542. *Ipecacuanha Alkaloids. Part III.* The Stereochemistry at Positions 1′ and 10 of Emetine.*

By A. R. Battersby, R. Binks, and G. C. Davidson.

Infrared evidence and conformational arguments are presented which strongly support conformation (VIII) as the thermodynamically most stable one for the benzoquinolizidine system (cf. VII).

The ester (VII; R = Me), prepared by degradation of *O*-methylpsychotrine, is shown to have an equatorial methoxyl group. It is established that no rearrangement occurs during preparation of this ester. The stereochemistry at positions 1′ and 10 in *O*-methylpsychotrine and emetine is thereby proved to be as in (XXII) and (XXIII), respectively.

Of the Ipecacuanha alkaloids,[1] particular interest attaches to emetine because of its importance in the treatment of amœbic dysentery. Its structure (I) was established by degradation [2] in 1949 and was confirmed by the synthesis of (±)-rubremetine [3] and of emetine itself,[4] but these studies gave no information about the stereochemistry of the alkaloid.

Our purpose in the present series of investigations is to elucidate the relative and absolute stereochemistry of emetine. It is clear that this knowledge will be of value in any explanation of the stereospecificity of emetine's pharmacological action and will also be of considerable interest in establishing the relation of emetine to other alkaloids, particularly those in the indole series, which are thought to have similar biogeneses.[5] Finally, work on the stereospecific synthesis of emetine requires first a knowledge of its stereochemistry.

Our degradative work which has been briefly described [6] in part, starts with *O*-methylpsychotrine (II). This occurs as a minor alkaloid in Ipecacuanha and a simple method for

* Part II, *J.*, 1959, 1748.

[1] Reviewed by Janot, " The Alkaloids," Ed. Manske and Holmes, Academic Press Inc., New York, 1953, Vol. III, p. 363.

[2] Pailer and Porschinski, *Monatsh.*, 1949, **80**, 94; Battersby and Openshaw, *J.*, 1949, 3207 and refs. therein.

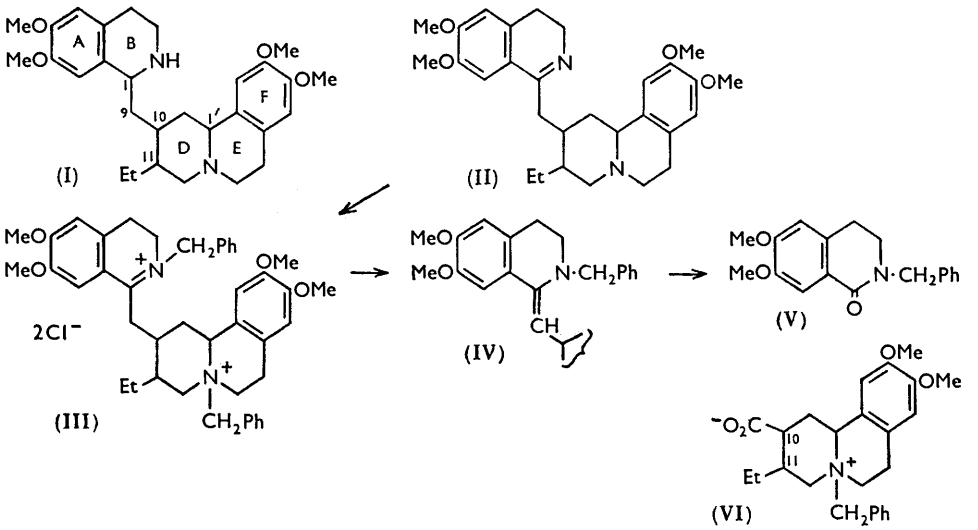
[3] Battersby and Openshaw, *Experientia*, 1950, **6**, 387; Battersby, Openshaw, and Wood, *J.*, 1953, 2463; Ban, *Pharm. Bull.* (*Japan*), 1955, **3**, 53.

[4] Evstigneeva, Livshits, Bainova, Zakharkin, and Preobrazhenskii, *J. Gen. Chem.* (*U.R.S.S.*), 1952, **22**, 1467.

