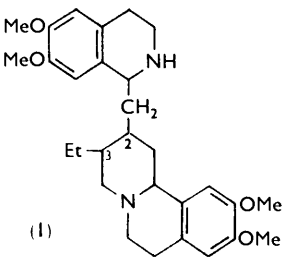
973. *The Synthesis of Emetine and Related Compounds. Part III.* The Reaction of Some Isoquinoline Derivatives with Acrylonitrile.*

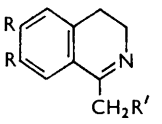
By H. T. Openshaw and Norman Whittaker.

The products of cyclisation of *N*-phenethyl-α-cyanoacetamide or its 3,4-dimethoxy-derivative with phosphoric oxide have been shown by spectroscopic methods to be the 1-cyanomethylene-1,2,3,4-tetrahydroisoquinolines (IV; R = H or OMe). Alcoholysis of these products gives the corresponding 1-ethoxycarbonylmethylene derivatives (IV; CO_2Et for CN; R = H or OMe). The salts of these bases possess the 3,4-dihydroisoquinolinium structure (IVa). Condensation of the isoquinoline (IV; R = H) with acrylonitrile gives a mono(cyanoethyl) (V) and a di(cyanoethyl) compound (VI). With alcoholic sodium ethoxide, or with toluene-*p*-sulphonic acid in toluene, the first of these is cyclised to the benzoquinolizine (VII; R = H), also formed by treatment of the second with alcoholic sodium ethoxide. Reaction of the isoquinolines (IV; R = H or OMe) with acrylonitrile in alcoholic sodium ethoxide, or of related amides (VIII; R = H or OMe) with phosphoric oxide, leads directly to the benzoquinolizine derivatives (VII; R = H or OMe). With hot aqueous acid, these quinolizines are converted into the lactams (IX; R = H or OMe; R′ = CN).

The various published syntheses[1] of the emetine skeleton (I) have involved the simultaneous or successive cyclisation of the isoquinoline and benzoquinolizine portions by the Bischler–Napieralski procedure. An alternative approach, which might offer advantages, would be by the direct linkage of an isoquinoline derivative with a suitable benzoquinolizine. Such a linkage might be achieved, for example, by Michael addition of a substituted 3,4-dihydro-1-methylisoquinoline (II) to a benzoquinolizine (III): moreover, if successful, this procedure should give a preponderance of the desired 2,3-*trans*-isomer.[1e]

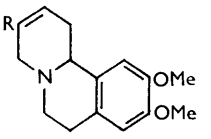


(I)



(II)

(III; R = Ac or CN)



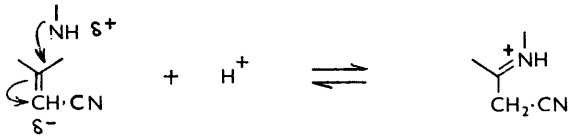
Accordingly, we have examined the possibility of using a derivative of 3,4-dihydro-1-methylisoquinoline as the reactive-methylene component of a Michael reaction with, in the first place, the highly reactive acrylonitrile. 3,4-Dihydro-6,7-dimethoxy-1-methylisoquinoline itself did not appear to react with acrylonitrile even in the presence of sodium ethoxide, and so the use of a more highly activated compound such as 1-cyanomethyl-3,4-dihydroisoquinoline (II; R = H, R′ = CN) seemed desirable.

Cyclisation of *N*-phenethyl-α-cyanoacetamide with phosphoric oxide gave a product of the expected composition, but ultraviolet (see Table) and infrared spectroscopy indicate

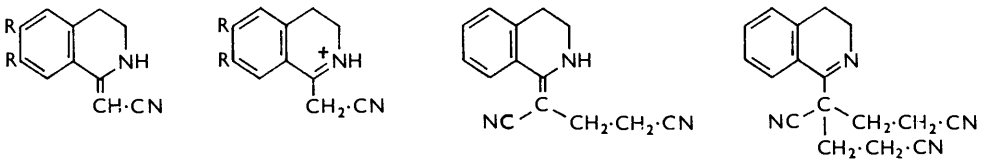
* Part II, *J.*, 1953, 2463.

