Studies on the Syntheses of Heterocyclic Compounds. Part DCL.† Total Synthesis of Corytenchirine

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(±)-Corytenchirine [*rac*-(8); 11-hydroxy-2,3,10-trimethoxy-8α-methyl-13aα*H*-berbine], isolated from *Corydalis ochotensis*, has been synthesised by two methods: (i) irradiation of the (*Z*)-1-benzylidenetetrahydroisoquinoline (3), derived from 1-(3-benzyloxy-4-methoxybenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (1), followed by reduction of the resulting dibenzoquinolizinylium salt (5) and debenzylation; and (ii) a Mannich reaction of 1,2,3,4-tetrahydro-1-(3-hydroxy-4-methoxybenzyl)-6,7-dimethoxyisoquinoline (18) with acetaldehyde. The 2,3,11-trimethoxy-isomer [*rac*-(10)] was also synthesised by the photochemical method. The stereochemistry of corytenchirine-type compounds is discussed.

FROM *Corydalis ochotensis* (Turez) in Taiwan, we isolated a molecular complex (base D) composed of (−)-corytenchirine (8) and (−)-corytenchine (17).[1] Corytenchirine was the first 8-methylberbine to be isolated from natural sources, and was tentatively assigned the structure (8). The relative stereochemistry at C-8 and C-13a was determined by the comparison of *O*-methylcorytenchirine (11) with coralydine (16),‡ but the possibility of the positionally isomeric structure (10) could not be excluded. The structure (8) has now been confirmed by synthesis *via* two different routes.

Condensation of 1-(3-benzyloxy-4-methoxybenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (1) [2a] with acetic anhydride in pyridine gave, in 94% yield, the 1-benzylidenetetrahydroisoquinoline (3), whose n.m.r. spectrum (solvent $CDCl_3$) showed the acetyl signal at δ 1.73 as singlet, indicating considerable shielding by the benzylidene phenyl group. Thus the product (3) was the *Z*-isomer. The enamide (3) was then irradiated with a high-pressure mercury lamp (450 W; Vycor filter) in the presence of hydriodic acid [3] in methanol–dioxan to afford the 8-methyldibenzoquinolizinylium iodide (5) in 56% yield. Reduction of the salt (5) with sodium borohydride, followed by preparative t.l.c. on silica gel, gave two stereoisomers of the 8-methylberbine in the ratio of 1 : 3. The stereochemistry of the former [*rac*-(7)] was shown to be the same as that of *O*-methylcorytenchirine (11) on the basis of i.r. ($CHCl_3$) (no absorption at 2 700—2 800 cm^{-1}) and n.m.r. [δ($CDCl_3$) 1.40 (3 H, d, *J* 6.5 Hz, 8-Me), 4.07 (1 H, q, *J* 6.5 Hz, 8-H), and 4.11 (1 H, dd, *J* 4 and 10 Hz, 13a-H)] data; the latter compound [*rac*-(12)] [$\nu_{max.}$($CHCl_3$) 2 700—2 800 cm^{-1} (*trans*-quinolizidine bands); δ($CDCl_3$) 1.54 (3 H, d, *J* 6.5 Hz, 8-Me)] had the same relative configuration as coralydine [*rac*-(16)]. The former product [*rac*-(7)] was debenzylated by refluxing with ethanolic hydrochloric acid; the product [*rac*-(8)] was identified as the racemate of corytenchirine as follows. The i.r. ($CHCl_3$) and n.m.r. (δ in $CDCl_3$) spectra of an equimolecular mixture of the synthetic material and (±)-corytenchine [*rac*-(17)] were identical with those of base D.

We eventually succeeded separating base D by high-pressure liquid chromatography to afford corytenchine (17) and corytenchirine (8), whose i.r. and n.m.r. spectra and h.p.l.c. behaviour were identical with those of the synthetic samples. Debenzylation of (12) yielded the stereoisomer (13) of corytenchirine.

The positional isomer (10) was synthesised according to the same procedure from 1-(4-benzyloxy-3-methoxybenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (2).[2b] Acetylation, followed by irradiation of the enamide (4) and a reduction of the resulting quaternary salt (6), furnished two stereoisomers, *rac*-(9) and *rac*-(14). Debenzylation gave the phenolic berbines, *rac*-(10) and *rac*-(15), respectively. The i.r. and n.m.r. spectra and t.l.c. behaviour of *rac*-(10) were different from those of corytenchirine (8).