[5] Woodward, *Nature*, 1948, **162**, 155; Robinson, *ibid.*, p. 206; Woodward, *Angew. Chem.*, 1956, **68**, 13.

[6] Battersby, Binks, Davidson, Davidson, and Edwards, *Chem. and Ind.*, 1957, 982.

its isolation from that source is given on p. 2708. This alkaloid can be reduced chemically to a mixture of emetine and isoemetine; the latter differs from emetine [7] only in the configuration at position 1. We find that this reduction is more readily achieved by catalytic hydrogenation of *O*-methylpsychotrine base in ethanol.[8] These results prove that *O*-methylpsychotrine and emetine have the same stereochemistry about rings D and E; knowledge derived from one therefore holds for the other.



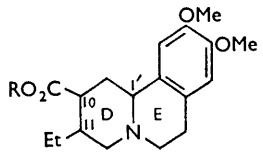
O-Methylpsychotrine with hot benzyl chloride yields the bisbenzylochloride (III) which in alkaline solution gave the iso-base (IV). This was very readily oxidised by potassium permanganate at −5° and, in addition to a water-soluble fraction, a crystalline neutral product, $C_{18}H_{19}O_3N$, was obtained in 53% yield. The latter was identical with our earlier preparation [9] of *N*-benzylcorydaline (V) and therefore the water-soluble product is presumably the quaternary betaine (VI). This was confirmed when hydrogenolysis of the crude betaine over palladium gave the crystalline amino-acid (VII; R = H) in 54% overall yield.

In order to study the configuration at $C_{(10)}$ in this amino-acid, the corresponding methyl ester (VII; R = Me) was heated with methanolic sodium methoxide under conditions selected to be considerably more vigorous than those which are known to invert the axial methoxycarbonyl group of ecgonine methyl ester.[10] Since our ester (VII; R = Me) was recovered unchanged, it follows that the methoxycarbonyl group is equatorial in the favoured conformation of the molecule.

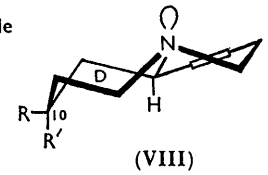
If one makes in this case the safe restriction that only the chair and the half-chair form of rings D and E respectively should be considered, there are three possible conformations, (VIII), (IX), and (X) for the benzoquinolizidine system in the ester (VII; R = Me). As required of different conformations of a molecule, (VIII), (IX), and (X) are interconvertible owing to the ease with which the nitrogen atom can undergo inversion. Conformation (X) with the bulky aromatic group axial should clearly be the least stable. The *trans*-form (VIII) should be more stable than the corresponding *cis*-form (IX) because in the latter arrangement there are present [11] the skew interactions which make *cis*-decalin thermodynamically less stable than *trans*-decalin. It is worth noting, however, that comparisons

[7] Pyman, *J.*, 1917, **111**, 419.
[8] Cf. Karrer, Eugster, and Ruttner, *Helv. Chim. Acta*, 1948, **31**, 1219.
[9] Battersby and Davidson, unpublished work.
[10] Findlay, *J. Amer. Chem. Soc.*, 1954, **76**, 2855.
[11] Cf. Cookson, *Chem. and Ind.*, 1953, 337.

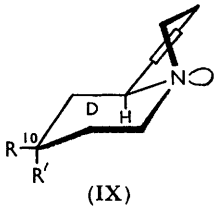
of stabilities of the possible conformations of quinolizidine (XI) with the thermodynamic stabilities of *cis*- and *trans*-decalin should consider the effect of the space requirement that the nitrogen electron pair exceeds that of a hydrogen atom.[12] This factor will act in favour of the *cis*-conformation (cf. IX), but it cannot outweight the forces which favour the *trans*-form (cf. VIII) because, though the bulk of a methyl group is accepted as greater than that of hydrogen or an electron pair,[12] *trans*-9-methyldecalin (XII) is thermodynamically more stable than the *cis*-isomer by 0·8 kcal. per mole.[13] Thus the foregoing consideration of non-bonded interactions leads to the conclusion that conformation (VIII) is the most stable one, and strong support comes from a study of infrared spectra in this series.



