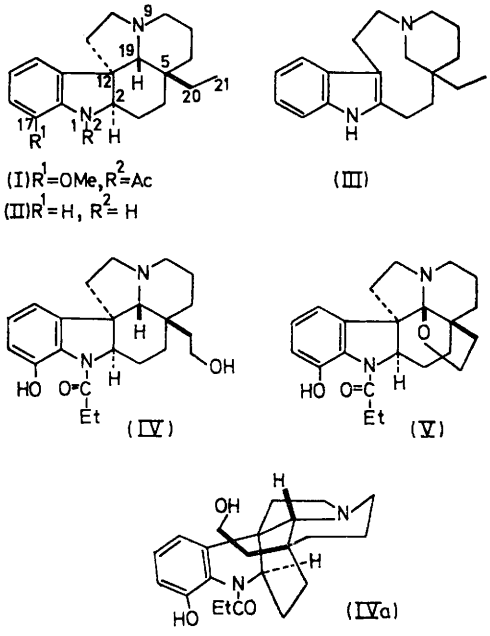
Studies on the Synthesis of *Aspidosperma* and Related Alkaloids. Part II.[1] A Synthetic Approach to the C-21 Oxygenated *Aspidosperma* Alkaloids

By **Ichizo Inoue** and **Yoshio Ban,*** Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo, Japan

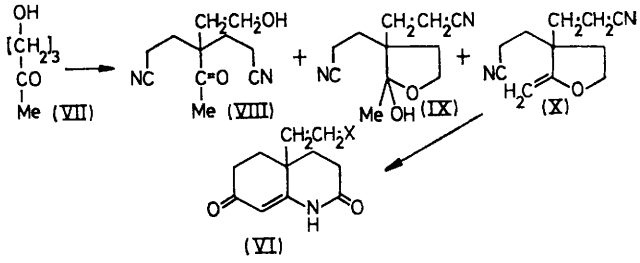
An attempt was made to extend the total synthesis of (±)-aspidospermine (I) to the synthesis of (±)-limaspermine (IV). An eleven-step scheme starting from 5-phenoxypentan-2-one (XIV) gave (±)-21-phenoxyisopalosine (XXXIX), which was treated with hydrobromic acid to furnish the quaternary salt (XLII). The formation of this salt suggests that the stereochemistry of our products is not identical with that of the natural alkaloid.

SYNTHESES of various *Aspidosperma* alkaloids and related compounds have been reported,[1-6] *e.g.* (±)-aspidospermine (I),[1-3] (±)-aspidospermidine (II),[4] and quebrachamine (III).[5] We describe here some results of an approach to the synthesis of the C-21 oxygenated alkaloids,[7] limaspermine (IV),[8] and haplocine (V).[9] These results should be of value for assignments of stereochemistry to the intermediates in the total syntheses of (±)-aspidospermine (I).[1b]



SCHEME 1

In extension of our method[1a] for synthesis of the alkaloid (±)-(I), the preparation of the tetrahydroquinolinedione (VI; X = OH), with an angular β-hydroxyethyl substituent, was attempted. Double cyanoethylation of 5-hydroxypentan-2-one (VII) afforded the ketone (VIII) in poor yield, together with



SCHEME 2

further transformation products (IX) and (X).[10] The hydroxy-group was therefore protected by formation of the phenyl ether (XIV). An improved synthesis of the latter [see (XI) ⟶ (XIV)] was achieved in the overall yield of 40—45% (*cf.* refs. 11 and 12).

The ketone (XIV) was readily transformed into (XV),[1] treatment of which with anhydrous dioxan saturated with dry hydrogen chloride, followed by addition of the calculated amount of water, gave the desired quinolinedione (VI; X = OPh), in good yield, presumably by way of the intermediates (XVI) and (XVII). The u.v. spectrum of (VI; X = OPh) in 50% ethanol shows absorption at 281 mμ (ε 31,400) (vinylogous imide[1a]), bathochromically shifted to 336 mμ (ε 39,310) in alkali, and showing a further, hyposchromic shift to 293 mμ (ε 31,280) after 2 hr. in alkaline solution. This behaviour is analogous to that of compound (VI; X = H) [$\lambda_{max.}$ (H_2O) 284 mμ (ε 36,830) ⟶ 334 mμ (ε 33,700) ⟶ 293 mμ (ε 37,030)], and could be reasonably explained[1a] in terms of the conversions (VI) ⟶

[1] (*a*) Part I, Y. Ban, Y. Sato, I. Inoue, M. Nagai, T. Oishi, M. Terashima, O. Yonemitsu, and Y. Kanaoka, *Tetrahedron Letters*, 1965, 2261; (*b*) preliminary communication of a part of this work: Y. Ban, I. Iijima, I. Inoue, M. Akagi, and T. Oishi, *ibid.*, 1969, 2067.

[2] (*a*) G. Stork and J. E. Dolfini, *J. Amer. Chem. Soc.*, 1963, **85**, 2872; (*b*) G. Stork, Special Lectures presented at the Third International Symposium on the Chemistry of Natural Products held in Kyoto, Japan (April 1964), Butterworths, London, 1964, p. 131.

[3] M. E. Kuehne and C. Bayha, *Tetrahedron Letters*, 1966, 1311.

[4] (*a*) J. E. D. Barton and J. Harley-Mason, *Chem. Comm.*, 1965, 298; *cf.* O. Kennard, K. A. Kerr, D. G. Watson, J. K. Fawcett and L. Riva di Sansevereino, *Chem. Comm.*, 1967, 1286; (*b*) J. Harley-Mason and M. Kaplan, *ibid.*, 1967, 915.

[5] J. P. Kutney, N. Abdurahman, P. Le Quesene, E. Piers, and I. Vlattas, *J. Amer. Chem. Soc.*, 1966, **88**, 3656.

[6] F. E. Ziegler and P. A. Zoretic, *Tetrahedron Letters*, 1968, 2639.

[7] The numbering system is due to M. Hesse, ' Indolalkaloide in Tabellen,' Springer-Verlag, Berlin, 1964.

[8] M. Pinar, W. von Philipsborn, W. Vetter, and H. Schmid, *Helv. Chim. Acta*, 1962, **45**, 2260.

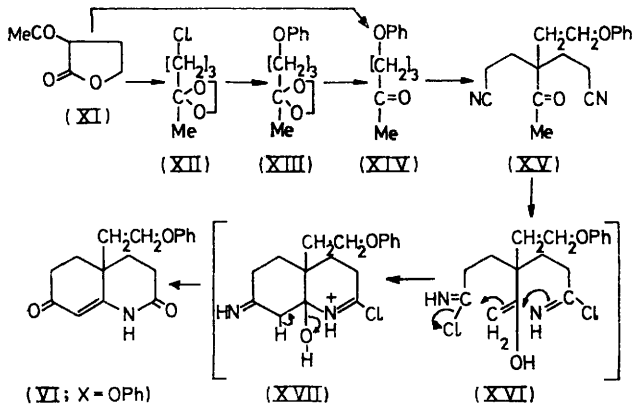
[9] M. P. Cava, S. K. Talapatra, K. Nomura, J. A. Weisbach, B. Douglas, and E. C. Shoop, *Chem. and Ind.*, 1963, 1242.

[10] L. Crombie, M. Manzoor-I-Khuda, and R. J. D. Smith, *J. Chem. Soc.*, 1957, 479.

[11] (*a*) N. Nau and D. H. Peacock, *J. Indian Chem. Soc.*, 1935. **12**, 318; (*b*) R. Robinson and H. S. Boyd-Barret, *J. Chem. Soc.*, 1932, 317; (*c*) G. B. Brown and C. W. H. Partridge, *J. Amer. Chem. Soc.*, 1945, **67**, 1423.

