

**704. The Structure of N<sub>β</sub>-Alkyl-β-carboline Anhydro-bases.**

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The structures of N<sub>β</sub>-alkyl-β-carboline anhydro-bases in the solid state and in solution are discussed in the light of their ultraviolet absorption spectra.

THE alkylation of β-carboline (I) and its C-substituted derivatives has been repeatedly studied<sup>1-4</sup> since 1919, when Perkin and Robinson recognised the alkaloid harmine (II) as the first member of this series.<sup>5</sup>

β-Carbolines react with alkyl iodides to give normal quaternary salts (III). With strong alkali these produce, not the quaternary hydroxides (IV), but yellow or orange anhydro-bases. Further alkylation of the anhydro-bases takes place at the indole-nitrogen atom, leading to salts (V) which on further treatment with alkali give the corresponding quaternary hydroxides, and when heated dry lose alkyl iodide from the basic nitrogen to give *ind-N*-alkylated β-carbolines (VI).<sup>6,4</sup>

The coloured anhydro-bases were originally formulated as (IX),<sup>5</sup> but are now regarded as resonance hybrids, with (IX) and (X) as the most important contributing structures.<sup>7</sup>

In recent years a number of alkaloids have been characterised as N<sub>β</sub>-alkyl-β-carboline anhydro-bases, in which C<sub>(1)</sub> and N<sub>β</sub> form part of a further ring.<sup>8</sup>

The anhydro-bases are all yellow or orange, their pK<sub>a</sub> lie between 10 and 11, and they are soluble in polar and non-polar solvents, the latter solutions being in general darker than the former. They crystallise with solvent of crystallisation which is difficult to remove and tend to give unsatisfactory analyses.<sup>9</sup>

Like all anhydro- and *pseudo*-bases, the β-carboline anhydro-bases do not form salts of their own, but yield, with one mol. of acid, the faintly yellow quaternary salts (III) of the parent base. The infrared spectra of these salts (*e.g.*, sempervirine chloride<sup>8a,10</sup>) show an indole-NH band (2.9 μ) which is absent from the spectra of the anhydro-bases themselves. This is now confirmed by comparison of the infrared spectra of β-carboline methiodide and 2-methyl-β-carboline anhydro-base. (I thank Dr. S. F. D. Orr, Chester Beatty Research Institute, for the determination and interpretation of these spectra.)

The fact that further alkylation of the anhydro-bases takes place at the indole-nitrogen

<sup>1</sup> Kermack, Perkin, and Robinson, *J.*, 1922, **121**, 1872.

<sup>2</sup> Hasenfratz, *Ann. Chim.*, 1927, **7**, 151; Kermack and Slater, *J.*, 1928, 789; Konovalova and Orechov, *Arch. Pharm.*, 1934, **272**, 748; Leonard and Elderfield, *J. Org. Chem.*, 1942, **7**, 556.

<sup>3</sup> Speitel and Schlittler, *Helv. Chim. Acta*, 1949, **32**, 860.

<sup>4</sup> Cook, Loudon, and McCloskey, *J.*, 1951, 1203.

<sup>5</sup> Perkin and Robinson, *J.*, 1919, **115**, 933.

<sup>6</sup> Iyer and Robinson, *J.*, 1934, 1635.

