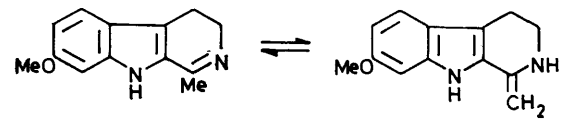
Reactions of Harmaline (4,9-Dihydro-7-methoxy-1-methyl-3*H*-pyrido-[3,4-*b*]indole) and its Derivatives. Part I. Reactions of Harmaline with Methyl Acrylate

By **Atta-ur-Rahman,**† University Chemical Laboratories, Lensfield Road, Cambridge CB2 1EW

The existence of an imine–enamine equilibrium in harmaline has been demonstrated by deuteriation studies; thus treatment with electrophilic olefins could bring about either *N*- or *C*-alkylation. At elevated temperatures, harmaline reacts with methyl acrylate to give 3,4,6,7-tetrahydro-10-methoxy-2*H*,12*H*-indolo[2,3-*a*]quinolizin-2-one (III). At room temperature, the major product is methyl 4-(3,4-dihydro-7-methoxy-β-carbolin-1-yl)butyrate (XI), which can be cyclized to 2,3,6,7-tetrahydro-10-methoxy-4*H*,12*H*-indolo[2,3-*a*]quinolizine-4-one (IV). With a large excess of methyl acrylate, the major product is methyl 3-(2,3,6,7-tetrahydro-10-methoxy-4-oxo-4*H*,12*H*-indolo[2,3-*a*]quinolizine-1-yl)propionate (XIV), formed along with a minor product resulting from the attack of three molecules of methyl acrylate on harmaline.

HARMALINE (4,9-dihydro-7-methoxy-1-methyl-3*H*-pyrido[3,4-*b*]indole) (I) is a simple indole alkaloid, occurring in the seeds of *Peganum harmala*.[1] The presence of the $CH_3{\cdot}CR{:}NR'$ grouping offers the possibility of either *N*- or *C*-alkylation with electrophilic olefins *via* the expected imine–enamine equilibrium in solution.

During studies carried out on the reactions of 2-methylharmaline with electrophilic olefins [2] it was noticed that when harmaline was subjected to t.l.c. on silica gel in chloroform–methanol (7 : 3) it separated into two greenish fluorescent bands.[3] Isolation and re-examination of each component gave material identical with harmaline and again separable into the same two components on t.l.c. It was suspected that these were the tautomeric imine and enamine forms of harmaline. Stronger evidence for the existence of the enamine form (II) in equilibrium with the imine in solution came from the n.m.r. spectrum of a solution in [$^2H_4$]methanol. Collapse of the *C*-methyl signal was observed, showing ready exchange with deuterium. This can be rationalized by the stepwise deuteriation of the *C*-methyl proton *via* rapid imine–enamine interconversion (Scheme 1). No olefinic proton signals were detectable, however, indicating the small contribution of the enamine form to the equilibrium mixture.



(I) (II)

When harmaline was refluxed with a small excess of methyl acrylate in methanol–benzene, the formation of a major new faster running compound was indicated by t.l.c. after 72 h. The product possessed a greyish green fluorescence in u.v. light, and crystallized as pale yellow crystals in 72% yield. Its u.v. spectrum showed longer wavelength absorptions at 370 and 390 nm, indicative of the extent of the conjugation of the indole nucleus with the adjacent chromophore. On acidification, these absorptions disappeared and a new absorption appeared at 410 nm. Subsequent basification resulted in the reversion of the spectrum to its original form. The i.r. spectrum showed the presence of a carbonyl group, $\nu_{max.}$ 1632 cm^{-1}, and the molecular ion in the mass spectrum appeared at *m/e* 268 as the parent peak. This suggested that one molecule of methyl acrylate had reacted with harmaline and the alkylated

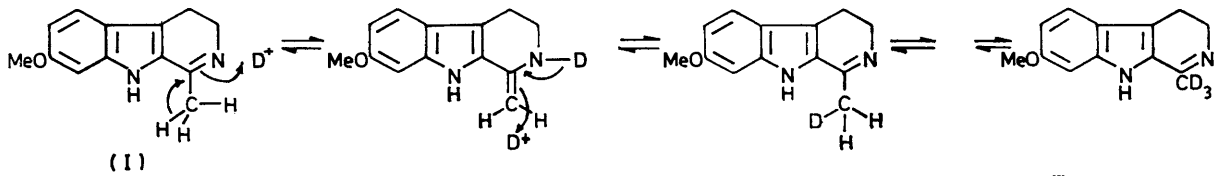
† *Present address:* Postgraduate Institute of Chemistry, University of Karachi, Karachi-32, West Pakistan.

