Reactions of Harmaline (4,9-Dihydro-7-methoxy-1-methyl-3*H*-pyrido-[3,4-*b*]indole) and its Derivatives. Part II.[1] Reinvestigation of Acetylharmaline

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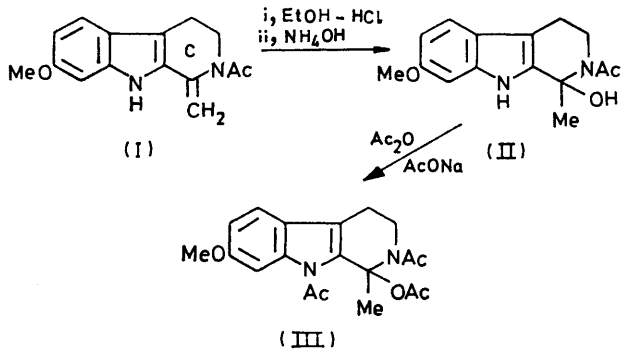
A reinvestigation of the acidic hydrolysis of acetylharmaline (2-acetyl-2,3,4,9-tetrahydro-7-methoxy-1-methylene-1*H*-pyrido[3,4-*b*]indole) (I) has shown that the product is not that of simple hydration of the exocyclic double bond, but is the result of cleavage of ring C, *i.e.* 3-(2-acetamidoethyl)-2-acetyl-6-methoxyindole (V). Further acetylation of this results in the 3-(2-diacetylaminoethyl) derivative (VI); no acetylation of the indole nitrogen atom is observed, contrary to a previous report. 1,2,3,5,6,11-Hexahydro-3-oxoindolizino[8,7-*b*]indol-4-ium tetrafluoroborate (XIV) was synthesised by a novel cyclisation–elimination reaction involving the treatment of *N*-succinimidotryptamine with triethyloxonium tetrafluoborate.

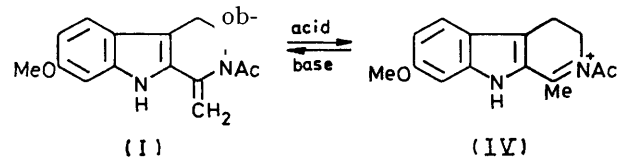
ACETYLHARMALINE (I) was first prepared by Fischer in 1897 by acetylation of harmaline with acetic anhydride and dry sodium acetate.[2] Fischer observed that treatment of acetylharmaline with ethanolic hydrogen chloride resulted in an immediate change in the colour of the originally colourless solution to yellow, green, and finally blue. Addition of concentrated ammonia to the blue solution precipitated a compound, m.p. 164—165°, to which Manske, Perkin, and Robinson assigned the structure (II).[3] Robinson also reported



(I) (II) (III)

that when 'hydroacetylharmaline' (II) was further acetylated by refluxing in acetic anhydride and sodium acetate, it was converted into the diacetyl derivative (III).

A reinvestigation of these reactions was considered necessary in view of the known lack of reactivity of the indole nitrogen atom to acetylation under the foregoing conditions. When acetylharmaline (I) was treated with ethanolic hydrogen chloride, a rapid blue colouration was observed. Basification with concentrated



(I) (IV)

ammonia afforded a colourless crystalline substance, m.p. 165—166°.

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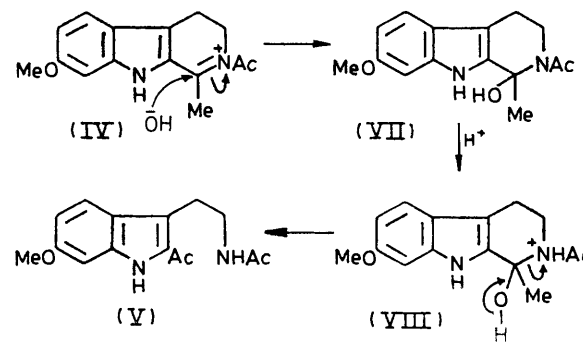
[1] Part I, preceding paper.

[2] O. Fischer, *Ber.*, 1897, **30**, 2481.

The u.v. spectrum of the product did not exhibit the characteristic bathochromic shift shown by acetylharmaline on acidification. This shift is attributed to the generation of the iminium ion (IV), and is typical of such conjugated indoles.[4] The spectrum was in accord with that expected for a 2-acyl-methoxyindole.

The n.m.r. spectrum ($CDCl_3$) showed no olefinic proton signals and contained sharp three-proton singlets at δ 1·88 (Ac), 2·58 (NAc), and 3·81 (aromatic OMe) p.p.m. The mass spectrum showed a molecular ion at *m/e* 274 with prominent loss of acetamide, supporting structure (V). Its formation may be rationalised in terms of attack of a molecule of water on the iminium ion (IV) followed by ring opening of the intermediate carbinol amide (VII).



