# Total Synthesis of the Alkaloids Rhoeadine and Alpinigenine

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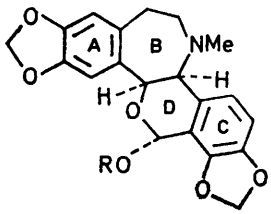
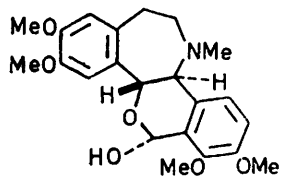
Rhoeadine (I) and alpinigenine (III) have been synthesised by a route involving the skeletal rearrangement of 1,2,3,4-tetrahydro-2-methyl-4′,5′:6,7-bismethylenedioxyisoquinoline-1-spiro-2′-indan-1′-ol (VII) into 5,6,7,7a-tetrahydro-2,3:10,11-bismethylenedioxy-7-methylbenz[*d*]indeno[1,2-*b*]azepine (VIII) by treatment with methanesulphonyl chloride and triethylamine. Oxidation of the indenoazepine (VIII) with osmium tetroxide gave 5,6,7,7a,12,12a-hexahydro-2,3:10,11-bismethylenedioxy-7-methylbenz[*d*]indeno[1,2-*b*]azepine-12,12a-diol (X), which was converted into (±)-rhoeagenine diol (XII) by treatment with sodium periodate followed by sodium borohydride. From 1,2,3,4-tetrahydro-2-methyl-4′,5′,6,7-tetramethoxy-1-spiro-2′-indan-1′-ol (XVII), (±)-alpinigenine diol (XXI) was synthesised. Oxidation of the diol (XXI) with manganese dioxide furnished (±)-alpinigenine (III).



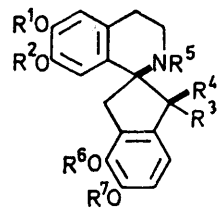
RHOEADINE (I) and rhoeagenine (II),[1] isolated from a variety of plants of the genus *Papaver* of the Papaveraceae, are characterised by a 3-benzazepine structure attached to a *cis*-fused six-membered acetal ring. We report here the first synthesis of the alkaloid (I).[2] † We also report the total synthesis of alpinigenine (III),[3] isolated from *Papaver alpinum* L. and *P. alpinum ssp. tatricum* Nyar., and also characterised by its 3-benzazepine skeleton. Alpinigenine differs from rhoeadine in




(I) R = Me
(II) R = H




(III)




(IV) $R^1 = R^2 = R^5 = H$, $R^3R^4 = O$, $R^6R^7 = CH_2$
(V) $R^1 = R^2 = H$, $R^3R^4 = O$, $R^5 = CO_2Et$, $R^6R^7 = CH_2$
(VI) $R^1R^2 = R^6R^7 = CH_2$, $R^3R^4 = O$, $R^5 = CO_2Et$
(VII) $R^1R^2 = R^6R^7 = CH_2$, $R^3 = OH$, $R^4 = H$, $R^5 = Me$
(XIV) $R^1 = R^2 = R^5 = H$, $R^3R^4 = O$, $R^6 = R^7 = Me$
(XV) $R^1 = R^2 = H$, $R^3R^4 = O$, $R^5 = CO_2Et$, $R^6 = R^7 = Me$
(XVI) $R^1 = R^2 = R^6 = R^7 = Me$, $R^3R^4 = O$, $R^5 = CO_2Et$
(XVII) $R^1 = R^2 = R^5 = R^6 = R^7 = Me$, $R^3 = OH$, $R^4 = H$

possessing a *trans*-fused acetal ring D and in substituents on rings A and C.

We planned to construct the 3-benzazepine skeleton from a benzylic spiroisoquinoline by a skeletal rearrangement involving an aziridinium ion. The spiroisoquinoline (IV),[4] an intermediate in the synthesis of ochotensine, was suitable for the present purpose.

Treatment of the spiroisoquinoline (IV) with ethyl chloroformate and triethylamine in dry tetrahydrofuran followed by alkaline hydrolysis of any *O*-ethoxycarbonyl group(s) furnished the urethane (V), which was converted in high yield into the bismethylenedioxyspiroisoquinoline (VI) by treatment with methylene iodide and potassium carbonate in dimethyl sulphoxide. Reduction of the oxo-isoquinoline (VI) with lithium aluminium hydride gave the hydroxy-spiroisoquinoline (VII) as the sole product. Structure (VII) (the key intermediate for our synthetic sequence) was confirmed by elemental analysis and the spectroscopic properties. Hydroxy-absorption at 3605 $cm^{-1}$ (dilute carbon disulphide solution) was not affected by the concentration, suggesting the *trans*-orientation of the hydroxy-group and the nitrogen atom. The n.m.r. spectrum showed signals at δ 5·81 (CH·O, singlet after treatment with deuterium oxide) and δ 2·40 (NMe, singlet).