The second synthesis of corytenchirine (8) was carried out by an intramolecular Mannich reaction of 1,2,3,4-tetrahydro-1-(3-hydroxy-4-methoxybenzyl)-6,7-dimethoxyisoquinoline (18) [2a] hydrochloride with acetaldehyde in hot acetic acid, which, interestingly, afforded corytenchirine [*rac*-(8)] as a main product in 45% yield and the stereoisomer [*rac*-(13)] in 10% yield, together with a trace of the 9,10-substituted berbines [*rac*-(20) and -(21)]. On the other hand, the berbine derivatives could not be obtained by a Mannich reaction of the 4-hydroxy-3-methoxybenzylisoquinoline (19) hydrochloride under the same conditions.

All the compounds of the corytenchirine series, having the protons at C-8 and C-13a *trans* to each other, showed no *trans*-quinolizidine bands in their i.r. spectra ($CHCl_3$) and the n.m.r. signal of the angular 13a-proton to low field of δ 4.11 (in $CDCl_3$), indicating a *cis*-quinolizidine form. The coralydine series, with *cis*-protons at C-8 and C-13a, exhibited *trans*-quinolizidine bands at 2 700—2 800 cm^{-1} and the 13a-proton signal to high field of δ 3.8. We have recently shown ^{13}C n.m.r. spectroscopy to be useful for determination of the

† Part DCXLIX, T. Kametani, T. Honda, T. Sugai, and K. Fukumoto, *Heterocycles*, 1976, **4**, 927.

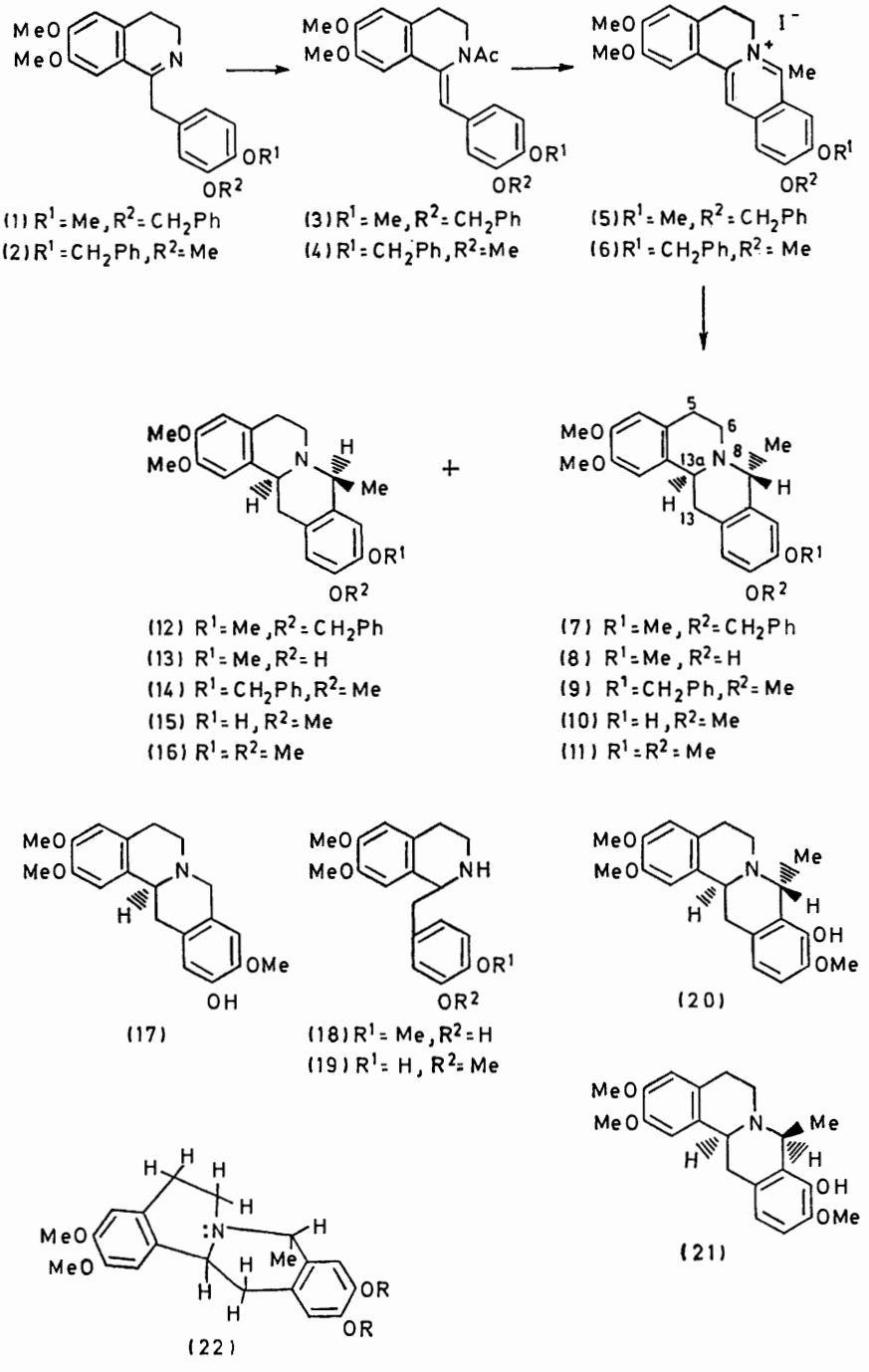
‡ Brossi and his co-workers have recently synthesised optically active *O*-methylcorytenchirine (11) from optically active tetrahydropapaverines, and shown the absolute configuration at C-13a position of (−)-corytenchirine, previously reported as *S* by us, to be correct (H. Bruderer, J. Metzger, and A. Brossi, *Helv. Chim. Acta*, 1975, **58**, 1719); we thank them for this information.

