857. *A Synthesis of* 1-*Ethyl*-1,2,3,5-*tetrahydro*-10-*methyl*-7,8-*methylenedioxy*-5-*oxobenzo*[f]*pyrrocoline, a Degradation Product of Lycorine.*

By Shuzo Takagi and Shojiro Uyeo.

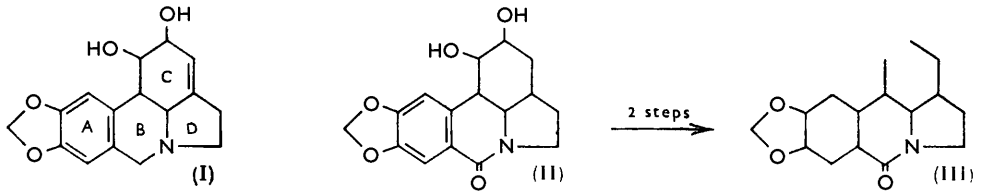
The structure of the compound (III), a degradation product of the alkaloid lycorine with the same number of carbon atoms as the natural product, has been established by synthesis of its racemate, providing further proof of the structure of the alkaloid.

Previously [1] we have shown that dihydrolycorinone (II) derived from the alkaloid, lycorine (I), undergoes oxidative scission of ring c with lead tetra-acetate or periodic acid to give a dialdehyde, which was smoothly converted through its bis(ethylene dithioacetal) into the derivative (III). We now record a synthesis of the racemate of compound (III), providing yet another proof of the structure of the alkaloid lycorine and its congeners.

Treatment of isosafrol (IV) with iodine and mercuric oxide according to Bougault's procedure [2] gave α-(3,4-methylenedioxyphenyl)propionaldehyde (V) which was characterised as its oxime and 2,4-dinitrophenylhydrazone. A Strecker reaction converted this aldehyde into 1-cyano-2-(3,4-methylenedioxyphenyl)propylamine (VI; R = H, R′ = CN) which with formic acid under reflux suffered partial hydrolysis of the cyano-group along with formylation of the amino-group to give 1-carbamoyl-*N*-formyl-2-(3,4-methylenedioxyphenyl)propylamine (VI; R = CHO, R′ = CO·NH_2); presence of

[1] Takagi, Taylor, Uyeo, and Yajima, *J.*, 1955, 4003.
[2] Bougault, *Bull. Soc. chim. France*, 1901, **25**, 856.

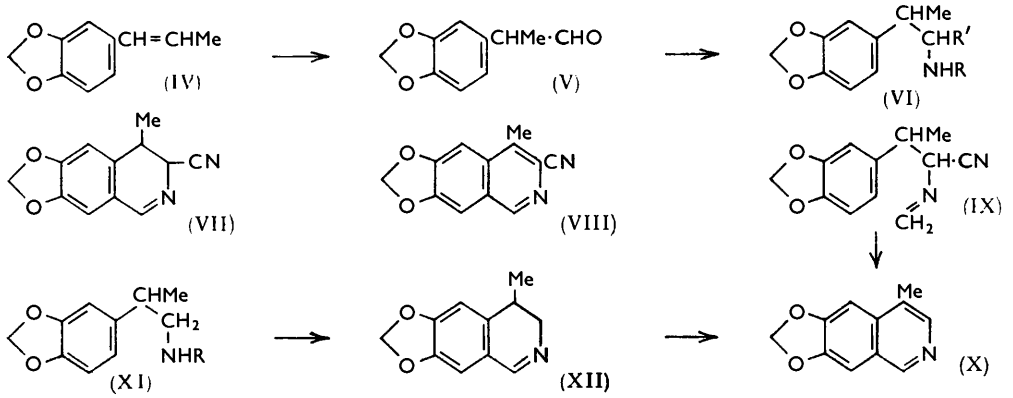
the amide group * was confirmed by its infrared spectrum which showed two strong carbonyl bands at 1661 and 1629 cm.$^{-1}$ but no CN band.



In our initial attempts to set up the A/B ring system of (III), we cyclised the amide (VI; R = CHO, R′ = CO·NH$_2$) with phosphorus oxychloride by the Bischler–Napieralski reaction. The product thus obtained in 30% yield was 3-cyano-3,4-dihydro-4-methyl-6,7-methylenedioxyisoquinoline (VII) which exhibited a CN band at 2217 cm.$^{-1}$ but no carbonyl absorption in the infrared spectrum. When the reaction was carried out in a xylene solution, however, a different compound, $C_{12}H_8N_2O_2$, containing two hydrogen atoms less than (VII), was the only isolable basic product. The ultraviolet spectrum of this compound exhibited bands which were quite different from those of (VII) and resembled those of isoquinoline (Fig. 1), and structure (VIII) was therefore assigned to it. The ready elimination of two hydrogen atoms by aerial oxidation from the obvious intermediate (VII) must be due, at least in part, to the electron-attracting effect of the cyano-group.

We next attempted to obtain 3-cyano-1,2,3,4-tetrahydro-4-methyl-6,7-methylenedioxyisoquinoline from the azomethine (IX) under the Pictet–Spengler conditions. The only product isolated in a crystalline form was, however, not the expected compound. It had the formula, $C_{11}H_9NO_2$, which was confirmed by the analytical values of the picrate and the ultraviolet spectrum of the base was comparable to that of (VIII) (Fig. 1), indicating that the compound was, not a tetrahydroisoquinoline, but an isoquinoline. The structure (X), indicated by these findings, was proved by the following unambiguous synthesis.

