497. *Emetine and Related Compounds. Part V.*[1] *Some Reactions of 3,4-Dihydroisoquinolines with Carbonyl Compounds.*

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Earlier structures suggested for the products of the reaction between the ester (V; R = CO_2Et) and formaldehyde have been revised. This ester and related compounds give tricyclic pyridones (IX; R = CO_2Et, etc.) with ethyl α-formylbutyrate.

The dihydroisoquinoline (XV) condenses with esters of acetonedicarboxylic acid to give unusual cyclisation products, tentatively formulated as (XVI; R^1 = H or CO_2Alk, R^2 = Alk).

A SYNTHESIS of the ring skeleton of emetine (III), by a method that differs in principle from earlier ones,[2,3] was envisaged as proceeding *via* the ester (I; R = $CHEt{\cdot}CO_2Et$) and the amide (II).

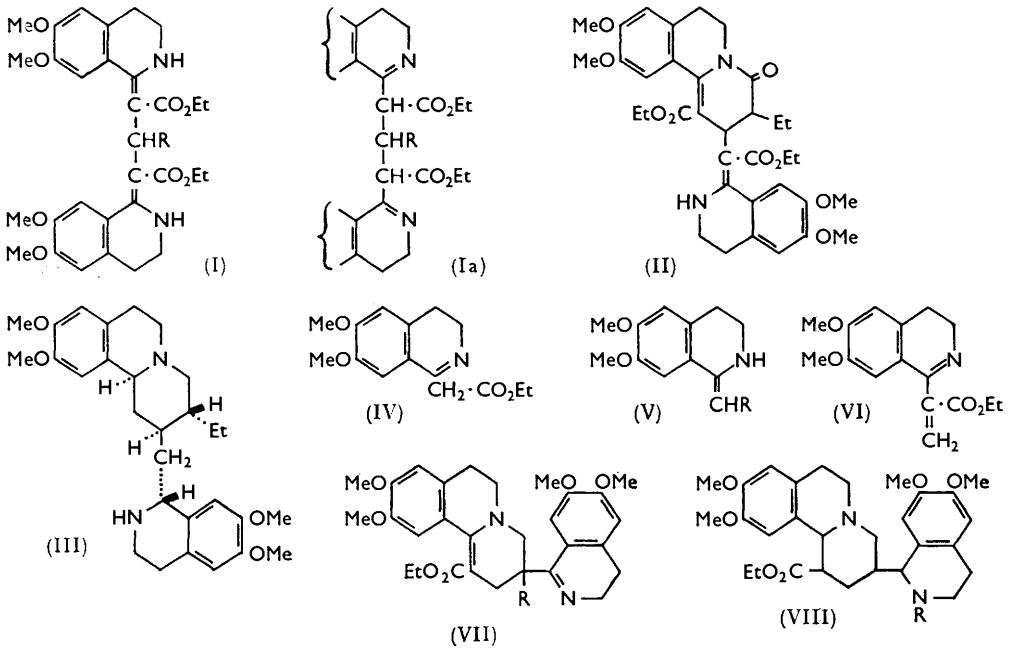
The related ester (Ia; R = H) has been described by Osbond [4] as the product of condensing one mol. of formaldehyde with two of the dihydroisoquinoline (IV). However, since the ultraviolet spectrum ($\lambda_{max.}$ 228·5, 270, and 330 mμ) clearly shows that the ester (IV) exists in neutral solution as the form (V; R = CO_2Et) having an exocyclic double bond,[5] it seemed possible that Osbond's product might also possess the alternative structure (I; R = H). Repetition of Osbond's reaction in aqueous acetic acid gave a crude ester from which pure material, with a melting point similar to that recorded previously, was isolated only with difficulty, in *ca.* 30% yield. In ethanol the reaction was much smoother and the yield over 90%. The product had an ultraviolet spectrum in ethanol identical with that of the ester (V; R = CO_2Et) and must therefore exist entirely in the form (I; R = H), having exocyclic double bonds. The spectra of these compounds in ethanolic hydrogen chloride were also identical ($\lambda_{max.}$ 248, 308, and 363 mμ) and showed that the corresponding salts had the endocyclic structures (Ia) and (IV).

