Total Synthesis of the Alkaloids (±)-Alpinigenine and (±)-*cis*-Alpinigenine

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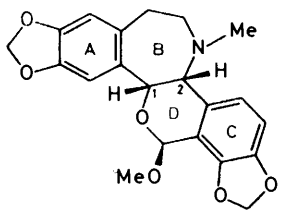
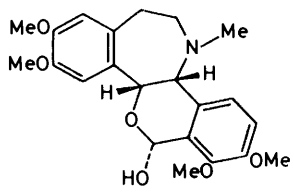
A stereoselective synthesis of the rhoeadine alkaloid (±)-*cis*-alpinigenine is described. Hofmann elimination of the known tetracyclic base (4) gave the *trans*-azecine (7) which afforded the diol (13) on oxidation with *N*-bromosuccinimide. Periodic acid cleavage of (13) yielded the dibenzaldehyde (14), which on photolysis resulted in the formation of (±)-*cis*-alpinigenine (20—30%) and (±)-alpinigenine (1%) involving *endo* (16) and *exo* (15) (4s + 2s) intramolecular additions respectively of the intermediate photodienol-E (Scheme 1).

THE rhoeadine alkaloids [1] occur widely in the genus *Papaver*. These tetracyclic bases are characterised by the presence of a 3-benzazepine unit *cis*- or *trans*-fused to a six-membered acetal or hemiacetal. Earlier investigations [2] have established the structure and stereochemistry of rhoeadine as (1). The constitution and absolute configuration of (+)-alpinigenine (3) and (+)-*cis*-alpinigenine (2) were recently established by a combination of chemical and physical methods.[3]

Our approach to the synthesis of rhoeadine alkaloids in general and (±)-*cis*-alpinigenine (2) in particular was based on the retrosynthetic scheme shown in Scheme 1. This disconnection process reduced the problem of choosing the appropriate starting material to the easily prepared and already known tetracyclic base (4) and avoided the necessity of preparing a 1,2,3,4-tetrasubstituted benzene precursor (ring C of the rhoeadine skeleton). The projected synthetic scheme also had the virtue of not involving protection and deprotection of



(1)



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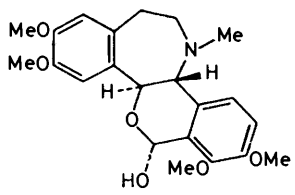
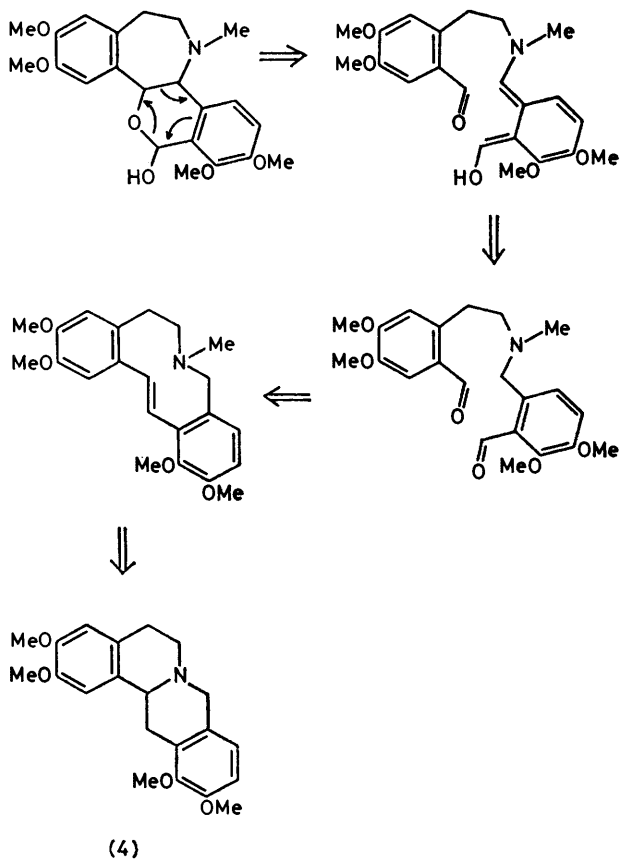


(3)

any functional group at any stage. Further, it directly leads to the D-ring of the alkaloid at the correct oxidation level.†