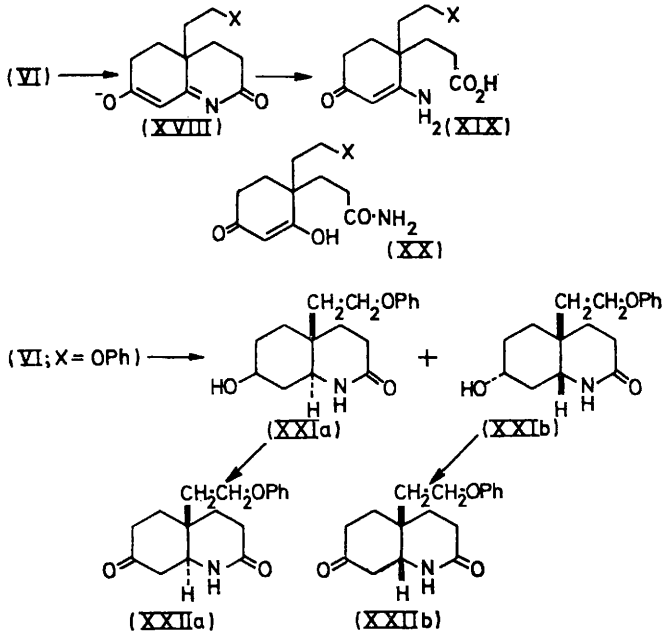
[12] M. M. H. Normant and C. Feugeas, *Compt. rend.*, 1959, 423.

(XVIII) ⟶ (XIX) (X = H or OPh). The possibility of (XX) instead of (XIX) as an end product was dismissed because of the lack of absorptions around 255—260 mμ (in water) and 280—285 mμ (in alkali).



SCHEME 3

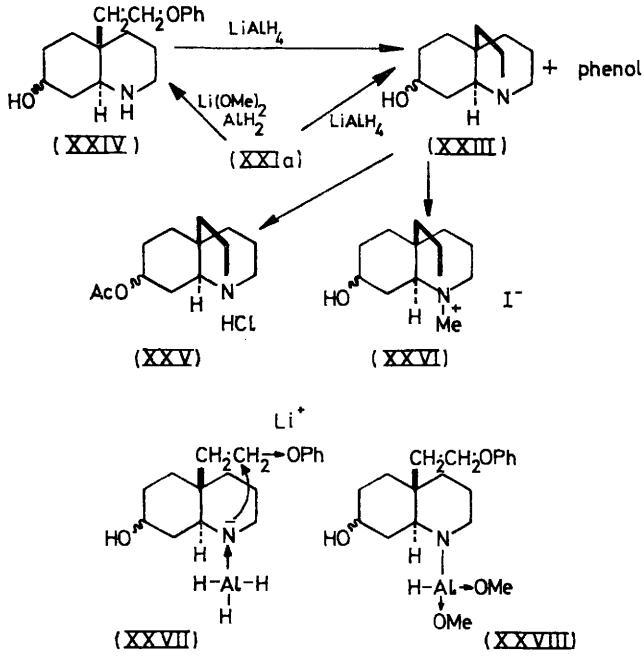
In view of this result, the dinitrile (X) was treated with hydrogen chloride in anhydrous ethanol or dioxan to give the quinolinediones (VI; X = OH or Cl). However the yields were poor and this approach was abandoned. Koelsch [13] has proposed that the first step of this reaction is hydrolysis to the diamide, which is then cyclised to the quinolinedione (the isolated diamide gives a better yield of the dione). However, the u.v. spectral behaviour of (VI; X = OPh) suggests that the



SCHEME 4

reaction of (XV) with anhydrous hydrogen chloride might proceed through a concerted mechanism involving the imido-chlorides (XVI) and (XVII).

Hydrogenation of (VI; X = OPh) over Adams catalyst in ethanolic alkali afforded the isomeric alcohols (XXIa), m.p. 220—222° (70·5%), and (XXIb), m.p. 163—165° (2·8%), with different stereochemistry at the ring junction. Oxidation of these with chromic acid afforded the epimeric keto-lactams (XXIIa), m.p. 187—189°, and (XXIIb), m.p. 97—99°, respectively. We have recently shown [1b] that (XXIa) and (XXIIa) have the *trans*-configuration and (XXIb) and (XXIIb) the *cis*.



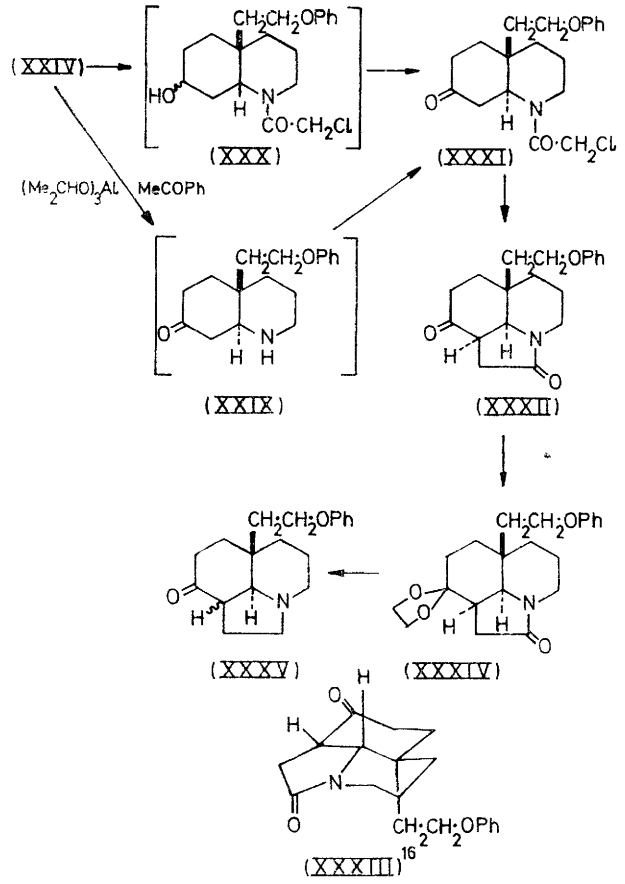
SCHEME 5

The major product (XXIa), the stereochemistry of which was unknown at the time, was chosen as starting material for the synthesis of the alkaloid, with the expectation that fission and recombination at C-12 and C-19 [*cf.* (XLa)] would take place during the Fischer indole cyclisation, according to the mechanism proposed by Stork.[2b]

Reduction of (XXIa) with lithium aluminium hydride in tetrahydrofuran did not yield the decahydroquinolinol (XXIV), but gave a basic product, m.p. 128—130°, M^+ 181, and phenol (70%). The structure of this product (XXIII) was established by conversion into the *O*-monoacetate hydrochloride (XXV), $\nu_{max.}$ 1720 cm.$^{-1}$ [(ester C=O); no amide carbonyl absorption], and into the corresponding methiodide (XXVI), m.p. 295—298°. The phenyl ether linkage is generally stable under reductive conditions; this anomalous hydrogenolytic cyclisation may be ascribed to the neighbouring group participation of the ring nitrogen with the aluminium atom of the hydride [see (XXVII)]. If this is correct, the introduction of electron-attracting groups into the metal hydride should suppress the cyclisation and favour the normal reduction [see

[13] C. F. Koelsch and H. M. Walker, *J. Amer. Chem. Soc.*, 1950, **72**, 346.