The hydroxy-spiroisoquinoline (VII) was subjected to the rearrangement reaction with methanesulphonyl chloride and triethylamine in anhydrous tetrahydrofuran to afford a mixture of two isomeric benzazepines, from which the desired benzazepine (VIII) was easily separated in 80% yield ‡ as its hydrochloride (sparingly soluble in water but soluble in chloroform). The n.m.r. spectrum of this hydrochloride in deuteriochloroform exhibited two singlets at δ 7·19 and 5·23 assigned to an olefinic proton and a benzylic proton adjacent to nitrogen, respectively, and the u.v. spectrum showed maxima at 230, 249, 257, and 335 nm (ε 19,500, 15,300, 13,600, and 16,300) unchanged on addition of base, confirming the structure (VIII). The corresponding free base was unstable and was converted into the isomeric benzazepine (IX) on chromatography on alumina. The benzazepine

† Recently, Brossi and his co-workers reported the synthesis of this type of alkaloid from a phthalide isoquinoline alkaloid (W. Klötzer, S. Teitl, and A. Brossi, *Helv. Chim. Acta.*, 1971, **54**, 2075; W. Klötzer, S. Teitler, J. F. Blount, and A. Brossi, *J. Amer. Chem. Soc.*, 1971, **93**, 4321).

‡ Although we previously reported [2] that the ratio of the products of this rearrangement reaction was 1 : 1, the yield of the 3-benzazepine (VIII) has been improved to 80% by a rapid work-up procedure.

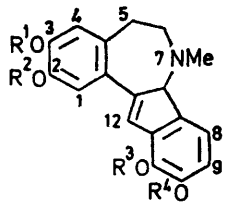
[1] F. Šantavý, M. Maturová, A. Němečková, H. B. Schröter, H. Proestisilova, and V. Preininger, *Planta. Med.*, 1960, **8**, 167; F. Šantavý, M. Maturová, A. Němečková, and M. Horák, *Coll. Czech. Chem. Comm.*, 1960, **25**, 1901.

[2] H. Irie, S. Tani, and H. Yamane, *Chem. Comm.*, 1970, 1713.

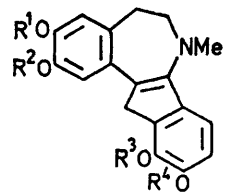
[3] M. Maturová, H. Potěšilova, F. Šantavý, A. D. Cross, V. Hanuš, and W. Doleiš, *Coll. Czech. Chem. Comm.*, 1967, **32**, 419.

[4] H. Irie, T. Kishimoto, and S. Uyeo, *J. Chem. Soc.* (*C*), 1968, 3051.

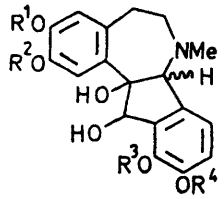
(IX) was stable; the n.m.r. spectrum exhibited no olefinic proton signal but a two-proton singlet at δ 3·77 assigned to benzylic protons. The u.v. spectrum confirmed the enamine structure (IX): maxima at 275 and



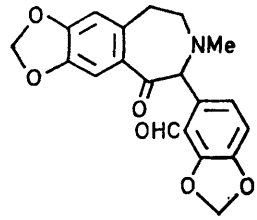
(VIII) $R^1R^2 = R^3R^4 = CH_2$
(XVIII) $R^1 = R^2 = R^3 = R^4 = Me$



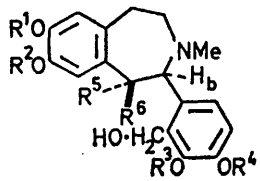
(IX) $R^1R^2 = R^3R^4 = CH_2$
(XIX) $R^1 = R^2 = R^3 = R^4 = Me$



(X) $R^1R^2 = R^3R^4 = CH_2$
(XX) $R^1 = R^2 = R^3 = R^4 = Me$



(XI)



(XII) $R^1R^2 = R^3R^4 = CH_2$, $R^5 = H$, $R^6 = OH$
(XIII) $R^1R^2 = R^3R^4 = CH_2$, $R^5 = OH$, $R^6 = H$
(XXI) $R^1 = R^2 = R^3 = R^4 = Me$, $R^5 = OH$, $R^6 = H_a$
(XXII) $R^1 = R^2 = R^3 = R^4 = Me$, $R^5 = H_a$, $R^6 = OH$
(XXIII) $R^1 = R^2 = R^3 = R^4 = Me$, $R^5R^6 = O$

346 nm (ε 10,000 and 24,300) were shifted to 244, 256, 318, and 346 nm (ε 23,600, 19,500, 16,500, and 18,000) in acidic solution.

Oxidation of the benzazepine (VIII) with osmium tetroxide in dry ether and pyridine gave the diol (X), the stereostructure of which has not been elucidated, though the glycol system is presumably *cis*-oriented in view of the properties of the reagent.