The known tetracyclic base (4), m.p. 160—162 °C, was prepared in excellent yield (four steps; 72% overall yield) from homoveratrylamine and *o*-homoveratric acid by standard procedures.[4] When refluxed in acetone solution with an excess of methyl iodide, this base quantitatively formed the corresponding quaternary

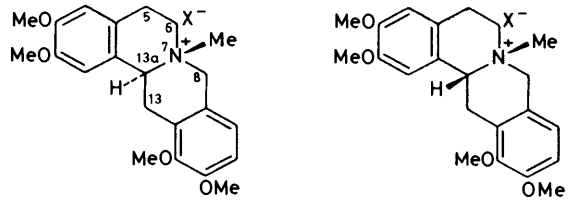


SCHEME 1

salt as a mixture of diastereoisomers. The ^{1}H n.m.r. spectrum of this mixture in deuteriodimethyl sulphoxide exhibited two *N*-methyl resonances (δ 3.20 and 2.81).

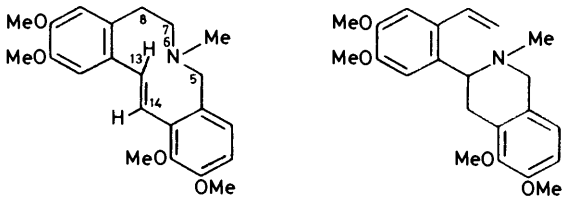
† All previously reported syntheses of the rhoeadine skeleton have followed a ring elaboration sequence A→B→C→D and necessitated adjustment of ring D to its proper oxidation level in the final step, with one exception (S. Prabhakar, A. M. Lobo, and I. M. C. Oliveira, *J. Chem. Soc., Chem. Commun.*, 1977, 419). For a review of other syntheses of rhoeadine alkaloids see T. Kametani and K. Fukumoto, *Heterocycles*, 1975, **3**, 931.

These were assigned the *cis* and *trans* configurations respectively on the basis of the chemical shifts of the signals due to the *N*-methyl groups.[5] These diastereoisomers could be separated by fractional crystallisation from aqueous ethanol into the *trans* isomer (5a), m.p. 254 °C (decomp.), and the *cis* isomer (6a), m.p. 248—249 °C (decomp.). However, for the reaction to follow, separation into the pure isomers was not necessary and the diastereoisomeric mixture could be used directly. The methiodides were converted into the corresponding methochlorides [6] which were then subjected to Hofmann elimination by the Russel procedure.[7] The resultant ten-membered tricyclic olefin (7) was obtained in 65% yield, the styrene (8) (13%), resulting from elimination of the other benzylic hydrogen, being a minor product. Both the ^{1}H n.m.r. [δ_A 6.9, δ_B 6.7 (q, J_{AB} 16 Hz)] among other signals and the u.v. [$\lambda_{max.}$ 286 nm (ε 11 900)] spectra confirmed the *trans* geometry of the olefin (7). Russel [7] was able to achieve the hydroxylation of the double bond of a closely related base (9) by treatment with *N*-bromosuccinimide in the presence of one equivalent of hydrochloric acid. In Russel's work [7] the diol (10) was accompanied by a quaternary salt (11) (30%). Formation of both (10) and (11) was rationalised on the basis of two concurrent reactions: one, an intramolecular transfer of the bromine atom from an initially formed $\equiv N^{+}-$ Br species to C-13 to give the benzyl bromide which eventually leads to the diol (10) [Scheme 2(*a*)], and the other, a concerted attack of Br^{+} (at C-13) and the nitrogen atom lone pair (at C-14) producing finally (11) [Scheme 2(*b*)]. In our hands the procedure of Russel led, after acidification with HCl, almost exclusively to the quaternary salt (12) with only traces of the requisite diol (13) being formed. However, systematic variation of conditions (temperature or solvent) did not increase the proportion of diol (13) in the mixture. Since the formation of (12) implied the participation of the nitrogen lone pair, it was reasoned that the use of an excess of mineral acid should suppress, if not completely prevent, the production of (12) and that the resulting product, being a benzylic bromohydrin, would solvolyse under aqueous conditions to the required diol (13).