[1] F. Goebel, *Annalen*, 1841, **38**, 363; R. H. F. Manske, W. H. Perkin, and R. Robinson, *J. Chem. Soc.*, 1927, 1.

[2] Atta-ur-Rahman, unpublished results.

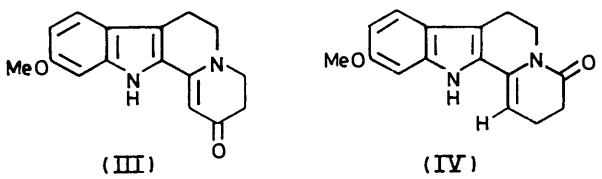
[3] Atta-ur-Rahman and T. Burney, M.Sc. Thesis, University of Karachi, 1970.

intermediate had then cyclised. If *N*-alkylation was followed by cyclisation, substance (III) would be obtained, whereas *C*-alkylation and cyclization would lead to structure (IV).



SCHEME 1

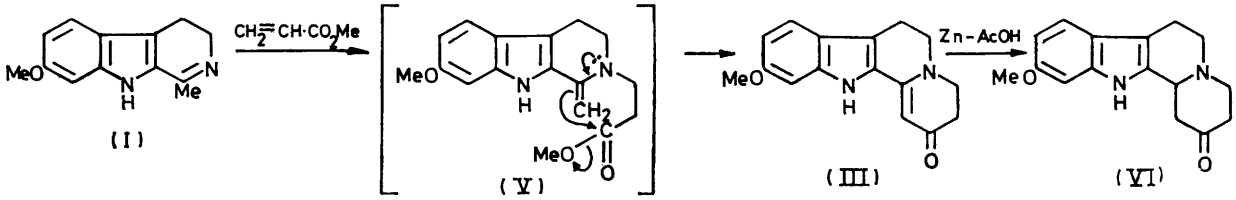
The low value for the C=O stretching frequency indicated structure (III) for the product, which was confirmed by the n.m.r. spectrum. A single olefinic



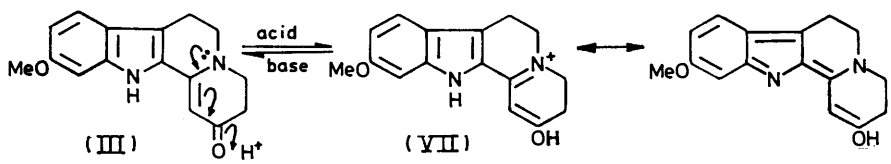
proton signal was visible at δ 5·51 p.p.m. as a sharp singlet. The signal for the corresponding olefinic proton in the lactam (IV) would be split by the adjacent methylene protons. Since the intermediate enamine (V) was not detectable during the course of the reaction, the rate-determining step must be the initial *N*-alkylation.* The enamino-ketone (III) was readily reducible with zinc and glacial acetic acid to the ketone (VI), which possessed the u.v. spectrum expected for a methoxyindole (Scheme 2).

The bathochromic shift observed in the u.v. spectrum of substance (III) on acidification may be rationalized by invoking the *O*-protonated structure (VII) (Scheme 3), which would be expected to absorb at higher wavelengths. Such shifts are characteristic of conjugated indoles such as (VIII), and are explained by postulating the generation of the iminium ion (IX) from the enamine (VIII) on acidification.[5] Harmaline itself undergoes a similar shift from 338 to 382 nm on acidification,[6] and this may be explained by the imine–iminium conversion indicated.