(XXVIII)]. Lithium alkoxyaluminium hydrides [14] were therefore used; lithium dimethoxyaluminium

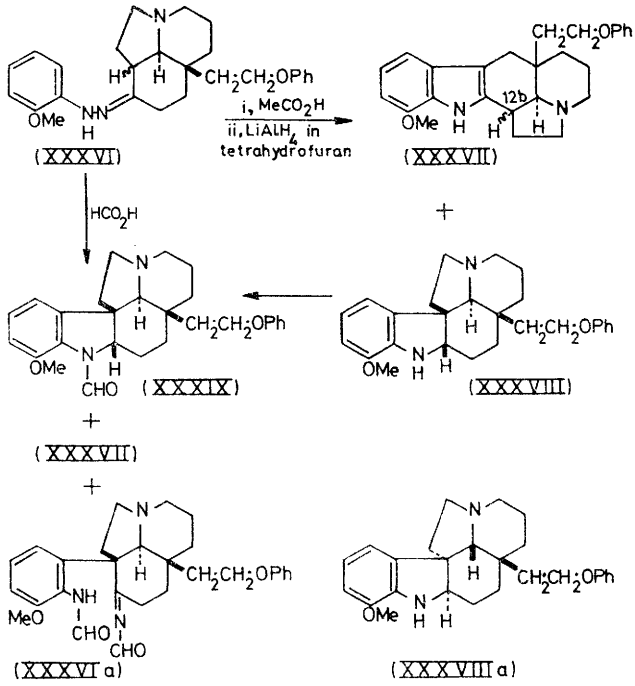


SCHEME 6

hydride proved to be the best for the reduction of (XXIa) to (XXIV) (76% yield).

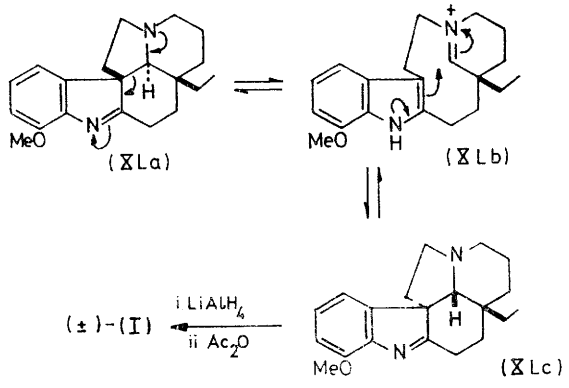
Oppenauer oxidation of (XXIV), followed by chloroacetylation gave the chloroacetyl-ketone (XXXI), m.p. 113—115°, $\nu_{max.}$ (Nujol) 1720 and 1670 cm.$^{-1}$, in relatively low yield (37%). Alternatively, selective chloroacetylation of the secondary amine (XXIV) followed by oxidation of the product (XXX) with 8N-chromium trioxide in acetone,[15] gave (XXXI) in 80% yield. Cyclisation of (XXXI) with potassium in t-butyl alcohol–benzene (1 : 1) gave the tricyclic keto-lactam (XXXII), m.p. 145—149°, $\nu_{max.}$ (Nujol) 1700, 1680, and 1670 cm.$^{-1}$, τ 6·35 (1H, d, J 10 c./sec., 3a-H) and 6·9 (1H, q, J 10 c./sec., 9a-H). These n.m.r. signals agree well with those of the tricyclic keto-lactam intermediate in the synthesis of (±)-aspidospermine,[1a] suggesting the stereochemistry of both to be the same.*

Treatment of (XXXII) with ethylene glycol afforded



SCHEME 7

the acetal (XXXIV), m.p. 68—74° (no i.r. absorption at 1720 cm.$^{-1}$). Reduction of (XXXIV) with lithium dimethoxyaluminium hydride followed by mild hydrolysis afforded the tricyclic keto-amine (XXXV), m.p. 64—66°, which showed strong Bohlmann bands in the i.r. spectrum.[16]



SCHEME 8

Fischer indolisation of *o*-methoxyphenylhydrazone (XXXVI), m.p. 101—103°, with polyphosphate ester [17] or with acetic acid,[18] followed by lithium aluminium hydride reduction and chromatography on alumina gave the indole (XXXVII), M^+ 402, with u.v. absorptions characteristic of the indole chromophore. Its con-

* The stereochemistry of the tricyclic keto-lactam was established as (XXXIII). The evidence for this will be published elsewhere (*cf.* ref. 1).

[14] (*a*) H. C. Brown and C. J. Shoaf, *J. Amer. Chem. Soc.*, 1964, **86**, 1079; (*b*) H. C. Brown and C. P. Garg, *ibid.*, 1964, **86**, 1085; (*c*) H. C. Brown and A. Tsukamoto, *ibid.*, 1964, **86**, 1089.

[15] K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 1946, 39.

[16] F. Bohlmann, *Chem. Ber.*, 1958, **91**, 2157.

[17] Y. Kanaoka, Y. Ban, O. Yonemitsu, K. Irie, and K. Miyashita, *Chem. and Ind.*, 1965, 473.

[18] Y. Ban and Y. Sato, *Chem. and Pharm. Bull.* (*Japan*), 1965, **13**, 1073.

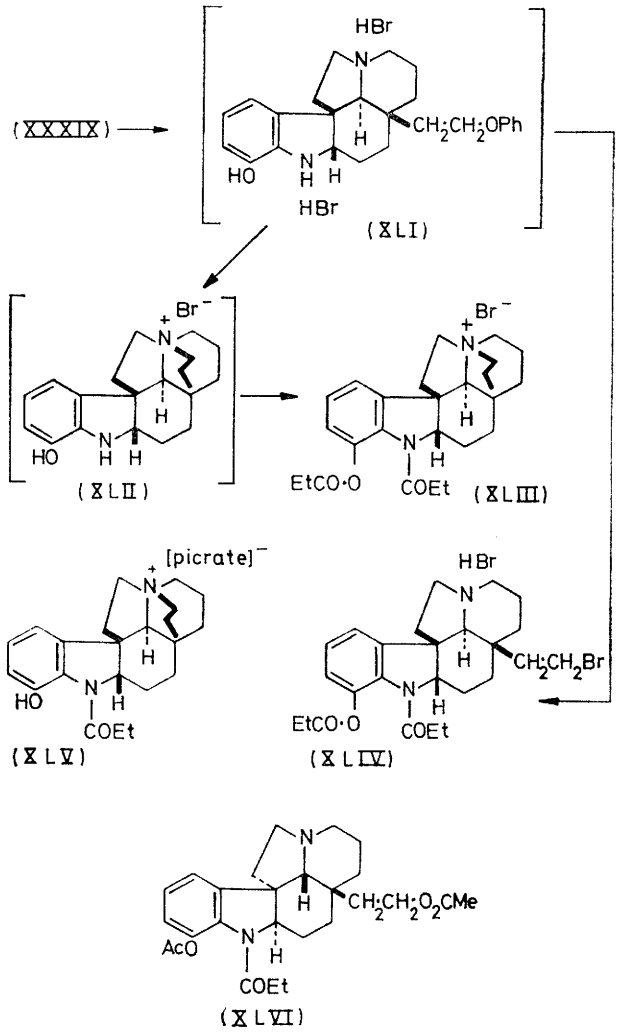
figuration at the ring junction should be the same as that of the initial compound, although epimerisation at C-12b could have occurred during the indolisation. A second fraction on further chromatography gave the indoline (XXXVIII) as a resin, which could not be crystallised, $\lambda_{max.}$ 247, 273, 279·5, and 292 mμ, almost corresponding to a combination of the absorptions of anisole and natural deacetylaspidospermine.

In view of the low yield of (XXXVIII) in the Fischer indolisation, anhydrous formic acid was used for cyclisation, as reported for the reaction with 2-ethylcyclohexanone.[19] The formylindoline (XXXIX), m.p. 159—162°, M^+ 432, was thus obtained in 16% yield; compounds (XXXVII) and (XXXVIa) were also produced, along with some of the initial keto-amine (XXXV). The n.m.r. spectrum of (XXXIX) ($CDCl_3$) shows a triplet at τ 5·1 due to the C-2 proton; however the natural alkaloids show a quartet at τ 5·5—6·0 for this proton ('*aspidosperma* finger-print'[20]). This difference should reflect the stereochemistry of the system.

Formylation of the indoline (XXXVIII) gave the formylindoline (XXXIX), m.p. 159—162°, identical with the sample prepared by the formic acid procedure. The identity of these compounds and the lack of '*aspidosperma* finger-print' makes it doubtful that they have the same stereochemistry as the natural alkaloids. Efforts to isolate the other indoline (XXXVIIIa) from the reaction mixture were unsuccessful.