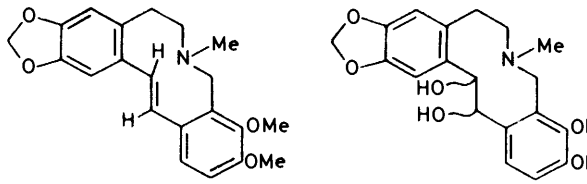


(5) (6)

a, X = I
b, X = Cl
c, X = OH



(7) (8)



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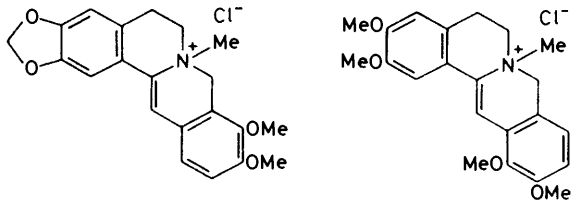
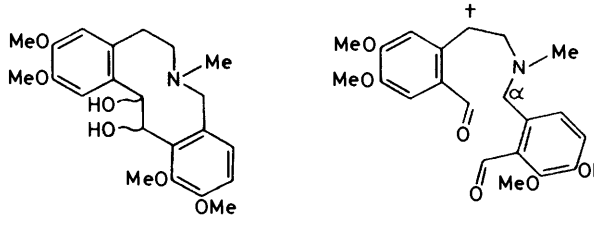
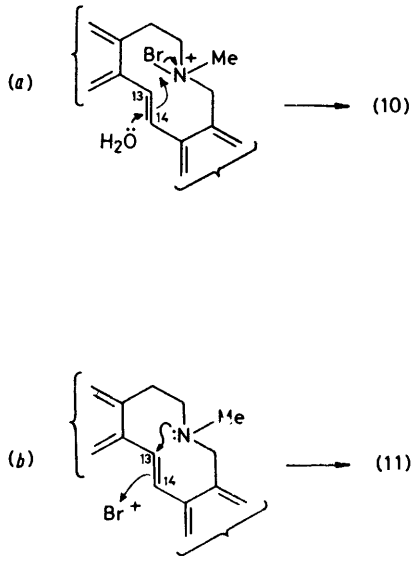


(11) (12)



(13) (14)

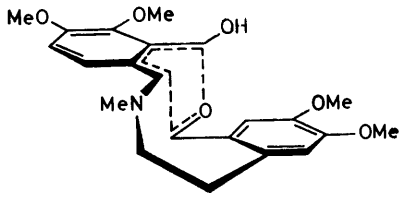


SCHEME 2

This modified procedure, involving treatment of the amino-olefin (7) with *N*-bromosuccinimide and an excess of 1N-HCl, stirring for 16 h at 25 °C, and subsequent basification, afforded the diol in yields varying between 60 and 70%. The ^{1}H n.m.r. spectrum of the material (m.p. 139—141 °C) contained signals at δ 5.17 (1 H, d, *J* 2 Hz) and 5.40 (1 H, d, *J* 2 Hz) and the i.r. spectrum a strong band at 3 490 cm^{-1}. Although the assumption of initial non-regiospecific *trans* addition of elements of HOBr can be safely made, the stereochemistry of the resulting diol is difficult to predict because of the solvolytic conditions that generated it. Inspection of molecular models shows that a relatively strain-free arrangement exists in which the two hydroxy-groups are oriented *cis* (dihedral angle *ca.* 50°). The diol (13), in 1N-H_2SO_4, was rapidly and quantitatively cleaved at 0—5 °C by periodic acid to the dialdehyde (14) which exhibited two singlets at δ 10.4 and 10.1, due to the two aldehyde protons, in its ^{1}H n.m.r. spectrum.