Reduction of the oxime of α-(3,4-methylenedioxyphenyl)propionaldehyde (V) with lithium aluminium hydride yielded the amine (XI; R = H) which with formic acid gave



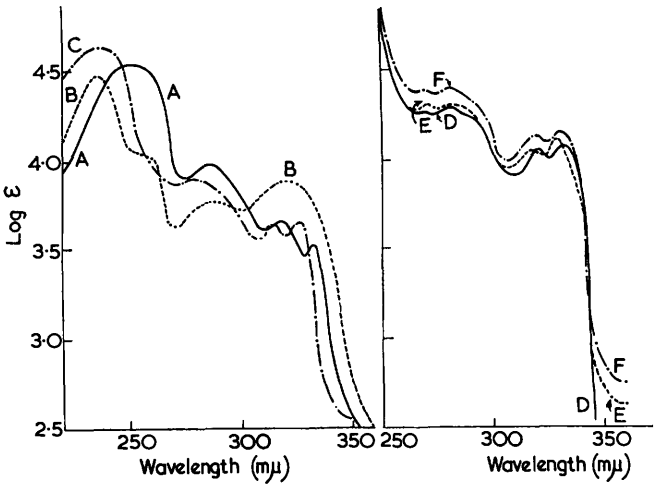
the formamide (XI; R = CHO). Bischler–Napieralski cyclisation of this furnished the 3,4-dihydroisoquinoline (XII) which on dehydrogenation with palladium–charcoal in cymene gave compound (X), identical with the sample obtained as above. How the isoquinoline (X) was formed under Pictet–Spengler conditions is not clear, but elimination

* We are very grateful to a Referee for suggesting this possibility.

of the elements of hydrogen cyanide from the first formed 3-cyano-1,2,3,4-tetrahydro-4-methyl-6,7-methylenedioxyisoquinoline could occur, followed by an aerial oxidation of the resulting 1,2-dihydroisoquinoline.

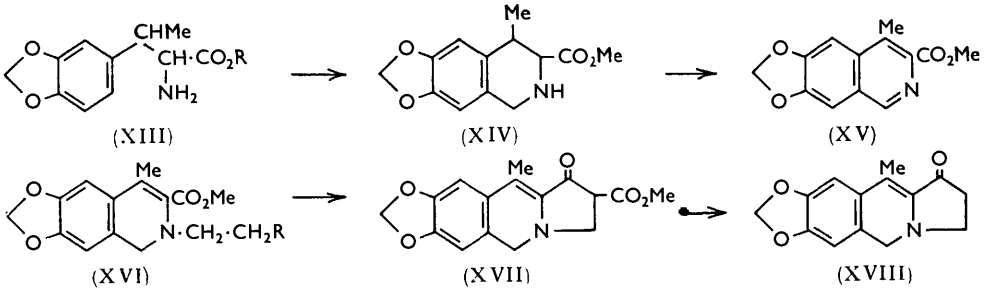
Since the cyclisations starting from the amino-nitrile (VI; R = H, R′ = CN) were unsatisfactory, we turned to the use of the amino-acid (XIII; R = H) which was readily available by hydrolysis of the amino-nitrile and conveniently isolated as its methyl ester (XIII; R = Me). A Pictet–Spengler cyclisation of this ester afforded a good yield of the 1,2,3,4-tetrahydroisoquinoline (XIV).

FIG. 1. FIG. 2.



FIGS. 1 and 2. *Absorption spectra of compounds* (A) VIII, (B) VII, (C) X, (D) XVI, R = CN, (F) XVIII, *and* (E) *oxime of* XVIII.

In order to build up ring C it was next desired to alkylate the nitrogen atom of the isoquinoline (XIV) with a β-halogenopropionate or a β-halogenopropionitrile. Leonard, Swann, and Fuller[3] have reported successful reaction of ethyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate with ethyl β-iodopropionate in xylene in the presence of potassium carbonate: under the comparable conditions, however, condensation of the tetrahydroisoquinoline (XIV) with methyl β-bromopropionate did not proceed well; also unsatisfactory was the quaternisation, with β-bromopropionitrile, of the isoquinoline (XV) [prepared

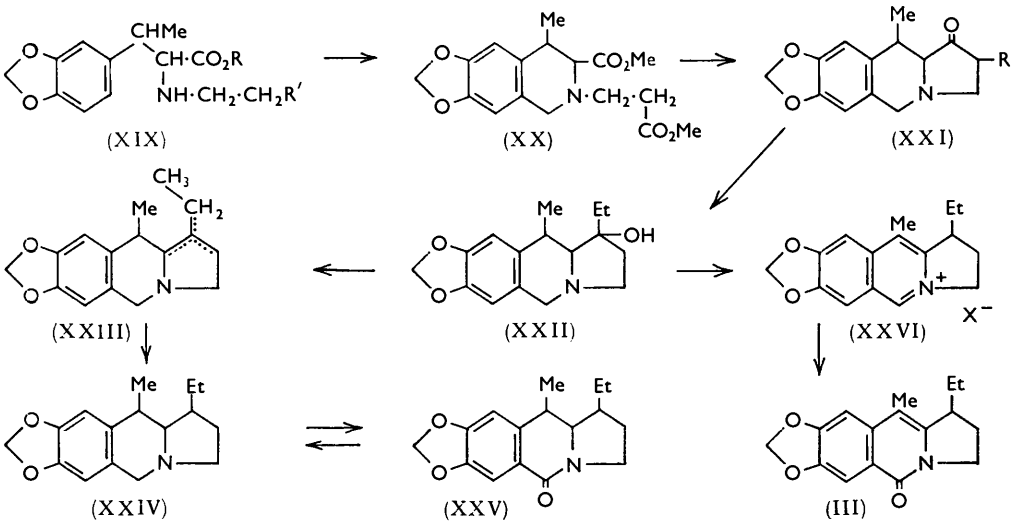


by boiling the ester (XIV) in xylene in the presence of palladium–charcoal and cinnamic acid].

