Studies on the Synthesis of Heterocyclic Compounds. Part 698.† An Alternative Protoberberine Synthesis; Total Synthesis of (±)-Xylopinine, (±)-Schefferine, (±)-Nandinine, (±)-Corydaline, and (±)-Thalictricavine

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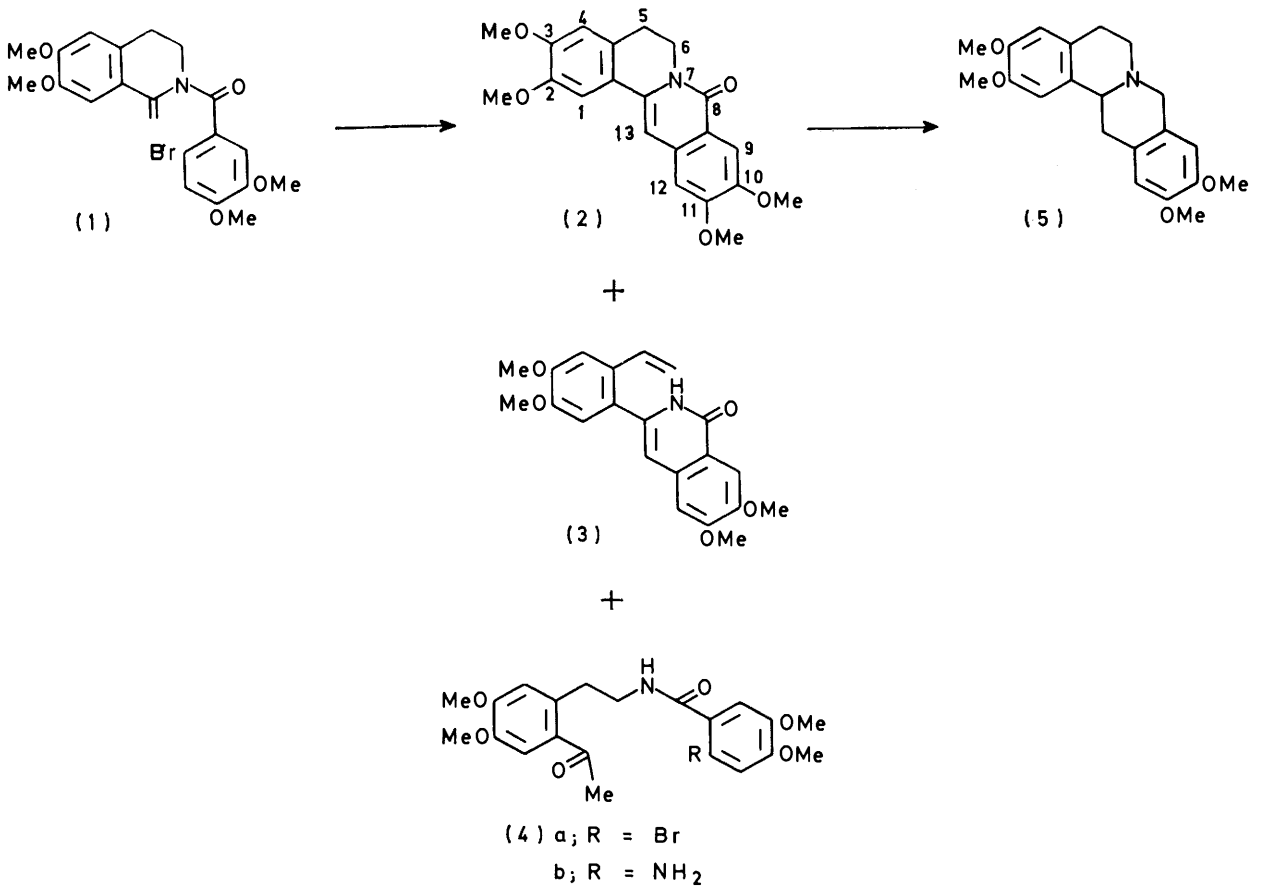
9,10-Disubstituted protoberberines were synthesised by photolysis of the corresponding bromo-enamides in high yields. The products were converted into (±)-xylopinine, (±)-schefferine, (±)-nandinine, (±)-corydaline, and (±)-thalictricavine. Xylopinine was also synthesised, together with the corresponding styrene derivative, from the corresponding enamide under benzyne reaction conditions.