Treatment of the diol (X) with sodium periodate gave a mixture, even though t.l.c. of the reaction mixture showed a single spot when the starting diol (X) had been consumed (*ca.* 5 min); apparently the keto-aldehyde (XI) decomposes during the usual work-up. Consequently, successive treatment of the diol (X) with sodium periodate and with sodium borohydride was carried out to furnish (±)-rhoeagenine diol (XII), m.p. 142—143°, whose i.r., ($CHCl_3$), mass, and n.m.r. spectra were identical with those of material[5] derived from rhoeagenine. Although t.l.c. of the final product showed the presence of a small amount of the stereoisomeric *trans*-diol (XIII), attempts to isolate it were not successful.

Since rhoeagenine diol had already been reconverted into rhoeagenine (II) and rhoeadine (I),[5] our work completes the total synthesis of these alkaloids.

During the synthesis just described, we thought it worthwhile to study further examples of the applicability of the rearrangement reaction, *i.e.* transformation of a spiroisoquinoline into a 3-benzazepine. We chose alpinigenine (III) as the target in which the acetal ring is *trans*-fused to the 3-benzazepine. Most of the reactions of the synthesis were carried out in the normal way.

A Pictet–Spengler cyclisation of 3,4-dihydroxyphenethylamine and 4,5-dimethoxyindane-1,2-dione in ethanol gave the spiroisoquinoline (XIV) in 70% yield, which was easily converted into the urethane (XV) by treatment with ethyl chloroformate and triethylamine in anhydrous tetrahydrofuran. Methylation of the phenolic function with methyl iodide and potassium carbonate in acetone furnished quantitatively the tetramethoxyspiroisoquinoline (XVI). Reduction with lithium aluminium hydride in tetrahydrofuran then gave the hydroxyspiroisoquinoline (XVII), identified as described in the case of (VII).

Treatment of the hydroxy-spiroisoquinoline (XVII) with methanesulphonyl chloride and triethylamine yielded a mixture of the isomeric benzazepines (XVIII) and (XIX), from which the desired benzazepine (XVIII) was easily separated in 60% yield as its hydrochloride.

Oxidation of the benzazepine (XVIII) with osmium tetroxide in ether gave the diol (XX). Treatment of the diol (XX) with sodium periodate at pH 4—5 at room temperature for 5 min followed by sodium borohydride furnished a mixture from which (±)-alpinigenine diol (XXI) (less than 10% yield) and the isomeric *cis*-diol (XXII) (50% yield) were isolated by preparative layer chromatography. These alcohols (XXI) and (XXII) were characterised as their picrates, m.p. 189—191 and 208—209°, respectively. The n.m.r. spectrum of (±)-alpinigenine diol (XXI) exhibited a typical AB-type quartet at δ 3·45 and 5·25 ($J$ 8 Hz), confirming the *trans* disposition of $H_a$ and $H_b$; the isomeric diol (XXII) showed an AB-type quartet at δ 4·08 and 5·08 ($J$ 3 Hz).

The yield of (±)-alpinigenine diol (XXI) was too low for oxidation to alpinigenine (III) to be performed. We therefore examined reagents other than sodium borohydride in order to improve the yield of *trans*-diol. Lithium perhydro-9b-boraphenalenylhydride[6] gave an acceptable result (40% yield).

Oxidation of the diol (XXI) was accomplished by treatment with activated manganese dioxide, to furnish (±)-alpinigenine (III), m.p. 172—173°, along with 3,4-dihydro-6,7-dimethoxy-2-methylisoquinolin-1-one,[7] 4,5-dimethoxyphthalide,[8] and the keto-alcohol (XXIII).

[5] F. Šantavý, J. L. Kaul, L. Hruban, L. Dolejš, V. Hanuš, K. Bláha, and A. D. Cross, *Coll. Czech. Chem. Comm.*, 1965, **30**, 335, 3479.

[6] H. C. Brown and W. C. Dickason, *J. Amer. Chem. Soc.*, 1970, **92**, 709.

[7] W. H. Perkin, jun., *J. Chem. Soc.*, 1916, **109**, 815.

[8] O. Salomon, *Ber.*, 1887, **20**, 883.

The i.r. ($CHCl_3$) and mass spectra of (±)-alpinigenine (III) were identical with those of natural material.

The structure of the keto-alcohol (XXIII) was suggested by its spectroscopic properties; the mass spectrum showed $M^+$ 401 ($C_{22}H_{27}NO_6$), the i.r. spectrum showed a carbonyl band at 1670 $cm^{-1}$, and the n.m.r. spectrum exhibited signals at δ 5·20 (2H, s, $ArCH_2$·OH) and 3·30 (1H, s, 6-H).

## EXPERIMENTAL

M.p.s were determined with a Yanagimoto microscope hot-stage apparatus. N.m.r. spectra were obtained with a Varian A-60 spectrometer (tetramethylsilane as internal standard). Mass spectra were determined with a Hitachi RMU-6D spectrometer with a direct heated inlet system.