We then tried to cyanoethylate the secondary amine (XIV), but the reaction proceeded neither in acetic acid nor in an alkaline solution with Triton B as condensing agent. On

[3] Leonard, Swann, and Fuller, *J. Amer. Chem. Soc.*, 1954, **76**, 3193.

the other hand, the base (XIV) with 2-bromoethyl cyanide in the presence of potassium carbonate gave a low yield of a cyanoethyl derivative which was isolated as the picrate, $C_{16}H_{16}N_2O_4,C_6H_3N_3O_7$. The free base, regenerated from this picrate, was soluble in



benzene and its ultraviolet spectrum indicated the presence of a double bond conjugated with the methylenedioxybenzene ring (Fig. 2); structure (XVI; R = CN) was therefore assigned to it. Hydrolysis of the cyano-group and simultaneous esterification with methanol and hydrochloric acid then afforded the diester (XVI; R = CO_2Me) which was cyclised by metallic potassium in xylene under the Dieckmann conditions. The resulting crude keto-ester (XVII) was saponified and decarboxylated in boiling hydrochloric acid to ketone (XVIII). As expected, the ultraviolet spectrum of this ketone resembled that of the nitrile (XVI; R = CN) (Fig. 2); its infrared spectrum exhibited a broad band at 3250 $cm.^{-1}$ (OH) but no bands were detected in the carbonyl region, suggesting that the keto-group exists under the conditions of the measurement entirely in the enol form although formation of an oxime leaves no doubt about the presence of a reactive carbonyl group in this compound. Although this ketone (XVIII) might have been expected to lead to the desired benzo[*f*]pyrrocoline (III) in four steps, the extremely low overall yield precluded its use. The following approach, which in essence reverses the order of some of the above steps, was more profitable.

Although the amino-nitrile (VI; R = H, R′ = CN) did not react with acrylonitrile under the conditions reported by McKinney and Uhuig,[4] the corresponding ester (XIII; R = Me) gave a good yield of compound (XIX; R = H, R′ = CN). Hydrolysis and esterification with methanolic hydrochloric acid, followed by treatment with formaldehyde and hydrochloric acid at pH 4 under the conditions of Pictet–Spengler cyclisation, then afforded the tetrahydroisoquinoline (XX), and Dieckmann ring closure was accomplished by the use of sodium hydride. The resulting keto-ester (XXI; R = CO_2Me) was decarboxylated in boiling hydrochloric acid, yielding the ketone (XXI; R = H) which exhibited in the infrared spectrum a carbonyl band at 1754 $cm.^{-1}$ characteristic of a five-membered cyclic ketone, in agreement with its expected structure.

With ethylmagnesium bromide in tetrahydrofuran this ketone gave the alcohol (XXII) which with boiling acetic anhydride gave an *O*-acetate rather than an olefin (XXIII). The acetate reverted to the tertiary alcohol (XXII) on hydrolysis in ethanolic sodium

[4] McKinney and Uhuig, *J. Amer. Chem. Soc.*, 1950, **72**, 2599.

hydroxide. By the use of phosphorus oxychloride in pyridine, however, the alcohol (XXII) gave the olefin (XXIII) which was hydrogenated to give the saturated compound (XXIV) (stereochemistry not established). Oxidation of this by potassium permanganate furnished the oily lactam (XXV): the lactam reverted to crystalline (XXIV) on reduction with lithium aluminium hydride. All attempts to convert the lactam into the desired product (III) by dehydrogenation with palladium–charcoal were unsuccessful: thus most of it was recovered after being heated with 30% palladium–charcoal in the presence of cinnamic acid in xylene at 160—170° for 2 hours, in cymene at 200° for 3 hours, or in ethyl cinnamate at 250° for 5 hours. We had noticed, however, that on working up the reaction mixture from the alcohol (XXII) and phosphorus oxychloride there remained unextracted in the aqueous layer a quaternary base which could be isolated as its sparingly soluble picrate. This base became the main product (yields up to 85%) when the alcohol (XXII) was treated with an excess of thionyl chloride in pyridine. The analytical values of the picrate and the ultraviolet spectra (Fig. 3) of the chloride derived from it indicated that it must have structure (XXVI; X = Cl), probably formed as a result of a shift of the double bond in (XXIII) accompanied by aerial oxidation of the resulting 1,4-dihydroisoquinoline. Potassium ferricyanide then oxidised the chloride (XXVI; X = Cl) to a neutral compound,

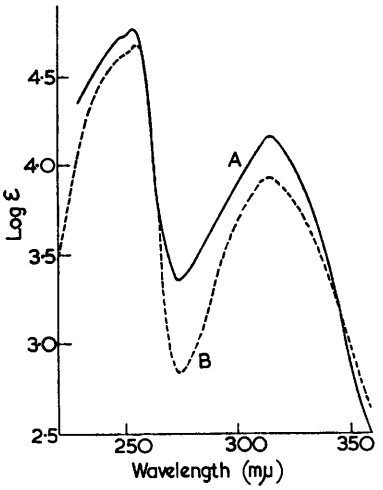


FIG. 3. *Absorption spectra of* (A) 4-*methyl*-6,7-*methylenedioxyisoquinoline methiodide and* (B) *compound* XXVI (X = Cl).

$C_{16}H_{17}NO_3$, m. p. 150°, which was shown to be the racemate of the degradation product (III) of lycorine by comparison of the infrared spectra in chloroform and the ultraviolet spectra in ethanol.

Preliminary attempts, so far without success, to resolve the amide (III) have centred on crystallisation of suitable quaternary salts (XXVI).

The synthesis of this compound provides an unambiguous proof of the structure of lycorine (I), since this was derived from the alkaloid, without loss of carbon atoms, under conditions that precluded molecular rearrangements.