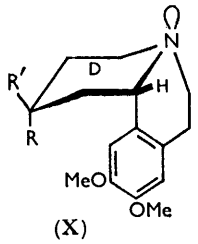
(VII)



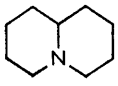
(VIII)



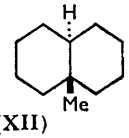
(IX)



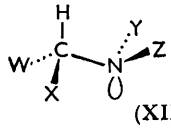
(X)



(XI)



(XII)



(XIII)

A large number of quinolizidine derivatives of known stereochemistry has been examined spectroscopically and it is found[14] that the infrared spectrum shows distinct absorption in the 2700—2800 cm.$^{-1}$ region only when the base contains at least two hydrogen atoms on the carbons attached to nitrogen arranged as in the system (XIII) with the C–H bond and the nitrogen electron pair *trans* and coplanar. This absorption also appears in the spectra of the indole alkaloids examined[15,16] which have an α-hydrogen atom at position 3 and *trans*-locked D, E rings. Again in these cases, the stereochemistry about the $C_{(3)}$–N system is unambiguously as in (XIII), when chair and half-chair rings are used, and two other hydrogen atoms are similarly orientated.

The many benzoquinolizidine bases (cf. VII) obtained in the present and subsequent work all show infrared absorption of medium intensity at 2750 ± 10 cm.$^{-1}$ which is not present in salts of the bases or in their 1′,*N*-unsaturated derivatives. Most of the spectra were determined with the base in solution or in the form of an amorphous film, so that the results are derived from molecules unconstrained by the intermolecular forces present in a crystal. Thus the favoured conformation of our benzoquinolizidine molecules must fulfil the stereochemical conditions described above for the reference compounds.* These requirements are met only by conformation (VIII) which can now be accepted confidently as the preferred one.

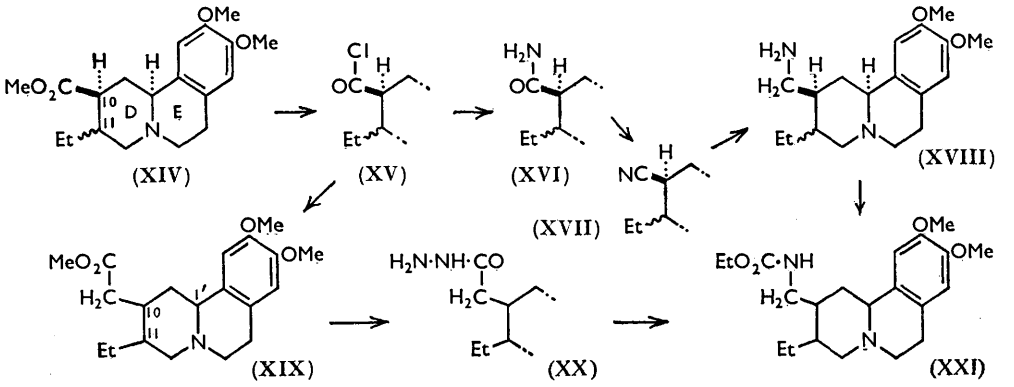
It follows that the ester (VII; R = Me), having an equatorial methoxycarbonyl group, must be represented by (VIII; R = CO_2Me, R′ = H) which in a planar representation

* It has recently been shown[17] that *N*-methyl groups give rise to an absorption band close to the one discussed above and presumably of similar origin. Confident assignment of an absorption in this region might therefore be difficult in some alkaloids. Our bases do not contain *N*-methyl groups, so this problem does not arise.

[12] Barton and Cookson, *Quart. Rev.*, 1956, **10**, 44 and refs. therein.
[13] Turner, *J. Amer. Chem. Soc.*, 1952, **74**, 2118.
[14] Bohlmann, *Angew. Chem.*, 1957, **69**, 641; *Chem. Ber.*, 1958, **91**, 2157.
[15] Wenkert and Roychaudhuri, *J. Amer. Chem. Soc.*, 1956, **78**, 6417.
[16] Neuss and Boaz, *J. Org. Chem.*, 1957, **22**, 1001.
[17] Hill and Meakins, *J.*, 1958, 760; Braunholtz, Ebsworth, Mann, and Sheppard, *J.*, 1958, 2780.