*Ethyl* 1,2,3,4-*Tetrahydro*-6,7-*dihydroxy*-4′,5′-*methylenedioxy*-1′-*oxoisoquinoline*-1-*spiro*-2′-*indane*-2-*carboxylate* (V).—The spiroisoquinoline (IV) [4] (245 mg) and triethylamine (0·5 ml) in tetrahydrofuran (200 ml) were treated with ethyl chloroformate (250 mg) with stirring at 0° for 30 min. Triethylamine hydrochloride was filtered off and the filtrate was concentrated under reduced pressure to dryness. The residue was stirred with aqueous 10% sodium hydroxide (30 ml) for 1 h at room temperature. The solution was washed with ether and acidified with dilute hydrochloric acid. The precipitate crystallised from ethanol to give the *urethane* (V) (200 mg), m.p. 277—279° (Found: C, 63·2; H, 4·8; N, 3·5. $C_{21}H_{19}NO_7$ requires C, 63·4; H, 4·8; N, 3·5%), $\nu_{max.}$ (Nujol) 3400 and 3150 (OH), and 1680 (CO) $cm^{-1}$, δ ([$^2H_5$]pyridine) 7·46 and 6·85 (2H, AB-type quartet, *J* 8 Hz, ArH), 6·96 and 6·68 (2H, s, ArH), 6·0 (s, O·$CH_2$·O), 4·06 (q, *J* 6 Hz, $CH_2$·$CH_3$), 3·60 (s, $CH_2Ar$), and 1·00 p.p.m. (t, *J* 6 Hz, $CH_2$·$CH_3$).

*Methylenation of the Urethane* (V).—The urethane (V) (143 mg), methylene iodide (0·4 ml) and potassium carbonate (230 mg) in dimethyl sulphoxide (5 ml) were heated with stirring at 70° under nitrogen for 4 h. The precipitate was filtered off and the solution concentrated under reduced pressure. The residue, after the usual work-up, gave the *bismethylenedioxyspiroisoquinoline* (VI) (75 mg), m.p. 186—189° (from ethanol) (Found: C, 64·8; H, 4·8; N, 3·5. $C_{22}H_{19}NO_7$ requires C, 64·5; H, 4·7; N, 3·4%), $\nu_{max.}$ (KBr) 1720 and 1690 (CO) $cm^{-1}$, δ ($CDCl_3$) 7·43 and 6·88 (2H, AB-type quartet, *J* 8 Hz, ArH), 6·60 and 6·12 (2H, s, ArH), 6·10 (s, O·$CH_2$·O), 4·13 and 4·17 (AB-type quartet, *J* 1 Hz, O·$CH_2$·O), 3·50 (s, $CH_2Ar$), 4·06 (q, *J* 7 Hz, $CH_2$·$CH_3$), and 1·08 p.p.m. (t, *J* 7 Hz, $CH_2$·$CH_3$).

1,2,3,4-*Tetrahydro*-2-*methyl*-4′,5′:6,7-*bismethylenedioxyisoquinoline*-1-*spiro*-2′-*indan*-1′-*ol* (VII).—The bismethylenedioxyisoquinoline (VI) (55 mg) in tetrahydrofuran (10 ml) was treated with lithium aluminium hydride (100 mg) under reflux for 2 h. The usual work-up gave the N-*methylhydroxyisoquinoline* (VII) (35 mg), m.p. 196—201° (from ethanol) (Found: C, 67·7; H, 5·4; N, 3·9. $C_{20}H_{19}NO_5$ requires C, 67·9; H, 5·4; N, 3·9%), $\nu_{max.}$ (KBr) 3460 (OH) $cm^{-1}$, $\nu_{max.}$ ($CS_2$) 3605 (OH) $cm^{-1}$, δ ($CDCl_3$) 6·75 (2H, s, ArH) 6·58(s) and 6·26(s) (2 × ArH), 6·06 and 5·83 (AB-type quartet, *J* 1 Hz, O·$CH_2$·O), 5·20br (m, C*H*·OH) (changed to a singlet at δ 5·21 by deuterium oxide treatment), 3·25 (s, $CH_2Ar$), and 2·40 p.p.m. (s, NMe).