Osbond [4] suggested structure (VI) for the compound derived from equimolar proportions of formaldehyde and the ester (IV) in aqueous acetic acid. However, we find that the material shows two carbonyl stretching peaks at 1725 and 1670 $cm.^{-1}$ in the infrared spectrum and that molecular-weight determinations by the Rast method give values

[1] Part IV, Ritchie, Preston, Walker, and Whiting, *J.*, 1962, 3385.
[2] Battersby and Turner, *J.*, 1960, 717, and references therein.
[3] Clark, Meredith, Ritchie, and Walker, *J.*, 1962, 2490.
[4] Osbond, *J.*, 1951, 3464.
[5] Cf. Openshaw and Whittaker, *J.*, 1961, 4939.

above 500. As the same product was obtained in high yield by treatment of the ester (I; R = H) with a further mol. of formaldehyde in acetic acid, the pentacyclic structure (VII; R = CO_2Et), arising from two mol. of formaldehyde and two of the ester (V; R = CO_2Et), is suggested. Further reaction of the ester (I; R = H) with formaldehyde did not occur in ethanol, which may account for the high yield of the former obtained in this solvent.

Alkaline hydrolysis of the diester (VII; R = CO_2Et) was accompanied by decarboxylation to give the monoester (VII; R = H), which absorbed two mol. of hydrogen in the presence of Adams catalyst to yield the saturated ester (VIII; R = H). The infrared



spectra of the two esters last mentioned showed single carbonyl stretching peaks at 1670 and 1725 cm.$^{-1}$, respectively. The presence of both secondary and tertiary amino-groups in (VIII; R = H) was shown by acetylation to the amide (VIII; R = Ac), which was characterised as the monopicrate.

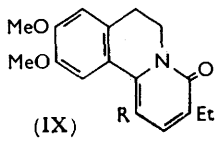
Although Osbond [6] failed to achieve satisfactory reaction between the ester (V; R = CO_2Et) and other aldehydes, we have found that ethyl α-formylbutyrate (XI) condenses with it in aqueous acetic acid at 100° to give a neutral product. The yield was 45% when two molar proportions of the ester were used and was increased to 70% with equimolar quantities. The compound was formulated as the pyridone (IX; R = CO_2Et), in keeping with its ultraviolet ($\lambda_{max.}$ 240, 283, and 350 mμ) and infrared spectra. Hydrolysis gave the acid (IX; R = CO_2H), which was decarboxylated at its melting point to the pyridone (IX; R = H).

The pyridone (IX; R = CN) was similarly formed from the nitrile (V; R = CN) in aqueous acetic acid, but the intermediate ester (X) was produced in refluxing toluene. This ester cyclised to the pyridone in acetic acid. High yields of the pyridone (IX; R = CN) were obtained from the tetrahydroisoquinoline (V; R = CN) and the diethyl acetal (XII) in aqueous acetic acid at 100°, but the ester (V; R = CO_2Et) suffered considerable hydrolysis and decarboxylation under these conditions and only *ca.* 35% of product (IX;

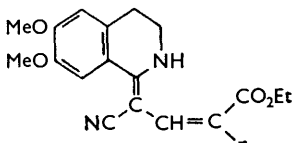
[6] Osbond, *J.*, 1952, 4785.

R = CO_2Et) was isolated. The enol ether (XIII) with the nitrile (V; R = CN) gave little pyridone (IX; R = CN) in aqueous acetic acid, but on condensation in benzene in the presence of sodium ethoxide yields of *ca.* 45% resulted.

Our failure to obtain the ester (I; R = $CHEt{\cdot}CO_2Et$) necessitated modifying our



(IX)



(X)

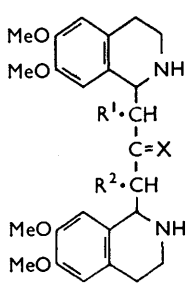
$CHO{\cdot}CHEt{\cdot}CO_2Et$ (XI)

$(EtO)_2CH{\cdot}CHEt{\cdot}CO_2Et$ (XII)

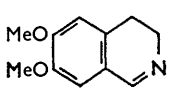
$EtO{\cdot}CH{=}CEt{\cdot}CO_2Et$ (XIII)

original synthetic scheme, so we sought to prepare the related triester (XIV; X = $:CEt{\cdot}CO_2Et$, $R^1 = R^2 = CO_2Et$) *via* the ketone (XIV; X = O, $R^1 = R^2 = CO_2Et$).