(IV) (VII) (V) (VIII)

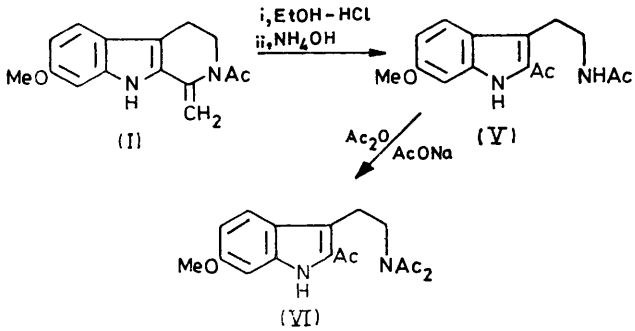
When the keto-amide (V) was refluxed in acetic anhydride and sodium acetate for several hours, it was converted into a faster-moving compound. Work-up afforded a crystalline solid, m.p. 158—160°. The u.v. spectrum indicated the presence of a 2-acylindole chromophore, the n.m.r. spectrum showed a six-proton singlet at δ 2·44 p.p.m. (NAc_2), and the i.r. spectrum showed carbonyl absorption at 1703 cm^{-1}. The mass spectrum included a molecular ion at *m/e* 316. On the basis of these data, structure (VI) was assigned.

We considered that the ring-opening reaction ob-

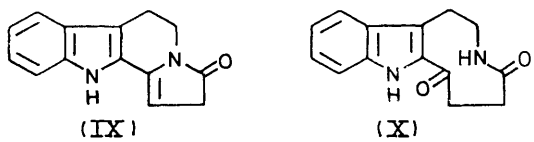
[3] R. H. F. Manske, W. H. Perkin, and R. Robinson, *J. Chem. Soc.*, 1927, 1; W. H. Perkin and R. Robinson, *J. Chem. Soc.*, 1912, **101**, 775; 1913, **103**, 1973; 1919, **115**, 933.

[4] R. N. Schut and T. J. Leipzig, *J. Heterocyclic Chem.*, 1966, **3**, 101.

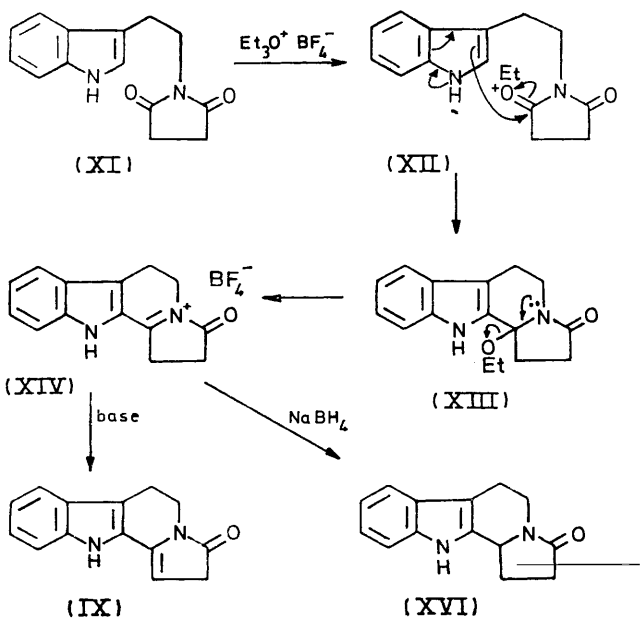
served might be applicable to the synthesis of the model compound (X) from the enamide (IX). Suitable transformations of the keto-amide (X) could lead to



the synthesis of *Strychnos* and *Aspidosperma* alkaloidal systems, which possess the same nine-membered ring as in (X).



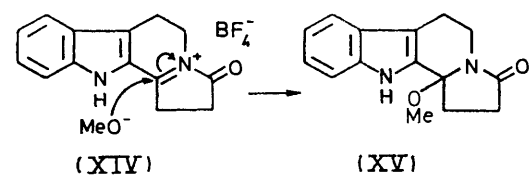
The imide (XI) was prepared by refluxing tryptamine and succinic anhydride in dry toluene for 12 h with use of a Dean and Stark apparatus. Wenkert had previously reported the failure of the imide (XI) to cyclise to the enamide (IX) under Bischler–Napieralski conditions.[5] It appeared that if the electrophilic character of the carbonyl group could be increased,



cyclisation on to the indole nucleus might be brought about, for example by alkylating the oxygen atom of the carbonyl group with Meerwein's reagent[6] to generate the oxonium (or iminium) compound (XII).