In syntheses of alkaloids, both photochemical reactions and benzyne reactions have played an important role, and the starting materials for these reactions are as often as not the same. We have already reported total syntheses of isoquinoline alkaloids by application of these reactions, from the same starting material, *e.g.* the synthesis of the aporphine alkaloid domesticine[1,2] and the morphinandienone alkaloid amurine.[1-3]

As an extension of this work, we have synthesised the protoberberine alkaloid (±)-xylopinine from the bromo-enamide (1), prepared in 70—80% yield by treating 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (8a) with 2-bromo-4,5-dimethoxybenzoyl chloride in the presence of triethylamine in benzene. Treatment of the bromo-enamide (1) with sodium amide in liquid ammonia gave three compounds, which were separated by column chromatography on silica gel.



The first, obtained in 15% yield was the known didehydrotetramethoxy-8-oxoberbine (2), which was also synthesised by photolysis of the bromo-enamide (1), in 80% yield. Thus, irradiation of a solution of the bromo-enamide (1) in benzene with a high-pressure mercury

† Part 697, T. Kametani, T. Higa, C. Van Loe, M. Ihara, and K. Fukumoto, *Heterocycles*, 1977, **6**, 255.

[1] T. Kametani, S. Shibuya, H. Sugi, O. Kusama, and K. Fukumoto, *J. Chem. Soc.* (*C*), 1971, 2446.

[2] T. Kametani, S. Shibuya, K. Kigasawa, M. Hiiragi, and O. Kusama, *J. Chem. Soc.* (*C*), 1971, 2712.

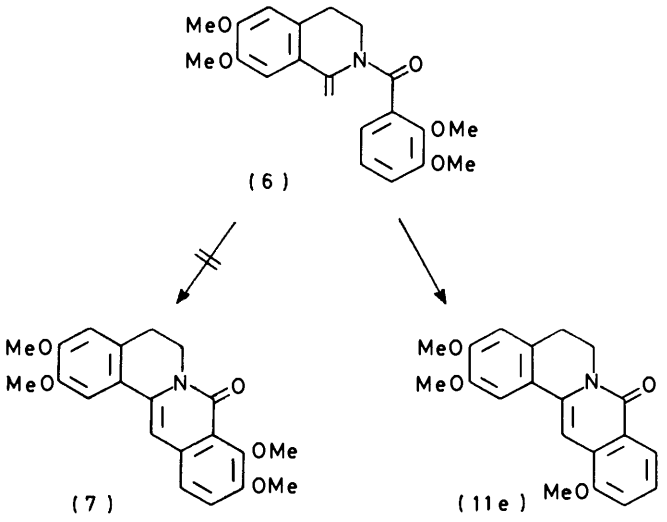
[3] T. Kametani, A. Ujiie, K. Takahashi, T. Nakano, T. Suzuki, and K. Fukumoto, *Chem. and Pharm. Bull.* (*Japan*), 1973, **21**, 766.

lamp equipped with Pyrex filter at room temperature for 3 h afforded the 8-oxoberbine (2) together with the hydrolysis product (4a). Treatment of the lactam (2) with phosphoryl chloride afforded the quaternary chloride, which was reduced with sodium borohydride in methanol to give (±)-xylopinine (5), identical with an authentic sample.[4,†]

The second product showed an ABX system characteristic of a styrene (δ 5.28, 5.66, and 6.76) in its n.m.r. spectrum, and its i.r. spectrum revealed the presence of a secondary amide group ($\nu_{max.}$ 3 400, 1 630, and 1 605 cm^{-1}). It was identified as the styrene derivative (3), formed by a Hofmann-like elimination reaction of compound (2).[5] This bond cleavage suggested the possibility of a biogenetic transformation from a protoberberine alkaloid to a benzophenanthridine alkaloid.[6,7]

The third product contained an acetophenone-type carbonyl group ($\nu_{max.}$ 1 660 cm^{-1}) and a secondary amide group (3 350 and 1 635 cm^{-1}) and showed an acetophenone methyl signal at δ 2.56 in its n.m.r. spectrum. These data indicated the structure (4b) of a hydrolysis product.