According to a mechanism proposed by Stork for his synthesis of (±)-aspidospermine (I), the fission and reformation of the C(12)–C(19) bond in the intermediate (XLa) initially formed in the Fischer indolisation with acetic acid, led to the thermodynamically stable isomer (XLc) *via* (XLb), from which the racemic product, with the same stereochemistry as the natural alkaloid (±)-(I), was produced through reduction with lithium aluminium hydride, followed by acetylation. Thus, the same product (±)-(I) was obtained from different diastereomeric intermediates in Stork's[2] and in our synthesis.[1]

Such a reversible mechanism, however, could not be expected in the reaction with formic acid, which should afford the product (XXXIX) with the same stereochemistry as the starting material (XXXVI); the simultaneous reduction and formylation of the kinetically controlled product corresponding to (XLa) by formic acid should prohibit the fission and formation of the bond. However, the main products [(XXXIX) and (XXXVIII)] obtained by both procedures have the same stereochemistry. Thus, the present result is apparently at odds with the previous synthesis of (±)-aspidospermine (I). This inconsistency could be ascribed to difficulties in isolation of the indoline (XXXVIIIa) with the same stereochemistry as natural limaspermine [(IV) ≡ (IVa)]; prolonged heating of (XXXVI) with acetic acid is perhaps necessary to effect the fission and recombination of the bond for production of the thermodynamically stable isomer.



SCHEME 9

The formylindoline (XXXIX) was hydrolysed with hydrobromic acid, then acylated with propionic anhydride, in the hope of obtaining compound (XLIV) *via* the intermediate (XLI). The crude hydrolysis product (XLII), however, on acylation, gave the quaternary bromide (XLIII) as a monohydrate, m.p. 174—177°, with u.v. spectrum [$\lambda_{max.}$ 255 (log ε 4·47) and 285sh (3·45) mμ; $\lambda_{max.}$ (0·05N-NaOH in 96% EtOH) 255sh (log ε 4·37) and 3·2 (4·28) mμ] similar to that of *OO*-diacetyl-limaspermine (XLVI), derived from the natural alkaloid (IV). The structure of this salt (XLIII) was confirmed by formation and analysis of the picrate (XLV), m.p. 89—90°. Formation of the quaternary salts (XLII and XLIII) indicates that the distance between the bridgehead nitrogen and the β-position of the angular bromoethyl group in (XXXIX) is short

[19] Y. Ban, T. Oishi, Y. Kishio, and I. Iijima, *Chem. and Pharm. Bull.* (*Japan*), 1967, **15**, 531.

[20] C. Djerassi, A. A. P. G. Archer, T. George, B. Gilbert, J. N. Shoolery, and L. F. Johnson, *Experientia*, 1960, **16**, 532.

enough for cyclisation. Such a relationship is not compatible with the stereochemistry of the natural alkaloid (IVa).

These results urged us to reinvestigate the stereochemistry of the intermediates in the syntheses of (+)-aspidospermine (I) proposed by Stork and by us. These studies will be reported later.

EXPERIMENTAL

M.p.s were determined with a Yamato apparatus. U.v. spectra were determined with a Hitachi EPS-3T recording spectrophotometer for solutions in 95% ethanol, unless otherwise stated. I.r. spectra were taken with a Koken DS-301 spectrophotometer for Nujol mulls, unless otherwise stated. N.m.r. spectra were measured at 60 Mc./sec. for solutions in deuteriochloroform, with tetramethylsilane as internal reference.

Cyanoethylation of 5-*Hydroxypentan*-2-*one* (VII).—Acrylonitrile (23·5 g., 0·445 mole) in t-butyl alcohol (15 ml.) was added with stirring to a cooled (−5 to −10°) solution of (VII) (30 g., 0·295 mole) and 30% methanolic potassium hydroxide (1·46 g.) in t-butyl alcohol (41 ml.) during 3·5 hr. The solution was stirred at the same temperature for an additional 2 hr., then poured into crushed ice (300 g.) and 10% hydrochloric acid (6 ml.). The mixture was extracted with benzene, and the extract was washed with saturated sodium chloride solution, dried (Na_2SO_4), and concentrated under reduced pressure to leave an oil. Fractional distillation gave fraction A, b.p. 180—220°/0·2 mm. (6·3 g.), and fraction B, b.p. 220—260°/0·2 mm. (13·0 g.).

Further fractionation of A gave 3,3-*bis*-(β-*cyanoethyl*)-2-*methylene tetrahydrofuran* (X) (4·4 g., 7·3%), b.p. 182—185°/2·5 mm., which was also obtained as a solid, m.p. 45—47·5°, by distillation of (IX) (see later) with a trace of toluene-*p*-sulphonic acid; τ 5·62 (1H, d *J* 3 c./sec.), 6·32 (1H, d, *J* 3 c./sec.), 5·94 (2H, t, *J* 7 c./sec.), and 7·4—8·3 (10H, m) (Found: C, 69·4; H, 7·5; N, 14·55. $C_{11}H_{14}N_2O_2$ requires C, 69·45; H, 7·4; N, 14·75%).

Further fractionation of B gave 3,3-*bis*-(β-*cyanoethyl*)-2-*hydroxy*-2-*methyl tetrahydrofuran* (IX) (2·4 g., 3·9%), which afforded colourless prisms, m.p. 92—94° (from benzene) (Found: C, 63·55; H, 7·7; N, 13·25. $C_{11}H_{16}N_2O_2$ requires C, 63·45; H, 7·45; N, 13·45%).

2,4-*Dinitrophenylhydrazone of* (VIII).—A solution of (X) (50 mg.) in 2N-sulphuric acid (4 ml.) was added to a solution of 2,4-dinitrophenylhydrazine (65 mg.) in bis-(2-methoxyethyl) ether (4 ml.) and the mixture was set aside at room temperature overnight. The crystals (82 mg.) deposited gave the 2,4-*dinitrophenylhydrazone* of (VIII) as dark red prisms, m.p. 168—170° (from methanol), $\nu_{max.}$ 3580, 3470, 3350, 2280, 1620, 1590, and 1340 cm.$^{-1}$ (Found: C, 52·55; H, 5·4; N, 21·9. $C_{17}H_{20}N_6O_5$ requires C, 52·55; H, 5·2; N, 21·65%).

5-*Chloropentan*-2-*one Ethylene Acetal* (XII).—A mixture of 5-chloropentan-2-one [21] (7·4 g., 0·062 mole), ethylene glycol (4·6 g., 0·074 mole), and benzene (50 ml.), with a trace of toluene-*p*-sulphonic acid was heated under reflux in a Cope apparatus for 6 hr. The cooled mixture was washed with aqueous sodium hydrogen carbonate and water, dried (Na_2SO_4), and distilled under reduced pressure to give the acetal (8·2 g., 80%) as a colourless oil, b.p. 81—84°/12 mm. (Found: C, 51·1; H, 8·0. Calc. for $C_7H_{13}ClO_2$: C, 51·05; H, 7·95%).

5-*Phenoxypentan*-2-*one Ethylene Acetal* (XIII).—A solution of (XII) (98 g., 0·597 mole) in absolute ethanol (100 ml.) was added with stirring to a solution of phenol (73 g., 0·775 mole) and sodium ethoxide (0·775 mole) in absolute ethanol (800 ml.), and the mixture was heated under reflux for 30 hr. After cooling, the inorganic precipitate was filtered off and the filtrate was concentrated under reduced pressure. The oily residue was extracted with benzene, and the extract was washed with 5% aqueous sodium hydroxide and with water, dried (Na_2SO_4), and distilled under reduced pressure to give the *phenoxy-derivative* (100 g., 75%), b.p. 120—128°/2 mm. (Found: C, 70·4; H, 8·35. $C_{13}H_{18}O_3$ requires C, 70·25; H, 8·15%).

5-*Phenoxypentan*-2-*one* (XIV).—A mixture of (XIII) (100 g.) and 5% hydrochloric acid (800 ml.) was heated at 80—90° for 1 hr., then cooled. The crystalline product was filtered off, washed with water, and dried to give the phenoxy-ketone (79 g., 99%), m.p. 53—55°, identical with an authentic sample (mixed m.p.).