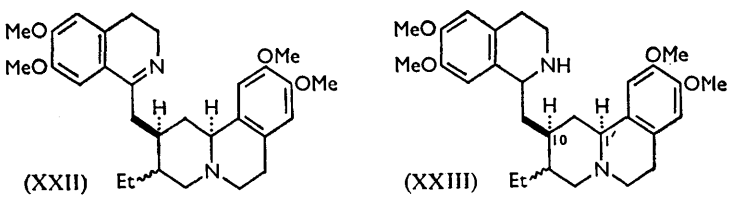
becomes (XIV); the *absolute* configuration shown has been selected for reasons presented elsewhere.[18]

Since the ester (XIV) has the more stable configuration at position 10, it is necessary to prove that inversion has not occurred during its preparation and isolation. This problem was studied as shown in the annexed scheme. The sodium salt derived from the ester



(XIV) reacted with oxalyl chloride to afford the acid chloride (XV). When this was subjected to Arndt–Eistert homologation, a reaction which is known to proceed with retention of configuration,[19] the ester (XIX) (below) was obtained. This result is in favour of the same stereochemistry for the two esters (XIV) and (XIX), but it was not considered to be fully satisfactory because of the low yield of the ester (XIX). A longer sequence of reactions gave the required conclusive proof.

The acid chloride (XV) with ammonia gave the amide (XVI) which was dehydrated by hot phosphoryl chloride to the nitrile (XVII). When the nitrile was reduced with lithium aluminium hydride, the amine (XVIII) was obtained and this, without purification, was converted by ethyl chloroformate into the urethane (XXI). The same urethane resulted from Curtius rearrangement of the hydrazide (XX) prepared from the ester (XIX) and which, in turn, was derived from protoemetine.[20] None of these transformations has affected any of the asymmetric centres and therefore it follows that the ester (XIV) and (XIX) have the same stereochemistry about rings D and E. Further, we proved earlier [20] that the ester (XIX) has the same stereochemistry as *O*-methylpsychotrine. Thus, this also holds for the ester (XIV) and it is established that no inversion has occurred in the reaction sequence used for its preparation. The stereochemistry shown in (XIV) can be used therefore to extend the structures of *O*-methylpysychotrine and emetine to (XXII) and (XXIII), respectively.



Recently, Brossi *et al.*[21] with Barash and Osbond [22] have interpreted the results obtained in the synthesis of the isomers of emetine, together with related experiments, on the basis

[18] Battersby and Garratt, *Proc. Chem. Soc.*, 1959, 86.
[19] Wiberg and Hutton, *J. Amer. Chem. Soc.*, 1956, **78**, 1640.
[20] Battersby and Harper, *J.*, 1959, 1748.
[21] Brossi, Cohen, Osbond, Plattner, Schnider, and Wickens, *Chem. and Ind.*, 1958, 491.
[22] Barash and Osbond, *ibid.*, p. 490.

of a stereochemistry for emetine having the opposite *relative* configuration at position 1′ to that shown in structure (XXIII), that is a *trans*-arrangement of the 1′- and the 10-hydrogen atom. This proposal is in conflict with our experiments [23] and Dr. Osbond has since very kindly sent to us, in advance of publication, a communication [24] describing new pharmacological tests on their synthetic emetine isomers. The results obtained are now in agreement with the stereochemistry shown in structure (XXIII).