It has been reported that irradiation of the enamide (6) did not lead to the 8-oxoberbine (7), with the natural oxygenation pattern, but to a demethoxy-8-oxoberbine (11e).[8] We have investigated the regioselectivity of the



synthesis of protoberberine alkaloids from the corresponding bromo-enamides by photocyclisation. The bromo-enamide (10a) was prepared from 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (8a) and 6-bromo-2,3-dimethoxybenzoyl chloride (9b) in the usual manner.[9] Irradiation in benzene solution for 5 h afforded the 9-bromo-8-oxoberbine (11a) as the major product together with the hydrolysis product (12a). On the other hand, irradiation in methanol for 5 h gave the 8-oxoberbine (11c) with the natural oxygenation pattern in 65% yield, the 12-methoxyberbine (11e) in 20% yield, and small amounts of (11a) and (12a). The lactam (11c) was reduced with lithium aluminium hydride and then sodium borohydride to give (±)-schefferine (13a), identical with an authentic sample.[10]

Similarly, irradiation of the enamide (10b) in benzene for 5 h gave the 9-bromo-12-methoxyberbine (11b) and the hydrolysis product (12b), whereas the reaction in methanol afforded the 8-oxoberbine (11d), the 12-methoxyberbines (11b) and (11f), and the hydrolysis product (12b) in the ratio *ca.* 4 : 2 : 1 : 1, respectively. The 8-oxoberbine (12b) was reduced to (±)-nandinine (13b), identical with an authentic specimen.[11] In the photocyclisation of the bromo-enamides (10a—d), 9-*O*-demethylation (berbine numbering) occurred selectively.

This photocyclisation of bromo-enamides was then applied successfully to the synthesis of 13-methylprotoberberine alkaloids. Photolysis of the bromo-enamide (10c), prepared from 1-ethyl-3,4-dihydro-6,7-dimethoxyisoquinoline (8c) and the benzoyl chloride (9b), in benzene for 5 h afforded the 8-oxoberbine (11g), the 9-bromo-8-oxoberbine (11i), and the hydrolysis product (12c) in the ratio 2 : 2 : 1; the reaction in methanol for 5 h gave the 8-oxoberbine (11g) as the only cyclisation product in 60% yield. This lactam was reduced with lithium aluminium hydride and then sodium borohydride to give the phenolic berbine (14a), which showed Bohlmann i.r. bands at 2 950—2 750 cm^{-1} and showed an axial proton signal at δ 4.26 (*J* 16 Hz).[12] Treatment of the phenolic base with diazomethane afforded (±)-corydaline (14c), m.p. 139—141° (lit.,[13] 139—141°).

Similarly, irradiation of the enamide (10d) in methanol for 5 h afforded the 8-oxoberbine (11h), the 9-bromo-12-methoxyberbine (11j), and the hydrolysis product (12d) in the ratio of 3 : 2 : 1. The 8-oxoberbine (11h) was converted into (±)-thalictricavine (14d) [14] by reduction followed by methylation.

When the cyclisation site was blocked by substituent groups, elimination occurred in the sequence OMe > Br > H, in accord with electron-releasing effects; [15] the reaction probably proceeds as shown in the Scheme.[16]

† (±)-Xylopinine [(±)-norcoralydine] occurs in two forms: granules, m.p. 145—145.5 °C and prisms, m.p. 155 °C (T. Kametani and M. Ihara, *J. Pharm. Soc. Japan*, 1967, **87**, 174).

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[6] F. von Buchhausen and H. W. Bersch, *Ber.*, 1930, **63**, 2520.
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[9] I. Ninomiya, T. Naito, and H. Takasugi, *J.C.S. Perkin I*, 1975, 1720, 1791.
[10] T. Kametani, M. Ihara, and T. Honda, *Chem. Comm.*, 1969, 1301; *J. Chem. Soc.* (*C*), 1970, 1060.
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[12] C. K. Yu, D. B. MacLean, R. G. A. Rodrigo, and R. H. F. Manske, *Canad. J. Chem.*, 1970, **48**, 3673.
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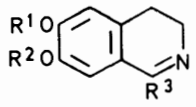
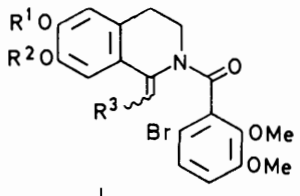
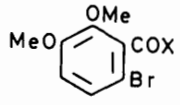
[15] C. K. Ingold, ' Structure and Mechanism in Organic Chemistry,' Cornell University Press, Ithaca, 1969.
[16] A. Gilbert, ' Photochemistry,' vol. 6, Chem. Soc. Specialist Periodical Report, 1975, p. 483.