[1] (*a*) Evstigneeva and Preobrazhensky, *Tetrahedron*, 1958, **4**, 223 and references cited therein; (*b*) Battersby and Openshaw, *Experientia*, 1950, **6**, 387; (*c*) Ban, *Pharm. Bull.* (*Japan*), 1955, **3**, 53; (*d*) Barash, Osbond, and Wickens, *J.*, 1959, 3530; (*e*) Battersby and Turner, *J.*, 1960, 717; (*f*) Brossi, Baumann, and Schnider, *Helv. Chim. Acta*, 1959, **42**, 1515; (*g*) Grüssner, Jaeger, Hellerbach, and Schnider, *ibid.*, 1959, **42**, 2431.

that this should be formulated as 1-cyanomethylene-1,2,3,4-tetrahydroisoquinoline (IV; R = H) rather than as 1-cyanomethyl-3,4-dihydroisoquinoline. It has characteristic absorption at 3332 and 3355 (N–H), and 2185 cm.$^{-1}$ (C≡N, conjugated) and in ethanol or acrylonitrile it has a strong absorption band at 328 mμ, whereas only a weak band at *ca.* 280 mμ (cf. 3,4-dihydro-1-methylisoquinoline) would be expected from the hypothetical 1-cyanomethyl-3,4-dihydroisoquinoline. Similarly, the spectroscopic results indicate that the ester obtained by alcoholysis of this nitrile is 1-ethoxycarbonylmethylene-1,2,3,4-tetrahydroisoquinoline, and that the already known [2,3] 6,7-dimethoxy-analogues of the nitrile and ester should be reformulated with an exocyclic double bond (*e.g.*, IV; R = OMe). When an alcoholic solution of the base (IV; R = OMe) is made 0·1N with respect to hydrogen chloride, its ultraviolet absorption spectrum changes, becoming similar to that of an acidic solution of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (II; R = OMe, R′ = H). Addition of a proton to the carbon atom bearing the cyano-group has occurred, with simultaneous redistribution of charge, giving the cation (IVa;



R = OMe). In contrast, the base (IV; R = H) has substantially the same spectrum in 0·1N-ethanolic hydrogen chloride as in ethanol, and is thus a weaker base than its dimethoxy-analogue; in N-ethanolic hydrogen chloride, however, the ion (IVa; R = H) is formed. The cyanomethylene compound (IV; R = H) is also a weaker base than 1-ethoxycarbonylmethylene-1,2,3,4-tetrahydroisoquinoline which forms the cation (IVa; R = H; CO_2Et for CN) in 0·1N-ethanolic hydrogen chloride. This is perhaps not unexpected, for the ethoxycarbonyl group has a weaker $-I$ effect than a cyano-group, and the adjacent carbon atom is consequently more basic.



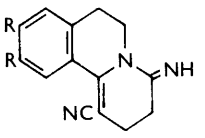
(IV) (IVa) (V) (VI)

Heating 1-cyanomethylene-1,2,3,4-tetrahydroisoquinoline (IV; R = H) with an excess of acrylonitrile at 100° for 6 hours gave a mono(cyanoethyl) compound, whilst prolonged heating gave also a di(cyanoethyl) compound. The latter is formulated as (VI), for it has no infrared absorption bands attributable to N–H or conjugated C≡N groups, and its ultraviolet spectrum is similar to that of a 1-alkyl-3,4-dihydroisoquinoline. Since the mono(cyanoethyl) compound gives the bis-product (VI) when heated with acrylonitrile, it follows that its cyanoethyl group is also located on the 1-substituent, and not on the ring nitrogen. The mono(cyanoethyl) compound, however, absorbs at 3325 (N–H), 2248 (C≡N, non-conjugated), and 2177 cm.$^{-1}$ (C≡N, conjugated), and its ultraviolet spectrum resembles that of the cyanomethylene compound (IV; R = H). The structure of the mono(cyanoethyl) compound is therefore (V).

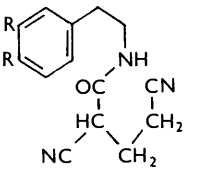
When the mono(cyanoethyl) compound (V) was treated with alcoholic sodium ethoxide at room temperature, or heated with toluene-*p*-sulphonic acid in toluene under reflux,

[2] Child and Pyman, *J.*, 1931, 36.
[3] Osbond, *J.*, 1951, 3464.