4-*Acetyl*-4-(β-*phenoxyethyl*)*heptanedinitrile* (XV).—Acrylonitrile (47·5 g., 0·89 mole) in tetrahydrofuran (45 ml.) was added with stirring at 2—10° to a solution of (XIV) (79 g., 0·455 mole) and 30% methanolic potassium hydroxide (8·9 ml.) in tetrahydrofuran (250 ml.) during 1·5 hr. The solution was stirred at the same temperature for a further 2 hr., then poured into ice–water (900 ml.) containing 10% hydrochloric acid (9 ml.). The mixture was extracted with ethyl acetate. The dried extracts were evaporated, and the residue gave colourless *prisms* (69·3 g., 61·7%), m.p. 88—91° [from methanol (300 ml.)] $\nu_{max.}$ 2300, 1700, 1600, 1500, and 1242 cm.$^{-1}$ (Found: C, 71·65; H, 7·05; N, 9·9. $C_{17}H_{20}N_2O$ requires C, 71·8; H, 7·1; N, 9·9%). Unchanged starting material (9·0 g.) was also recovered.

Conversion of the Phenoxy-nitrile (XV) *into the Quinolinedione* (VI; X = OPh).—A solution of (XV) (40 g.) in absolute dioxan (1200 ml.) was saturated with anhydrous hydrogen chloride at 4—12° and set aside at 0° for 4 days, after which the u.v. absorption band at 296 mμ had reached its maximum intensity. Dioxan (20 ml.) and water (2·5 ml.) were then added and the mixture was kept at the same temperature for a further 2 days. After addition of more aqueous dioxan (20 ml.), the mixture was left at room temperature for another day, then heated on a boiling water bath for 3 hr., and concentrated to dryness under reduced pressure. The residue was dissolved in chloroform and washed with water (washings A), aqueous sodium hydrogen carbonate, and with water, and dried (Na_2SO_4). Evaporation afforded the crude product (39 g.), which gave the *quinolinedione* (13·65 g.) as pale yellow leaflets, m.p. 190—191·5° [from methanol (450 ml.)]. Washings A were heated at 95—100° for 3 hr. to furnish more product (8 g.). A further crop (3·3 g.) was obtained from the mother liquor of recrystallisation (total yield 24·95 g., 62%), $\lambda_{max.}$ (50%, EtOH) 281 (ε 31,400) mμ, $\lambda_{max.}$ (0·1N-NaOH in 50% EtOH) 336 (ε 39,310) mμ (3 min. after addition of alkali), 293 (ε 31,280) (2 hr. after addition of alkali) mμ (Found: C, 71·6; H, 6·65; N, 4·8. $C_{17}H_{19}NO_3$ requires C, 71·55; H, 6·7; N, 4·9%).

4a-(β-*Chloroethyl*)-4,4a,5,6-*tetrahydroquinoline*-2(1H),-7(3H)-*dione* (VI; X = Cl).—A solution of (X) (500 mg.,

[21] G. W. Cannon, R. C. Ellis, and J. R. Leal, *Org. Synth.*, 1951, **31**, 74.

2·6 mmoles) in absolute dioxan (15 ml.) was saturated with anhydrous hydrogen chloride at −10° and kept at 0° for 30 hr. Then water (0·188 ml.) was added and the mixture was kept at 5° for a further 6 days. It was then heated at 90° for 3 hr., and concentrated under reduced pressure. The residue was extracted with chloroform and the dried extract was concentrated to give an oil (154 mg.). Chromatography on alumina afforded the *chloro-quinolinedione*, m.p. 212—213°, as colourless needles, $\lambda_{max.}$ 283 mμ (Found: C, 58·25; H, 6·15; N, 6·35. $C_{11}H_{14}ClNO_2$ requires C, 58·05; H, 6·2; N, 6·15%).

4a-(β-*Hydroxyethyl*)-4,4a,5,6-*tetrahydroquinoline*-2(1H),-7(3H)-*dione* (VI; X = OH).—A solution of (X) (264 mg., 1·37 mmole) and anhydrous ethanol (138 mg., 3·0 mmoles) in absolute ether (10 ml.) was saturated with anhydrous hydrogen chloride at 0—5° and kept at 0° for 6 days. An amorphous powder obtained on evaporation was treated at 25—30° with freshly prepared potassium t-butoxide (4·2 mmoles) in t-butyl alcohol (30 ml.), and the mixture was refluxed for 1 hr. The residue after evaporation of the solvent was taken up in 2% hydrochloric acid (19 ml.) and heated on a boiling water bath for 1·5 hr. The cooled mixture was washed with chloroform and the aqueous layer was adjusted to pH 5·0 with dilute hydrochloric acid, then evaporated to dryness under reduced pressure. The residue was extracted with ethanol and the extracts were concentrated to give an oil (100 mg.), which on chromatography on alumina afforded the *hydroxy-derivative* as colourless needles, m.p. 172—175° (from ethanol–benzene), $\lambda_{max.}$ 283 mμ (Found: C, 63·15; H, 7·15. $C_{11}H_{15}NO_3$ requires C, 63·15; H, 7·25%).

Catalytic Hydrogenation of the Quinolinedione (VI; X = OPh).—A suspension of the dione (21 g., 0·0735 mole), Adams catalyst (2·1 g.), and sodium hydroxide (1·47 g., 0·0367 mole) in ethanol (2·1 l.) was hydrogenated at room temperature and atmospheric pressure. The filtrate and washings were neutralised with 10% hydrochloric acid and evaporated to dryness. The semi-solid was re-crystallised from ethanol to give the *hydroxy-derivative*, isomer (XXIa) as colourless needles (14·2 g., 70·5%), m.p. 220—222°, $\nu_{max.}$ 3380, 3200, 1640, 1600, 1585, 1245, 1230, 1050, 1030, 830, and 755 cm.$^{-1}$ (Found: C, 70·35; H, 7·9; N, 5·0. $C_{17}H_{23}NO_3$ requires C, 70·55; H, 8·0; N, 4·85%).

From the mother liquors, the other isomer (XXIb) (568 mg., 2·8%), pale yellow *prisms*, m.p. 155—161°, was obtained together with unchanged starting material (1·33 g., 6·3%). It was washed with 2% aqueous sodium hydroxide and recrystallised from ethanol to give a sample, m.p. 163—164°, $\nu_{max.}$ 3260sh, 3160, 1636, 1600, 1585, 1245, 1175, 1100, 1060, 1025, 875, and 760 cm.$^{-1}$ (Found: C, 70·45; H, 8·0; N, 4·9. $C_{17}H_{23}NO_3$ requires C, 70·55; H, 8·0; N, 4·85%).

Chromic Acid Oxidation of the Hydroxy-lactam (XXIa) *to the Keto-lactam* (XXIIa).—To a solution of (XXIa) (1·45 g., 5 mmoles) in acetone (400 ml.) was added 8N-chromic acid (2·8 ml.) with stirring at 5° during 15 min., and the mixture was stirred at the same temperature for a further 15 min., then at room temperature for 1 hr. Isopropyl alcohol (5 ml.) was added and the mixture was treated with sodium hydrogen carbonate (2·0 g.) for 30 min., filtered to remove the inorganic precipitate, and concentrated to an oil, which was taken up in chloroform. The solution was washed with aqueous sodium hydrogen carbonate and with water, dried, and concentrated. The residue gave the *keto-lactam* (397 mg., 27·5%) as colourless needles, m.p. 187—189° (from ethanol), $\nu_{max.}$ 3180, 3080, 1725, 1660, 1610, 1585, 1250, 1035, and 750 cm.$^{-1}$ (Found: C, 71·15; H, 7·4; N, 5·0. $C_{17}H_{21}NO_3$ requires C, 71·05; H, 7·35; N, 4·85%).

