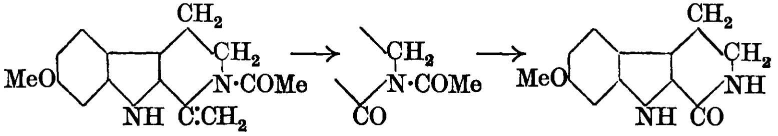
CCCXCVI.—*Harmine and Harmaline. Part X. The Synthesis of 7- and 8-Methoxyketotetrahydro-β-carbolines and the Constitution of Acetylharmaline.*

By HERBERT S. BOYD BARRETT, (the late) WILLIAM HENRY PERKIN, jun., and ROBERT ROBINSON.

NISHIKAWA, PERKIN, and ROBINSON (Part VIII, J., 1924, **125**, 657) concluded that acetylharmaline must have the formula (I), since, on oxidation with permanganate in acetone, it yielded a neutral substance $C_{14}H_{14}O_3N_2$ (replacement of CH_2 by O).

On hydrolysis with alcoholic potassium hydroxide, an amino-acid, $C_{12}H_{14}O_3N_2$, and a well-characterised, neutral substance, $C_{12}H_{12}O_2N_2$, were isolated; the constitution (II) was assigned to the latter.

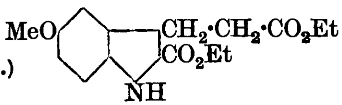


(I.) (II.)

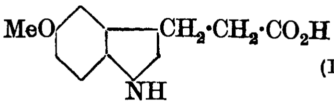
The correctness of this view has now been confirmed by the synthesis of the substance (II), and thus there can be no doubt that acetylharmaline must be represented, as already suggested, by the expression (I).

The synthesis of (II) was effected by an application of the method of Manske and Robinson (J., 1927, 240) for the preparation of a ketotetrahydrocarboline. In order to gain experience, a preliminary investigation of an isomeric series was made.

The p-*methoxyphenylhydrazone* of *ethyl hydrogen α-ketoadipate*, $MeO{\cdot}C_6H_4{\cdot}NH{\cdot}N{:}C(CO_2Et){\cdot}[CH_2]_3{\cdot}CO_2H$, derived from the coupling of ethyl *cyclo*pentanonecarboxylate with *p*-methoxybenzenediazonium chloride in alkaline solution, was transformed, by boiling alcoholic sulphuric acid, into *ethyl* β-2-*carbethoxy*-5-*methoxyindole*-3-*propionate* (III). The dicarboxylic acid obtained on hydrolysis lost carbon dioxide on heating, with formation of β-5-*methoxyindole*-3-*propionic acid* (IV).

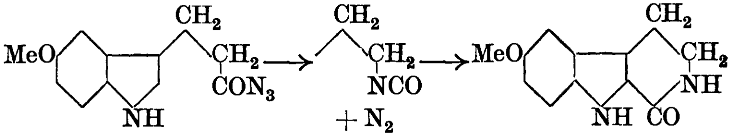


(III.)



(IV.)

The hydrazide of (IV) gave rise to an *azide* (V), from which the ketotetrahydrocarboline (VI) was obtained by the action of hydrogen chloride in chloroform–toluene solution.



(V.) (VI.)

The properties of (VI) are very different from those of the harmaline derivative (II), and this fact is of considerable interest, because the methoxy-group is in the position in which it occurs in the indole nucleus of physostigmine (Barger and Stedman; M. and M. Polonowski; Späth). Thus, the proofs of identity of synthetical 6-methoxyindole derivatives with members of the harmala group are now supplemented for the first time by a proof of non-identity of a 5-methoxyindole derivative with an appropriate degradation product of harmaline.

Starting with *m*-anisidine and proceeding as already described, except that the indole ring was closed by the agency of hydrogen chloride in alcoholic solution, we ultimately obtained 2-*keto*-8-*methoxytetrahydro*-β-*carboline*.* This proved to be identical with the above-mentioned harmaline derivative, $C_{12}H_{12}O_2N_2$, to which the constitution (II) was allotted.

EXPERIMENTAL.

p-*Methoxyphenylhydrazone of Ethyl Hydrogen α-Ketoadipate*.—A diazonium solution was prepared from *p*-anisidine (51 g.), concentrated hydrochloric acid (100 c.c.), ice (200 g.), and sodium nitrite (28 g.): potassium hydroxide (48 g.) was dissolved in water (600 c.c.). One half of the latter solution was shaken with ethyl *cyclo*pentanonecarboxylate (63 g.), and a small volume of the undissolved oil taken up in benzene. The aqueous layer was added to crushed ice (400 g.), and the benzene layer shaken with the remainder of the alkali. About half of the diazo-solution was then added to the solution of the ester, and one minute later the rest of the alkali, followed by the second half of the diazo-solution, was introduced. After 5 minutes, concentrated hydrochloric acid (100 c.c.) was added, and the sticky precipitate was repeatedly washed by decantation and then dried. Great difficulty was experienced in crystallising this *hydrazone*, but ultimately it was obtained in clusters of light yellow needles, m. p. 97° (Found: N, 9·1. $C_{15}H_{20}O_5N_2$ requires N, 9·1%), from light petroleum, in which it was sparingly soluble in the cold.