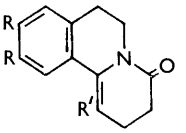
cyclisation occurred with formation of the amidine (VII; R = H). This product also resulted when the di(cyanoethyl) compound (VI) was heated with alcoholic sodium ethoxide, and, in good yield, on direct condensation of 1-cyanomethylene-1,2,3,4-tetrahydroisoquinoline (IV; R = H) with acrylonitrile in alcoholic sodium ethoxide. The structure given for the amidine is supported by light-absorption data, and was confirmed by an alternative synthesis. α-Ethoxycarbonylglutaronitrile was condensed with phenethylamine, and the resulting amide (VIII; R = H) was heated with phosphoric oxide in boiling toluene; cyclodehydration and further ring-closure occurred, yielding the amidine (VII; R = H). Replacement of phenethylamine by its 3,4-dimethoxy-derivative in this reaction sequence gave the corresponding product (VII; R = OMe), which was also obtained in excellent yield when 1-cyanomethylene-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (IV; R = OMe) was condensed with acrylonitrile in alcoholic sodium ethoxide. On being heated with aqueous mineral acid or aqueous acetic acid, the amidines (VII; R = H or OMe) were hydrolysed to the lactams (IX; R = H or OMe, R′ = CN).



(VII)



(VIII)



(IX)

Addition of acrylonitrile in alcoholic sodium ethoxide to 1-ethoxycarbonylmethylene-1,2,3,4-tetrahydroisoquinoline occurred less readily than to the 1-cyanomethylene derivative (IV; R = H). The analogous ethoxycarbonylamidine was obtained, however, as a gum which was converted, by hydrolysis, into a crystalline lactam (IX; R = H, R′ = CO_2Et).

When acrylonitrile was replaced by 1-cyanocyclohexene in the above reactions, no condensation occurred. It therefore seemed unlikely that a compound of structure (III) would react, and work along these lines was not pursued further.

Ultraviolet absorption spectra.

Compound	Solvent	$\lambda_{max.}$ (mμ)	ε
(IV; R = H)	EtOH	247, 328	14,300, 11,300
	Acrylonitrile	248, 329	14,500, 10,800
	0·1N-HCl–EtOH	248, 326	12,300, 10,000
	N-HCl–EtOH	285, 321 *	11,500, 3550
(IV; R = H; CO_2Et for CN)	EtOH	248, 335	14,200, 14,400
	0·1N-HCl–EtOH	281, 317 *	13,100, 2670
(II; R = R′ = H)	EtOH	250, 280 *	8800, 1460
	0·1N-HCl–EtOH	272, 310 *	11,900, 1800
(IV; R = OMe)	EtOH	227, 272, 320	23,300, 10,300, 17,300
	0·1N-HCl–EtOH	216, 250, 315, 365	10,800, 15,100, 10,700, 8900
(IV; R = OMe; CO_2Et for CN)	EtOH	227, 268,* 273, 331	23,100, 8400, 8740, 20,800
	0·1N-HCl–EtOH	247, 309, 362	17,200, 9550, 9430
(II; R = OMe, R′ = H)	EtOH	227, 272, 308	23,600, 7570, 6660
	0·1N-HCl–EtOH	245, 303, 354	18,400, 9300, 8910
(V)	EtOH	234, 245, 325	11,650, 10,900, 10,500
	0·1N-HCl–EtOH		
	Acrylonitrile	243, 326	11,800, 12,300
(VI)	EtOH	253, 284	8300, 1600
(VII; R = H)	0·1N-NaOH–EtOH	249, 320	14,250, 10,900
(VII; R = OMe)	0·1N-NaOH–EtOH	236, 249,* 282, 317	18,300, 14,300, 10,500, 16,300
(IX; R = H, R′ = CN)	EtOH	244, 308	13,400, 9900
(IX; R = OMe, R′ = CN)	EtOH	215, 225, 240, 280, 329	17,500, 16,600, 18,300, 9390, 13,800
(IX; R = H, R′ = CO_2Et)	EtOH	235, 302	13,800, 8670

* Inflexion.