Chromic Acid Oxidation of the Hydroxy-lactam (XXIb) *to the Keto-lactam* (XXIIb).—A mixture of sodium dichromate dihydrate (450 mg., 1·5 mmole), acetic acid (1 ml.), conc. sulphuric acid (1 ml.), and water (2·6 ml.) was added to a stirred and cooled solution of (XXIb) (287 mg., 1 mmole) in acetic acid (5 ml.). The mixture was stirred at the same temperature for 15 min., poured on crushed ice, and extracted with chloroform. The extracts were washed with aqueous sodium hydrogen carbonate and water, dried (Na_2SO_4), and evaporated to leave an oil which was chromatographed on alumina (15 g.). Elution with benzene–ethanol (20 : 1) gave a paste (83 mg.) which yielded the *keto-lactam* (55 mg., 19·3%) as colourless needles, m.p. 97—99° (from di-isopropyl ether–acetone), $\nu_{max.}$ 3180, 1725, 1645, 1600, 1585, 1235, 1030, and 750 cm.$^{-1}$ (Found: C, 71·0; H, 7·3; N, 4·95. $C_{17}H_{21}NO_3$ requires C, 71·05; H, 7·35; N, 4·85%).

Reduction of the Hydroxy-lactam (XXIa) *with Lithium Aluminium Hydride*.—Finely powdered (XXIa) (2·89 g., 0·01 mole) was added in portions to a stirred suspension of lithium aluminium hydride (2·89 g., 0·075 mole) in absolute tetrahydrofuran (200 ml.) cooled in ice. The mixture was then heated under reflux for 16 hr., cooled in ice, and treated with water (20 ml.); the inorganic precipitate was filtered off. The dried filtrate was concentrated to an oil, which was taken up in 5% hydrochloric acid and washed with benzene. The acidic layer was made alkaline with potassium carbonate and the resulting mixture was extracted with chloroform. The extracts were dried (K_2CO_3) and evaporated, and the residue gave the tricyclic derivative (XXIII) (1·285 g., 70%) as colourless *prisms* (hygroscopic), m.p. 128—130° (from acetone), $\nu_{max.}$ 3160, 1136, 1069, 1040, 1007, 985, 950, 867, and 720 cm.$^{-1}$, *m/e* 181 (M^+) (Found: C, 73·25; H, 10·5; N, 7·9. $C_{11}H_{19}NO$ requires C, 72·9; H, 10·55; N, 7·75%).

The *methiodide* (XXVI) formed colourless prisms, m.p. 295—298° (from isopropyl alcohol), $\nu_{max.}$ 3380, 1310, 1290, 1065, 1040, 1010, 970, 910, 880, 850, and 805 cm.$^{-1}$ (Found: C, 44·7; H, 6·8; N, 4·25. $C_{12}H_{22}INO$ requires C, 44·6; H, 6·85; N, 4·35%).

Acetylation of the Reduction Product (XXIII).—A mixture of (XXIII) (50 mg.) and acetic anhydride (1 ml.) was heated on a boiling water bath for 30 min. The excess of acetic anhydride was evaporated off under reduced pressure and the residue was diluted with ice-cold water and washed with chloroform. The aqueous phase was made alkaline with potassium carbonate and extracted with chloroform, and the dried extracts were evaporated to an oil (49 mg.). Dry hydrogen chloride was passed into a solution of this in absolute ether, to give almost colourless crystals (48 mg.) of the *monoacetate hydrochloride* (XXV), m.p. 295—298° (from isopropyl alcohol), $\nu_{max.}$ 2400—2700, 1720, 1265, and 1025 cm.$^{-1}$ (Found: C, 60·0; H, 8·5; N, 5·4. $C_{13}H_{22}ClNO_2$ requires C, 60·1; H, 8·55; N, 5·4%).

Reduction of the Hydroxy-lactam (XXIa) *with Lithium Dimethoxyaluminium Hydride*.—Methanol (16 g., 0·5 mole) in absolute tetrahydrofuran (100 ml.) was added to a stirred solution of lithium aluminium hydride (9·5 g., 0·25 mole) in absolute tetrahydrofuran (900 ml.) at 0°;

after 15 min. stirring finely powdered (XXIa) (14·5 g., 0·05 mole) was added in portions. The mixture was boiled under reflux for 4 hr., was cooled to 0—10°, and decomposed with tetrahydrofuran (100 ml.) containing water (36 ml.). The inorganic precipitate was filtered off and the filtrate was dried (K_2CO_3), filtered, and concentrated. The crystalline residue (11·0 g.) gave the *hydroxy-amine* (XXIV) (10·3 g., 76%) as colourless leaflets, m.p. 150—151·5° [from ethyl acetate (110 ml.)], $\nu_{max.}$ 3200, 1600, 1580, 1500, 1250, 1110, 1060, 1025, 935, 870, 800, and 755 cm.$^{-1}$ (Found: C, 74·3; H, 9·05; N, 4·95. $C_{17}H_{25}NO_2$ requires C, 74·15; H, 9·15; N, 5·1%).

Reduction of the Hydroxy-amine (XXIV) *with Lithium Aluminium Hydride*.—A mixture of (XXIV) (40 mg.) and lithium aluminium hydride (40 mg.) in absolute tetrahydrofuran (10 ml.) was refluxed for 16 hr. It was worked up as in the previous experiment to give phenol (17 mg.) and a basic product (XXIII) (25 mg.), identified by comparison (i.r. spectrum) with an authentic sample prepared by reduction of (XXIa) with lithium aluminium hydride.

Preparation of the Chloroacetyl-ketone (XXXI) *from the Hydroxy-amine* (XXIV).—*Method A*. To a solution of (XXIV) (1·69 g., 6·1 mmoles) in chloroform (50 ml.), stirred and cooled at 0—5°, a solution of chloroacetyl chloride (1·05 g., 9·2 mmoles) in chloroform (15 ml.) and aqueous N-sodium hydroxide (15·35 ml.) were added simultaneously. The mixture was stirred at 0—2° for 35 min., then at room temperature for 21 hr. The chloroform layer was separated, washed with water, dried (Na_2SO_4), and evaporated to leave the crude product (XXX) (2·26 g.), which was pure enough (t.l.c.) for the next reaction; $\nu_{max.}$ ($CHCl_3$) 3640, 3450, 1657, 1600, and 1590 cm.$^{-1}$.

To a stirred solution of (XXX) (1·53 g., 4·4 mmoles) in acetone (120 ml.) at 0—2° was added 8N-chromic acid (2·45 ml., 6·5 mmoles) and the mixture was stirred at the same temperature for 5 min., and at room temperature for 30 min. It was then treated with isopropyl alcohol (4 ml.) to decompose the excess of reagent, and made alkaline with sodium hydrogen carbonate (650 mg.).

After filtration, the solution was concentrated to dryness and the residue was taken up in benzene and washed with water, aqueous sodium hydrogen carbonate, and water again.

The dried benzene solution was concentrated to leave a residue (1·51 g.) which yielded the ketone (XXXI) (1·22 g., 80%) as colourless needles, m.p. 115·5—117° (from benzene–di-isopropyl ether), $\nu_{max.}$ 1710, 1670, 1600, 1585, 1500, 1235, 1175, and 1155 cm.$^{-1}$ (Found: C, 65·2; H, 6·95; N, 4·25. $C_{19}H_{24}ClNO_3$ requires C, 65·2; H, 6·9; N, 4·0%).