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* For the nomenclature of the carbolines, see Gulland, Robinson, Scott, and Thornley (preceding paper).

Ethyl β-2-*Carbethoxy*-5-*methoxyindole*-3-*propionate* (III).—The crude methoxyphenylhydrazone (90 g.), prepared as described in the last section, was mixed with alcohol (190 c.c.) and concentrated sulphuric acid (28 c.c.), and the whole refluxed for 2½ hours. The mixture was diluted with water, and the product collected, dried, and distilled, b. p. 230—240°/1 mm. (yield, 31 g.). This *ester* crystallised from alcohol in stout, colourless needles, m. p. 110° (Found : C, 63·8; H, 6·9. $C_{17}H_{21}O_5N$ requires C, 63·9; H, 6·6%). It is sparingly soluble in cold ethyl alcohol and readily soluble in benzene, ether, and ethyl acetate. On hydrolysis with 10% alcoholic sodium hydroxide and subsequent isolation in the usual manner, β-2-carboxy-5-methoxyindole-3-propionic acid was readily obtained; it crystallised from water in colourless prisms, m. p. 225° (decomp.). It is readily soluble in alcohol, ether, and benzene.

β-5-*Methoxyindole*-3-*propionic Acid* (IV).—The decomposition of the foregoing dicarboxylic acid was most conveniently effected by heating in diphenylamine solution until evolution of carbon dioxide ceased. The monocarboxylic *acid* crystallised from water, containing a little alcohol, in colourless rectangular plates, m. p. 136° (yield, 7 g. from 10 g.) (Found : C, 65·7; H, 6·2. $C_{12}H_{13}O_3N$ requires C, 65·8; H, 5·9%). It is readily soluble in alcohol and benzene, and moderately readily soluble in hot water. The *methyl* ester (5 g.) separated from a cold solution of the acid (7 g.) in pure methyl alcohol containing 10% of hydrogen chloride. The solid was collected, washed with aqueous sodium carbonate and water, and dried; it crystallised from aqueous methyl alcohol in colourless plates, m. p. 100° (Found : C, 67·1; H, 7·0. $C_{13}H_{15}O_3N$ requires C, 67·0; H, 6·5%). This ester is readily soluble in alcohol, benzene, and light petroleum, but is insoluble in water. With *p*-dimethylaminobenzaldehyde in aqueous-alcoholic hydrochloric acid solution, it gives a magenta coloration, especially on heating. The appearance of the coloration in the cold was only noted when the concentration of hydrochloric acid exceeded a certain value.

The *hydrazide*, $MeO{\cdot}C_6H_3{\colon}C_2H_2N{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}NH_2$, was obtained by heating a mixture of the methyl ester (12 g.) and hydrazine hydrate (5 g. of 95%) at 150°. The product (10 g.) crystallised from alcohol in colourless prisms, m. p. 146° (Found : N, 18·3. $C_{12}H_{15}O_3N_3$ requires N, 18·0%). This derivative is moderately readily soluble in alcohol, ether or benzene and also in hot water, separating on cooling.

2-*Keto*-7-*methoxy*-2 : 3 : 4 : 5-*tetrahydro*-β-*carboline* (VI).—β-5-Methoxyindole-3-propionhydrazide (2 g.) was dissolved in acetic acid (15 c.c.) and water (20 c.c.); ice (50 g.) and sodium nitrite (1 g. in 10 c.c. of water) were added. The liquid became milky, and in a few minutes pasty, owing to the separation of the yellow crystalline azide (V). This was collected, washed with water, drained as far as possible, and dissolved in cold chloroform (50 c.c.). The solution was dried by calcium chloride and filtered, and the filter washed with toluene (75 c.c.); the liquid was then warmed gently until evolution of nitrogen slackened, and finally boiled for ½ hour after the gas evolution ceased. Dry hydrogen chloride was passed for 2 minutes through the hot solution, which was then boiled, and the gas passed through for 1 minute. The solution was boiled again and cooled at once; crystals then separated. These were collected and dissolved in acetic acid (charcoal); on addition of hot water to the filtered solution, the *carboline* gradually separated. It crystallised from much ethyl acetate in pointed hexagonal prisms, m. p. 280° (Found: C, 66·4; H, 5·4; N, 12·9. $C_{12}H_{12}O_2N_2$ requires C, 66·7; H, 5·6; N, 12·9%). The ketohydrocarboline dissolves in concentrated sulphuric acid to an orange-yellow solution, exhibiting a characteristic green fluorescence; on warming, the colour fades almost completely, and later the solution turns brown. It is slightly soluble in hot water, and sparingly soluble in most organic solvents except acetic acid, from a solution in which it is not immediately precipitated by water. The colour of the yellow solution in concentrated hydrochloric acid is discharged on addition of water, and the substance is immediately precipitated.