*Rearrangement of the* N-*Methylhydroxyisoquinoline* (VII).—Methanesulphonyl chloride (150 mg) was added to a solution of the foregoing hydroxyisoquinoline (VII) (200 mg) and triethylamine (150 mg) in tetrahydrofuran (50 ml) with stirring at 0°. The precipitate was filtered off and the filtrate concentrated to dryness. The residue was taken up in dilute hydrochloric acid and extracted with chloroform. The extract was washed with water, dried ($Na_2SO_4$), and concentrated to dryness to leave the *hydrochloride* (160 mg) of 5,6,7,7a-*tetrahydro*-2,3:10,11-*bismethylenedioxy*-7-*methylbenz*[d]*indeno*[1,2-b]*azepine* (VIII), m.p. 209—211° (from ethanol) (Found: C, 62·6; H, 5·3; N, 3·7. $C_{20}H_{17}NO_4$,HCl,0·6$H_2O$ requires C, 62·7; H, 5·1; N, 3·7%), $M^+$ 335, $\nu_{max.}$ ($CHCl_3$) 2400 (NH) $cm^{-1}$, $\lambda_{max.}$ (EtOH) 230, 249, 257, and 335 nm (ε 19,500, 15,300, 13,600, and 16,300), δ (HCl salt in $CDCl_3$) 7·84 and 6·74 (2H, AB-type quartet, *J* 8 Hz, ArH), 7·19, 7·06, and 6·63 (all s, 2 × ArH and olefinic H), 6·03(s) and 6·00(s) (2 × O·$CH_2$·O), 5·23 (s, N·CH), and 2·74 p.p.m. (s, NMe). The aqueous layer was basified with sodium carbonate and extracted with chloroform. The extract was washed with water, dried ($Na_2SO_4$) and evaporated to leave the isomeric 5,6,7,12-*tetrahydrobenzindenoazepine* (IX) (15 mg), m.p. 220—222° (from ethanol) (Found: C, 70·9; H, 5·3; N, 4·4. $C_{20}H_{17}NO_4$,·0·25$H_2O$ requires C, 70·7; H, 5·2; N, 4·1%), $M^+$, 335 $\lambda_{max.}$ (EtOH) 275 and 346 nm (ε 10,000 and 24,300) $\lambda_{max.}$ (EtOH–HCl) 244, 256, 318, and 346 nm (ε 23,600, 19,500, 16,500, and 18,000), δ ($CDCl_3$) 6·57 and 6·99 (2H, AB-type quartet, *J* 8 Hz, ArH), 6·89(s) and 6·63(s) (2 × ArH), 5·96(s) and 5·91(s) (2 × O·$CH_2$·O), 2·38 (s, NMe), and 3·77 p.p.m. (s, $CH_2Ar$).

*Oxidation of the Tetrahydrobenzindenoazepine* (VIII) *with Osmium Tetroxide*.—Compound (VIII) (130 mg) (regenerated from its hydrochloride by shaking in aqueous sodium carbonate with ether) was treated in dry ether (30 ml) with osmium tetroxide (100 mg) and dry pyridine (100 mg) for 72 h at room temperature. Evaporation under reduced pressure left a residue which was refluxed with sodium sulphite (500 mg) in aqueous ethanol for 3 h. The mixture was filtered and the filtrate was concentrated to dryness. The residue was taken up in water and extracted with chloroform, and the extract was washed with water, dried, and evaporated to give 5,6,7,7a,12,12a-*hexahydro*-2,3:10,11-*bismethylenedioxy*-7-*methylbenz*[d]*indeno*[1,2-b]*azepine*-12,12a-*diol* (97 mg) (X), m.p. 208—211° (Found: C, 65·1; H, 4·9; N, 3·6. $C_{20}H_{19}NO_6$ requires C, 65·0; H, 5·2; N, 3·8%), $\nu_{max.}$ (KBr) 3450 and 3350 (OH) $cm^{-1}$, $M^+$ 369, δ ($CDCl_3$) 7·45(s) and 6·61(s) (2 × ArH), 6·85 (2H, s, ArH), 6·03(s) and 5·93(s) (2 × O·$CH_2$·O), 2·28 (s, NMe), 5·56 (s, C*H*·OH), and 4·48 p.p.m. (s, N·CH).

(±)-*Rhoeagenine Diol* (XII).—The glycol (X) (50 mg) was treated with sodium periodate (50 mg) in dilute hydrochloric acid (5 ml) at 0° for 5 min, then the solution was basified with sodium hydrogen carbonate, diluted with ethanol, treated with sodium borohydride (200 mg) with stirring at room temperature for 30 min, and heated on a water-bath for 30 min. After decomposition of the excess of the reagent with acetic acid, the solution was basified with sodium carbonate, and extracted with chloroform. The extract was washed with water and dried. Removal of the solvent gave (±)-rhoeagenine diol, m.p. 142—143°, identical with material [5] from natural sources [i.r. ($CHCl_3$), n.m.r. ($CDCl_3$), and mass spectra and t.l.c. behaviour], δ ($CDCl_3$), 6·65 and 6·85 (2H, AB-type quartet, *J* 8 Hz, ArH), 6·64(s) and 6·59(s) (2 × ArH), 5·90(s) and 5·94(s) (2 × O·$CH_2$·O), 4·00 (d, *J* 2 Hz, N·CH), 4·96 (d, *J* 2 Hz, HO·C*H*), 4·67 (s, $CH_2$·OH), and 2·25 p.p.m. (s, NMe), $M^+$ 371.

*4,5-Dimethoxyindane-1,2-dione*.— 2-Hydroxyimino-4,5-dimethoxyindan-1-one [9] (10 g), 37% formalin (40 ml), and centrated hydrochloric acid (10 ml) were stirred for 10 min at 100°. Water was added to the cooled mixture, and the deposited crystals were filtered off to give *4,5-dimethoxyindane-1,2-dione* (8 g), m.p. 143—144° (from benzene) (Found: C, 64·4; H, 4·9. $C_{11}H_{10}O_4$ requires C, 64·1; H, 4·9%), $\nu_{max.}$ ($CHCl_3$) 1765 and 1703 $cm^{-1}$ (CO), δ ($CDCl_3$) 7·72 and 7·05 (2H, AB-type quartet, *J* 8 Hz, ArH), 4·03 and 3·92 (2 × OMe), and 3·56 p.p.m. (s, O=C–$CH_2$Ar).