Method B. A mixture of (XXIV) (1·0 g., 3·6 mmoles), aluminium t-butoxide (2·02 g., 8·2 mmoles), cyclohexanone (20 ml.) and absolute toluene (65 ml.) was heated under reflux for 16 hr. and then concentrated to its half volume under reduced pressure. The mixture was extracted with dilute hydrochloric acid (1 : 1; 70 ml.) and the acidic layer was separated and heated on a boiling water bath for 1 hr. The cooled mixture was made basic with sodium carbonate and extracted with chloroform. The extract was dried (K_2CO_3) and concentrated to an oil (XXIX) (636 mg.). This was dissolved in chloroform (20 ml.) and treated at 0° with a solution of chloroacetyl chloride (312 mg., 2·8 mmoles) in chloroform (5 ml.) and with aqueous N-sodium hydroxide (3·45 ml.) for 1·5 hr. The chloroform phase was separated, washed with 5% hydrochloric acid, aqueous sodium hydrogen carbonate, and water, dried (Na_2SO_4), and evaporated to give an oil, which crystallised on treatment with di-isopropyl ether to afford the ketone (XXXI). This yielded colourless needles (477 mg., 37%), m.p. 113—117° (from benzene–di-isopropyl ether), identical (i.r. spectrum) with a sample prepared by method A.

Cyclisation of the Chloroacetyl-ketone (XXXI) *to the Tricyclic Keto-lactam* (XXXII).—A solution of (XXXI) (950 mg., 2·7 mmoles) in t-butyl alcohol–benzene (1 : 1; 54 ml.) was added with stirring to a freshly prepared solution of potassium t-butoxide (2·98 mmoles) in t-butyl alcohol (55 ml.) during 4 hr. The mixture was stirred overnight, then at 40° ± 3° for a further 2 hr. It was neutralised with 10% hydrochloric acid and the solvent was evaporated off under reduced pressure, leaving an oil. This was taken up in benzene and washed with 5% hydrochloric acid, aqueous sodium hydrogen carbonate, and water. The dried benzene phase was concentrated, leaving a solid (738 mg.) which yielded the *keto-lactam* (376 mg., 44%) as colourless needles, m.p. 145—149° (from ethyl acetate), of the ethyl acetate solvate. For analysis this was dried at 100°/2 mm. for 7 hr.; $\nu_{max.}$ 1700, 1680, 1670, 1600, 1585, 1030, and 760 cm.$^{-1}$, τ 3·0 (5H, m), 5·85 (1H, q), 6·05 (2H, t), 6·35 (1H, d, J 10 c./sec.), 6·9 (1H, q, J 10 c./sec.), and 7·1—8·9 (13H, m) (Found: C, 72·85; H, 7·15; N, 4·85. $C_{19}H_{23}NO_3$ requires C, 72·8; H, 7·4; N, 4·45%).

Conversion of the Tricyclic Keto-lactam (XXXII) *into the Tricyclic Keto-amine* (XXXV).—A mixture of (XXXII) (20 g., 0·064 mole), ethylene glycol, toluene-*p*-sulphonic acid (500 mg.), and absolute benzene (350 ml.) was heated under reflux for 45 hr. with continuous removal of water by azeotropic distillation. The cooled mixture was treated with powdered sodium carbonate (5 g.) for 1 hr., washed with water, dried (K_2CO_3), and concentrated to an oil, which yielded colourless needles (100%), m.p. 68—74° (from ethyl acetate) (Found: C, 70·45; H, 7·95; N, 3·6. $C_{21}H_{27}NO_4$ requires C, 70·55; H, 7·6; N, 3·9%).

The crude product (XXXIV) in absolute tetrahydrofuran (300 ml.) was added at 0° to a solution of lithium aluminium hydride (12·1 g., 0·32 mole) and methanol (20·5 g., 0·64 mole) in absolute tetrahydrofuran (900 ml.). The mixture was stirred at 0° for 30 min., then heated under reflux for 4 hr., cooled, and decomposed with tetrahydrofuran–water (4 : 1; 200 ml.). The inorganic precipitate was filtered off and the filtrate was concentrated to give an oil. This was taken up in 5% hydrochloric acid (160 ml.) and warmed at 80—90° for 30 min. The cooled mixture was extracted with methylene chloride and the combined extracts were washed with 5% aqueous sodium hydroxide. The dried organic phase was evaporated to give the *keto-amine* (15·1 g., 78%) as colourless needles, m.p. 63—66° (from n-hexane), $\nu_{max.}$ 2800, 2700, 2600, 1718, 1600, 1585, 1490, 1270, 1240, and 760 cm.$^{-1}$ (Found: C, 76·1; H, 8·35; N, 4·9. $C_{19}H_{25}NO_2$ requires C, 76·2; H, 8·4; N, 4·7%).

Conversion of the Tricyclic Keto-amine (XXXV) *into the* o-*Methoxyphenylhydrazone* (XXXVI).—A mixture of (XXXV) (7·1 g., 0·0245 mole), *o*-methoxyphenylhydrazine (3·654 g., 0·0265 mole), and ethanol (60 ml.) was heated under reflux for 40 min. On cooling, an oil separated, which gradually crystallised giving the *hydrazone* (9·6 g.,

93%) as brown needles, m.p. 101—103° (from ethanol), $\nu_{max.}$ 3425, 2800, 2625, 1600, 1510, 1245, 1117, 1020, and 745 cm.$^{-1}$ (Found: C, 74·35; H, 7·95; N, 9·7. $C_{26}H_{33}N_3O_2$ requires C, 74·45; H, 7·95; N, 10·0%).

Reaction of the o-Methoxyphenylhydrazone (XXXVI) *under the Conditions of the Fischer Indole Synthesis.—Formic acid method.* A mixture of (XXXVI) (2·1 g., 5 mmoles) and 99—100% formic acid (21 ml.) was heated at 120° for 20 min., then concentrated under reduced pressure, and the residual oil was dissolved in cold water (50 ml.) and made basic with sodium hydrogen carbonate. The basic mixture was extracted with chloroform, dried, and evaporated to afford a brown paste (1·964 g.). This was chromatographed on alumina (77 g.); elution with benzene–ethyl acetate (20 : 1; 100 ml.) gave the keto-amine (XXXV) as crystals (173 mg., 11·5%), m.p. 60—66° (from hexane) and an unidentified compound (10 mg.), m.p. 235—237°. The next 400 ml. of eluate afforded a yellow oil which gave the *pentacyclo-compound* (XXXIX) (292 mg., 13·4%) as colourless leaflets, m.p. 159—162° (from di-isopropyl ether), $\nu_{max.}$ ($CHCl_3$) 2880, 2810, 2720, 1650, 1600, 1590, 1490, 1300, 1170, 1080, 1050, and 1030 cm.$^{-1}$, $\lambda_{max.}$ 261 (log ε 4·17), 277sh (3·85), and 288sh (3·44) mμ, $\lambda_{min.}$ 236 (3·73) mμ, τ 0·6 (s, 1H), 2·5—32 (m, 8H), 5·1 (t, 1H), 5·9 (t, 2H), 6·05 (s, 3H), and 6·4—9·2 (m, 17H), *m/e* 432 (M^+), 338, 310, 298, and 216 (Found: C, 74·95; H, 7·5; N, 6·45. $C_{27}H_{32}N_2O_3$ requires C, 74·97; H, 7·45; N, 6·5%).

Elution with ethyl acetate then afforded colourless *leaflets*, m.p. 199—200·5°, identified as (XXXVIa) by elemental analyses and i.r. spectral data (Found: C, 70·5; H, 6·6; N, 8·65. $C_{28}H_{33}N_3O_4$ requires C, 70·7; H, 7·0; N, 8·85%).

Use of formic acid dried over anhydrous copper sulphate gave (XXXIX) in improved yield (16%). The indole (XXXVII) was also isolated in this experiment (3·5%).