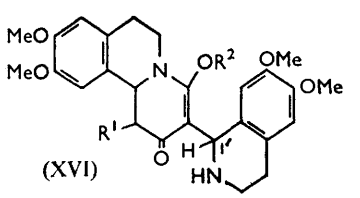
We have already described the reaction of 3,4-dihydro-6,7-dimethoxyisoquinoline (XV) with acetonedicarboxylic acid, to give the symmetrical ketone (XIV; X = O, $R^1 = R^2 = H$).[7] However, ethyl acetonedicarboxylate (1 mol.) with this base (XV) (2 mol.) gave, in good yield, a crystalline product whose ultraviolet spectrum had a strong absorption band at 293 mμ (ε 32,800) and so differed from the expected ketone (XIV; X = O, $R^1 = R^2 = CO_2Et$). Ethyl, methyl, and benzyl hydrogen acetonedicarboxylate gave a series of closely related compounds with absorption maxima at 287—292 mμ. Their infrared spectra showed that the alkoxyl group of the ester had been retained, but that the carbonyl stretching peak at 1725 $cm.^{-1}$ was absent. The stretching frequency of the ketonic carbonyl group was shifted from 1710 to 1680 $cm.^{-1}$ and a strong band had appeared at 1570 $cm.^{-1}$. These compounds have been tentatively assigned the structures (XVI; $R^1 = H$, $R^2 = Et$, Me, or CH_2Ph), and the product from ethyl acetonedicarboxylate that of the corresponding ester (XVI; $R^1 = CO_2Et$, $R^2 = Et$). Analytical figures and molecular-weight determinations were in good agreement with these formulations, and



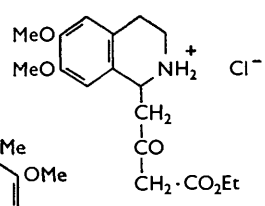
(XIV)



(XV)



(XVI)



(XVII)

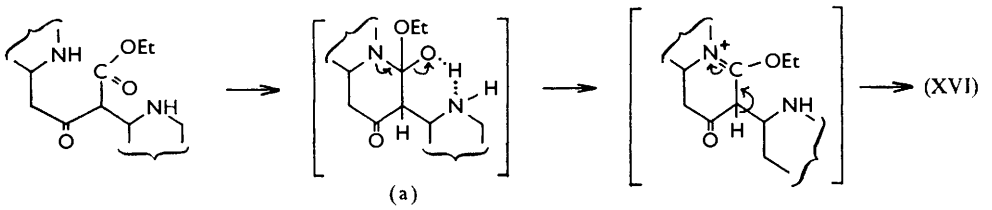
Zeisel determinations demonstrated the presence of six alkoxyl groups in the product (XVI; $R^1 = CO_2Et$, $R^2 = Et$), five in (XVI; $R^1 = H$, $R^2 = Et$ or Me), and four in (XVI; $R^1 = H$, $R^2 = CH_2Ph$) (the benzyloxy-group being inert under the conditions of analysis). The number and nature of the alkoxyl groups were also apparent from the nuclear magnetic resonance spectra of these compounds. Two single-proton resonance bands with τ 4·9—5·1 and 4·55—4·65 were tentatively correlated with the doubly allylic 1'-hydrogen atom and the hydrogen atom of the secondary amine, shifted towards the low field as a result of bonding with the carbonyl group.

Ester (XVI; $R^1 = CO_2Et$, $R^2 = Et$) was rapidly degraded to the dihydroisoquinoline (XV) in aqueous hydrochloric acid, but ketone (XVI; $R^1 = H$, $R^2 = Et$) was converted

[7] Chapman, Holton, Ritchie, Walker, Webb, and Whiting, *J.*, 1962, 2471.

by careful treatment with ethanolic hydrogen chloride into the ester hydrochloride (XVII).[7]

Cyclisation between an ester group and a secondary amine in the primary reaction product (XIV; X = O, R^1 = CO_2Alk or H, R^2 = CO_2Alk), to give compounds such as (XVI) instead of the expected amide, would be of mechanistic interest. Professor D. H. R. Barton, F.R.S., has suggested the following scheme, in which hydrogen bonding of a hydroxyl group with the second nitrogen atom in the intermediate (a) provides a special path for the elimination of hydroxyl rather than ethoxyl.