Ethyl β-2-*Carbethoxy*-6-*methoxyindole*-3-*propionate* (analogous to III).—The coupling of *m*-methoxybenzenediazonium chloride with ethyl *cyclo*pentanonecarboxylate was like that of the *p*-derivative, and, on the same scale, 90 g. of a crude methoxyphenylhydrazone were obtained. The substance was not crystallised, but the whole was dissolved in alcohol (150 c.c.), and the solution saturated with hydrogen chloride and kept in a well-closed vessel over-night. The vacuum-distilled *ester* (20 g.) crystallised from alcohol in colourless plates, m. p. 109° (Found: C, 63·9; H, 7·3. $C_{17}H_{21}O_5N$ requires C, 63·9; H, 6·6%); the solubilities and other properties were similar to those of the isomeride (above). On hydrolysis with 10% alcoholic sodium hydroxide and subsequent isolation of the acid, β-2-*carboxy*-6-*methoxyindole*-3-*propionic acid*, which crystallised from water, containing acetic acid, in long, colourless, prismatic needles, m. p. 221° (decomp.) (Found: C, 58·9; H, 5·0. $C_{13}H_{13}O_5N$ requires C, 59·3; H, 5·1%), was obtained. The substance is moderately readily soluble in alcohol, acetone, and acetic acid.

β-6-*Methoxyindole*-3-*propionic Acid*,

$$MeO\cdot C_6H_3\vdots C_2H_2N\cdot CH_2\cdot CH_2\cdot CO_2H.$$

—When the dicarboxylic acid was heated to 220°, it suffered smooth decomposition. The resulting monocarboxylic *acid* crystallised from water in colourless rhombic plates, m. p. 165° (Found : C, 65·7; H, 6·1. $C_{12}H_{13}O_3N$ requires C, 65·8; H, 5·9%). This acid is moderately readily soluble in most organic solvents; it can be crystallised from methyl alcohol. The *methyl* ester could not be obtained by the usual methods of esterification with acid catalysts but was readily prepared in excellent yield by the use of diazomethane in ethereal solution: it crystallised from methyl alcohol in thin colourless plates, m. p. 69° (Found : C, 67·3; H, 6·8. $C_{13}H_{15}O_3N$ requires C, 67·0; H, 6·5%). The reaction with *p*-dimethylaminobenzaldehyde in aqueous-alcoholic hydrochloric acid solution results in a deep greenish-blue coloration; this is produced much more readily, even in the cold, than the magenta coloration in the isomeric series, and it is remarkable that the influence of the change of position of the methoxy-group should be so pronounced.

The *hydrazide* was obtained in the usual manner; it crystallised from water in colourless pearly plates, m. p. 143° (Found : N, 17·9. $C_{12}H_{15}O_3N_3$ requires N, 18·0%).

2-*Keto*-8-*methoxy*-2 : 3 : 4 : 5-*tetrahydro*-β-*carboline* (II).—This substance was prepared from harmaline, as described by Nishikawa, Perkin, and Robinson (*loc. cit.*) (Specimen A). It was synthesised from the foregoing hydrazide as described for the isomeride, except that the solid that separated from the chloroform–toluene solution on the passage of hydrogen chloride was removed, and the filtrate again heated with further passage of the gas. The combined precipitates were extracted with ether in a Soxhlet apparatus; the soluble portion crystallised from alcohol in colourless prisms (Specimen B), m. p. 198° (Found : C, 66·5; H, 5·7; N, 13·1. $C_{12}H_{12}O_2N_2$ requires C, 66·7; H, 5·6; N, 12·9%). A mixture of specimens A and B also melted at 198°, and the reactions and other properties of the two specimens were identical. Especially characteristic was the behaviour with sulphuric acid : a greenish-yellow solution was momentarily produced, and this became pure yellow, but, unlike the isomeride, exhibited no fluorescence. On heating, the colour disappeared completely, and the solution then exhibited an intense violet fluorescence when observed in ultra-violet light; under these conditions, the isomeride still fluoresces green. On further heating, the colour changed through greenish-brown to bluish-red.

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UNIVERSITY COLLEGE, LONDON. [*Received, November 7th,* 1929.]