Experimental

Ultraviolet spectra were determined with a Hilger Uvispek instrument. Infrared spectra were measured for potassium chloride dispersions, by means of a Unicam S.P. 100 spectrophotometer with grating accessory, at a computed spectral slit width of *ca.* 3 cm.$^{-1}$. Solids were dried *in vacuo* over silica gel.

1-*Cyanomethylene*-1,2,3,4-*tetrahydroisoquinoline* (IV; R = H).—A solution of *N*-phenethyl-α-cyanoacetamide [4] (70 g.) in hot toluene (1260 ml.) was heated until 70 ml. of toluene had distilled. The solution was refluxed and, with occasional shaking, treated with portions of phosphoric oxide (140, 140, and 95 g.) at intervals of 30 min. After a further 30 min., the mixture was cooled, decomposed with ice-water (1500 ml.), and stirred, with cooling, until all the solid had dissolved (*ca.* 3 hr.). The liquid was filtered (Hyflo), the aqueous layer separated, and the toluene layer extracted with 2N-hydrochloric acid (2 × 350 ml.). The combined aqueous solution was washed with ether (2 × 500 ml.), and agitated with a vigorous current of nitrogen to remove traces of ether. The solution was basified with concentrated aqueous potassium hydroxide, with cooling, and the precipitated solid was collected, washed with water, and dried. The yellow solid (33 g.) was digested with hot light petroleum (b. p. 80 100°) (2800 ml.), and the petroleum solution was decanted from a dark residue, reheated, decolorised (activated charcoal), and set aside, giving pale yellow prisms (24·6 g.), m. p. 98·5—99°, of 1-*cyanomethylene*-1,2,3,4-*tetrahydroisoquinoline* (Found: C, 78·0; H, 6·1; N, 16·4. $C_{11}H_{10}N_2$ requires C, 77·6; H, 5·9; N, 16·45%).

Reaction of 1-*Cyanomethylene*-1,2,3,4-*tetrahydroisoquinoline* (IV; R = H) *with Acrylonitrile*.—(*a*) A mixture of the base (IV; R = H) (2 g.) and acrylonitrile (1·24 g., 2 mol.) was heated in a sealed tube at 100° for 6 hr. Crystals separated from the cooled liquid. The mixture was digested with warm ether (25 ml.) and cooled to 0°, and the crystals (1·88 g.), m. p. 135—137°, were collected. Recrystallisation from methanol afforded colourless flat needles (1·58 g.) of 1-(1,3-*dicyanopropylidene*)-1,2,3,4-*tetrahydroisoquinoline* (V), m. p. 137—138° (Found: C, 75·75; H, 5·75; N, 18·5. $C_{14}H_{13}N_3$ requires C, 75·3; H, 5·85; N, 18·8%). From the ethereal liquors some unchanged starting material was isolated.

(*b*) When the base (IV; R = H) (20 g.) and acrylonitrile (18·6 g., 3 mol.) were heated together under reflux for 30 hr., the temperature of the solution increased from 83° to 93°. After cooling, the mass of crystals was taken up in hot benzene (300 ml.), 100 ml. of solvent were distilled, and the residual solution was set aside to give colourless crystals of the product (V) (16·88 g.), m. p. 136·5—138°. The benzene liquors were evaporated *in vacuo* and a solution of the residual gum in methanol was evaporated. The residual gum was dissolved in hot methanol (20 ml.) and set aside, giving crystals (9·4 g.) of m. p. 92—99° [m. p. 80—95° in admixture with (IV; R = H)]. These, recrystallised from methanol, afforded colourless prisms (8·56 g.), m. p. 98—99·5°, of 1-(1,3-*dicyano*-1-2′-*cyanoethylpropyl*)-3,4-*dihydroisoquinoline* (VI) (Found: C, 73·8; H, 5·75; N, 20·6. $C_{17}H_{16}N_4$ requires C, 73·9; H, 5·85; N, 20·3%). The di(cyanoethyl) compound (VI) (0·25 g.), m. p. 97—98·5°, and unchanged compound (V) (0·44 g.), m. p. 133—135°, also resulted from heating a mixture of the mono-derivative (V) (1 g.) and acrylonitrile (0·48 g., 2 mol.) in a sealed tube at 100° for 9 hr.

