield 24 g., 76%.

iso*Amyl* 1-*Keto*-2 : 3-*dihydropentindole*-2-*glyoxylate* (I, R = $CO{\cdot}CO_2C_5H_{11}$).—*iso*Amyl oxalate was prepared in 92% yield by refluxing a mixture of oxalic acid (143 g.), *iso*amyl alcohol (220 g.), and carbon tetrachloride (200 c.c.) in a flask fitted with a device which retained the water distilling out with carbon tetrachloride. The ester boiled at 144°/14 mm. Sodium (1·3 g.) was dissolved in boiling *iso*amyl alcohol (30 c.c.), the solution added to a mixture of 1-keto-2 : 3-dihydropentindole (8·6 g.) and *iso*amyl oxalate (12 g.), and the mixture heated on the water-bath for 4 hours. Water and excess of sulphuric acid were added to the cooled mixture, followed by ethyl alcohol to facilitate filtration. The yellow solid was crystallised from glacial acetic acid, giving iso*amyl* 1-*keto*-2 : 3-*dihydropentindole*-2-*glyoxylate*, m. p. 184—185° (decomp.) (Found : C, 68·6; H, 6·3; N, 4·6. $C_{18}H_{19}O_4N$ requires C, 69·0; H, 6·1; N, 4·5%); yield 9·5 g., 60%.

Ethyl 1-*Keto*-1 : 2 : 3 : 4-*tetrahydrocarbazole*-2-*glyoxylate* (II, R = $CO{\cdot}CO_2Et$).—A mixture of 1-keto-1 : 2 : 3 : 4-tetrahydrocarbazole (20 g.) and ethyl oxalate (16 g.) was treated at 0° with a solution of sodium ethoxide from sodium (2·5 g.) and anhydrous alcohol (50 c.c.), and the product worked up and crystallised as for (I, R = $CO{\cdot}CO_2Et$). *Ethyl* 1-*keto*-1 : 2 : 3 : 4-*tetrahydrocarbazole*-2-*glyoxalate* was obtained as yellow crystals, m. p. 155—156° (Found : C, 67·9; H, 5·55; N, 5·3. $C_{16}H_{15}O_4N$ requires C, 67·35; H, 5·3; N, 4·9%); yield 23 g., 75%. A solution of the compound in alcohol gave an intense brown colour on addition of ferric chloride.

Ethyl 1-*Keto*-1 : 2 : 3 : 4-*tetrahydrocarbazole*-2-*carboxylate*.—The preceding ester (20 g.) was heated under reflux at 200—220°. When gas-evolution slackened, the bath temperature was raised to 240° and maintained thereat till no more gas was evolved. The resulting reddish oil solidified on cooling, and after crystallisation from ethyl alcohol (charcoal), gave *ethyl* 1-*keto*-1 : 2 : 3 : 4-*tetrahydrocarbazole*-2-*carboxylate* as colourless needles, m. p. 145—146° (Found : C, 69·6; H, 6·2; N, 5·5. $C_{15}H_{15}O_3N$ requires C, 70·0; H, 5·9; N, 5·45%); yield 10·8 g., 60%. A solution of this compound in ethyl alcohol gave a green colour on addition of ferric chloride.

6-*Bromo*-1-*keto*-1 : 2 : 3 : 4-*tetrahydrocarbazole*.—Bromine (2 c.c.) was added slowly to a vigorously stirred mixture of 1-keto-1 : 2 : 3 : 4-tetrahydrocarbazole (5 g.) in chloroform (60 c.c.) and calcium carbonate (4 g.), and stirring was thereafter continued for 1½ hours. Hydrochloric acid was added, and the residual solid was filtered off and crystallised from alcohol, 6-bromo-1-keto-1 : 2 : 3 : 4-tetrahydrocarbazole being obtained, m. p. 220—221°, undepressed on admixture with a specimen prepared by the method of Mears, Oakeshott, and Plant (*loc. cit.*), who give m. p. 222—224°. A further quantity of the compound was obtained by separating the chloroform layer, drying it over calcium chloride, and evaporating it to dryness.

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