When harmaline was treated with a small excess of methyl acrylate at room temperature, it was converted into a new substance which was isolated as a pale yellow gum in 90% yield after chromatography. The u.v. spectrum of the product was strikingly similar to that of harmaline and showed similar shifts in acid and in base. The mass spectrum showed the molecular ion at *m/e* 300, indicating the involvement of one molecule

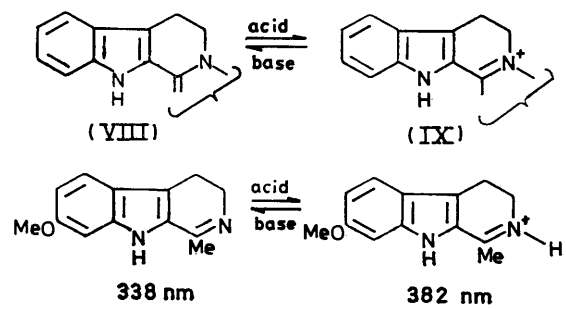


SCHEME 2



SCHEME 3

each of methyl acrylate and harmaline. The n.m.r. spectrum ($CDCl_3$) showed no olefinic proton signals.



* Similar intramolecular *C*-acylations of enamines have been described.[4]

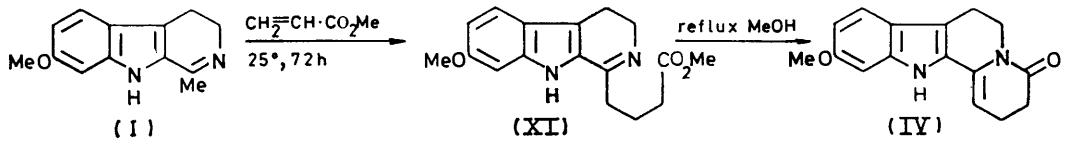
[4] A. I. Meyers and J. C. Sircar, *J. Heterocyclic Chem.*, 1965, **2**, 329; W. Sobotka, W. N. Beverung, G. G. Munoz, J. C. Sircar, and A. I. Meyers, *J. Org. Chem.*, 1965, **30**, 3667.

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

[6] I. D. Spencer, *Canad. J. Chem.*, 1959, **37**, 1851.

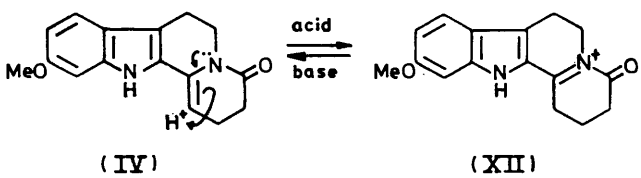
Hence the product could not be the *N*-alkylated enamine ester (V). The spectroscopic data were consistent with structure (XI). An exact mass measurement on the molecular ion (M^+ 300·1473) agreed with that calculated for the formula $C_{17}H_{20}N_2O_3$. Thus by lowering the temperature at which the reaction is conducted, *C*-alkylation can be made to predominate over *N*-alkylation in harmaline.

When the ester (XI) was refluxed in methanol, it was quantitatively converted into a new product



SCHEME 4

which crystallized readily. The substance appeared as a violet spot under u.v. light on a t.l.c. plate, in contrast to the ester (XI), which possessed a bright green fluorescence. The u.v. spectrum showed absorptions at 317 and 330 nm, indicative of the nature of the chromophore. Addition of acid produced a new



absorption at 425 nm, although this was not simultaneously accompanied by collapse of peaks at 317 and 330 nm. The understandably smaller contribution of the iminium ion (XII) on acidification as compared