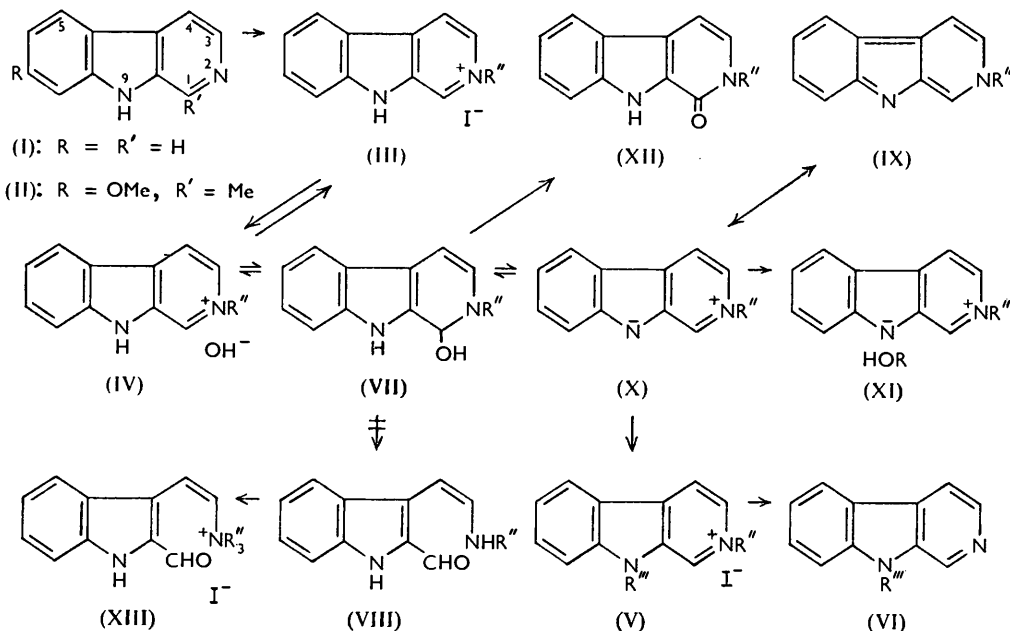
<sup>7</sup> Armit and Robinson, *J.*, 1925, **127**, 1604.

<sup>8</sup> Woodward and Witkop, *J. Amer. Chem. Soc.*, 1949, **71**, 379; Elderfield and Grey, *J. Org. Chem.*, 1951, **16**, 506; Schlittler and Schwarz, *Helv. Chim. Acta*, 1950, **33**, 1463; Karrer and Schmid, *Angew. Chem.*, 1955, **67**, 361.

<sup>9</sup> Schwarz and Schlittler, *Helv. Chim. Acta*, 1951, **34**, 629.

<sup>10</sup> Witkop, *J. Amer. Chem. Soc.*, 1953, **75**, 3361.

atom is best interpreted by regarding the dipolar amphion (X) as the reacting form. If the compounds were of structure (IX), and not resonance hybrids, they should be diacidic, for in this formulation both nitrogen atoms would be basic. No instance of the addition to the anhydro-bases of two mols. of either acid or alkyl halide has been reported.



The ultraviolet spectra of the compounds confirm their anhydro-base character. In aqueous 0.1N-hydrochloric acid, the anhydro-bases give curve *B* of Fig. 1. Except for a bathochromic shift of 10  $m\mu$ , due to the introduction of an *N*-alkyl substituent into the chromophoric system, this curve is of the same shape as that given by  $\beta$ -carboline (I) in 0.1N-acid (curve *A*, Fig. 1). A slight further shift to longer wavelengths is found in the absorption of *ind-N*-alkylated quaternary  $\beta$ -carbolinium salts (V) (curve *C*, Fig. 1). The curves in Fig. 1 represent the absorption spectra of  $\beta$ -carbolinium ions (III, V) of increasing degree of nitrogen alkylation.

Aqueous or alcoholic solutions of  $\beta$ -carbolinium salts are only faintly yellow and exhibit a bright blue or blue-purple fluorescence.

An aqueous or alcoholic solution of the anhydro-bases yields the same curve (curve *B*, Fig. 1). This accords with the behaviour of all *pseudo*- and anhydro-bases so far studied, which in ionising solvents give ultraviolet spectra identical with those of their parent salts,<sup>11</sup> a measure of their readiness to revert, whenever possible, to the more stable salt structure.

In non-ionising solvents (*e.g.*, ether or chloroform), or in aqueous or alcoholic sodium hydroxide of pH > 11.5, curve *D* of Fig. 2 is obtained. The same curve was also given by a solid film of 2-methyl- $\beta$ -carboline anhydro-base, formed on a quartz slide by high-vacuum sublimation in the presence of phosphoric oxide. (I am indebted to Dr. J. E. S. Bradley, Middlesex Hospital Medical School, for this result.) Curve *D* is that of the free anhydro-base.