The instability of these compounds made them of little value in our projected synthesis of emetine, and the scheme was abandoned. None of the intermediates described in this paper showed useful activity against *Entamoeba histolytica* when tested on infected weanling rats.

Experimental

Diethyl αα′-Di-(1,2,3,4-tetrahydro-6,7-dimethoxy-1-isoquinolylidene)glutarate (I; R = H).—1-Ethoxycarbonylmethylene-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (V; R = CO_2Et) (11·1 g.), ethanol (80 ml.), 0·2M-ethanolic piperidine acetate (20 ml.), and 10% aqueous formaldehyde (6·4 ml.) were kept overnight at room temperature. The ester (I; R = H) was filtered off, washed with ethanol and ether, and dried at 100°; it formed prisms (10·6 g., 93·5%), m. p. 180·5—182° (lit.,[4] m. p. 182—183°), $\lambda_{max.}$ (in EtOH) 228·5, 270, and 330 mμ (ε 46,800, 16,400, and 37,500) (in EtOH–HCl) 248, 308, and 363 mμ (ε 32,800, 19,300, and 19,300).

Diethyl 3-(3,4-Dihydro-6,7-dimethoxy-1-isoquinolyl)-3,4,6,7-tetrahydro-9,10-dimethoxy-2H-benzo[a]*quinolizine-1,3-dicarboxylate* (VII; R = CO_2Et).—(*a*) Ester (V; R = CO_2Et) (5 g.), 38% w/v aqueous formaldehyde (1·42 ml.), and 50% aqueous acetic acid (50 ml.) were kept at room temperature for 5 hr., and the mixture was then slowly neutralised at 5° with 30% aqueous sodium hydroxide. The pale yellow precipitate (4·87 g.), m. p. 175—178°, crystallised from ethyl acetate to give the *ester* (VII; R = CO_2Et) (3·5 g.), m. p. 180—183° (Found: C, 65·9; H, 6·6; N, 4·8. $C_{32}H_{38}N_2O_8$ requires C, 66·4; H, 6·6; N, 4·8%) (Osbond [4] records m. p. 179—181° for his product), $\lambda_{max.}$ (in EtOH) 229, 280, 310, and 354 mμ (ε 40,000, 14,400, 15,500, and 10,000) (in EtOH–HCl) 250, 314, and 370 mμ (ε 21,000, 17,700, and 15,100). (*b*) Ester (I; R = H) (0·44 g.), 10% aqueous formaldehyde (0·24 ml.), and 50% aqueous acetic acid (5 ml.), treated as in (*a*), gave the ester (VII; R = CO_2Et) (0·28 g.), m. p. and mixed m. p. 182—183°.

Ethyl 3-(3,4-Dihydro-6,7-dimethoxy-1-isoquinolyl)-3,4,6,7-tetrahydro-9,10-dimethoxy-2H-benzo[a]*quinolizine-1-carboxylate* (VII; R = H).—The diester (VII; R = CO_2Et) (2 g.) was heated in refluxing 5% ethanolic potassium hydroxide (30 ml.) for 2 hr. The gum obtained on removal of the solvent was taken up in dilute hydrochloric acid and reprecipitated in granular form with dilute sodium hydroxide solution. Recrystallisation from ethanol gave the *monoester* (VII; R = H) (1·13 g.) as prisms, m. p. 173—174° (Found: C, 68·45; H, 6·75; N, 5·5%; *M*, 504. $C_{29}H_{34}N_2O_6$ requires C, 68·75; H, 6·8; N, 5·5%; *M*, 507), $\lambda_{max.}$ (in EtOH) 226, 278, 309, and 352 mμ (ε 47,000, 15,500, 16,800, and 10,600) (in EtOH–HCl) 249, 310, and 365 mμ (ε 21,000, 18,300, and 20,900).

The *picrate* separated from ethanol–dimethylformamide as needles, m. p. 194—195° (decomp.) (Found: C, 50·8; H, 4·0; N, 11·7. $C_{41}H_{40}N_8O_{20}$ requires C, 51·0; H, 4·1; N, 11·6%).