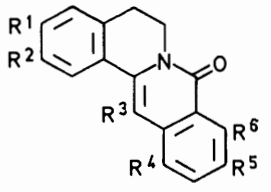
(8) a; $R^1 = R^2 = R^3 = Me$
b; $R^1R^2 = CH_2$, $R^3 = Me$
c; $R^1 = R^2 = Me$, $R^3 = Et$
d; $R^1R^2 = CH_2$, $R^3 = Et$

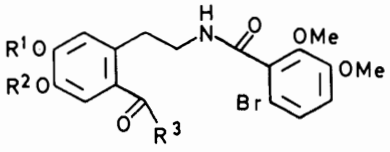


(10) a; $R^1 = R^2 = Me$, $R^3 = H$
b; $R^1R^2 = CH_2$, $R^3 = H$
c; $R^1 = R^2 = R^3 = Me$
d; $R^1R^2 = CH_2$, $R^3 = Me$



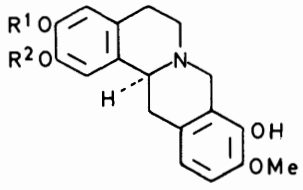
(9) a; X = OH
b; X = Cl



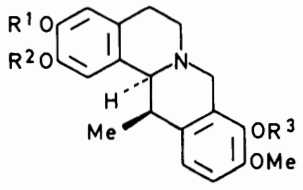


(12) a; $R^1 = R^2 = R^3 = Me$
b; $R^1R^2 = CH_2$, $R^3 = Me$
c; $R^1 = R^2 = Me$, $R^3 = Et$
d; $R^1R^2 = CH_2$, $R^3 = Et$

(11) a; $R^1 = R^2 = R^4 = OMe$, $R^3 = R^5 = H$, $R^6 = Br$
b; $R^1R^2 = CH_2$, $R^3 = R^5 = H$, $R^4 = OMe$, $R^6 = Br$
c; $R^1 = R^2 = R^5 = OMe$, $R^3 = R^4 = H$, $R^6 = OH$
d; $R^1R^2 = CH_2$, $R^3 = R^4 = H$, $R^5 = OMe$, $R^6 = OH$
e; $R^1 = R^2 = R^4 = OMe$, $R^3 = R^5 = R^6 = H$
f; $R^1R^2 = CH_2$, $R^4 = OMe$, $R^3 = R^5 = R^6 = H$
g; $R^1 = R^2 = R^5 = OMe$, $R^3 = Me$, $R^4 = H$, $R^6 = OH$
h; $R^1R^2 = CH_2$, $R^3 = Me$, $R^5 = OMe$, $R^4 = H$, $R^6 = OH$
i; $R^1 = R^2 = R^4 = OMe$, $R^3 = Me$, $R^5 = H$, $R^6 = Br$
j; $R^1R^2 = CH_2$, $R^3 = Me$, $R^4 = OMe$, $R^5 = H$, $R^6 = Br$



(13) a; $R^1 = R^2 = Me$
b; $R^1R^2 = CH_2$

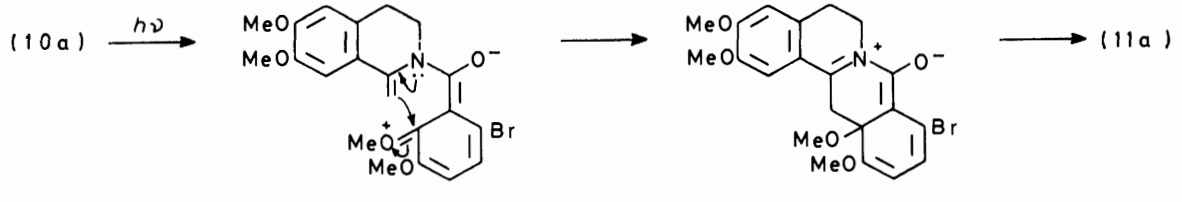


(14) a; $R^1 = R^2 = Me$, $R^3 = H$
b; $R^1R^2 = CH_2$, $R^3 = H$
c; $R^1 = R^2 = R^3 = Me$
d $R^1R^2 = CH_2$, $R^3 = Me$