Fig. 3 shows the absorption spectra of the anhydro-base in aqueous or alcoholic ammonia or sodium hydroxide solutions of pH between 9.0 and 12.5. At pH values below 10.5, the curves obtained are identical with that given by the  $\beta$ -carbolinium ion (curve *B*, Fig. 1); the compound therefore exists as the quaternary ammonium hydroxide (IV). At pH values above 11.5, the absorption is that of the anhydro-base (curve *D*, Fig. 2). With

<sup>11</sup> Dobbie, Lauder, and Tinkler, *J.*, 1903, **83**, 598; Dobbie and Tinkler, *J.*, 1904, **85**, 1005; Steiner, *Bull. Soc. Chim. biol.*, 1924, **6**, 231; Bills and Noller, *J. Amer. Chem. Soc.*, 1948, **70**, 957.

increasing pH, at values between 10.5 and 11.5, the peaks due to the  $\beta$ -carbolinium ion at 255, 305, and 375  $m\mu$  gradually weaken in intensity and finally disappear, while the maxima due to the anhydro-base, at 275 and 325  $m\mu$ , appear as inflexions and increase finally to their full intensities. This indicates an equilibrium between quaternary hydroxide (IV) and anhydro-base, at pH values between 10.5 and 11.5.

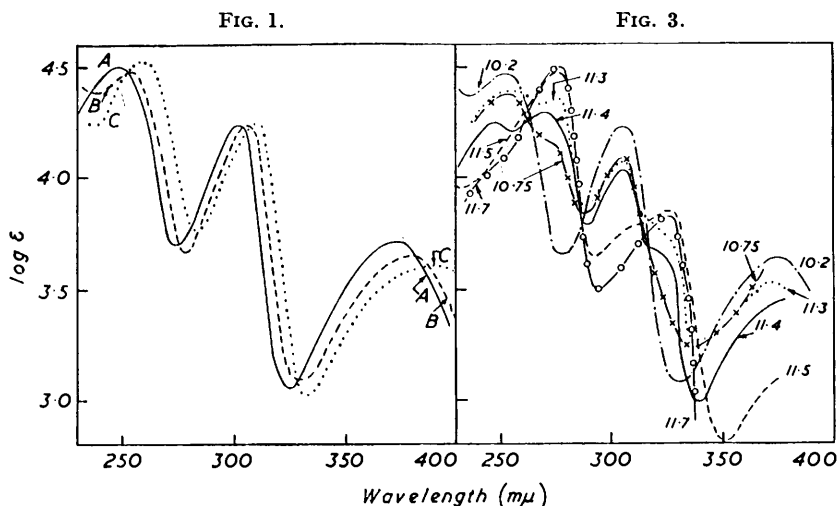


FIG. 1. A,  $\beta$ -Carboline hydrochloride. B,  $\beta$ -Carboline methiodide. C, 9-Methyl- $\beta$ -carboline propiodide. (All in EtOH.)

FIG. 3. 1 : 2-Dimethyl- $\beta$ -carboline anhydro-base in aqueous solutions of pH 9.5—11.7.

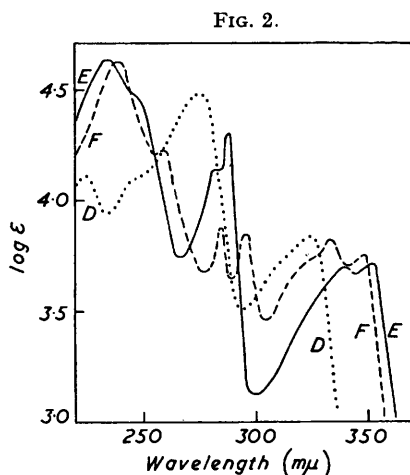


FIG. 2. D, 2-Methyl- $\beta$ -carboline anhydro-base (solid film). E,  $\beta$ -Carboline in EtOH. F, 1 : 2-Dihydro-2-methyl-1-oxo- $\beta$ -carboline in EtOH.

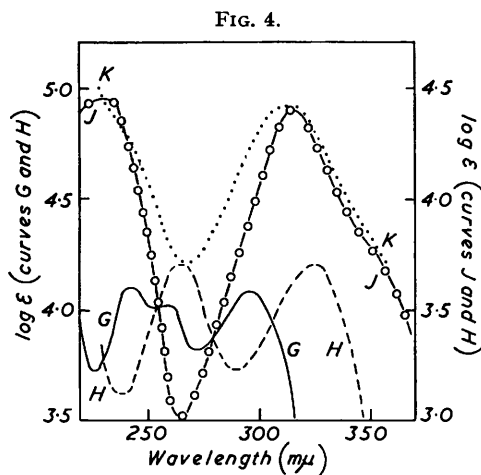
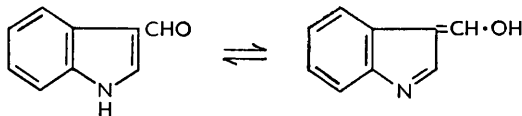