EXPERIMENTAL

α-(3,4-*Methylenedioxyphenyl*)*propionaldehyde* (V).—Iodine (64 g.) was added to a stirred mixture of isosafrole (40 g.), yellow mercuric oxide (60 g.), and a small amount of iodine in ether saturated with water, in small portions during 30 min., with cooling in ice. Additional mercuric oxide (10 g.) was added, and stirring was continued at 13—15° for about 4 hr., until the colour of iodine disappeared. Mercuric salts were filtered off, and a solution of sodium hydrogen sulphite (70 g.) and potassium iodide (8 g.) in water (120 ml.) was added to the filtrate, which was stirred until precipitation of the bisulphite addition compound of the

aldehyde was complete. The adduct, m. p. 175°, was dissolved in water, basified with aqueous sodium carbonate, and extracted with benzene. Drying (Na_2SO_4) and evaporation of the benzene extract and distillation of the residue gave α-(3,4-*methylenedioxyphenyl*)*propionaldehyde* (33·8 g.), b. p. 95—95·5°/0·32 mm. (Found: C, 67·3; H, 5·8. $C_{10}H_{10}O_3$ requires C, 67·4; H, 5·7%). The 2,4-*dinitrophenylhydrazone* formed orange prisms (from ethyl acetate), m. p. 140° (Found: C, 53·6; H, 4·0; N, 15·4. $C_{16}H_{14}N_4O_6$ requires C, 53·6; H, 3·9; N, 15·6%). The *oxime* was prepared in the usual manner and formed prisms (from ethanol), m. p. 72° (Found: C, 62·0; H, 5·7; N, 7·1. $C_{10}H_{11}NO_3$ requires C, 62·2; H, 5·7; N, 7·3%).

1-*Cyano*-2-(3,4-*methylenedioxyphenyl*)*propylamine* (VI; R = H, R′ = CN).—To a solution of the aldehyde (V) (10 g.) in ethanol (20 ml.) was added, with stirring, 50% sodium cyanide solution (10 ml.), 27% aqueous ammonia (20 ml.), and ammonium chloride (5 g.), the temperature rising and the mixture separating into two layers. More water was added, when necessary, until ammonium chloride passed completely into the aqueous layer. The mixture was heated with frequent shaking in a sealed vessel at 50—60° for 10 hr., then cooled, diluted with water, and extracted with benzene. The benzene layer was washed with water and extracted with 10% hydrochloric acid which immediately began to deposit crystals of the *hydrochloride* (cf. VI; R = H, R′ = CN) (10·2 g.). Recrystallisation from ethanol gave needles, m. p. 187—188° (decomp.) (Found: C, 54·8; H, 5·4; N, 11·5. $C_{11}H_{12}N_2O_2$,HCl requires C, 54·9; H, 5·4; N, 11·6%). This gave the free *base* as needles, m. p. 88° (from ethanol) (Found: C, 64·4; H, 5·8; N, 13·5. $C_{11}H_{12}N_2O_2$ requires C, 64·7; H, 5·9; N, 13·7%).

1-*Carbamoyl*-N-*formyl*-2-(3,4-*methylenedioxyphenyl*)*propylamine* (VI; R = CHO, R′ = $CO{\cdot}NH_2$).—1-Cyano-2-(3,4-methylenedioxyphenyl)propylamine (VI; R = H, R′ = CN) (1·4 g.) was heated with 85% formic acid (9 ml.) at 180° for 2 hr. After cooling, the mixture was poured on ice, then set aside at 0° overnight, and the precipitate was collected. Crystallisation from acetone gave the *diamide* (VI; R = CHO, R′ = $CO{\cdot}NH_2$) as scales (1·3 g.), m. p. 219—220° (decomp.) (Found: C, 57·4; H, 5·7. $C_{12}H_{14}N_2O_4$ requires C, 57·6; H, 5·6%).

3-*Cyano*-3,4-*dihydro*-4-*methyl*-6,7-*methylenedioxyisoquinoline* (VII).—The diamide (VI; R = CHO, R′ = $CO{\cdot}NH_2$) (0·3 g.) was heated in phosphorus oxychloride (5 ml.) on a water bath until evolution of hydrogen chloride ceased. The mixture was evaporated under reduced pressure and the residue taken up in water (10 ml.), filtered, and washed with benzene. The aqueous layer was basified with aqueous sodium hydroxide and extracted with benzene. The extracts were washed with water, dried, and concentrated to give a residue which was chromatographed in benzene on alumina (7 g.). Elution with benzene gave the *dihydroisoquinoline* (VII) (83 mg.), needles (from benzene), m. p. 177—178° (Found: C, 67·0; H, 4·8; N, 13·1. $C_{12}H_{10}N_2O_2$ requires C, 67·3; H, 4·7; N, 13·1%).

3-*Cyano*-4-*methyl*-6,7-*methylenedioxyisoquinoline* (VIII).—The diamide (VI; R = CHO, R′ = $CO{\cdot}NH_2$) (0·3 g.) and phosphorus oxychloride (1·5 ml.) in dry xylene (10 ml.) were heated on a water bath for 30 min. After cooling, the mixture was extracted with 5% hydrochloric acid (50 ml.) which was basified and extracted with chloroform. The chloroform extract was washed with water, dried, and evaporated to give a residue (0·16 g.) which was chromatographed in chloroform on alumina (2 g.). The chloroform eluate gave the *base* (VIII) (40 mg.) which crystallised from benzene as needles, m. p. 173—175° (Found: C, 67·5; H, 3·8. $C_{12}H_8N_2O_2$ requires C, 67·9; H, 3·8%).

4-*Methyl*-6,7-*methylenedioxyisoquinoline* (X).—(*a*; cf. below) Addition of 37% formaldehyde solution (0·3 ml.) to an aqueous solution (5 ml.) of the hydrochloride (0·3 g.) of the amino-nitrile (VI; R = H, R′ = CN) in water (5 ml.) caused immediate precipitation of the azomethine (IX) which formed scales (from acetone), m. p. 222—223° (decomp.). A solution of the azomethine (0·3 g.) in methanol (50 ml.) was adjusted to pH 4·0 with hydrochloric acid; 37% aqueous formaldehyde (0·5 ml.) was then added, and the whole was kept at 30° for 64 hr. The mixture was neutralised with aqueous sodium hydroxide and evaporated, and the residue was dissolved in 10% hydrochloric acid (10 ml.) and washed with chloroform. The aqueous layer was basified with 20% aqueous sodium hydroxide (10 ml.) and extracted with chloroform which was washed with water, dried, and evaporated. Chromatography of the residue (0·24 g.) in chloroform over alumina (2 g.) and elution with chloroform gave the *compound* (X) (60 mg.), needles (from ether), m. p. 113—114° (Found: C, 70·4; H, 4·7. $C_{11}H_9NO_2$ requires C, 70·6; H, 4·9%). The *picrate* formed needles (from methanol), m. p. 235° (decomp.) (Found: C, 49·0; H, 2·7. $C_{17}H_{12}N_4O_9$ requires C, 49·0; H, 2·8%).