When a solution of the imide (XI) in dichloromethane was stirred at room temperature for 42 h with an excess of triethyloxonium tetrafluoroborate, a yellow product was obtained in over 80% yield. The u.v. spectrum of the substance in methanol or ethanol did not indicate any significant conjugation of the indole nucleus. However the spectrum of a solution in dichloromethane or dry dioxan exhibited strong absorption at 386 nm which disappeared on basification. The i.r. spectrum exhibited carbonyl absorption at 1795 cm^{-1}, and the n.m.r. spectrum showed a significant downfield shift of the $N{\cdot}CH_2$ signal to δ 4·2 p.p.m. No olefinic proton signal was visible; hence the expected product (IX) had not been obtained. All the physical data, however, fitted structure (XIV).

The non-appearance of high-wavelength u.v. absorption in methanol or ethanol is explicable in terms of attack of the solvent alcohol to afford the adduct (XV), which would have a normal indolic u.v. spectrum.



The high value of the C=O stretching frequency is also indicative of the non-amidic character of the carbonyl group, due to the non-availability of the lone pair of electrons on the nitrogen atom for conjugation. The positive charge on the nitrogen atom explains the strong deshielding of the methylene protons.

Structure (XIV) was confirmed by reduction with sodium borohydride or hydrogenation over platinum oxide to give the known amide (XVI).[7]

Attempted hydrolytic ring opening of compound (XIV) resulted in appreciable decomposition. No compound possessing a 2-acylindole-type u.v. spectrum was obtained, and preliminary experiments indicated that cleavage of ring D was occurring, to afford an imino acid.

The foregoing alternative to the Bischler–Napieralski procedure for cyclodehydration of imides offers considerable advantages, particularly with five-membered cyclic imides which do not undergo dehydrative ring closures as easily as the corresponding six-membered compounds. It should find wide application, particularly in syntheses of alkaloid and aza-steroid systems.

EXPERIMENTAL

3-(2-*Acetamidoethyl*)-2-*acetyl*-6-*methoxyindole* (V).—Acetylharmaline (I) (500 mg, 1·96 mmol) was dissolved in

[5] E. Wenkert, S. Garrat, and K. G. Dave, *Canad. J. Chem.*, 1964, **42**, 489.

[6] H. Meerwein, E. Battenberg, H. Gold, P. Pfeil, and G. Willfang, *J. prakt. Chem.*, 1940, (2) **154**, 83; H. Meerwein, *Org. Synth.*, 1966, **46**, 113.

[7] S. Corsana and S. Algieri, *Ann. Chim.* (*Italy*), 1960, **50**, 75.

ethanolic 5% hydrogen chloride (10 ml). The solution rapidly became blue. Concentrated ammonium hydroxide solution (5 ml) was added, and a whitish solid precipitated out. Water (10 ml) and ethanol (10 ml) were added and the solution was evaporated to dryness to leave a reddish gum and white crystals of ammonium chloride. Water (15 ml) and ethyl acetate (25 ml) were added and the aqueous solution was extracted with ethyl acetate (2 × 25 ml). The extracts were dried and evaporated. The aqueous mother liquor was further extracted with dichloromethane (25 ml). The dichloromethane extract was dried and added to the organic material obtained from the ethyl acetate extracts. The mixture was evaporated to leave a reddish gum. Ethyl acetate (2 ml) was added and scratching initiated crystallisation. The colourless *crystals* obtained (0·3 mg, 56%) had m.p. 165—166°. Repeated recrystallisations from ethyl acetate afforded two crystalline forms, light brown rhombic crystals, m.p. 165—166°, and colourless needles, m.p. 148° (spectroscopically and chromatographically identical), $\lambda_{max.}$ (MeOH) 335, 258, and 215 nm (ε 22,750, 7810, and 24,600), $\lambda_{min.}$ 278 and 250 nm (ε 1460 and 6960), $\lambda_{max.}$ (MeOH–HCl) 335, 256, and 215 nm (ε 22,900, 7970, and 25,600), $\lambda_{min.}$ 278 and 250 nm (ε 1495 and 7300), $\lambda_{max.}$ (MeOH–NaOH) 335, 257, and 216 nm (ε 22,400, 7950, and 24,900), $\lambda_{min.}$ 280 and 250 nm (ε 1650 and 7025), δ ($CDCl_3$) 3·28 (2H, t, 3-CH_2), 3·53 (2H, t, N·CH_2), and 3·81 p.p.m. (3H, s, OMe); *m/e* 28, 83, 91, 117, 129, 139, 141, 160, 188, 202, 215, 230, and 274 (Found: C, 65·7; H, 6·5; N, 10·1. $C_{15}H_{18}N_2O_3$ requires C, 65·7; H, 6·6; N, 10·2%).