FIG. 4. G, 3-Formylindole (G) in EtOH or 0.1N-HCl in aq. EtOH; (H) in 0.1N-NaOH in aq. EtOH. J, 2-Formylindole in EtOH.<sup>13</sup> K, 3 : 4-Dihydro-1 : 2-dimethyl- $\beta$ -carboline anhydro-base in  $\text{CHCl}_3$ , or 3 : 4-dihydro-1-methyl- $\beta$ -carboline methiodide in 0.1N-NaOH in aq. EtOH.<sup>14</sup>

This interpretation is at variance with that of Schwarz and Schlittler,<sup>9</sup> who claim to have demonstrated an equilibrium between (IX) and (X). These structures are not tautomeric, however, but are canonical forms of a resonance hybrid and thus chemically and spectroscopically indistinguishable. From the observation that the anhydro-bases give curve B of Fig. 1 in aqueous or alcoholic solution, these authors conclude that in

ionising solvents the substances exist as pseudo-bases (VII) in equilibrium with amino-aldehyde (VIII), or as solvated molecules (XI).

None of the compounds (VII), (VIII), and (XI) would be likely to give a curve of type *B*. The *pseudo*-base (VII) can be considered as a 3-vinylindole, and although no ultraviolet spectrum of such a structure appears to have been published it would probably



be similar to that given by 3-formylindole in acid or alcoholic solution (curve *G*, Fig. 4). [The bathochromic shift shown by this compound in alkali (curve *H*, Fig. 4) is probably due to enolisation, accompanied by a change in the chromophoric system.<sup>12</sup>]

Analogous similarities are found of the ultraviolet absorption spectra of 2-formylindole (curve *J*<sup>13</sup>, Fig. 4) and 3 : 4-dihydro-1 : 2-dimethyl-β-carboline anhydro-base<sup>14</sup> (a 2-vinylindole) (curve *K*, Fig. 4), and of those of benzaldehyde and styrene.<sup>15</sup>

Structure (VIII) includes a chromophore similar to that of 1 : 2-dihydro-2-methyl-1-oxo-β-carboline (XII) (curve *F*, Fig. 2) (cf. ref. 16), while the chromophore of the compound (XI) is identical with that of (X) and would give curve *D* of Fig. 2. If the aldehyde (VIII) were a hydrated tautomeric contributor to the anhydro-base, further alkylation should occur at N<sub>β</sub>, yielding quaternary salts of structure (XIII). In fact further alkylation takes place at the indole nitrogen atom.<sup>1-4</sup> The alkylation products, quaternary salts of 9-alkyl-β-carboline (V) (*e.g.*, 9-propyl-β-carboline methiodide, obtained from 2-methyl-β-carboline anhydro-base and propyl iodide, and 9-methyl-β-carboline propiodide, from 2-propyl-β-carboline anhydro-base and methyl iodide) give β-carbolinium curves, identical in acid, neutral, and alkaline alcoholic solutions (curve *C*, Fig. 1), showing the shift to longer wavelengths, discussed above.

There is thus no evidence for the existence of an aldehyde-amine form (VIII), postulated<sup>9</sup> by analogy with the classical work on *N*-alkylpyridine and quinoline.<sup>17</sup>

The only evidence for the existence of a *pseudo*-base (VII) as a hydrated form of the anhydro-base is not spectroscopic but chemical: β-carboline methiodide is oxidised by weakly alkaline potassium ferricyanide to the 1 : 2-dihydro-1-oxo-derivative (XII).<sup>1</sup>

## EXPERIMENTAL

β-Carboline (norharman), m. p. 198—200° (hydrochloride, m. p. 234—236°), and 1-methyl-β-carboline (harman), m. p. 235—237°, were prepared<sup>3, 18, 19</sup> from tryptophan.

β-Carboline Alkiodides.—Norharman (0.5 g.) and methyl iodide (1 ml.) in benzene (200 ml.) and nitrobenzene (20 ml.) was kept for 24 hr. at 37°; the methiodide separated in 95% yield. It recrystallised from water as slightly yellow prisms, m. p. 243—244° (cf. ref. 3).