*1,2,3,4-Tetrahydro-6,7-dihydroxy-4′,5′-dimethoxyisoquinoline-1-spiro-2′-indan-1′-one* (XIV).—4,5-Dimethoxyindane-1,2-dione (8·24 g) and 3,4-dihydroxyphenethylamine hydrobromide (9·92 g) were refluxed with stirring in ethanol (300 ml) under nitrogen for 5 h. The mixture was evaporated under reduced pressure and the residue crystallised from ethanol. The crystals were taken up in water, and solution was basified with aqueous ammonia. The precipitate crystallised from ethanol to give the *spiroisoquinoline* (XIV) (12 g), m.p. 222—223° (Found: C, 66·9; H, 5·8; N, 4·0. $C_{19}H_{19}NO_5$ requires C, 66·8; H, 5·6; N, 4·1%), $\nu_{max.}$ (Nujol) 3410, 3247 (OH and NH), and 1710 $cm^{-1}$ (CO), δ [$(CD_3)_2$N·CDO] 7·51 and 7·23 (2H, AB-type quartet, *J* 8 Hz, ArH), 6·57(s) and 6·14(s) (2 × ArH), 4·01 and 3·88 (each 3H, s, OMe), 3·36 (s, $CH_2$Ar), 6·0—5·0br (m, 2 × OH), and 3·22—2·5 p.p.m. (4H, m, $CH_2$·$CH_2$Ar).

*Ethyl 1,2,3,4-Tetrahydro-6,7-dihydroxy-4′,5′-dimethoxy-1′-oxoisoquinoline-1-spiro-2′-indane-2-carboxylate* (XV).—The foregoing spiroisoquinoline (XIV) (500 mg) and triethylamine (1 ml) in tetrahydrofuran (200 ml) were treated with ethyl chloroformate (500 mg) with stirring at 0° for 30 min. The same work-up as in the case of (V) gave the *urethane* (XV) (430 mg), m.p. 271—273° (from ethanol) (Found: C, 62·5; H, 5·6; N, 3·4. $C_{21}H_{23}NO_7$ requires C, 62·8; H, 5·9; N, 3·5%), $\nu_{max.}$ (Nujol) 3400, 3100 (OH), and 1680 (CO) $cm^{-1}$, δ ([$^2H_5$]pyridine) (80°) 7·63 and 7·01 (2H, AB-type quartet, *J* 8 Hz, ArH), 6·95(s) and 6·61(s) (2 × ArH), 4·70 (2H, s, $CH_2$Ar), 3·88 (6H, s, 2 × OMe), 4·08 (q, *J* 7 Hz, N·$CO_2$·$CH_2$·$CH_3$), and 1·0 p.p.m. (t, *J* 7 Hz, N·COO·$CH_2$·$CH_3$).

*Methylation of the Urethane* (XV).—The urethane (XV) (4 g), methyl iodide (20 g), and potassium carbonate (20 g) were heated in acetone (200 ml) under reflux with stirring for 5 h. The usual work-up gave the *tetramethoxyspiroisoquinoline* (XVI) (4 g), m.p. 144—146° (Found: C, 65·6; H, 6·4; N, 3·2. $C_{24}H_{27}NO_7$ requires C, 65·3; H, 6·2; N, 3·2%), $\nu_{max.}$ ($CHCl_3$) 1715 and 1680 (CO) $cm^{-1}$, δ ($CDCl_3$) 7·60 and 7·01 (2H, AB-type quartet, *J* 8 Hz, ArH), 6·66(s) and 6·18(s) (2 × ArH), 3·61 (s, $CH_2$Ar), and 3·98, 3·93, 3·83, and 3·46 p.p.m. (each s, OMe).

*1,2,3,4-Tetrahydro-4′,5′,6,7-tetramethoxyisoquinoline-1-spiro-2′-indan-1′-ol* (XVII).—The tetramethoxyisoquinoline (XVI) (4 g) in tetrahydrofuran (500 ml) was treated with lithium aluminium hydride (2 g) under reflux for 4 h. The usual work-up gave the N-*methylhydroxyisoquinoline* (XVII) (3 g) as needles, m.p. 173—174° (from ethanol) (Found: C, 68·7; H, 7·3; N, 3·6. $C_{22}H_{27}NO_5$ requires C, 68·5; H, 7·0; N, 3·6%), $\nu_{max.}$ (Nujol) 3425 (OH), $\nu_{max.}$ ($CS_2$) 3606 (OH) $cm^{-1}$, δ ($CDCl_3$) 6·99 and 6·79 (2H, AB-type quartet, *J* 8 Hz, ArH) 6·59(s) and 6·21(s) (2 × ArH), 5·28 (s, CH·O), 3·89, 3·86, 3·83, and 3·44 (each s, OMe), and 2·45 p.p.m. (s, NMe).