EXPERIMENTAL

M.p.s were measured with a Yanagimoto microapparatus, i.r. spectra with a Hitachi EPI-3 recording spectrophotometer, and n.m.r. spectra with a JEOL JNM–PMX 60 spectrometer.

General Procedure for Irradiation of the Enamides.—A solution of the enamide (2 g) in methanol (or benzene) was irradiated for 5 h with a Riko 400 W mercury lamp equipped with Pyrex filter at room temperature. The solvent was evaporated off and the residue was chromatographed on silica gel (50 g) with benzene and benzene–ethyl acetate as eluants. The m.p.s and yields of the products are shown in the Table.



SCHEME

The bromo-enamides (1) and (10a—d) were prepared according to Ninomiya's methods; [9] their m.p.s are given in the Table but they were too unstable for micro-analysis.

Reaction of the Enamide (1) *with Sodium Amide.*—A solution of the enamide (1) (2.0 g) and sodium amide [from sodium (0.8 g)] in liquid ammonia (500 ml) was stirred at −33 °C for 3 h. The solvent was removed and the residue treated with an excess of crystalline ammonium chloride and extracted with chloroform. The extract was washed with saturated ammonium chloride solution and water, dried (Na_2SO_4), and evaporated. The resulting gum was chromatographed on silica gel (40 g). Elution with benzene (fractions 2—5; each 100 ml) gave the lactam (2) as needles (240 mg, 15%), m.p. 192—194° (lit.,[8] 196.5—198°; lit.,[9] 187—188°) (from methanol), $\nu_{max.}$ ($CHCl_3$) 1 640, 1 605, and 1 585 cm^{-1}, δ ($CDCl_3$) 2.90 (2 H, t, *J* 5 Hz, 5-H_2), 3.88 (3 H, s, OMe), 3.96 (9 H, s, 3 × OMe), 4.35 (2 H, t, *J* 5 Hz, 6-H_2), and 6.70, 6.87, 6.92, 7.18, and 7.65 (each 1 H, s, ArH and 13-H). Elution with benzene–ethyl acetate (9 : 1 v/v) (fractions 7—11; each 100 ml) gave 3-(*4,5-dimethoxy-2-vinylphenyl*)-*6,7-dimethoxyisoquinolin*-1(2H)-*one* (3) as needles (570 mg, 35%), m.p. 197—200° (from methanol) (Found: C, 68.45; H, 5.9; N, 3.6. $C_{21}H_{21}NO_5$ requires C, 68.65; H, 5.75; N, 3.8%), $\nu_{max.}$ ($CHCl_3$) 3 400, 1 630, and 1 605 cm^{-1}, δ ($CDCl_3$) 3.89, 3.94, 3.98, and 4.03 (each 3 H, s, 4 × OMe), 5.28 (1 H, q, *J* 2 and 11 Hz, :C*H*H *trans* to Ar), 5.66 (1 H, q, *J* 2 and 17 Hz, :CH*H cis* to Ar), 6.76 (1 H, dd, *J* 11 and 17 Hz, C*H*=CH_2), and 6.42, 6.93, 6.99, 7.13, and 7.78 (each 1 H, s, ArH and 13-H). Elution with benzene–ethyl acetate (8 : 2 v/v) (fractions 14—19; each 100 ml) gave N-(*2-acetyl-4,5-dimethoxyphenethyl*)-*2-amino-4,5-dimethoxybenzamide* (4b) as needles (720 mg, 40%), m.p. 148—150° (from methanol) (Found: C, 62.65; H, 6.7; N, 6.95. $C_{21}H_{26}N_2O_6$ requires C, 62.65; H, 6.5; N, 6.95%), $\nu_{max.}$ ($CHCl_3$) 3 350, 1 660, and 1 635 cm^{-1}, δ ($CDCl_3$) 2.56 (3 H, s, CO·CH_3), 3.17 (2 H, t, *J* 6 Hz, ArCH_2·CH_2), 3.67 (2 H, t, *J* 6 Hz, CH_2·CH_2·NH), 3.83 (6 H, s, 2 × OMe), 3.92 (6 H, s, 2 × OMe), and 6.10, 6.76, 6.86, and 7.12 (each 1 H, s, ArH).