The *propiodide*, needles, m. p. 201—202° (from water), was obtained similarly (Found: C, 49.5; H, 4.5. C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>I requires C, 49.7; H, 4.5%); so was 1-methyl-β-carboline methiodide, m. p. 298—300° (from water) (Found: C, 48.1; H, 3.9. C<sub>13</sub>H<sub>13</sub>N<sub>2</sub>I requires C, 48.1; H, 4.0%).

2-Methyl-β-carboline Anhydro-base.<sup>3</sup>—A hot aqueous solution of β-carboline methiodide was treated with an excess of warm 20% aqueous sodium hydroxide. On cooling, the yellow anhydro-base, m. p. 212—214°, p*K*<sub>a</sub> 10.6, crystallised. When recrystallised from a little water, a hydrate, m. p. 81—82°, was obtained; this loses water on further heating, and then resolidifies and remelts at 212—214°.

2-Propyl-β-carboline anhydro-base, m. p. 179—180°, p*K*<sub>a</sub> 10.6, was obtained similarly from

<sup>12</sup> Cf. Majima and Kotake, *Ber.*, 1925, **58**, 2037; Baker and Happold, *Biochem. J.*, 1940, **34**, 657.

<sup>13</sup> Taylor, *Helv. Chim. Acta*, 1950, **33**, 164.

<sup>14</sup> Spenser, unpublished result.

<sup>15</sup> Gillam and Stern, "An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry," Edward Arnold Ltd., London, 1954, p. 126.

<sup>16</sup> Johnson, Larsen, Holley, and Gerzon, *J. Amer. Chem. Soc.*, 1947, **69**, 2364.

<sup>17</sup> Hantzsch and Kalb, *Ber.*, 1899, **32**, 3109; Kaufmann and Strübin, *Ber.*, 1911, **44**, 680.

<sup>18</sup> Jacobs and Craig, *J. Biol. Chem.*, 1936, **113**, 759.

<sup>19</sup> Harvey, Miller, and Robson, *J.*, 1941, 153.

$\beta$ -carboline propiodide. Recrystallisation from water gives a hydrate, m. p. 75—80°, which on further heating resolidifies and remelts at 179—180°.

1 : 2-Dimethyl- $\beta$ -carboline anhydro-base, greenish-yellow needles,<sup>18</sup> m. p. 184—185°,  $pK_a$  10.6, was obtained in the same way from harman methiodide.

9-Propyl- $\beta$ -carboline Methiodide.—2-Methyl- $\beta$ -carboline anhydro-base, in benzene, was treated with excess of propyl iodide and kept at 37° for 48 hr.; the *salt* crystallised; it recrystallised from water as yellow needles, m. p. 238—239° (Found: C, 51.2; H, 5.0.  $C_{15}H_{17}N_2I$  requires C, 51.1; H, 4.9%). A mixed m. p. with  $\beta$ -carboline methiodide showed a depression of 30°.

9-Methyl- $\beta$ -carboline propiodide was obtained similarly from 2-propyl- $\beta$ -carboline anhydro-base and methyl iodide and the *salt* recrystallised from water as yellow needles, m. p. 262—263° (Found: C, 51.3; H, 5.1.  $C_{15}H_{17}N_2I$  requires C, 51.1; H, 4.9%).

1 : 2-Dihydro-2-methyl-1-oxo- $\beta$ -carboline<sup>1</sup> (XII).—A 4% aqueous solution of potassium ferricyanide was added slowly to a hot solution of  $\beta$ -carboline methiodide (0.9 g.) and potassium carbonate (2.0 g.), until a drop of the acidified mixture gave a Prussian-blue colour with ferrous sulphate. The warm solution was repeatedly extracted with benzene, and the combined extracts were washed with *n*-hydrochloric acid (2  $\times$  20 ml.) and dried (KOH). Removal of solvent gave the lactam (0.12 g.), which on recrystallisation from ethanol was obtained in colourless needles,<sup>1,18</sup> m. p. 261—263°.

*Ultraviolet Absorption Spectra*.—These were determined on a Unicam S.P. 500 spectrophotometer, with solutions which were 5.0 ( $\pm 0.5$ )  $\times 10^{-5}M$ .

I am indebted to Dr. W. Robson, King's College, London, for advice and encouragement.

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[Received, March 7th, 1956.]