*Rearrangement of the N-Methylhydroxyisoquinoline* (XVII). Methanesulphonyl chloride (500 mg) was added to a solution of the hydroxyisoquinoline (XVII) (1 g) and triethylamine (1 g) in tetrahydrofuran (300 ml) with stirring at 0°. The precipitate was filtered off and the filtrate was concentrated to dryness; the residue was taken up in dilute hydrochloric acid and extracted with chloroform. The extract was washed with a small amount of water, dried ($Na_2SO_4$), and concentrated to dryness to leave the *hydrochloride* (650 mg) of *5,6,7,7a-tetrahydro-2,3,10,11-tetramethoxy-7-methylbenz*[d]*indeno*[1,-b]*azepine* (XVIII) m.p. 198—200° (from ethanol) (Found: C, 61·2; H, 6·8; N, 3·2. $C_{22}H_{25}NO_4$,HCl,1·5$H_2O$ requires C, 61·2; H, 6·5; N, 3·2%), $M^+$ 367, $\nu_{max.}$ ($CHCl_3$) 2300 ($N^+H$) $cm^{-1}$, $\lambda_{max.}$ (EtOH) 258 and 342 nm (ε 23,400 and 18,500), δ ($CDCl_3$) 8·08 and 6·83 (2H, AB-type quartet, *J* 8 Hz, ArH), 7·38(s), 7·15(s), and 6·18(s) (2 × ArH and olefinic H), 3·98, 3·96, 3·91, and 3·90 (4 × OMe), 5·23 (s, N·CH), and 2·38 p.p.m. (s, NMe).

The aqueous layer was basified with sodium carbonate and extracted with chloroform. The extract was washed with water and dried. Removal of the solvent left the *5,6,7,12-tetrahydro-isomer* (XIX) (300 mg), m.p. 133—134° (from ethanol) (Found: C, 71·8; H, 7·0; N, 3·8. $C_{22}H_{25}NO_4$ requires C, 71·9; H, 6·9; N, 3·8%), $\lambda_{max.}$ (EtOH) 262 and 340 nm (ε 16,800 and 34,200), $\lambda_{max.}$ (EtOH–HCl) 238 and 324 nm (ε 28,200 and 29,600), δ ($CDCl_3$) 7·18 and 6·85 (2H, AB-type quartet, *J* 8 Hz, ArH), 7·06(s) and 6·68(s) (2 × ArH), 3·83 (s, $CH_2$Ar), 3·98, 3·95, 3·88, and 3·87 (each s, OMe), and 3·00 p.p.m. (s, NMe).

*Oxidation of the Tetrahydrobenzindenoazepine* (XVIII).—Compound (XVIII) (117 mg) was treated with osmium tetroxide (90 mg) as for compound (VIII); the same work-up gave the *glycol* (110 mg) (XX), m.p. 163—164° (from ethanol), (Found: C, 65·1; H, 6·8; N, 3·6. $C_{22}H_{27}NO_6$,·0·25$H_2O$ requires C, 65·0; H, 6·8; N, 3·4%), $M^+$ 401, $\nu_{max.}$ ($CHCl_3$) 3450 (OH) $cm^{-1}$, $\lambda_{max.}$ (EtOH) 233 and 284 nm (ε 20,300 and 6200), δ ($CDCl_3$) 7·11 and 6·90 (2H, AB-type quartet, *J* 8 Hz, ArH), 7·51(s) and 6·65(s) (2 × ArH), 5·65 (s, O·CH), 4·48 (s, N·CH), 3·96, 3·91, and 3·86 (each s, OMe), and 2·25 p.p.m. (s, NMe).

*Alpinigenine Diol* (XXI).—(*a*) The glycol (XX) (220 mg) was treated with sodium periodate (130 mg) in dilute hydrochloric acid (5 ml) at 0° for 10 min, then the solution was basified with sodium hydrogen carbonate and diluted with ethanol. The whole was treated with sodium borohydride (100 mg) with stirring at room temperature for 30 min, and heated on a water-bath for 30 min. After decomposition of the excess of reagent with acetic acid, the solution was basified with sodium carbonate, and extracted with chloroform. The organic layer was washed with water and dried. Removal of the solvent left an oily residue (200 mg) which was subjected to preparative layer chromatography on a silica gel plate. The faster-running substance (XXI) was characterised as its *picrate*, m.p. 189—191° (from ethanol) (Found: C, 53·1; H, 5·1; N, 8·8. $C_{22}H_{29}NO_6$,$C_6H_3N_3O_7$ requires C, 53·1; H, 4·9; N, 8·7%); $M^+$ 403, the free base was identical with alpinigenine diol * from natural sources [3] (attempts to crystallise the free base were unsuccessful), $\nu_{max.}$ ($CHCl_3$) 3350—3550 (OH) $cm^{-1}$, δ ($CDCl_3$) 7·11 and 6·85 (2H, AB-type quartet, *J* 9 Hz, ArH), 7·20(s) and 6·66(s) (2 × ArH), 5·25 (d, *J* 8 Hz, O·C*H*·CH·N), 3·45 (d, *J* 8 Hz, N·CH), 5·10 and 4·73 (AB-type quartet, $ArCH_2$·O), 3·86 and 3·83 (4 × OMe), and 2·03 p.p.m. (s, NMe). The slower-running substance (XXII) was also characterised as its *picrate*, m.p. 208—210° (Found: C, 53·1; H, 5·0; N, 8·7%),

* Alpinigenine diol derived from alpinigenine was supplied by Professor H. Rönsch.