Acetic acid method. A mixture of (XXXVI) (1·26 g., 3 mmoles) and acetic acid (18 ml.) was heated at 90—95° for 30 min. The cooled mixture was poured into ice-cold water (100 ml.), made slightly alkaline with sodium hydrogen carbonate and extracted with methylene chloride. The solvent was evaporated off to give an oil (1·165 g.). A solution of this (1·115 g.) in absolute tetrahydrofuran (60 ml.) was added to a solution of lithium aluminium hydride (1·05 g.) in absolute tetrahydrofuran (50 ml.) at 0° during 15 min., and the mixture was heated under reflux for 5 hr. It was then decomposed with moist tetrahydrofuran [50 ml. containing water (4 ml.)] below 7°. The inorganic precipitate was filtered off and the filtrate was dried (K_2CO_3) and evaporated to a brown oil (872 mg.). This was chromatographed on alumina (70 g.); the fraction (250 ml.) eluted with benzene–ethyl acetate (20 : 1) gave an oil (151 mg,) which gave a violet colour with cerium sulphate reagent. Preparative t.l.c. (kieselgel HF 254) gave the indoline (XXXVIII) (62 mg.), $\lambda_{max.}$ 244, 273, 277, and 291 mμ, $\lambda_{max.}$ (dil. HCl–EtOH) 271 and 277 mμ, $\nu_{max.}$ ($CHCl_3$) 3400, 2800, 2700, 1600, 1490, 1460, 1390, 1060, 1050, 1030, and 1720 (impurity) cm.$^{-1}$.

The indoline (XXXVIII) (62 mg.) was formylated with a mixture of 98% formic acid (1 ml.) and acetic anhydride (0·5 ml.). The product was concentrated under reduced pressure and the residue was taken up in cold water and made alkaline with sodium hydrogen carbonate. Extraction with ether gave crystals (60 mg.) which afforded the formyl-indoline (XXXIX) (9 mg.) as colourless leaflets, m.p. 159—161° (from di-isopropyl ether–hexane); more of this product (9 mg.) was obtained from the mother liquor. The formylindoline was identical (mixed m.p. and i.r. spectra) with that obtained by the formic acid method.

Elution with benzene–ethyl acetate (20 : 1; 300 ml.) furnished an inseparable mixture of oils. Elution with benzene–ethyl acetate (7 : 3; 200 ml.) then afforded an oil (176 mg.) which yielded the indole (XXXVII) (from ethanol) (81 mg., 6·7%), m.p. 78—82°. An analytically pure sample melted at 85—103° and contained ethanol of solvation (1 mol.) which could not be removed by drying at 40—45°/2 mm. for 8 hr.; $\lambda_{max.}$ 273 (log ε 3·98), 279 (3·96), and 290sh (3·68) mμ, $\lambda_{min.}$ 246·5 (3·56) and 277·5 (3·96) mμ, $\nu_{max.}$ 3675, 3500, 3275, 1620, 1600, 1590, 1500, 1240, 1030, 780, 750, and 725 cm.$^{-1}$, *m/e* 402 (M^+), 306, 305, 198, and 94 (Found: C, 75·1; H, 7·9; N, 6·55. $C_{26}H_{30}N_2O_2,C_2H_5OH$ requires C, 74·95; H, 8·1; N, 6·25%).

Polyphosphate ester method A solution of (XXXVI) (420 mg., 1 mmole) and polyphosphate ester (2·1 g.) in chloroform (2·1 ml.) was heated under reflux on a boiling water bath for 5 hr. The cooled solution was poured into ice-cold water and the resulting mixture was treated as in the previous experiment. Chromatography afforded the indoline (XXXVIII) (20 mg.) and the indole (XXXVII) (72 mg., 16%), identical with the products obtained by the acetic acid method.

Hydrolysis of the Formylindoline (XXXIX) *to the Indoline* (XXXVIII).—A mixture of (XXXIX) (100 mg., 0·23 mmole) and dilute hydrochloric acid (conc. HCl–H_2O, 1 : 2; 3 ml.) was heated under reflux for 3 hr. It was concentrated under reduced pressure to an oil, which was dissolved in water (10 ml.). The solution was made alkaline with potassium carbonate to yield colourless crystals, which gave the *indoline* (63 mg., 67·5%) as prisms, m.p. 89—91° (from di-isopropyl ether–n-hexane, $\lambda_{max.}$ 246 (log ε 3·88), 272 (3·50), 279 (3·52), and 290 (3·39) mμ, $\lambda_{min.}$ 235 (3·77), 269 (3·45), 276 (3·45), and 285 (3·38) mμ, $\lambda_{max.}$ (0·1N-HCl in 96% EtOH) 271 (3·56) and 278 (3·53) mμ, $\lambda_{min.}$ (0·1N-HCl in 96% EtOH) 239 (2·76) and 275 (3·45 mμ), $\nu_{max.}$ ($CHCl_3$) 3400, 2800, 2700, 1600, 1490, 1460, 1390, 1060, 1050, and 1030 cm.$^{-1}$ (Found: C, 77·1; H, 7·95; N, 7·1. $C_{26}H_{32}N_2O_2$ requires C, 77·2; H, 7·95; N, 6·95%).

Acylation of the Indoline (XXXVIII) *with Propionic Anhydride.*—A mixture of (XXXVIII) (40 mg.) and propionic anhydride (0·5 ml.) was heated on a boiling water bath for 3 hr. The excess of reagent was evaporated off under reduced pressure leaving an oil. To this was added aqueous sodium hydrogen carbonate, and the oil which separated was extracted with methylene chloride. The dried extracts were concentrated to give an oily product (36 mg.). This was chromatographed on alumina (2·0 g.); elution with benzene–ethyl acetate (20 : 1) gave the pure product (29 mg.) (t.l.c.), which could not be crystallised, $\nu_{max.}$ (film) 2800, 2700, 1630, 1600, 1590, 1485, 1450, 1395, 1290, 1265, 1170, 1050, and 1030 cm.$^{-1}$, $\lambda_{max.}$ 257, 279sh, and 290sh mμ. The i.r. and u.v. spectra were similar to those of natural aspidospermine. The *picrate* (25 mg.) gave yellow prisms, m.p. 188—189·5° (from ether–ethyl acetate) (Found: C, 60·85; H, 5·7; N, 9·9. $C_{29}H_{36}N_2O_3$,-$C_6H_3N_3O_7$ requires C, 60·95; H, 5·7; N, 10·15%).

Treatment of the Formylindoline (XXXIX) *with* 47% *Hydrobromic Acid.*—A mixture of (XXXIX) (100 mg., 0·23 mmole) and 47% hydrobromic acid (20 ml.) was heated

at 150° ± 5° (bath) for 12 hr., then concentrated to dryness under reduced pressure to leave an amorphous product (127 mg.), which was dried and treated with propionic anhydride (1 ml.) at 95° for 3 hr. The mixture was concentrated to dryness under reduced pressure. Trituration of the residue with ether afforded the crude product (115 mg.), which gave the quaternary salt (XLIII) (80 mg., 69%) as colourless *needles*, m.p. 177—181° (from ethyl acetate–acetone). An analytical sample melted at 174—177°, $\nu_{max.}$ 3600—3200, 1760, 1670, 1650, 1610, 1595, 1410, 1300, 1150, 1060, 785, and 745 cm.$^{-1}$, $\lambda_{max.}$ (96% EtOH) 255 (log ε 4·47) and 285sh (3·45), $\lambda_{min.}$ (96% EtOH) 232 (4·05) mμ, $\lambda_{max.}$ (0·05N-NaOH in 96% EtOH) 312 (4·28) and 255sh (4·37), $\lambda_{min.}$ (0·05N-NaOH in 96% EtOH) 283 (3·73) mμ (Found: C, 59·1, H, 7·15; Br, 15·65; N, 6·45. $C_{25}H_{33}BrN_2O_3,H_2O$ requires C, 59·15; H, 6·95; Br, 15·75; N, 5·5%).

The picrate (XLV) was precipitated from the quaternary hydroxide with aqueous picric acid (the hydroxide was liberated from the quaternary bromide with aqueous potassium carbonate); it gave yellow prisms, m.p. 87—89° (from ethyl acetate–ethanol) (Found: C, 57·15; H, 5·6; N, 11·2. $C_{28}H_{31}N_5O_9,C_2H_5OH$ requires C, 57·4; H, 5·95; N, 11·15%).

We thank Mrs. T. Toma and Miss A. Maeda for elemental analyses, and Miss Y. Kishio for measurement of n.m.r. spectra. We also thank the United States Public Health Service for a grant.

[9/789 *Received*, *May* 13*th*, 1969]