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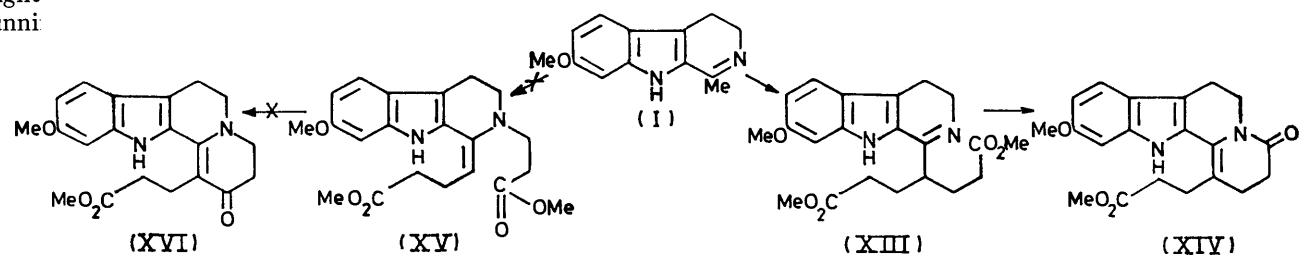
light. The latter crystallized readily on concentration of the solution. The major product was then obtained (85% yield) by chromatography over activity I alumina. Its u.v. spectrum was similar to that of harmaline and underwent the same bathochromic shift on acidification. The mass spectrum showed the molecular ion at *m/e* 386, indicating that two molecules of methyl acrylate had taken part in the alkylation under these conditions. An exact mass measurement of the molecular ion agreed with the formula $C_{21}H_{26}N_2O_5$. Structure (XIV) was confirmed by the n.m.r. spectrum. The absence of olefinic proton signals provided further evidence against the alternative structure (XV) (Scheme 5).

Attempted column chromatography of the diester (XIII) over a silicic acid CC7 column resulted in complete conversion into a new faster-moving substance. Evaporation of the eluates afforded a crystalline solid which appeared as a violet spot on t.l.c. The u.v. spectrum was the same as that of the product (IV) obtained previously, and indicated that cyclization of the amine diester (XIII) to the enamide (XIV) proceeds readily under the specified conditions. The same cyclization could be effected by prolonged refluxing of the diester (XIII) in dioxan. In subsequent preparations, the ester (XIV) was obtainable directly without isolation of the intermediate diester (XIII), by first



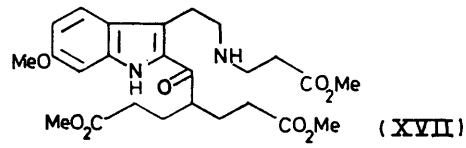
SCHEME 5

to substances in which the adjacent destabilizing amidic carbonyl group is absent could account for this observation. An appropriately coupled olefinic proton resonated at δ 5·66 p.p.m. in the n.m.r. spectrum of the substance, confirming that it was the amide (IV), isomeric with the enamino-ketone (III) obtained previously. The mass spectral cleavage pattern was also in accord with structure (IV) (Scheme 4).

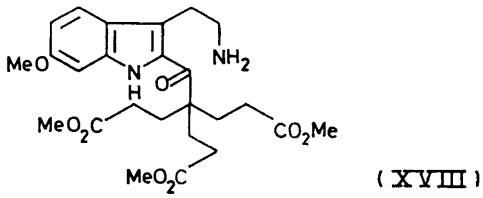
When harmaline was treated with a large excess of methyl acrylate at room temperature for 48 h, t.l.c. indicated the formation of a major new product possessing a bright green fluoresence in u.v. light, and a minor, faster-running product, which appeared violet in u.v. leaving the mixture at room temperature for 48—72 h and then refluxing it in dioxan.

The u.v. spectrum of the minor crystalline product was reminiscent of a 2-acylindole, undergoing no shifts in acid or base. The mass spectrum indicated a molecular weight of 490, indicating possible trialkylation and hydrolysis of harmaline. Two likely structures appeared to be (XVII) and (XVIII). The n.m.r. spectrum (C_6D_6) showed one ester function in a slightly different environment from the other two [δ 3·42 (3H) and 3·45 (6H) p.p.m.] and was in accord with structure (XVII). The triester (XVIII) would be expected to show a much simpler spectrum. Moreover, the presence

of a substantial M^+ −73 (M − $CH_2{\cdot}CO_2Me$) fragment in the mass spectrum afforded further proof of structure (XVII).