2-(3,4-*Methylenedioxyphenyl*)*propylamine* (XI; R = H).—The oxime (9 g.) of the aldehyde

(V) in ether (50 ml.) was refluxed with lithium aluminium hydride (2·7 g.) for 5 hr. After cooling, the excess of reagent was destroyed by water, and the ethereal layer extracted with 5% hydrochloric acid. The acid extract was basified with aqueous ammonia and extracted with ether. This second ether solution was dried and evaporated to dryness, to give the amine (XI; R = H) as an oil (7·8 g.). The *hydrogen oxalate* had m. p. 177—178° (from ethanol) (Found: C, 53·4; H, 5·6; N, 5·1. $C_{10}H_{13}NO_2,C_2H_2O_4$ requires C, 53·5; H, 5·6; N, 5·2%). The *N*-formyl derivative (XI; R = CHO) was prepared by heating the amine (6 g.) with 85% formic acid (3 ml.) at 170—190° for 2 hr. and distilled under reduced pressure as an oil (4·8 g.), $\nu_{max.}$ 1685 cm.$^{-1}$ (film).

3,4-*Dihydro*-4-*methyl*-6,7-*methylenedioxyisoquinoline* (XII).—The preceding *N*-formyl derivative (4·6 g.) and phosphorus oxychloride (14 g.) were refluxed in xylene (20 ml.) for 40 min. Addition of light petroleum (b. p. 30—60°) caused separation of a brown oil which was taken up in water, washed with ether, basified with aqueous sodium hydroxide, and extracted with chloroform. The chloroform extract was dried and evaporated and the residue distilled under reduced pressure, to give the dihydroisoquinoline (XII) as an oil (1·4 g.). The *picrate* formed needles (from methanol), m. p. 181—182° (Found: C, 48·9; H, 3·4; N, 13·3. $C_{11}H_{11}NO_2,C_6H_3N_3O_7$ requires C, 48·8; H, 3·4; N, 13·4%).

4-*Methyl*-6,7-*methylenedioxyisoquinoline* (X).—(*b*; cf. above) The dihydroisoquinoline (XII) (0·2 g.), regenerated from its picrate, was heated in *p*-cymene (5 ml.) in the presence of 30% palladium–charcoal (0·3 g.) under nitrogen at 200° for 1 hr. After being kept at room temperature overnight, the catalyst and crystals which separated were collected and extracted with chloroform which was then shaken with 5% hydrochloric acid. The *p*-cymene layer was also extracted with 5% hydrochloric acid. The combined aqueous layers were basified with aqueous ammonia and extracted with ether which was dried and evaporated. The residue was passed in chloroform through a column of alumina. Evaporation of the chloroform eluate and crystallisation from benzene gave the isoquinoline (X) as needles (50 mg.), m. p. 116—118° (Found: C, 70·5; H, 4·7; N, 7·6%). The picrate formed yellow needles (from methanol), m. p. 235—237° (decomp.) (Found: C, 49·1; H, 2·9; N, 13·6%). This base and its picrate showed no depression of m. p.s on admixture with respective preparations described above. The infrared and ultraviolet spectra were also identical. The methiodide was prepared in the usual manner and crystallised from acetone: it had m. p. 267—268° (decomp.).

Methyl α-*Amino*-β-(3,4-*methylenedioxyphenyl*)*butyrate* (XIII; R = Me).—1-Cyano-2-(3,4-methylenedioxyphenyl)propylamine hydrochloride (10 g.) in methanol (100 ml.) was saturated with dry hydrogen chloride and refluxed on a water bath for 20 hr. The methanol was evaporated under reduced pressure and the residue taken up in water (100 ml.). This solution was filtered, basified with sodium carbonate, and extracted with ether. The ethereal extract was dried and evaporated and the residue (6·1 g.) distilled at 154—158°/0·27 mm., giving the oily ester (XIII; R = Me). The ester, in ether, gave its *hydrochloride*, deliquescent needles, m. p. 175° (from ethanol–ether) (Found: C, 53·1; H, 5·2; N, 4·8. $C_{12}H_{15}NO_4$,HCl requires C, 52·8; H, 5·5; N, 5·1%). The *picrate* formed yellow needles (from methanol), m. p. 178° (decomp.) (Found: C, 46·3; H, 3·7; N, 11·8. $C_{12}H_{15}NO_4,C_6H_3N_3O_7$ requires C, 46·4; H, 3·9; N, 12·0%).

Methyl 1,2,3,4-*Tetrahydro*-4-*methyl*-6,7-*methylenedioxyisoquinoline*-3-*carboxylate* (XIV).—A solution of the butyrate (XIII; R = Me) (1·3 g.) in 10% hydrochloric acid (10 ml.) was adjusted to pH 3·5 with aqueous sodium hydroxide. 37% Aqueous formaldehyde (2 ml.) was then added to the solution and the whole kept at 30° for 30 hr. After addition of 35% hydrochloric acid (1 ml.), the mixture was heated on a water bath for 30 min., filtered from some resin, washed with ether, and basified with sodium carbonate, and the precipitated solid was collected, washed with water, and dried, to give the *tetrahydroisoquinoline* (XIV) (1·1 g.). This crystallised from methanol as needles, m. p. 171—172° (Found: C, 62·9; H, 5·8. $C_{13}H_{15}NO_4$ requires C, 62·6; H, 6·1%). The *hydrochloride*, m. p. 247° (decomp.) (Found: C, 54·3; H, 5·5. $C_{13}H_{15}NO_4$,HCl requires C, 54·6; H, 5·6%), and the *picrate*, m. p. 226° (decomp.) (Found: C, 47·7; H, 3·6; N, 11·8. $C_{13}H_{15}NO_4,C_6H_3N_3O_7$ requires C, 47·7; H, 3·8; N, 11·7%), both crystallised as needles from methanol.