1-*Cyano*-3,4,6,7-*tetrahydro*-4-*imino*-2H-*benzo*[a]*quinolizine* (VII; R = H).—(*a*) A solution of the mono(cyanoethyl) compound (V) (9·3 g.) in hot ethanol (180 ml.) was cooled quickly, and the resulting suspension of fine crystals was added to a solution of sodium (9·3 g.) in ethanol (270 ml.). The crystals dissolved immediately, and soon the product began to crystallise. After 1 hr. at room temperature, the alcohol was evaporated *in vacuo*, and the residual solid was shaken with ice-cold water (450 ml.) and benzene (450 ml.). The benzene solution was separated, washed with water, and then extracted with 0·25N-acetic acid (2 × 400 ml.). The combined extract was gradually basified with aqueous potassium hydroxide, with seeding, and the resulting crystals were collected and washed with water. The dried product (8·9 g.), m. p. 146—147°, crystallised from alcohol (50 ml.), yielding colourless flat needles (7·77 g.) of pure *amidine* (VII; R = H) which began to melt at 140°, then resolidified, with m. p. 147—148° (Found: C, 75·6; H, 5·65; N, 18·85. $C_{14}H_{13}N_3$ requires C, 75·3; H, 5·85; N, 18·8%), $\nu_{max.}$ 2190 (C≡N, conjugated), 3299 cm.$^{-1}$ (N–H).

(*b*) A solution of toluene-*p*-sulphonic acid (0·85 g.) in hot toluene (25 ml.) was distilled until 5 ml. of liquid had been collected, and the residual anhydrous solution was heated with

[4] Leonard and Boyer, *J. Amer. Chem. Soc.*, 1950, **72**, 2980.

the mono(cyanoethyl) compound (V) (1 g.) under reflux for 1 hr. At first an oil was formed, but this soon gave place to crystals of the toluene-*p*-sulphonate of the amidine (VII; R = H). The cooled mixture was shaken with water (25 ml.), and the crystals were collected (solid A). The aqueous filtrate was separated from the toluene layer, washed once with toluene, then basified with aqueous potassium hydroxide, and the precipitated solid was collected (solid B). A stirred suspension of solid A in water (200 ml.) was basified with potassium hydroxide, and the resulting base was collected, combined with solid B, and shaken with water (60 ml.) containing just more than the equivalent amount of glacial acetic acid. The resulting solution was filtered from a brown sediment and basified with potassium hydroxide, with seeding, giving crystals of the amidine (VII; R = H) (0·74 g.), which began to melt at 140°, then resolidified, with m. p. 147—148°.

(*c*) The amidine (VII; R = H) (0·42 g.) resulted when the di(cyanoethyl) compound (VI) (1 g.) was heated with a solution of sodium (1 g.) in anhydrous ethanol (25 ml.) under reflux for 30 min.

(*d*) A stirred solution of sodium (0·54 g.) in ethanol (30 ml.) was treated with the isoquinoline compound (IV; R = H) (4 g.) and acrylonitrile (1·38 g.), and kept at 50—60° under nitrogen for 2 hr. The cooled product was worked up in the manner of (*a*), giving the amidine (VII; R = H) (4·18 g.) of the same m. p.

(*e*) An equimolecular mixture of phenethylamine (14·6 g.) with α-ethoxycarbonylglutaronitrile [5] (20 g.) was heated rapidly to 126° (alcohol then began to distil) and then during 30 min. to 180°. The residual crude amide (VIII; R = H) (29·4 g.) was cooled slightly and dissolved in toluene (530 ml.), and the solution was heated until 30 ml. of liquid had distilled. The toluene solution was heated under reflux and treated with phosphoric oxide (59 g., 59 g., and 40 g.), and the product was isolated in the manner described for the preparation of base (IV; R = H). The crude orange-brown base (5·4 g.) was twice crystallised from acetone, giving colourless prisms (1·73 g.) of the amidine (VII; R = H) which began to melt at 140°, then resolidified, with m. p. 147—148°. Recrystallisation from alcohol afforded flat needles of the same m. p., alone and in admixture with amidine obtained by method (*a*) (Found: C, 75·3; H, 5·85; N, 18·9%).