Experimental

For general directions, see Part I of this series.[25]

Isolation of O-*Methylpsychotrine* (II).—The crude bases (60 g.) recovered [25] from the mother-liquors obtained in the extraction of emetine, were dissolved in warm ethanol (400 ml.) containing hydrated oxalic acid (40 g.). The precipitated hydrogen oxalates were collected from the warm solution and then heated to the b. p. with ethanol (150 ml.). A mixture of *O*-methylpsychotrine and emetamine hydrogen oxalates (20·5 g.) crystallised from the cold solution. This mixture was distributed between ethyl acetate (250 ml.) and aqueous phosphate buffer (500 ml.) made from 0·5M-KH_2PO_4 (5 vol.) and 0·5M-K_2HPO_4 (3 vol.). The separated aqueous layer was shaken again with ethyl acetate (50 ml.), and the combined organic solutions were extracted with fresh buffer (4 × 250 ml.). After the combined aqueous layers had been made strongly alkaline, the precipitated base was extracted into ether–chloroform (5 : 1 by vol.; 4 × 250 ml.). Evaporation of the dried extracts left a gum (18 g.) which was dissolved in dry ether, and the solution was filtered. The filtrate was concentrated to a thin syrup; *O*-methylpsychotrine crystallised (12 g.; m. p. 121—123°). Brindley and Pyman [26] record m. p. 123—124° (corr.).

Crude emetamine was obtained by evaporation of the above combined solutions in ethyl acetate.

O-*Methylpsychotrine Bisbenzylochloride* (III).—A solution of *O*-methylpyschotrine (5 g.) in freshly distilled benzyl chloride (30 ml.) was heated at 80° for 12 hr. Half of the benzyl chloride was then evaporated at 0·1 mm. and the residual solution was poured into dry ether (300 ml.). The precipitated solid *salt* was powdered under the ether, washed several times with ether by decantation, and then dried at 100° *in vacuo* (7·28 g., 96%) (Found: C, 70·8; H, 7·3; N, 3·6. $C_{43}H_{52}O_4N_2Cl_2$ requires C, 70·6; H, 7·2; N, 3·8%).

Oxidation of O-*Methylpsychotrine Bisbenzylochloride*.—A stirred solution of the bisbenzylochloride (6 g.) in rigorously purified dioxan (100 ml.) and water (100 ml.) at 0° was treated with 2N-sodium hydroxide (10 ml.). The solution was then cooled to −5° and aqueous potassium permanganate (150 ml. containing 3 g.) was added dropwise under the surface during 45 min. with stirring. After filtration of the resultant suspension and washing of the pad with warm dilute sodium hydroxide and acetone, the filtrate was adjusted to pH 2 with concentrated hydrochloric acid (*A*).

Five similar oxidations of the bisbenzylochloride (total 33 g.) were carried out and the solutions from the six runs were combined at stage (*A*) above. The organic solvents were evaporated and the aqueous suspension was extracted thrice with ethyl acetate; the aqueous layer was reserved (*B*). After the ethyl acetate solution had been washed with dilute hydrochloric acid and water, it was dried and evaporated to leave a gum which was extracted with hot ether. Concentration of the extract afforded *N*-benzylcorydaline (V) as needles (7·22 g., 53%), m. p. 96—99° undepressed on admixture with an authentic sample.[9]

The aqueous solution (*B*) was extracted with chloroform (3 × 100 ml.), the combined chloroform solutions were shaken with 0·5N-sodium hydroxide (3 × 100 ml.), and the alkaline extracts were acidified and added to the main aqueous solution. This was evaporated to dryness, and the residue was dried for 1 day over phosphoric oxide *in vacuo* and then extracted with boiling ethanol until the insoluble material contained nothing organic. Water (20 ml.) and hydrated sodium acetate (10 g.) were added to the combined extracts (400 ml.) which were then shaken with 10% palladised charcoal (2 g.) and hydrogen at room temperature and pressure. Uptake

[23] Battersby, *Chem. and Ind.*, 1958, 1324.
[24] Osbond, *ibid.*, 1959, 257.
[25] Battersby, Davidson, and Harper, *J.*, 1959, 1744.
[26] Brindley and Pyman, *J.*, 1927, **130**, 1067.