Methyl 4-*Methyl*-6,7-*methylenedioxyisoquinoline*-3-*carboxylate* (XV).—The tetrahydroisoquinoline (XIV) (0·3 g.), cinnamic acid (0·36 g.), and 30% palladium–charcoal (0·2 g.) in xylene (20 ml.) were heated in a current of carbon dioxide at 160—170° for 2 hr. The mixture was filtered and the filtrate extracted with 5% hydrochloric acid. The acidic extracts were washed with ether, basified with sodium carbonate, and extracted with benzene. The benzene extracts

were washed with water, dried, and evaporated, to give a residue (0·21 g.) which on crystallisation from methanol gave the *isoquinoline* (XV) as needles, m. p. 183° (Found: C, 63·5; H, 4·4; N, 5·7; OMe, 12·5. $C_{13}H_{11}NO_4$ requires C, 63·7; H, 4·5; N, 5·7; OMe, 12·7%).

Methyl 2-*Cyanoethyl*-1,2-*dihydro*-4-*methyl*-6,7-*methylenedioxyisoquinoline*-3-*carboxylate* (XVI; R = CN).—The tetrahydroisoquinoline (XIV) (0·34 g.), 2-bromoethyl cyanide (0·25 g.), and anhydrous potassium carbonate (0·25 g.) were heated with occasional stirring on the water bath for 8 hr., then cooled. Water (20 ml.) was added, and the mixture was extracted with benzene which was washed with water, dried, and evaporated to dryness. The residue (0·19 g.) distilled at 160—175° (bath temp.)/0·8 mm. The distillate (0·1 g.) was converted into its *picrate*, needles (from methanol), m. p. 274° (decomp.) (Found: C, 49·7; H, 3·2; N, 13·1. $C_{16}H_{16}N_2O_4,C_6H_3N_3O_7$ requires C, 49·9; H, 3·6; N, 13·2%). The free base (XVI; R = CN) was regenerated by passing a chloroform solution of the picrate through alumina, and crystallised from ether as needles, m. p. 87—90°.

1,2,3,5-*Tetrahydro*-10-*methyl*-7,8-*methylenedioxy*-1-*oxobenzo*[f]*pyrrocoline* (XVIII).—The distillate (0·4 g.) consisting of (XVI; R = CN) in methanol (30 ml.) was saturated with dry hydrogen chloride and refluxed with constant bubbling of dry hydrogen chloride at a slow rate through the mixture for 6 hr. The methanol was then evaporated under reduced pressure and the residue taken up in water (50 ml.). This solution was filtered, basified with sodium carbonate, and extracted with benzene. The benzene extract was dried and evaporated, and the residue (0·22 g.) distilled at 128—132°/0·3 mm., giving the diester (XVI; R = CO_2Me) as a pale yellow, viscous oil (0·2 g.). This (0·2 g.) was added in dry toluene (2 ml.) to a suspension of powdered potassium (0·15 g.) in toluene (5 ml.), and the whole was heated on a water bath with occasional shaking for 2 hr. After cooling, the excess of the potassium was destroyed with ethanol, then concentrated hydrochloric acid (15 ml.) was added to the mixture and the whole heated on the water bath for 3 hr. After evaporation to dryness under reduced pressure, the residue was taken up in water (50 ml.), basified with sodium carbonate, and extracted with benzene. The extracts were washed with water, dried, and evaporated to dryness, to give a residue which was distilled at 180—220° (bath temp.)/0·6 mm. Crystallisation of the distillate (20 mg.) from ether yielded the *pyrrocoline* (XVIII) as needles, m. p. 91—92° (Found: C, 68·8; H, 5·9; N, 6·2. $C_{14}H_{13}NO_3$ requires C, 69·1; H, 5·4; N, 5·8%). The *oxime* formed needles (from water), m. p. 85—90°, which was raised to m. p. 99—100° by drying in a vacuum over phosphorus pentoxide (Found, after drying: N, 8·8. $C_{14}H_{14}N_2O_3,3H_2O$ requires N, 9·0%).

α-(2-*Cyanoethylamino*)-β-(3,4-*methylenedioxyphenyl*)*butyric Acid* (XIX; R = H, R′ = CN).—Methyl α-amino-β-(3,4-methylenedioxyphenyl)butyrate (4·2 g.) and sodium hydroxide (0·66 g.) in water (10 ml.) were stirred at room temperature for 30 min. Acryolnitrile (0·91 g.) was then added with cooling and the whole stirred for a further 3 hr. After being kept overnight at 0°, the mixture was heated at 50° for 1 hr., then cooled, washed with ether, and acidified with 35% hydrochloric acid (1·4 ml.). The precipitate was collected, washed with water and ether, and dried, to give the *butyric acid* (XIX; R = H, R′ = CN) (3·5 g.). Crystallisation from water gave needles, m. p. 191—192°, soluble in acids and alkaline solutions and giving a positive ninhydrin test (Found: C, 57·7; H, 6·1; N, 9·8. $C_{14}H_{16}N_2O_4,H_2O$ requires C, 57·1; H, 6·2; N, 9·5%).

Methyl α-(2-*Methoxycarbonylethylamino*)-β-(3,4-*methylenedioxyphenyl*)*butyrate* (XIX; R = Me, R′ = CO_2Me).—The butyric acid (XIX; R = H, R′ = CN) (6 g.) in methanol (70 ml.) was saturated with dry hydrogen chloride. After being refluxed for 10 hr., the mixture was evaporated and the residue taken up in water (100 ml.), filtered, washed with ether, basified with sodium carbonate, and extracted with ether. The ethereal extracts were dried and evaporated to dryness, to give a residue (3·1 g.) which was distilled at 145—165° (bath temp.)/0·05 mm., yielding the *ester* (XIX; R = Me, R′ = CO_2Me) as a viscous oil (Found: C, 59·3; H, 6·6; OMe, 19·2. $C_{16}H_{21}NO_6$ requires C, 59·4; H, 6·6; 2OMe, 19·2%).