With the dialdehyde (14) in hand we were in a position to attempt the double ring-closure (rings B and D) that could lead directly to the rhoeadine skeleton. The dialdehyde (14) contains two benzylic positions having acidic hydrogens, further activated by an *ortho*-aldehyde group. Although the benzylic carbanion α to the nitrogen atom should be thermodynamically less stable, in relation to the other position (carbon marked †), nevertheless base-catalysed cyclisation was attempted. Treatment of the dialdehyde with potassium t-butoxide in dimethyl sulphoxide or lithium tetramethylpiperidide in tetrahydrofuran resulted in the appearance of the red colour of the benzyl anion, but no product corresponding to the rhoeadine skeleton could be detected in the reaction mixture under a variety of conditions. Primary and/or secondary *o*-alkylbenzaldehydes are known to generate dienols on photolysis by intramolecular 1,5-hydrogen abstraction and the dienols have been trapped with suitable dienophiles either intra- or inter-molecularly.[8] However, it has also been well established that triplet states of ketones and aldehydes are quenched by charge-transfer interactions with amines.[9] Wagner [10] has recently described the importance of protic solvents in decreasing charge-transfer processes in γ-aminoketones and the role of such protic solvents in catalysing the rearrangement of exciplexes into 1,4-diradicals which are the species responsible for generating dienols in *o*-alkyl aromatic compounds. In the case of the dialdehyde (14) it was expected that a regioselective, if not a regiospecific, formation of the 1,4-diradical (17) would occur because of the additional stabilisation offered by the α-nitrogen.

Intermolecular capture of a dienol by an aromatic aldehyde group has been reported by Tchir [11] in the photolysis of *o*-tolualdehyde. Considering these and anticipating that intramolecular (4s + 2s) *endo*-cyclisation (16) involving the *E*-dienol (Scheme 1) would lead directly to (±)-*cis*-alpinigenine and *exo*-addition (15) to the thermodynamically less stable [3] (±)-alpinigenine, the γ-aminobenzylaldehyde (14) was photolysed (37 °C) in degassed t-butyl alcohol. A rapid photoreaction occurred (2.5—3 h). From among at least seven photoproducts (t.l.c.) that were formed, (±)-*cis*-alpinigenine (m.p. 180—182 °C) was isolated in 20—30% yield, by evaporating the solvent, purifying the residue over a column of alumina, and crystallising from ethyl acetate. The t.l.c. properties and i.r. spectrum ($CHCl_3$) were identical with those of (+)-*cis*-alpinigenine and the ^{1}H n.m.r. spectrum with that of the (±)-*cis*-alkaloid. From the mother-liquor, by careful column and preparative layer chromatography, (±)-alpinigenine was isolated in 1% yield, identical with the natural product (i.r. and ^{1}H n.m.r. spectra and t.l.c.).



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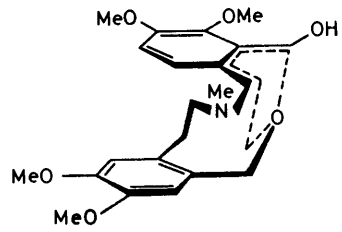

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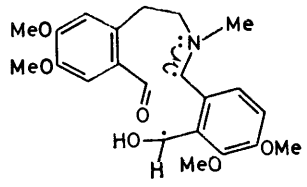

(17)

EXPERIMENTAL

U.v. spectra were recorded for solutions in cyclohexane on a Perkin-Elmer 124 instrument and ^{1}H n.m.r. spectra

were recorded for solutions in deuteriochloroform, unless otherwise stated, with tetramethylsilane as internal standard on a JEOL JNM-PS-100 or a Brüker CXP 300-MHz spectrometer. I.r. spectra were recorded on a Perkin-Elmer 457 instrument. Melting points were determined with a Kofler hot-stage apparatus. T.l.c. was carried out on silica gel (GF_{254}) (0.5-mm layer for preparative work). Microanalyses were performed at Alfred Bernhardt's Mikroanalytisches Laboratorium, W. Germany.

cis- *and* trans-2,3,11,12-*Tetramethoxy*-7-*methyl*-5,6,7,8,13,13a-*hexahydrodibenzo*[a,g]*quinolizinium Iodides* (5a *and* 6a).—2,3,11,12-Tetramethoxy-5,6,7,8,13,13a-hexahydrodibenzo[*a*,*g*]quinolizine [4] (4) (7.5 g) and methyl iodide (12 ml) in acetone (225 ml) were refluxed (1 h), then cooled in an ice-bath (½ h) and the crystals were collected by filtration. The mixture of cis- and trans-*methiodides* (10.5 g) m.p. 232—245 °C (decomp.), was used as such for the ensuing reaction. A small amount of the above sample was crystallised twice from ethanol (95%) to afford the pure trans-*methiodide* (5a), m.p. 254 °C (decomp.), δ[$(CD_3)_2SO$] 2.81 (Found: C, 53.2; H, 5.7; N, 2.7. $C_{22}H_{28}INO_4$ requires C, 53.1; H, 5.6; N, 2.8%). Evaporation of the original filtrate yielded a sticky solid which was crystallised from ethanol (95%) to give crystals (3.81 g), m.p. 237—242 °C (decomp.). On crystallisation thrice from ethanol (95%), the same solid (50 mg) yielded the pure *cis* isomer (6a) (20 mg), m.p. 248—249 °C (decomp.), δ[$(CD_3)_2SO$] 3.20 (Found: C, 53.1; H, 5.7; N, 2.75. $C_{22}H_{28}INO_4$ requires C, 53.1; H, 5.6; N, 2.8%). In a separate experiment, the residue, obtained after treatment with methyl iodide and evaporation of acetone, was washed with anhydrous ether and dried. The ^1H n.m.r. spectrum of the crude product exhibited NMe singlets at δ 3.2 and 2.8 (relative ratio by integration 2 : 3).