of gas (1·4 l.) ceased after 15 hr. and the solution was then filtered. Evaporation of the filtrate left a gum which was dissolved in dilute hydrochloric acid, and the solution was basified. This was extracted thrice with ethyl acetate, and the aqueous layer was acidified to Congo Red and then evaporated to dryness. After the residue had been dried over phosphoric oxide *in vacuo* for 1 day, it was extracted with several portions of boiling ethanol to dissolve all the organic material. Evaporation of the extracts left a gum which was heated under reflux for 5 hr. with methanol (500 ml.) and concentrated sulphuric acid (20 ml.). Methanol (400 ml.) was distilled off and the solution was poured on ice and aqueous sodium carbonate. Ether-extraction of the resultant alkaline suspension gave, by the usual working up, a gum (9·29 g.) which was extracted (2 × 200 ml.) with hot light petroleum (b. p. 40—60°). The insoluble residue was dissolved in ether (5 ml.), and light petroleum (150 ml.) was added to precipitate an amorphous solid (0·36 g.) which was rejected. The three solutions in light petroleum were combined and extracted with 2N-hydrochloric acid (3 × 100 ml.) to give an acidic aqueous solution (*C*) which was heated under reflux for 14 hr. and then evaporated to 75 ml. Addition of concentrated hydrochloric acid (7 ml.) caused separation of the *amino-acid hydrochloride* (cf. VII; R = H) as prisms (6·6 g.), m. p. 264—266° (decomp.), unchanged by recrystallisation from a mixture of concentrated hydrochloric acid (1 vol.) and water (3 vol.). Concentration of the original mother liquor gave more of the same salt (total yield, 9·03 g., 54%). The amino-acid hydrochloride also separated as fine needles from a rapidly cooled solution, but on being kept in contact with the mother-liquor these changed into compact prisms (Found: C, 61·0; H, 7·3; N, 3·8. $C_{18}H_{26}O_4NCl$ requires C, 60·75; H, 7·4; N, 3·9%), $[\alpha]_D^{20}$ −46·5° ± 1° (*c* 3·1 in water).

In a similar degradation of *O*-methylpsychotrine (10 g.), solution (*C*) above was made alkaline with potassium carbonate, and the crude amino-ester (VII; R = Me) was extracted with ether. Evaporation of the ether left a gum (3·6 g.) which was distilled in a short-path still at 150° (bath)/0·2 mm. The distillate (2·9 g.) was heated under reflux with 0·2N-barium hydroxide (75 ml.) for 7½ hr. and the cooled solution was treated with exactly one equiv. of 0·5N-sulphuric acid. After the barium sulphate had been filtered off, the solution was evaporated to dryness to leave the *amino-acid* (VII; R = H) as prisms which, crystallised from ethanol or from water (1·5 g.), had m. p. 193—200° (decomp.), strongly dependent on the rate of heating; a slow temperature rise gave m. p. 185—194° (Found, in material dried at 110°: C, 63·4; H, 8·0; N, 3·7. $C_{18}H_{25}O_4N,H_2O$ requires C, 64·1; H, 8·1; N, 4·1%).

The Amino-ester (VII; R = Me).—A solution of the foregoing amino-acid hydrochloride (1 g.) in methanol (50 ml.) containing concentrated sulphuric acid (2 ml.) was heated under reflux for 12 hr. Part of the methanol (40 ml.) was then distilled off and the solution was poured on ice and sodium carbonate. Ether-extraction then afforded the *amino-ester* (VII; R = Me) as a gum (0·9 g., 97%) which crystallised from light petroleum (b. p. 40—60°) as rosettes of needles, m. p. 73·5—75·5° (Found, in material dried at 56°: C, 68·9; H, 8·2; N, 4·4. $C_{19}H_{27}O_4N$ requires C, 68·5; H, 8·2; N, 4·2%).

Action of Sodium Methoxide on the Amino-ester (VII; R = Me).—A solution of the above ester (0·11 g.) in methanolic sodium methoxide (2 ml.), made by dissolving sodium (0·29 g.) in methanol (51 ml.), was heated under reflux for 11 hr. 2N-Hydrochloric acid (0·3 ml.) was then added, the solution was evaporated to dryness, and the residue was heated under reflux with 2N-hydrochloric acid (10 ml.) for 24 hr. This solution was then evaporated to dryness and the residue was dried in *vacuo* for 24 hr. before it was dissolved quantitatively in a mixture (5 ml.) of ethanol (3 vol.) and water (1 vol.) for the determination of rotation. $[\alpha]_D^{20}$ was −45·5° ± 1° calculated as amino-acid hydrochloride (cf. VII; R = H). Concentration of the solution yielded the unchanged amino-acid hydrochloride (cf. VII; R = H) (0·08 g.), m. p. and mixed m. p. 264—266° (decomp.), $[\alpha]_D^{19}$ −45° ± 1°.