Methyl β-(1,2,3,4-*Tetrahydro*-3-*methoxycarbonyl*-4-*methyl*-6,7-*methylenedioxy*-2-*isoquinolyl*)-*propionate* (XX).—A solution of the ester (XIX; R = Me, R′ = CO_2Me) (4·4 g.) in water (30 ml.) containing 35% hydrochloric acid (1 ml.) was adjusted to pH 4·0 with aqueous sodium hydroxide. 37% Aqueous formaldehyde (13 ml.) was then added and the whole kept at 32° for 4 days. After addition of 35% hydrochloric acid (1 ml.), the mixture was heated on a water bath for 30 min., filtered from resin, washed with ether, basified with sodium carbonate, and extracted with ether. The ethereal extracts were combined, washed with water, dried, and evaporated to dryness, to give a residue (3·2 g.) which was chromatographed in benzene

over alumina. Elution with benzene gave a pale yellow oil (XX) which resisted crystallisation. The hydrochloride was very deliquescent. The *picrolonate* prepared in the usual manner formed yellow needles, m. p. 180—181°, from acetone–ether (Found: C, 54·2; H, 4·9; N, 11·5; OMe, 10·5. $C_{17}H_{21}NO_6$,$C_{10}H_8N_4O_5$ requires C, 54·1; H, 4·9; N, 11·7; 2OMe, 10·4%).

1,2,3,5,10,10a-*Hexahydro*-10-*methyl*-7,8-*methylenedioxy*-1-*oxobenzo*[f]*pyrrocoline* (XXI; R = H).—To a stirred suspension of sodium hydride (1 g.) in dry toluene (20 ml.) was added a solution of the ester (XX) (7·2 g.) in dry toluene (20 ml.) in two portions at 90°, the second portion being added dropwise after evolution of hydrogen had been observed. After addition of a few drops of ethanol, the mixture was heated at that temperature with stirring for 4 hr. The excess of the sodium hydride was destroyed with ethanol, concentrated hydrochloric acid (270 ml.) added, and the whole boiled under reflux with stirring for 3 hr., a negative ferric chloride test being then obtained. The mixture was evaporated to dryness, diluted with water (200 ml.), and filtered from resin, and the filtrate basified with sodium carbonate and extracted with ether. The extracts were combined, washed with water, dried, and evaporated to give a residue (5·7 g.). Two crystallisations of this residue from methanol gave the *ketone* (XXI; R = H) as yellow needles (3·9 g.), m. p. 150—151° (decomp.). It gave a positive Zimmermann test (Found: C, 68·3; H, 6·1; N, 6·1. $C_{14}H_{15}NO_3$ requires C, 68·6; H, 6·2; N, 5·7%). The *oxime* was prepared in methanol and formed prisms (from methanol), m. p. 216—217° (decomp.) (Found: C, 64·5; H, 6·2; N, 10·4. $C_{14}H_{16}N_2O_3$ requires C, 64·6; H, 6·2; N, 10·8%).

1-*Ethyl*-1,2,3,5,10,10a-*hexahydro*-1-*hydroxy*-10-*methyl*-7,8-*methylenedioxybenzo*[f]*pyrrocoline* (XXII).—To a Grignard solution prepared from magnesium (1·5 g.) and ethyl bromide (4·2 g.) in tetrahydrofuran (20 ml.) was added with stirring the ketone (XXI; R = H) (3 g.) in tetrahydrofuran (80 ml.). Stirring was continued under reflux for 4 hr. The solvent was then removed and the residue decomposed with ice-water and hydrochloric acid and filtered. The filtrate was made alkaline with aqueous ammonia and extracted with chloroform. This extract was washed with water, dried, and evaporated, to give a residue (2·5 g.) which was chromatographed in benzene (12 ml.) over alumina (25 g.). Benzene and chloroform eluates gave the *alcohol* (XXII) as scales, m. p. 149—150° (from methanol) (Found: C, 69·5; H, 7·6; N, 5·0. $C_{16}H_{21}NO_3$ requires C, 69·8; H, 7·7; N, 5·1%). The O-*acetate* was prepared by treatment of the alcohol (XXII) (0·4 g.) with acetic anhydride at 150° for 1 hr. and formed needles, m. p. 125°, from methanol (Found: C, 67·8; H, 7·4. $C_{18}H_{23}NO_4$ requires C, 68·1; H, 7·3%).

1-*Ethyl*-2,3-*dihydro*-10-*methyl*-7,8-*methylenedioxy*-3H-*benzo*[f]*pyrrocolinium Salts* (XXVI).—(i) To a solution of the alcohol (XXII) (0·7 g.) in dry pyridine (6 ml.) was added, with cooling in ice-water, phosphorus oxychloride (0·4 ml.), and the mixture was heated on a water bath for 40 min. After being kept at room temperature overnight, the mixture was added to ice-water and evaporated to dryness. The residue was dissolved in water (50 ml.), basified with aqueous ammonia, and extracted with ether. Evaporation gave the olefin (XXIII) as an oil (0·19 g.). The alkaline aqueous layer was weakly acidified with hydrochloric acid and filtered, and a saturated sodium picrate solution was added. The picrate thus formed was collected, washed with ether, and passed in acetone (40 ml.) through alumina (5 g.). Elution with acetone and crystallisation from acetone gave the *picrate* (cf. XXVI) as yellow needles (0·34 g.), m. p. 175—176° (decomp.) (Found: C, 54·6; H, 4·1; N, 11·4. $C_{16}H_{18}NO_2$,$C_6H_2N_3O_7$ requires C, 54·5; H, 4·2; N, 11·6%). The hydrochloride was prepared by passage of the picrate in methanol through a column of Amberlite IRA 400 ion-exchange resin (OH^- form), followed by acidification with hydrochloric acid and concentration. Crystallisation from acetone–methanol gave hygroscopic needles, m. p. 184—186°.