Ethyl 1,2,3,4,6,7-Hexahydro-9,10-dimethoxy-3-(1,2,3,4-tetrahydro-6,7-dimethoxy-1-isoquinolyl)-11bH-benzo[a]*quinolizine-1-carboxylate* (VIII; R = H).—Ester (VII; R = H) (1·75 g.) in glacial acetic acid (20 ml.) was shaken under hydrogen at room temperature and pressure with

Adams catalyst (70 mg.) until 2·1 mol. of hydrogen had been absorbed. After removal of the catalyst and the solvent, the residue was taken up in water and neutralised with 2N-sodium hydroxide, to give a grey amorphous powder (1·53 g.), m. p. 184—188°. Recrystallisation from chloroform–ether gave the *ester* (VIII; R = H) as needles, m. p. 197—198° (Found: C, 67·7; H, 7·2; N, 5·7. $C_{29}H_{38}N_2O_6$ requires C, 68·2; H, 7·5; N, 5·5%), $\lambda_{max.}$ (in EtOH) 283 mμ (ε 7300).

The acetyl derivative (VIII; R = Ac) was obtained as an amorphous powder and was converted into the *picrate*. This crystallised from ethanol–dimethylformamide as prisms, m. p. 207—208° (decomp.) (Found: C, 56·4; H, 5·5; N, 8·7. $C_{37}H_{43}N_5O_{14}$ requires C, 56·8; H, 5·6; N, 9·0%).

Ethyl α-Formylbutyrate (XI).—The diethyl acetal [8] (XII) (20·3 g.) was hydrolysed overnight at room temperature in 2N-hydrochloric acid (100 ml.) and ethanol (10 ml.). The solution was extracted with ether (4 × 30 ml.), and the combined organic extracts were washed with 2N-sodium hydroxide (4 × 30 ml.). Acidification of the alkaline phase with concentrated hydrochloric acid gave the aldehyde (XI) as a colourless oil (8·75 g.) that was isolated by extraction with ether and distillation; it had b. p. 65—67°/15 mm. (lit.,[9] b. p. 64—66°/16 mm.), n_D^{20} 1·4320.

Ethyl β-Ethoxy-α-ethylacrylate (XIII).—The diethyl acetal (XII) (10 g.) was heated with potassium hydrogen sulphate (0·1 g.) till evolution of ethanol was complete. The residue was distilled *in vacuo*, giving the ester (XIII) as a pale oil (6·6 g.), b. p. 98—100°/16 mm. (lit.,[10] b. p. 103—105°/20 mm.), n_D^{25} 1·4470.

Ethyl 3-Ethyl-6,7-dihydro-9,10-dimethoxy-4-oxo-4H-benzo[a]*quinolizine-1-carboxylate* (IX; R = CO_2Et).—(*a*) Ester (V) (R = CO_2Et) (3·2 g.), ethyl α-formylbutyrate (1·6 g.), and 50% aqueous acetic acid (10 ml.) were heated at 100° for 5 hr. The solution was cooled, then diluted with water (10 ml.), and the crystalline precipitate (3·46 g.) was collected. Crystallisation from ethanol afforded the *pyridone ester* (IX; R = CO_2Et), m. p. 167·5—168·5° (Found: C, 67·2; H, 6·4; N, 4·4%; *M*, 342. $C_{20}H_{23}NO_5$ requires C, 67·2; H, 6·5; N, 3·9%; *M*, 357), $\lambda_{max.}$ (in EtOH) 240, 283, and 350 mμ (ε 15,000, 8800, and 19,600).

(*b*) Ester (V) (5 g.) and the diethyl acetal (XII) (4·2 ml.) were heated at 100° for 3 hr. in 50% aqueous acetic acid (40 ml.). The pyridone ester (IX; R = CO_2Et) (1·33 g.), m. p. 165—167°, separated on cooling.

3-Ethyl-6,7-dihydro-9,10-dimethoxy-4-oxo-4H-benzo[a]*quinolizine-1-carboxylic Acid* (IX; R = CO_2H).—A solution of ester (IX; R = CO_2Et) (0·48 g.) in 5% ethanolic potassium hydroxide (10 ml.) was heated under reflux for 45 min. and the solvent was then removed *in vacuo*. An aqueous solution of the residue was acidified with dilute hydrochloric acid, giving a precipitate (0·38 g.), m. p. 251—253° (decomp.). This *acid* (IX; R = CO_2H) separated from ethanol–dimethylformamide in prisms of unchanged m. p. (Found: C, 65·8; H, 5·8; N, 4·7%; equiv., 362. $C_{18}H_{19}NO_5$ requires C, 65·6; H, 5·8; N, 4·3%; equiv., 329), $\lambda_{max.}$ (in EtOH) 243, 278, and 357 mμ (ε 14,500, 8250, and 20,300).