A second sample (0·11 g.) of the amino-ester (VII; R = Me) was handled as above, but the treatment with sodium methoxide was omitted. $[\alpha]_D^{20}$ of the final solution was −43·4° ± 1° calculated as above.

Arndt–Eistert Homologation.—The foregoing amino-acid hydrochloride (534 mg., 1·5 mmol.), which had been dried at 100° over phosphoric oxide *in vacuo* for 7 hr., was dissolved in water (10 ml.) and treated with 0·5N-sodium hydroxide (6 ml.). Evaporation of the solution to dryness left a crystalline residue which was powdered in an agate mortar and dried at 100° over phosphoric oxide in *vacuo* for 1·5 hr. This mixture of salts (517 mg.) was stirred at room temperature in dry benzene (30 ml.) while freshly distilled oxalyl chloride (0·169 ml.) in benzene (2·5 ml.) was added during 5 min.; the oxalyl chloride was then washed in with more benzene

(5 ml.). After the suspension had been stirred for 0·5 hr., most of the solid had dissolved and the last traces were removed by filtration through a filter stick in an apparatus completely protected against moisture. The resultant clear solution was added to an ethereal solution of diazomethane (*ca.* 0·7 g.), kept overnight at room temperature, and evaporated to dryness at 10°, to leave the diazo-ketone as a gum (286 mg.).

Silver oxide, freshly prepared from silver nitrate (0·25 g.), was washed many times with water, methanol, and finally with anhydrous methanol. The product was added to a solution of the above diazo-ketone in anhydrous methanol (10 ml.) at 50°; nitrogen evolution (26 ml.) was complete in 2 hr. After the solution had been filtered, it was evaporated to dryness and the residue was dissolved in ether (2 ml.) containing a few drops of methanol to give a clear solution. This was mixed with light petroleum (50 ml.), b. p. 40—60°, then kept until the petroleum solution was clear, and the solution was decanted; the same procedure was repeated twice on the petroleum-insoluble matter. The combined extracts were shaken with 0·2N-hydrochloric acid (2 × 15 ml.), the aqueous solution was extracted with ether (3 × 50 ml.), then basified with potassium carbonate and extracted again with ether (3 × 50 ml.). Evaporation of the latter ethereal solution gave a gum (122 mg.) which was extracted thoroughly with boiling light petroleum (b. p. 40—60°); the combined extracts were concentrated to 2 ml., crystallisation occurring to give needles, m. p. 93—94°, depressed to 58—65° on admixture with the methyl ester (VII; R = Me).

The crystalline ester and the gum obtained by evaporation of its mother-liquor were hydrolysed separately by boiling 2N-hydrochloric acid (5 ml.). Concentration of both solutions (to 0·5 ml.) yielded crystals of the homologated amino-acid hydrochloride (46·3 mg., 15 mg., respectively; 11%), and both crops when dried at room temperature had m. p. and mixed m. p. 179—183°, after sintering at 176°. After a sample of the former crop had been dried at 40° for 3 hr., the m. p. was 199—202°, after slight sintering.

Part (24·3 mg.) of the combined crops of hydrochloride above was converted as earlier into the methyl ester (23·5 mg.) which crystallised from light petroleum (b. p. 40—60°) to give the amino-ester (XIX), m. p. 93—94° undepressed on admixture with an authentic sample.[20] The two samples of (XIX) gave identical *X*-ray powder diagrams.