2-*Acetyl*-3-(2-*diacetylaminoethyl*)-6-*methoxyindole* (VI).—The keto-amide (V) (100 mg, 0·36 mmol) was dissolved in freshly distilled acetic anhydride (2 ml). Sodium acetate (100 mg; freshly sublimed) was added and the solution was refluxed in a stream of dry nitrogen for 6—7 h, cooled, and evaporated with addition of portions of ethyl alcohol to remove residual acetic anhydride. Water (2 ml) and then ethyl acetate (5 ml) were added. The aqueous solution was extracted with ethyl acetate (2 × 5 ml); the organic washings were combined, dried, and evaporated to give a brown gum. The gum was redissolved in ethyl acetate and filtered through an alumina column (6 in) under suction. The column was washed thoroughly with ethyl acetate. T.l.c. (9 : 1 $CHCl_3$–MeOH; silica gel) indicated the presence of a single product, R_F 0·7, in the eluate. Evaporation and crystallisation (from ethyl acetate) afforded a crystalline *solid*, m.p. 158—160° (71%), $\nu_{max.}$ (Nujol) 1703 (C=O) and 3320 cm^{-1} (NH); $\lambda_{max.}$ (MeOH) 335, 258, and 215 nm, $\lambda_{min.}$ 277 and 249 nm; δ ($CDCl_3$) 2·45 (6H, s, NAc_2), 2·68 (3H, s, Ac), 3·4 (2H, m, 3-CH_2), 3·94 (2H, m, N·CH_2), and 3·87 p.p.m. (3H, s, OMe); *m/e* 43, 202, 215, and 316 (Found: C, 64·7; H, 6·4; N, 8·9. $C_{17}H_{20}N_2O_4$ requires C, 64·5; H, 6·3; N, 9·0%).

1,2,3,5,6,11-*Hexahydro*-3-*oxoindolizino*[8,7-b]*indol*-4-*ium Tetrafluoroborate* (XIV).—3-(2-Succinimidoethyl)indole (XI) (1·0 g, 4·1 mmol) was dissolved in anhydrous dichloromethane. Triethyloxonium tetrafluoroborate * (4·5 g, 0·024 mol) was added under anhydrous conditions and the solution was stirred in the dark for 42 h at 25 °C. The yellow *precipitate* (650 mg) was filtered off; the mother liquor deposited a further 50 mg in 36 h. The solution was then filtered through silica gel (60—100 mesh) under suction in a sintered column (12 in). Initial washings afforded a greenish impurity. Subsequent eluates provided more product (total 750 mg, 85%). The product fractions were checked by t.l.c. and combined. Recrystallisation from dichloromethane afforded a specimen of m.p. 207°, $\nu_{max.}$ (Nujol) 1630 (C=C), 1795 (C=O), 2320 cm^{-1} (NH), $\lambda_{max.}$ (neutral CH_2Cl_2) 395 nm, $\lambda_{max.}$ (CH_2Cl_2–NaOH) 311 and 324 nm, $\lambda_{max.}$ (anhydrous dioxan, neutral or acidic) 228, 282, 294, 311, 324, and 387 nm, $\lambda_{min.}$ 267, 287, 300, and 319 nm, $\lambda_{max.}$ (MeOH) 333, 320, 290, 282, and 224 nm, (ε 3580, 4130, 6060, 6500, and 31,000), $\lambda_{min.}$ 328, 310, 288, and 252 nm (ε 3220, 3560, 5500, and 3580), δ (CD_3·CN) 2·31 (2H, narrow m, CH_2·CO), 2·97 (2H, narrow m, CH_2·C=N^+), 3·5 (2H, t, 6-H_2), and 4·19 p.p.m. (2H, t, 5-H_2); *m/e* 167, 195, 224, and 225 (Found: C, 53·8; H, 4·4; N, 9·3. $C_{14}H_{13}BF_4N_2O$ requires C, 53·8; H, 4·2; N, 9·0%).

1,5,6,11b-*Tetrahydro*-11H-*indolizino*[8,7-b]*indol*-3(2H)-*one* (XVI).—The fluoroborate (XIV) (100 mg, 0·03 mmol) was dissolved in anhydrous tetrahydrofuran (3 ml). Sodium borohydride (25 mg, 0·66 mmol) was added and the solution was stirred at room temperature for 3½ h, then evaporated. Water (1 ml) and ethyl acetate (2 ml) were added and the aqueous layer was extracted with ethyl acetate (2 ml). The organic extracts were dried and evaporated to afford a crystalline solid (96 mg, 95%), identical with the authentic amide (XVI).[7]

Hydrogenation over platinum oxide also afforded the amide (XVI), in 80% yield.

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* Stored under anhydrous ether at −30 °C. When a sample was required, the ether was removed quickly under vacuum, and the compound was rapidly weighed.