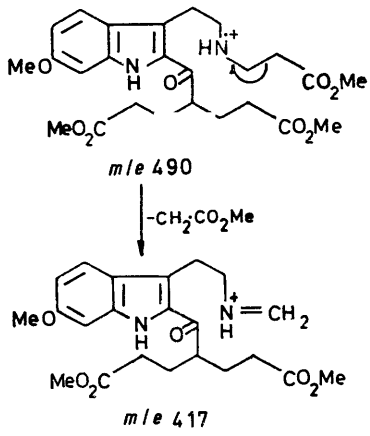


(XVII)

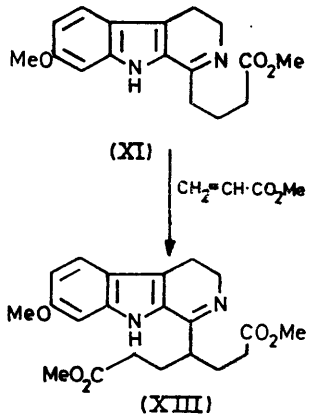


(XVIII)

Finally, when the ester (XI) was treated with an excess of methyl acrylate at room temperature for 48 h, it



was completely converted into the diester (XIII), as expected.



(XI)

(XIII)

Thus by suitable manipulation of quantities of reagent and conditions, it is possible to control the direction of the addition of methyl acrylate. This approach provides a simple method for the introduction of an extra ring into β-carboline systems, corresponding to ring D in yohimbine and eburnamine. Use of appropriately substituted electrophilic olefins might make it possible to extend the method to the syntheses of more complex alkaloidal structures of the *Yohimbe* and *Hunteria* series. Many of the methoxyindoles synthesized are of potential pharmacological importance and are to be studied.

EXPERIMENTAL

Evaporations were carried out with a Büchi rotary evaporator (flask temperature ≤40°). Thin-layer chromatograms were run on silica gel (GF-254) in chloroform–methanol (9 : 1). Spots were detected with a u.v. lamp or by developing with iodine. U.v. spectra were measured with a Unicam SP 800 spectrophotometer, n.m.r. spectra with a Varian 100 MHz instrument, and mass spectra with an A.E.I. MS902 spectrometer.

3,4,6,7-*Tetrahydro*-10-*methoxy*-4H,12H-*indolo*[2, ... *inolizin*-2-*one* (III).—Harmaline (100 mg, 0·47 mmol) was dissolved in anhydrous methanol (10 ml) and benzene (10 ml) mixture by gentle heating. Methyl acrylate (54 μl, 0·55 mmol) was added and a slow stream of dry nitrogen was blown through the solution, which was refluxed in the dark for 24 h. T.l.c. then showed a faster-running product and some unchanged harmaline. More methyl acrylate (54 μl, 0·55 mmol) was added and the solution was refluxed for a further 48 h. Evaporation and crystallisation from methyl alcohol gave pale yellow *crystals* (92 mg, 72%), m.p. 264—265°; $\nu_{max.}$ (Nujol) 1632 (C=O) and 1620 (C=C) cm^{-1}; $\lambda_{max.}$ (MeOH) 390, 370, and 266 nm (ε 43,279, 41,614, and 5394), $\lambda_{min.}$ 380, 285, and 259 nm (ε 38,702, 1706, and 4577), $\lambda_{max.}$ (MeOH–HCl) 410, 252, and 215 nm (ε 24,140, 8322, and 28,998), $\lambda_{min.}$ 290 and 240 nm (ε 2497 and 7075), $\lambda_{max.}$ (MeOH–NaOH) 390, 370, and 265 nm (ε 34,956, 33,648, and 6658), $\lambda_{min.}$ 380, 274, and 255 nm (ε 31,620, 2496, and 6442); δ ($CD_3{\cdot}OD$) 5·5 (1H, s, olefinic) and 3·79 p.p.m. (3H, s, OMe); *m/e* 120, 184, 225, 253, and 268 (Found: C, 71·5; H, 5·8; N, 10·2. $C_{16}H_{16}N_2O_2$ requires C, 71·6; H, 6·0; N, 10·4%).