(±)-*Xylopinine* (5).—A mixture of the lactam (2) (95 mg) and phosphoryl chloride (3 ml) was refluxed for 2 h, then evaporated. The residue was dissolved in methanol (20 ml) under nitrogen and sodium borohydride (30 mg) was added in small portions with stirring at 0 °C. After stirring at the same temperature for 30 min, the solution was evaporated and the residue was extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give (±)-xylopinine (5) (70 mg, 80%) as needles, m.p. 144—145° (lit.,[4] 144—145°) (from methanol–ether), identical with an authentic specimen.

(±)-*Schefferine* (13a).—A mixture of the lactam (11c) (200 mg), lithium aluminium hydride (500 mg), and tetrahydrofuran (50 ml) was refluxed for 3 h with stirring. After cooling to 0 °C, the excess of hydride was decomposed with water, and the resulting mixture was filtered through Celite. To the filtrate was added sodium borohydride (1 g) in portions with stirring at room temperature, and the mixture was stirred for 1 h at the same temperature. The solvent was distilled off and the residue was extracted with chloroform; the extract was washed with water, dried (Na_2SO_4), and evaporated to give a pale yellowish solid, recrystallisation of which afforded (±)-schefferine [10] (13a) (126 mg, 65%), m.p. 147—148° (lit.,[10] 147—148°) (from methanol), identical with an authentic sample.

(±)-*Nandinine* (13b).—Reduction of the lactam (11d) (150 mg) in the same manner as above gave (±)-nandinine (13b) (99 mg, 68%) as needles, m.p. 184—186° (lit.,[11] 183—185°) (from ethanol), identical with an authentic sample.

6-Bromo-2,3-dimethoxybenzoic Acid (9a).—To a stirred solution of 2,3-dimethoxybenzoic acid (5 g) in acetic acid (100 ml) was added bromine (5.3 g) in acetic acid (10 ml) dropwise at room temperature. After stirring for 3 h, the mixture was poured into water, and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated to leave the acid (9a) (6 g, 81%), m.p. 83—85° (lit.,[17] 83—85°) (from benzene–n-hexane), identical with an authentic specimen, $\nu_{max.}$ ($CHCl_3$) 1 725 cm^{-1}, δ ($CDCl_3$) 3.83 (3 H, s, OMe), 3.86 (3 H, s, OMe), 6.80 (1 H, d, *J* 9 Hz, ArH), and 7.26 (1 H, d, *J* 9 Hz, ArH).

Compound *	Yield (%)	M.p. (°C) (solvent)	Compound *	Yield (%)	M.p. (°C) (solvent)
(1)	80	224—226 (MeOH)	(11f)	25	218—220 (MeOH)
(10a)	80	199—202 (benzene–ether)	(11g)	60	236—238 (EtOH)
(10b)	85	161—163	(11h)	55	209—211 (MeOH)
(10c)	80	162—163 (benzene–n-hexane)	(11i)	40	142—143 (MeOH)
(10d)	85	145—147.5 (ether–n-hexane)	(11j)	55	194—196 (MeOH)
(11a)	63	198—200 (MeOH)	(12a)	11	179—180 (MeOH)
(11b)	72	267—269 (MeOH)	(12b)	10	155—157 (MeOH)
(11c)	65	176—178 (MeOH)	(12c)	16	150—151 (EtOH)
(11d)	60		(12d)	15	219—220 (MeOH)
(11e)	20	218—220 (MeOH) (lit.,[8] 219—220°)	(4a)	12	183—183 (MeOH)

* I.r. and n.m.r. data for compounds (1) and (10a—d) and n.m.r. data and microanalyses for compounds (11a—j), (12a—d), and (4a) are listed in Supplementary Publication No. SUP 22011 (6 pp.). For details see Notice to Authors No. 7, *J.C.S. Perkin I*, 1976, Index issue.