3-Ethyl-6,7-dihydro-9,10-dimethoxy-4H-benzo[a]*quinolizin-4-one* (IX; R = H).—The acid (IX; R = CO_2H) (1 g.) was heated at 260—270° until evolution of gas had ceased. Elution of the product from alumina (30 g.) (Peter Spence's grade H) with benzene–chloroform (1 : 1) gave the *pyridone* (IX; R = H), which crystallised from benzene–light petroleum as prisms (0·5 g.), m. p. 126—128°. Recrystallisation from the same solvent mixture gave material with m. p. 129—130° (Found: C, 71·8; H, 6·7; N, 5·2. $C_{17}H_{19}NO_3$ requires C, 71·6; H, 6·7; N, 4·9%), $\lambda_{max.}$ 266 and 346 mμ (ε 7800 and 22,300).

Ethyl γ-Cyano-α-ethyl-γ-(1,2,3,4-tetrahydro-6,7-dimethoxy-1-isoquinolylidene)crotonate (X).—A mixture of the nitrile (V; R = CN) (10 g.), ethyl α-formylbutyrate (5 ml.), and toluene (150 ml.) was heated under reflux overnight in a Dean and Stark apparatus. The solvent was removed *in vacuo* and the residue was digested with 2N-hydrochloric acid and ether. Crystallisation of the insoluble powder from ethanol gave the *ester* (X) as yellow plates (5·35 g.), m. p. 154—156°. A further crystallisation raised the m. p. to 159—160°, which was strongly depressed on admixture with the pyridone (IX; R = CN) (Found: C, 67·4; H, 6·8; N, 8·3. $C_{20}H_{24}N_2O_4$ requires C, 67·4; H, 6·8; N, 7·9%). The ester had $\lambda_{max.}$ (in EtOH) 228, 283, 304, and 390 mμ (ε 19,200, 11,700, 11,200, and 20,000).

[8] Deno, *J. Amer. Chem. Soc.*, 1947, **69**, 2233.
[9] Legrand and Lozac'h, *Bull. Soc. chim. France*, 1955, 79.
[10] B.P. 778,495.

1-*Cyano*-3-*ethyl*-6,7-*dihydro*-9,10-*dimethoxy*-4H-*benzo*[a]*quinolizin*-4-*one* (IX; R = CN).—(*a*) Nitrile (V; R = CN) (2 g.), ethyl α-formylbutyrate (0·83 ml.), and 66% aqueous acetic acid (20 ml.) were heated together at 100° for 4 hr. Removal of the solvent *in vacuo* and trituration with 2N-hydrochloric acid gave a brown powder (0·77 g.; m. p. 145—149°) that crystallised from ethanol as long needles of the *cyanopyridone* (IX; R = CN), m. p. 154—155° (Found: C, 0·2; H, 5·8; N, 9·0. $C_{18}H_{18}N_2O_3$ requires C, 69·7; H, 5·8; N, 9·0%), $\lambda_{max.}$ (in EtOH) 240, 48, 283, and 352 mμ (ε 15,600, 16,400, 8800, and 21,500).

(*b*) When the nitrile (V; R = CN) (5 g.) was treated with the acetal (XII) (5 ml.) for 24 hr. at 100° as in the preceding example the cyanopyridone (IX; R = CN) (4·65 g.), m. p. 150—152°, resulted.

(*c*) The nitrile (V; R = CN) (1 g.), the enol ether (XIII) (0·6 ml.), and sodium ethoxide (0·[illegible] g.) were heated for 3 hr. in refluxing benzene (20 ml.). The cyanopyridone (IX; R = CN) (0·61 g.), m. p. 149—151°, was isolated as in previous examples.

(*d*) The ester (X) (0·3 g.), heated at 100° overnight in acetic acid (5 ml.), gave the crude pyridone (IX; R = CN) (0·2 g.), m. p. 145—150°. Recrystallisation from ethanol raised the m. p. to 150—152°.