Methyl 4-(3,4-*Dihydro*-7-*methoxy*-β-*carbolin*-1-*yl*)*butyrate* (XI).—Harmaline (250 mg, 1·17 mmol) was dissolved in 1 : 1 methanol–benzene (10 ml). Methyl acrylate (125 μl, 1·4 mmol) was added. Dry nitrogen was bubbled through the solution for 1 min. The flask was then stoppered and kept in the dark at 25° for 72 h. T.l.c. [$CHCl_3$–MeOH (9 : 1)] showed the presence of a major product (R_F, 0·1) along with some unchanged harmaline. More methyl acrylate (60 μl, 0·7 mmol) was added and the solution was left for a further 72 h at room temperature. T.l.c. then showed the complete conversion of harmaline. The solution was evaporated and the brownish gum chromatographed on an alumina column. Elution first with benzene ethyl acetate and later with ethyl acetate–methanol mixtures afforded a pale yellow *gum* (310 mg, 90%), which was homogeneous on t.l.c. and appeared as a bright greenish fluorescent spot in u.v. light; $\nu_{max.}$ (Nujol) 1740 (C=O) and 3360 (NH) cm^{-1}; $\lambda_{max.}$ (MeOH) 332 and 215 nm (ε 9680 and 20,670), $\lambda_{min.}$ 280 nm (ε 2941) $\lambda_{max.}$ (MeOH–HCl) 380, 332, and 215 nm (ε 6836, 7630, and 20,800), $\lambda_{min.}$ 345 and 280 nm (ε 5560 and 2540), $\lambda_{max.}$ (MeOH–NaOH) 330 and 215 nm (ε 10,410 and 20,350), $\lambda_{min.}$ 280 nm (ε 3736); δ ($CDCl_3$) 3·86 (3H, s, CO_2Me) and

3·74 p.p.m. (3H, s, OMe); *m/e* 170, 185, 199, 241, 269, and 300; M^+ 300·1473 ($C_{17}H_{20}N_2O_3$ requires *M*, 300·1473).

2,3,6,7-*Tetrahydro*-10-*methoxy*-4H,12H-*indolo*[2,3-a]*quinolizin*-4-*one* (IV) —The ester (XI) (20 mg, 0·075 mmol) was dissolved in methanol and refluxed for 12 h. T.l.c. indicated complete conversion into a faster-running compound, R_F 0·9. Evaporation *in vacuo* afforded a crystalline *mass*, which was recrystallized from methanol (yield 19 mg), m.p. 216°; $\lambda_{max.}$ (MeOH) 330, 317, and 233 nm (ε 23,550, 21,750, and 29,400), $\lambda_{min.}$ 324 and 278 nm (ε 20,500 and 5050), $\lambda_{max.}$ (MeOH–NaOH) 330, 317, and 230 nm (ε 20,800, 19,110, and 28,800), $\lambda_{min.}$ 323 and 280 nm (ε 18,100 and 5210), $\lambda_{max.}$ (MeOH–HCl) 425, 331, 317, and 233 nm (ε 4450, 20,065, 18,850, and 26,450), $\lambda_{min.}$ 355, 323, and 280 nm (ε 520, 17,810, and 4790); δ [$(CD_3)_2CO$] 5·66 (1H, m, olefinic) and 3·74 (3H, s, OMe); *m/e* 120, 134, 225, 239, 253, and 268 (Found: C, 71·6; H, 6·0; N, 10·5. $C_{16}H_{16}N_2O_2$ requires C, 71·7; H, 5·8; N, 10·5%).