1-*Cyanomethylene*-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (IV; R = MeO).—Cyclisation of *N*-(3,4-dimethoxyphenethyl)-α-cyanoacetamide by Osbond's method [3] gave the isoquinoline (IV; R = MeO) as needles, m. p. 170—171°, $\nu_{max.}$ 2182 (C≡N, conjugated) and 3339 cm.$^{-1}$ (N–H).

1-*Cyano*-3,4,6,7-*tetrahydro*-4-*imino*-9,10-*dimethoxy*-2H-*benzo*[a]*quinolizine* (VII; R = MeO).—(*a*) A solution of sodium (1 g.) in ethanol (60 ml.) was treated with the isoquinoline compound [3] (IV; R = MeO) (10 g.), and then with acrylonitrile (2·54 g.). The mixture was heated under nitrogen on the steam-bath for 30 min., then cooled, and the resulting crystals were collected and washed with alcohol, giving 10·27 g., m. p. 156—158°, of the amidine (VII; R = MeO). The alcoholic liquors were evaporated, the residual solid was shaken with water (200 ml.) and benzene (200 ml.), and the benzene solution was washed with water, then extracted with water (200 ml.) containing glacial acetic acid (3 ml.). The acid extract was basified with aqueous potassium hydroxide, with seeding, giving pale yellow crystals (1·55 g.), m. p. 156—157·5°, of less pure amidine. The major product, recrystallised from alcohol (60 ml.), gave colourless prisms (8·72 g.), m. p. 158—159°, of pure *amidine* (VII; R = MeO) (Found: C, 67·95; H, 5·95; N, 14·65. $C_{16}H_{17}N_3O_2$ requires C, 67·8; H, 6·05; N, 14·85%).

(*b*) An equimolecular mixture of 3,4-dimethoxyphenethylamine (16·4 g.) with α-ethoxycarbonylglutaronitrile [5] (15 g.) was heated quickly to 120°, and then during 30 min. to 180°. The residual crude amide (VIII; R = MeO) was heated *in vacuo* on the steam-bath, to remove traces of alcohol, and dissolved in hot toluene (250 ml.). The toluene solution was heated until 10 ml. of liquid had distilled and treated under reflux with three 30 g. portions of phosphoric oxide at intervals of 30 min. After a further 30 minutes' refluxing, the mixture was cooled, stirred with ice, and kept at an alkaline pH by periodical addition of strong aqueous sodium hydroxide, with external cooling in ice-water. When, after *ca.* 3 hr., all lumps had disintegrated, the liquid was filtered (Hyflo), and the insoluble residue was washed with water and toluene. The toluene layer was separated, washed with water, and extracted with a solution of glacial acetic acid (10 ml.) in water (200 ml.). Basification of the extract with sodium hydroxide gave a thick oil which soon solidified, and the solid was collected, pulverised, and then washed with water. The dried solid (7·31 g.) crystallised from alcohol (35 ml.) as pale yellow-brown

[5] Rogers, U.S.P. 2,460,536/1949.

prisms (5·2 g.), m. p. 158—159°, of almost pure amidine (VII; R = MeO). It did not prove possible to remove completely the trace of coloured impurity present in these prisms. A lukewarm solution in benzene (400 ml.) was treated with a little activated alumina, filtered, and extracted with a solution of glacial acetic acid (4 ml.) in water (300 ml.). The extract was basified with sodium hydroxide, giving a pale yellow solid which crystallised from alcohol as pale yellow prisms, almost colourless when powdered, of m. p. 158—159°, alone and in admixture with the amidine obtained by method (*a*).