[9] W. H. Perkin and R. Robinson, *J. Chem. Soc.*, 1914, **105**, 2376.

$M^+$ 403 (free base) $\nu_{max.}$ ($CHCl_3$) 3350—3500 (OH) $cm^{-1}$, $\delta$ ($CDCl_3$) 6·93 and 6·70 (2H, AB-type quartet, $J$ 9 Hz, ArH), 6·68(s) and 6·65(s) (2 × ArH) 5·08 (s, $J$ 3 Hz, O·CH), 4·08 (d, $J$ 3 Hz, N·CH), 4·76 (s, $CH_2Ar$), 3·90, 3·83, 3·82, and 3·73 (each s, OMe), and 2·23 p.p.m. (s, NMe).

(*b*) The glycol (XX) (200 mg) was oxidised as in (*a*). After basified with sodium hydrogen carbonate, the mixture was extracted with ether, and the extract was washed with water, dried, and evaporated to dryness under reduced pressure below 0°. The residue was taken up in dry tetrahydrofuran (50 ml) and the solution was treated with lithium perhydro-9b-boraphenalenylhydride (600 mg) for 1 h at 0°. The whole was diluted with 3N-sodium hydroxide (5 ml) and 30% hydrogen peroxide (5 ml) and stirred at room temperature for 1 h. The tetrahydrofuran layer was separated and concentrated to dryness; the residue was taken up in dilute hydrochloric acid and the solution was washed with ether, basified with sodium carbonate, and extracted with chloroform. The extract was washed with water, dried, and evaporated to dryness; the residue which was subjected to preparative layer chromatography as before to give (±)-alpinigenine diol (XXI) (80 mg) and the *cis*-diol (XXII) (100 mg).

*Oxidation of* (±)-*Alpinigenine Diol.*—(±)-Alpinigenine diol (XXI) (50 mg) was treated with manganese dioxide (500 mg) in chloroform (7 ml) for 30 min at room temperature. After removal of the reagent, the solution was evaporated to dryness. The residue was taken up in dilute hydrochloric acid and the solution was heated on a water-bath for 30 min, washed with ether, basified with sodium carbonate, and extracted with ether. The extract was washed with water, dried, and concentrated; the residue was chromatographed in benzene on alumina. Elution with benzene first gave *2,3,4,5-tetrahydro-2-(2-hydroxymethyl-3,4-dimethoxyphenyl)-7,8-dimethoxy-3-methyl-3-benzazepin-1-one* (XXIII) (10 mg), m.p. 187—190° (Found: C, 65·7; H, 6·5; N, 3·3. $C_{22}H_{27}NO_6$ requires C, 65·8; H, 6·7; N, 3·5%), $\nu_{max.}$ (KBr) 1670 $cm^{-1}$ (CO), $\lambda_{max.}$ (EtOH) 230, 275, and 310 nm ($\varepsilon$ 20,100, 7400, and 6100), $\delta$ ($CDCl_3$) 6·93(s) and 6·71(s) (2 × ArH), 6·78 (2H, s, ArH), 5·20 (s, $O{\cdot}CH_2$), 3·30 (s, N·CH), and 3·95, 3·88, and 3·82 p.p.m. (4 × OMe), and then (±)-alpinigenine (5 mg), m.p. 172—173° (from ethyl acetate–light petroleum), identical [i.r. spectrum ($CHCl_3$)] with an authentic sample.

The ether washing was washed with water, dried, and evaporated to dryness and the residue which was chromatographed in benzene on alumina. Elution with benzene gave 4,5-dimethoxyphthalide (5 mg), m.p. 125—128° (lit.,[8] 123—124°), and then 3,4-dihydro-6,7-dimethoxy-2-methylisoquinolin-1-one (8 mg), m.p. 122—123 (lit.,[7] 126—127°).

We thank Drs. F. Šantavý (Institute of Chemistry of the Medical Faculty, Palacký University, Olomouc, Czechoslovakia) and H. Rönsch (Forschungszentrum für Molekularbiologie und Medizin, Institut für Biochemie der Pflanzen, Weinberg, Deutsche Demokratische Republik) for samples of rhoeadine and alpinigenine. We also thank Professor S. Uyeo of this Faculty for encouragement and Dr. T. Shingu for the n.m.r. measurements.

[2/1088 *Received*, 15*th May*, 1972]