trans-1,2,10,11-*Tetramethoxy*-6-*methyl*-5,6,7,8-*tetrahydrodibenz*[c,g]*azecine* (7).—The above iodides (10.5 g) in hot methanol (400 ml) were cooled in an ice-bath while hydrogen chloride was bubbled through the solution. After saturation (*ca.* 3 h) the mixture was refluxed gently (30 min) and then the solvent removed under reduced pressure. The solid was washed with anhydrous ether and dried to give the methochlorides (5b) and (6b) (8.2 g) which were dissolved in distilled water (400 ml) and filtered from a small amount of insoluble material. The filtrate [7] was run through a column of IRA-400 resin (58 g) [which had been previously treated with 10% sodium hydroxide (1 100 ml) and washed with an equal volume of distilled water]. The eluate was collected in an atmosphere free of carbon dioxide. The column was then washed with distilled water (750 ml) and the combined fractions were evaporated under reduced presure [12] (*ca.* 40 mmHg) at 95 °C. The residue was maintained at 95 °C for a further 0.5 h and then dried under high vacuum (2 h). The solid was extracted thrice with hot ethyl acetate (dried over anhydrous K_2CO_3) (170 ml), and the extract was concentrated under reduced pressure, treated with n-hexane (40 ml), and cooled to give crystals of the *stilbene* (7). Recrystallisation (from ethyl acetate) afforded the trans-*azecine* (4.5 g). Recrystallisation (from benzene–n-hexane) provided a pure sample, m.p. 142—143 °C, $\lambda_{max.}$ 286 nm (ε 11 900), δ 6.92 (2 H, q, J_{AB} 16 Hz, *trans*-CH=CH–), 2.7 (4 H, s, 7- and 8-H), 2.2 (3 H, s, NMe), and 3.5 (2 H, s, 5-H) (Found: C, 71.7; H, 7.4; N, 3.7. $C_{22}H_{27}NO_4$ requires C, 71.55; H, 7.3; N, 3.8%). Evaporation of the mother-liquor, chromatography of the residue on silica gel, and elution with chloroform–ethanol (0.6%, v/v) afforded the styrene (8) as an oil (13%). The derived *methiodide* prepared in the usual manner had m.p. 209—212 °C (decomp.) (from methanol–diethyl ether) (Found: C, 52.2; H, 5.7; N, 2.55. $C_{23}H_{30}INO_4 \cdot H_2O$ requires C, 52.2; H, 6.05; N, 2.65%).

1,2,10,11-*Tetramethoxy*-6-*methyl*-5,6,7,8,13,14-*hexahydrodibenzo*[c,g]*azecine*-13,14-*diol* (13).—The *trans*-stilbene (7) (1.05 g) in hydrochloric acid (1N; 15 ml) was cooled in an ice-bath and a suspension of finely powdered *N*-bromosuccinimide (660 mg) in ice–water (90 ml) was added with stirring (40 min). The mixture was stirred overnight. The resulting solution was adjusted to pH 9 with 3N-sodium hydroxide, the product was extracted with chloroform (4 × 30 ml), and the combined extracts were washed with saturated brine and dried ($MgSO_4$). Evaporation of the solvent gave the crude *diol* (13) which was purified by filtration through a short column of alumina using chloroform–ethanol (1%) as eluant. Crystallisation (from chloroform–diethyl ether–n-hexane) yielded needles of the diol (688 mg), m.p. 139—141 °C, $\nu_{max.}$ (Nujol) 3 490 cm^{-1}, δ 2.2 (3 H, s, NMe), 5.17 (1 H, d, *J* 2 Hz), and 5.40 (1 H, d, *J* 2 Hz) (Found: C, 65.55; H, 7.3; N, 3.55. $C_{22}H_{29}NO_6$ requires C, 65.5; H, 7.1; N, 3.5%).