9-*De*-O-*methylcorydaline* (14a).—Reduction of the lactam (11g) (500 mg) as in the case of (±)-schefferine (13a) afforded 9-*de*-O-*methylcorydaline* (14a) (360 mg, 74%) as prisms, m.p. 192—193° (from methanol) (Found: C, 71.0; H, 7.05; N, 3.45. $C_{21}H_{25}NO_4$ requires C, 70.95; H, 7.1; N, 3.95%), $\nu_{max.}$ ($CHCl_3$) 3 550 and 2 950—2 750 cm^{-1} (Bohlmann bands), δ ($CDCl_3$) 0.98 (3 H, d, *J* 7 Hz, *C*-Me), 3.50 (1 H, d, *J* 16 Hz, 8-H), 3.88 (9 H, s, 3 × OMe), 4.26 (1 H, d, *J* 16 Hz, 8-H), 6.61 (1 H, s, ArH), 6.72 (1 H, s, ArH), and 6.75 (2 H, s, 2 × ArH).

9-*De*-O-*methylthalictricavine* (14b).—Reduction of the lactam (11h) (500 mg) as above gave 9-*de*-O-*methylthalictricavine* (14b) (343 mg, 71%) as needles, m.p. 180—182° (from methanol) (Found: C, 69.5; H, 5.95; N, 4.0. $C_{20}H_{21}NO_4$,-0.5H_2O requires C, 68.95; H, 6.35; N, 4.0%), $\nu_{max.}$ ($CHCl_3$) 3 550 and 2 950—2 750 cm^{-1} (Bohlmann bands), δ ($CDCl_3$) 0.93 (3H, d, *J* 7 Hz, *C*-Me), 3.46 (3 H, d, *J* 7 Hz, 8-H), 5.92 (2H, s, O·CH_2·O), 6.56 (1 H, s, ArH), and 6.72 (2 H, s, 2 × ArH).

(±)-*Corydaline* (14c).—To a solution of 9-de-*O*-methylcorydaline (14a) (50 mg) in methanol (5 ml) was added an excess of diazomethane [from *N*-methyl-*N*-nitrosotoluene-*p*-sulphonamide (5 g)] in ether (50 ml) and the mixture was

[17] T. Kametani, T. Honda, H. Inoue, and K. Fukumoto, *Heterocycles*, 1975, **3**, 1091.

kept at room temperature for 18 h. Removal of the solvent and the excess of diazomethane left a pale yellow solid, which was recrystallised to give (±)-corydaline (14c) (38 mg, 73%) as needles, m.p. 139—141° (from ethanol), $\nu_{max.}$ ($CHCl_3$) 2 950—2 750 cm^{-1} (Bohlmann bands), δ ($CDCl_3$) 0.93 (3 H, d, *J* 7 Hz, *C*-Me), 3.46 (1 H, d, *J* 16 Hz, 8-H), 3.86 (12 H, s, 4 × OMe), 4.20 (1 H, d, *J* 16 Hz, 8-H), 6.58 (1 H, s, ArH), 6.66 (1 H, s, ArH), and 6.79 (2 H, s, 2 × ArH).

(±)-*Thalictricavine* (14d).—Methylation of the phenolic base (14b) (50 mg) as above gave (±)-thalictricavine (14d) (32 mg, 61%) as needles, m.p. 149° (lit.,[14] 149°) (from chloroform–methanol), $\nu_{max.}$ ($CHCl_3$) 2 950—2 750 cm^{-1} (Bohlmann bands), δ ($CDCl_3$) 0.97 (3 H, d, *J* 7 Hz, *C*-Me), 3.50 (1 H, d, *J* 16 Hz, 8-H), 3.86 (6 H, s, 2 × OMe), 4.23 (1 H, d, *J* 16 Hz, 8-H), 5.89 (2 H, s, $O{\cdot}CH_2{\cdot}O$), 6.55 (1 H, s, ArH), 6.64 (1 H, s, ArH), and 6.81 (2 H, s, 2 × ArH), identical with an authentic sample provided by Dr. Y. Kondo.

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