Preparation of the Amide (XVI).—A benzene solution of the amino-acid chloride (XV) was prepared as above, though without filtration, on the 1 mmol. scale. An excess of dry ammonia was passed through the solution, and the benzene was evaporated to leave a solid which was dissolved in 0·2N-hydrochloric acid (8 ml.). The acidic solution was filtered and basified with ammonia, to precipitate a solid (239 mg.), m. p. 239—240°, which was collected and washed with water. Recrystallisation once from aqueous ethanol, containing 30% of ethanol, gave the *amide* (XVI) as prisms, m. p. 243—244° (decomp.) (Found: C, 68·2; H, 8·4. $C_{18}H_{26}O_3N_2$ requires C, 67·9; H, 8·2%).

The Benzoquinolizidine Nitrile (XVII).—The foregoing amide (146 mg.) was heated for 35 min. with freshly distilled phosphorus oxychloride (1·2 ml.) in a bath at 112—123°. Ice (10 g.) was then added to the cooled solution and, when the decomposition of the phosphorus oxychloride was complete, the solution was made strongly alkaline with sodium carbonate. The precipitated solid was collected, washed with water, and dried (136 mg.; m. p. 157—158°). Recrystallisation from aqueous ethanol, containing 30% of ethanol, afforded the *nitrile* (XVII) as fine needles, m. p. 158—159° (Found: C, 71·9; H, 8·3; N, 9·4. $C_{18}H_{24}O_2N_2$ requires C, 72·0; H, 8·1; N, 9·3%).

Preparation of the Hydrazide (XX).—A mixture of the methyl ester [20] (XIX) (0·1 g.) and anhydrous hydrazine (0·5 ml.) was heated on the steam-bath, and anhydrous methanol (15 drops) was added to give a clear solution. This was heated on the steam-bath for 24 hr., then cooled, and the crystals were collected, washed with water, and dried [82 mg.; m. p. 206—207° (decomp.)]. The m. p. of the *hydrazide* was unchanged by recrystallisation from ethanol (Found: C, 65·2; H, 8·5. $C_{19}H_{29}O_3N_3$ requires C, 65·6; H, 8·4%).

Preparation of the Ethyl Urethane (XXI).—(a) *From the foregoing hydrazide.* A solution of dry hydrogen chloride (7·3 mg.) in anhydrous ethanol (0·35 ml.) was added to a suspension of the above hydrazide (34·6 mg.) in anhydrous ethanol (1 ml.). The resultant clear solution was treated at 0° during 2 min. with pentyl nitrite (13·8 mg.) in ethanol (1·01 ml.). After the mixture had warmed to room temperature, it was kept for 1 hr. and then heated under reflux for 24 hr. The solution was concentrated to 0·5 ml., made alkaline with ammonia, and treated with water until turbid. Crystals (34·1 mg.), m. p. 138—140°, separated and were recrystallised

from aqueous ethanol, to give the *ethyl urethane* (XXI) as needles, m. p. 139·5—140·5° (Found: C, 67·4; H, 8·6. $C_{21}H_{32}O_4N_2$ requires C, 67·0; H, 8·6%).

(b) *From the nitrile* (XVII). The nitrile was dried at 78° for 3 hr. over phosphoric oxide in *vacuo* and then added as a solution in anhydrous ether (20 ml.) during 5 min. to a suspension of lithium aluminium hydride (0·1 g.) in ether (10 ml.). After the mixture had been heated under reflux for 1·5 hr., it was cooled and treated with water (0·15 ml.), then with 20% aqueous sodium hydroxide (0·1 ml.), and finally with water (0·5 ml.). The granular precipitate was filtered off and washed with much hot ether. Evaporation of the dried ethereal solution left a gum (99 mg.). This was dissolved in dry purified dioxan (2·5 ml.) and treated at room temperature with triethylamine (0·08 ml.) in dioxan (0·5 ml.), followed by ethyl chloroformate (0·12 ml.) in dioxan (0·12 ml.). The mixture was heated at 50—55° for 30 min., then diluted with water (3 ml.) and freed from dioxan by evaporation. Basification of the resultant solution with ammonia precipitated a solid (88 mg.), m. p. 135—137°, raised to 138·5—139·5° by recrystallisation from aqueous ethanol. The m. p. was unchanged on admixture with the urethane (XXI) from (*a*) above and the two samples of urethane had identical infrared spectra (Nujol).

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