N-(2-*Formyl*-3,4-*dimethoxybenzyl*)-N-(2-*formyl*-4,5-*dimethoxyphenethyl*)*methylamine* (14).—The diol (13) (290 mg) in dilute sulphuric acid (1N; 1.5 ml) was cooled in an ice-bath and treated with periodic acid (260 mg) in water (2.6 ml). The reaction was complete in 10 min (t.l.c. control). The solution was neutralised with 3N-sodium hydroxide and the product was extracted with ethyl acetate (5 × 5 ml), washed with water, and dried ($MgSO_4$). Evaporation of the solvent yielded the *dialdehyde* (14) as an oil (280 mg), $\nu_{max.}$ (film) 2 800 and 1 690 cm^{-1}, δ 10.4 (1 H, s) and 10.1 (1 H, s). The derived *methiodide*, prepared in the usual manner, had m.p. 196—198 °C (decomp.) (from methanol–*NN*-dimethylformamide), δ[$(CD_3)_2SO$] 10.46 (1 H, s), 10.1 (1 H, s), 4.96 (2 H, s, $ArCH_2NMe_2$), 3.00 [6 H, s, $-\overset{+}{N}(CH_3)_2$] (Found: C, 50.75; H, 5.6; N, 2.5. $C_{23}H_{30}INO_6$ requires C, 50.8; H, 5.55; N, 2.6%).

(a) (+)-cis-*Alpinigenine* (2).—The dialdehyde (14) [from the diol (13), 500 mg] was dissolved in dry t-butyl alcohol (180 ml) in a Pyrex flask, dry nitrogen was bubbled through the solution (½ h), and the solution was then photolysed (3.5 h, t.l.c. control), using a Phillips HPR-125 lamp as the external source of radiation. The internal temperature was maintained at 37 °C by means of external cooling. The solvent was evaporated under reduced pressure, the brown residue was freed completely from the solvent by dissolving it in benzene and evaporating to dryness, the process being repeated twice. The residue was redissolved in the minimum amount of hot benzene and decanted from insoluble material. Removal of solvent and crystallisation of the remaining solid (from ethyl acetate–diethyl ether–n-hexane) yielded brown crystals (187 mg) which consisted essentially of (±)-*cis*-alpinigenine. Further crystallisation (from ethyl acetate) afforded needles of the alkaloid with m.p. 176—179 °C. An additional quantity (23 mg) could be isolated from the mother-liquor by preparative t.l.c. [benzene–chloroform–methanol (7 : 2 : 1 v/v/v)]. A portion of the material (m.p. 176—179 °C) was chromatographed on a short column of alumina and eluted with chloroform–diethyl ether–n-hexane (3 : 2 : 5 v/v/v). Evaporation of the eluate and crystallisation afforded needles of (±)-*cis*-alpinigenine, m.p. 180—182 °C (lit.,[13] 183—184 °C). The

i.r. spectrum was identical with an authentic sample of (+)-*cis*-alpinigenine and the ^{1}H n.m.r. spectrum ($CDCl_3$) with a spectrum of (±)-*cis*-alpinigenine.[13] The t.l.c. properties of the active and racemic compounds were identical on different solvent systems. Both samples developed at the same rate the characteristic red colour on the chromatoplates on spraying with concentrated sulphuric acid.