(ii) To a stirred solution of the alcohol (XXII) (0·32 g.) in dry pyridine (6·3 ml.) was added thionyl chloride (0·5 ml.) with cooling. Stirring was continued for 10 min. and then the mixture was left at room temperature for 2 hr. After evaporation under reduced pressure, a solution of the residue in water (50 ml.) was filtered, basified with aqueous ammonia, and extracted with ether. Concentration of the ethereal extract gave the olefin (XXIII) as an oil (15 mg.). The aqueous layer was treated with sodium picrate as described in (i), yielding the picrate (cf. XXVI) (0·48 g.), m. p. and mixed m. p. 173—175°.

Attempts to resolve the base by the use of (+)-tartaric acid, (−)-dibenzoyltartaric acid, (+)-camphoric acid, (−)-quinic acid, or (+)-di-*p*-toluoyltartaric acid failed.

1-*Ethyl*-1,2,3,5,10,10a-*hexahydro*-10-*methyl*-7,8-*methylenedioxybenzo*[f]*pyrrocoline* (XXIV).—A solution of the olefin (XXIII) (0·5 g.) in acetic acid (25 ml.) was shaken with hydrogen in the

presence of Adams catalyst (90 mg.) (uptake 71 ml. in 40 min.). The mixture was filtered, and the combined filtrate and washings were evaporated under reduced pressure. The residue was taken up in water, basified with aqueous ammonia, and extracted with ether. The ethereal extract was washed with water, dried, and concentrated, to give a residue (485 mg.) which was chromatographed in benzene–light petroleum (b. p. 30—60°) (1 : 1) over alumina (2 g.). Elution with benzene–light petroleum (b. p. 30—60°) (1 : 1) gave the *pyrrocoline* (XXIV) (330 mg.) which crystallised from light petroleum as plates, m. p. 92—95° (Found: C, 73·9; H, 8·1. $C_{16}H_{21}NO_2$ requires C, 74·1; H, 8·2%).

1-*Ethyl*-1,2,3,5,10,10a-*hexahydro*-10-*methyl*-7,8-*methylenedioxy*-5-*oxobenzo*[f]*pyrrocoline* (XXV).—To a solution of the base (XXIV) (66 mg.) in acetone (12 ml.) was added with stirring a 1% solution of potassium permanganate in acetone (7·2 ml.) at 1—2°. Stirring was continued for a further 3 hr. and the mixture kept at room temperature overnight. After removal of manganese dioxide, the filtrate was evaporated to dryness and the residue taken up in benzene, washed with 3% hydrochloric acid, water, and aqueous sodium hydrogen carbonate, dried, recovered (62 mg.), and distilled at 180—185° (bath temp.)/0·01 mm. The viscous distillate was the *lactam* (XXV) (55 mg.) which was analysed after one redistillation (Found: C, 70·1; H, 7·1; N, 5·0. $C_{16}H_{19}NO_3$ requires C, 70·3; H, 7·0; N, 5·1%).

The *lactam* (XXV) (60 mg.) and lithium aluminium hydride (70 mg.) in tetrahydrofuran (5 ml.) were heated under reflux for 4 hr. Working up in the usual manner gave a base which after chromatography and recrystallisation had m. p. 92°, undepressed on admixture with a sample of the base (XXIV) described above.

Attempted Dehydrogenation of the Lactam (XXV).—(i) The lactam (228 mg.), cinnamic acid (0·12 g.), and 30% palladium–charcoal (70 mg.) in xylene (15 ml.) were heated in a stream of carbon dioxide at 160—170° for 2 hr. The mixture was filtered and washed with 5% aqueous sodium hydrogen carbonate and water, dried, and evaporated, to give a residue (200 mg.) which was purified by passing through alumina. A benzene eluate gave an oil which was identical with the starting material (ultraviolet and infrared spectra; paper chromatography). (ii) Lactam (63 mg.), cinnamic acid (83 mg.), and 30% palladium–charcoal (70 mg.) in *p*-cymene (10 ml.) were heated under nitrogen at 200° for 3 hr.; starting material (36 mg.) was recovered. (iii) Dehydrogenation in ethyl cinnamate at 250° for 5 hr. and chromatography on alumina gave starting material as the main fraction, with minute amounts of two compounds, m. p. 125—127° and 215—220°, severally, whose infrared spectra were quite different from that of the lactam (III); these compounds were not investigated further.

1-*Ethyl*-1,2,3,5-*tetrahydro*-10-*methyl*-7,8-*methylenedioxy*-5-*oxobenzo*[f]*pyrrocoline* (III).—To a solution of the quaternary chloride (cf. XXVI) (54 mg.) in 50% aqueous ethanol (2 ml.) was added one of potassium ferricyanide (0·22 g.) and potassium hydroxide (40 mg.) in water (4 ml.). After being heated on a water bath for 3 hr., the mixture was neutralised with dilute sulphuric acid and evaporated to dryness. The residue was dissolved in water (30 ml.) and extracted with benzene, and the benzene extract washed with dilute sulphuric acid and water, dried, and evaporated to give a further residue (31 mg.). This was chromatographed in benzene over alumina (3 g.). Elution with benzene gave the lactam (III) which on crystallisation from benzene–light petroleum (b. p. 30—60°) formed needles, m. p. 150° (Found: C, 71·0; H, 6·4; N, 5·3. Calc. for $C_{16}H_{17}NO_3$: C, 70·8 H, 6·3; N, 5·2%). The infrared spectrum in chloroform was identical with that of a sample from natural sources. The ultraviolet spectra of the two samples were superimposable.

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School of Pharmacy, Osaka University, Japan.
[Present addresses: Mukogawa Women's University, Hyogo (S. T.).
Faculty of Pharmacy, Kyoto University, Kyoto (S. U.).] [*Received, March 13th*, 1961.]