Dimethyl 4-(3,4-*Dihydro*-7-*methoxy*-β-*carbolin*-1-*yl*)*heptanedioate* (XIII) *and Dimethyl* 4-{6-*Methoxy*-3-[2-(2-*methoxycarbonylethylamino*)*ethyl*]*indol*-2-*ylcarbonyl*}*heptanedioate* (XVII).—Harmaline (500 mg, 2·33 mmol) was dissolved in 1 : 1 methanol–benzene (25 ml). Methyl acrylate (2·0 g, 24 mmol) was added and the solution was stirred in an atmosphere of nitrogen in the dark for 48 h at 25°. T.l.c. indicated complete conversion into a major product (R_F 0·35), possessing a bright green fluorescence, and a minor product (XVII) (R_F 0·9) which appeared violet in u.v. light. On evaporation the minor product crystallized as *needles*, m.p. 123—124° (80 mg). The mother liquor was chromatographed over an alumina column to afford a chromatographically homogenous pale yellow *product* (XIII) (750 mg, 85%), $\nu_{max.}$ 1730 (CO_2Me) and 3320 cm^{-1} (NH), $\lambda_{max.}$ (MeOH) 334 and 223 nm (ε 16,920 and 21,680), $\lambda_{min.}$ 280 and 215 nm (ε 3701 and 20,620), $\lambda_{max.}$ (MeOH–HCl) 400, 334, 325, and 315 nm, $\lambda_{min.}$ 335 and 280 nm, $\lambda_{max.}$ (MeOH–NaOH) 334 and 222 nm (ε 16,215 and 20,800), $\lambda_{min.}$ 280 and 215 nm ($\varepsilon_{min.}$ 3348 and 19,400), δ ($CDCl_3$) 3·7 (6H, s, 2 × CO_2Me) and 3·86 p.p.m. (3H, s, OMe); *m/e* 55, 90, 227, 281, 300, 313, 355, and 386; M^+ 386·1845 ($C_{21}H_{26}N_2O_5$ requires *M*, 386·1841).

Compound (XVII) showed $\nu_{max.}$ 1735 (CO_2Me) and 3320 cm^{-1} (NH); $\lambda_{max.}$ (MeOH) 335, 260, and 215 nm (ε 22,400, 7150, and 22,150), $\lambda_{min.}$ 280 and 250 nm (ε 1140 and 5810) (no shifts in acidic or basic media); δ [$(CD_3)_2CO$] 3·62 p.p.m. (3H, s, CO_2Me); *m/e* 202, 417, and 490 (Found: C, 61·2; H, 6·9; N, 5·7. $C_{25}H_{34}N_2O_8$ requires C, 61·4; H, 6·8; N, 5·8%).

Methyl 3-(2,3,6,7-*Tetrahydro*-10-*methoxy*-4-*oxo*-4H,12H-*indolo*[2,3-a]*quinolizin*-1-*ylpropionate* (XIV).—The diester (XIII) (250 mg, 0·66 mmol) was subjected to chromatography over a silicic acid CC7 column and eluted with benzene–ethyl acetate (95 : 5). The later fractions contained a new compound of higher R_F value (0·8) (t.l.c. on silica gel). Evaporation afforded a crystalline solid (230 mg, 98%), m.p. 161—162° (from ethyl acetate).

The same conversion could be effected by refluxing a solution of the ester (XIII) in dioxan for 6 h. The *ester* (XIV) had $\nu_{max.}$ (Nujol) 1740 (ester C=O) and 3328 cm^{-1} (NH); $\lambda_{max.}$ (MeOH) 334, 320, and 235 nm (ε 25,473, 25,309, and 31,225), $\lambda_{min.}$ 327, 278, and 215 (ε 23,665, 6245, and 20,872), $\lambda_{max.}$ (MeOH–HCl) 430, 334, 320, and 220 nm (ε 14,955, 12,983, 12,654, and 22,350), $\lambda_{min.}$ 365, 328, 285, and 215 nm (ε 1314, 11,997, 3944, and 21,364), $\lambda_{max.}$ (MeOH–NaOH) 334, 320, 304, and 228 nm (ε 10,390, 10,300, 7900, and 29,800), $\lambda_{min.}$ 328, 310, and 280 nm (ε 9890, 7590, and 5440); δ (CD_2Cl_2) 3·7 (3H, s, CO_2Me), 3·82 (3H, s, OMe), and 3·96 p.p.m. (2H, t, $N{\cdot}CH_2$); *m/e* 83, 281, 282, and 354 (Found: C, 67·8; H, 6·2; N, 7·9. $C_{20}H_{22}N_2O_4$ requires C, 67·8; H, 6·2; N, 7·9%).

Alkylation of the Ester (XI) *with Methyl Acrylate*.—The ester (XI) (4 mg, 0·013 mmol) was dissolved in methanol (0·1 ml). Methyl acrylate (40 mg, 0·46 mmol) was added, and the stoppered tube was left in the dark for 48 h. T.l.c. showed complete conversion into a faster-moving product. Spectroscopic examination and direct comparison showed that the product (4·3 mg) was identical with the diester (XIII) obtained earlier.

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