1-*Cyano*-3,4,6,7-*tetrahydro*-4-*oxo*-2H-*benzo*[a]*quinolizine* (IX; R = H, R′ = CN).—When a solution of the amidine (VII; R = H) (0·52 g.) in water (10 ml.) containing glacial acetic acid (1 ml.) was heated on the steam-bath, colourless plates soon began to separate. After 30 minutes' heating, the suspension was cooled, diluted with water, and filtered, yielding 0·49 g. of the *lactam* (IX; R = H, R′ = CN), which almost completely melted at 146—147°, then resolidified, with m. p. 149—150°. The aqueous filtrate liberated ammonia on being heated with potassium hydroxide. The *lactam* depressed the m. p. of the starting material and crystallised from light petroleum (b. p. 80—100°) in colourless long flat needles of the above m. p. (Found: C, 74·75; H, 5·15; N, 12·55; O, 7·40. $C_{14}H_{12}N_2O$ requires C, 75·0; H, 5·4; N, 12·5; O, 7·15%), $\nu_{max.}$ 1674 (C=O), 2198 cm.$^{-1}$ (C≡N, conjugated). The lactam (IX; R = H, R′ = CN) was also produced when a solution of the amidine (VII; R = H) in dilute aqueous hydrochloric acid was heated on the steam-bath.

1-*Cyano*-3,4,6,7-*tetrahydro*-9,10-*dimethoxy*-4-*oxo*-2H-*benzo*[a]*quinolizine* (IX; R = MeO, R′ = CN).—A solution of the amidine (VII; R = MeO) (1·16 g.) in water (20 ml.) containing glacial acetic acid (2 ml.) was heated on the steam-bath for 1 hr., yielding the *lactam* (IX; R = MeO, R′ = CN) (1·14 g.), m. p. 146—147·5°. Recrystallisation from alcohol afforded colourless prisms, m. p. 146·5—147·5° (Found: C, 67·75; H, 5·5; N, 9·95. $C_{16}H_{16}N_2O_3$ requires C, 67·6; H, 5·65; N, 9·85%).

1-*Ethoxycarbonylmethylene*-1,2,3,4-*tetrahydroisoquinoline* (IV; R = H; CO_2Et for CN) was prepared from the cyanomethylene compound (IV; R = H) in the manner described by Osbond [3] for the alcoholysis of base (IV; R = MeO). On distillation, the ester was obtained as a pale yellow oil, b. p. 140°/0·08 mm. (Found: C, 72·05; H, 7·0; N, 6·75. $C_{13}H_{15}NO_2$ requires C, 71·85; H, 6·95; N, 6·45%).

1-*Ethoxycarbonyl*-3,4,6,7-*tetrahydro*-4-*oxo*-2H-*benzo*[a]*quinolizine* (IX; R = H, R′ = CO_2Et).—A solution of sodium (0·21 g.) in dry ethanol (6 ml.) was treated with 1-ethoxycarbonylmethylene-1,2,3,4-tetrahydroisoquinoline (2 g.) and acrylonitrile (0·74 g.) and set aside at room temperature for 17 hr. The alcohol was evaporated *in vacuo*, the residue was shaken with benzene and water, and the benzene layer was washed with water and extracted with dilute aqueous acetic acid. The extract was basified with potassium hydroxide, giving an oil, which was taken up in ether. The ethereal solution was washed with water and evaporated, and the residual gum was heated with water (15 ml.) and glacial acetic acid (1 ml.) on the steam-bath for 30 min. The resulting crystals (0·14 g.), m. p. 123—125°, recrystallised from light petroleum (b. p. 80—100°), giving colourless prisms of the *lactam* (IX; R = H, R′ = CO_2Et), m. p. 124·5—125·5° (Found: C, 71·1; H, 6·25; N, 5·3. $C_{16}H_{17}NO_3$ requires C, 70·85; H, 6·3; N, 5·15%).

1-*Ethoxycarbonylmethylene*-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (IV; R = MeO; CO_2Et for CN).—Alcoholysis of base (IV; R = MeO) by Osbond's method,[3] and crystallisation of the product from light petroleum (b. p. 60—80°), and then from alcohol, gave colourless prisms of the ester (IV; R = MeO; CO_2Et for CN), m. p. 86—87°, $\nu_{max.}$ 1651 (C=O) and 3305 cm.$^{-1}$ (N–H). Infrared absorption maxima for a 0·01M-solution in carbon tetrachloride were the same. The C=O stretching frequency is *ca.* 60 cm.$^{-1}$ lower than that of a simple αβ-unsaturated ester, suggesting a resonance-stabilised interaction of the carbonyl-oxygen and the amino-hydrogen atom.

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