(b) *Isolation of* (±)-*Alpinigenine* (3).—The dialdehyde (14) [from the diol (13), 868.5 mg] in t-butyl alcohol (300 ml) was photolysed as above. The residue was chromatographed was on neutral alumina (30 g) and eluted with n-hexane–dichloromethane–diethyl ether (5 : 3 : 2 v/v/v). Fractions containing the isomer (2) were combined, evaporated, and crystallised to give (±)-*cis*-alpinigenine, m.p. 180—181 °C (from benzene–diethyl ether). The column was eluted with dichloromethane–methanol (5% v/v). Evaporation and crystallisation (from benzene–diethyl ether) of the dark residue, in the presence of Norit, provided an additional amount of (2). The mother-liquors from the above two crystallisations were evaporated and re-chromatographed on alumina using the same solvent system. Fractions (10 ml each) were examined after evaporation of the eluate by ^{1}H n.m.r. (100 MHz) for (±)-alpinigenine, and those containing the characteristic doublets [3] at δ 5.80 (1 H, *J* 9 Hz, 1-H) and 4.03 (1 H, *J* 9 Hz, 2-H), were combined and evaporated and the residue was repurified by preparative t.l.c. (benzene–acetone 9 : 2 v/v). Three developments separated traces of the *cis* isomer from the *trans*, possessing a higher R_F value. Extraction of the band corresponding to (3) with ethyl acetate, and crystallisation from the same solvent, provided needles of (±)-alpinigenine (3) (8.5 mg, 1%), m.p. 168—169 °C (lit.,[14] 172—173 °C). The ^{1}H n.m.r. (300 MHz) and the i.r. ($CHCl_3$) spectra were identical with those of the natural product, as were also the t.l.c. properties in three different solvent systems [ethyl acetate–n-hexane (5 : 7v/v), 3 developments; benzene–acetone (5 : 1 v/v), 4 developments; benzene–acetone–methanol (7 : 2 : 1 v/v)].

We thank the Foundation Calouste Gulbenkian and the Instituto Nacional de Investigação Científica for financial support (to I. M. C. O. and M. R. T. respectively), Junta Nacional de Investigação Científica e Tecnológica for a grant, Prof. H. Rönsch for a sample of (+)-*cis*-alpinigenine and (+)-alpinigenine, and Prof. R. Rodrigo for copies of ^{1}H n.m.r. and i.r. spectra of (±)-*cis*-alpinigenine.

[0/1097 *Received*, 11*th July*, 1980]

REFERENCES

[1] M. Shamma, ' The Isoquinoline Alkaloids,' Academic Press, New York, 1972, p. 399.
[2] F. Santavy, J. L. Kaul, L. Hruban, L. Dolejs, V. Hanus, R. Bláha, and A. D. Cross, *Coll. Czech. Chem. Commun.*, 1965, **35**, 3479 and 3712; J. Hrbek, jun., F. Santavy, and L. Dolejs, *ibid.*, 1970, **35**, 3712; F. Santavy, J. Hrbek, jun., and K. Bláha, *ibid.*, 1967, **32**, 4452.
[3] H. Rönsch, A. Guggisberg, M. Hesse, and H. Schmid, *Helv. Chim. Acta*, 1977, **60**, 2402.
[4] E. Späth and E. Mosettig, *Liebigs Ann. Chem.*, 1923, **433**, 138; S. Chakravarti and M. Swaminathan, *J. Indian Chem. Soc.*, 1934, **11**, 107.
[5] T. Kametani, A. Ujiie, Shyh-Pyng Huang, M. Ihara, and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 1977, 394.
[6] A. P. Phillips and R. Baltzly, *J. Am. Chem. Soc.*, 1952, **74**, 5231.
[7] P. B. Russel, *J. Am. Chem. Soc.*, 1956, **78**, 3115.
[8] P. G. Sammes, *Tetrahedron*, 1976, **32**, 405.
[9] S. G. Cohen, A. Parola, and G. H. Parsons, *Chem. Rev.*, 1973, **73**, 141.
[10] P. J. Wagner, A. E. Kemppainen, and T. Jellink, *J. Am. Chem. Soc.*, 1972, **94**, 7512; P. J. Wagner and D. A. Ersfeld, *ibid.*, 1976, **98**, 4515.
[11] D. M. Findlay and M. F. Tchir, *J. Chem. Soc., Chem. Commun.*, 1974, 514.
[12] F. L. Pyman, *J. Chem. Soc.*, 1913, **103**, 817.
[13] K. Orito, R. H. Manske, and R. Rodrigo, *J. Am. Chem. Soc.*, 1974, **96**, 1944.
[14] H. Irie, S. Tani, and H. Yamane, *J. Chem. Soc., Perkin Trans. 1*, 1972, 2986.