Methyl 1,2,6,7-*Tetrahydro*-4,9,10-*trimethoxy*-2-*oxo*-3-(1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-*isoquinolyl*)-11bH-*benzo*[a]*quinolizine*-1-*carboxylate* (XVI; $R^1 = CO_2Me$, R^2 = Me).—3,4-Dihydro-6,7-dimethoxyisoquinoline (XV) (15·28 g.), pyridine (60 ml.), and methyl acetonedicarboxylate (6·96 g.) were kept for 24 hr. at room temperature. Removal of the solvent *in vacuo* and addition of ethanol to the gummy residue gave the *ester* (XVI; $R^1 = CO_2Me$, R^2 = Me) (9·24 g.) as white crystals, m. p. 181—182·5° (Found: C, 64·8; H, 6·4; N, 5·0; OMe, 34·8%; *M*, 530. $C_{29}H_{34}N_2O_8$ requires C, 64·7; H, 6·4; N, 5·2; OMe, 34·6%; *M*, 539), $\lambda_{max.}$ (in EtOH) 292·5 mμ (ε 33,000).

The 4-*ethoxy*-1-*ethoxycarbonyl compound* (XVI; $R^1 = CO_2Et$, R^2 = Et), obtained as above, but from ethyl acetonedicarboxylate, had m. p. 178—179° (Found: C, 65·6; H, 6·7; N, 5·3; Alkoxyl, as OMe, 33·2%; *M*, 590. $C_{31}H_{38}N_2O_8$ requires C, 65·7; H, 6·8; N, 4·9; Alkoxyl, 32·9%; *M*, 567), $\lambda_{max.}$ (in EtOH) 293 mμ (ε 32,800).

1,2,6,7-*Tetrahydro*-4,9,10-*trimethoxy*-3-(1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-*isoquinolyl*)-11bH-*benzo*[a]*quinolizin*-2-*one* (XVI; R^1 = H, R^2 = Me).—The dihydroisoquinoline (XV) (15·28 g.) in ethanol (25 ml.) was added to a solution of the methyl hydrogen acetonedicarboxylate [from acetonedicarboxylic anhydride [11] (4 g.) and methanol (1·5 g.) in ether (10 ml.)]. After 18 hr. at 0° the white crystals were collected and leached with hot ethanol, to give the *methoxy-ketone* (XVI; R^1 = H, R^2 = Me) (16·37 g.), m. p. 176—177° (Found: C, 67·8; H, 6·9; N, 5·8; OMe, 31·9%; *M*, 480. $C_{27}H_{32}N_2O_6$ requires C, 67·5; H, 6·7; N, 5·8; OMe, 32·2%; *M*, 480·5), $\lambda_{max.}$ (in EtOH) 290·5 mμ (ε 35,100).

The 4-*ethoxy-compound* (XVI; R^1 = H, R^2 = Et), from the ethyl ester, had m. p. 170—172° (Found: C, 67·8; H, 7·0; N, 5·7; Alkoxyl, as OMe, 31·4%; *M*, 490. $C_{28}H_{34}N_2O_6$ requires C, 68·0; H, 6·9; N, 5·7; Alkoxyl, 31·4%; *M*, 495), $\lambda_{max.}$ (in EtOH) 287—290 mμ (ε 35,600).

The 4-*benzyloxy-compound* (XVI; R^1 = H, $R^2 = CH_2Ph$) had m. p. 181·5—182·5° (Found: C, 71·4; H, 6·6; N, 4·8; OMe, 22·9%; *M*, 530. $C_{33}H_{36}N_2O_6$ requires C, 71·2; H, 6·5; N, 5·0; OMe, 22·4%; *M*, 555), $\lambda_{max.}$ (in EtOH) 292 mμ (ε 35,900).

Hydrolysis of the Ester (XVI; $R^1 = CO_2Et$, R^2 = Et).—The ester (1 g.) was heated for a few minutes in 0·2N-hydrochloric acid, and the solution was then evaporated to dryness, to give the hydrochloride of the dihydroisoquinoline (XV) as a yellow solid, m. p. 197—198° (decomp.).

Hydrolysis of the Ester (XVI; R^1 = H, R^2 = Et).—The ester (0·29 g.) was warmed on the steam-bath in ethanolic hydrogen chloride (2 ml.) at pH 3, and the solution was then evaporated to dryness. Recrystallisation of the residue from ethanol gave the keto-ester hydrochloride (XVII) (0·12 g.), m. p. 175°.

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