[1] S.-T. Lu, T.-L. Su, T. Kametani, A. Ujiie, M. Ihara, and K. Fukumoto, *J.C.S. Perkin I*, 1976, 63.

[2] (*a*) T. Kametani, K. Nyu, S. Ikeda, T. Tominaga, and R. Iwashiro, *J. Pharm. Soc. Japan*, 1973, **93**, 1120; (*b*) T. Kametani, K. Nyu, S. Ikeda, T. Tominaga, and R. Iwashiro, *ibid.*, p. 1116.

[3] G. R. Lenz and N. C. Yang, *Chem. Comm.*, 1967, 1136.

preferred conformation of berbine alkaloids having substituents only on aromatic rings.[4] The γ-effect was also a powerful aid in the conformational analysis of methyl carbon atom in *O*-methylcorytenchirine (11) indicates one form (22) of two possible *cis*-conformations,[4] in which rings B and C assume a half-chair form.



8-methylberbines. The assignments of sp^3 carbon signals of *O*-methylcorytenchirine (11), coralydine (16), and the *O*-benzyl derivative (14) are summarised in the Table. Unusual shielding of C-6, C-13a, and the C-8

[4] T. Kametani, A. Ujiie, M. Ihara, K. Fukumoto, and M. Koizumi, *Heterocycles*, 1975, **3**, 371; *J. Org. Chem.*, 1975, **40**, 3280.

EXPERIMENTAL

I.r. and u.v. spectra were taken with Hitachi 215 and Hitachi 124 recording spectrometers, respectively. N.m.r. spectra were measured with JNM-PMX-60 (60 MHz) and JNM-PS-100 (100 MHz) instruments (for solutions in deuteriochloroform with tetramethylsilane as internal standard). Mass spectra were measured with a Hitachi

RMU-7 mass spectrometer. High pressure liquid chromatography (h.p.l.c.) was carried out with a Water Associates ALC/GDC202/R401 instrument (6000 pumping system).

Carbon-13 chemical shifts of sp^3 carbon atoms of *O*-methylcorytenchirine (11), coralydine (16), and the *O*-benzyl derivative (14) (δ_C in p.p.m. from Me_4Si)

	(11)	(16)	(14)
C-5	29.2	29.1	29.6
C-6	46.8	46.7	46.9
C-8	58.8	58.9 *	58.9
C-13	35.3	36.0	36.7
C-13a	50.0	58.6 *	58.9
C(8)Me	17.7	21.3	21.7
OMe	55.4	55.4 and 55.6	55.9
OCH_2Ph			71.6

* Assignments may be reversed.

(Z)-2-*Acetyl*-1-(3-*benzyloxy*-4-*methoxybenzylidene*)-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (3).—A mixture of the 3,4-dihydroisoquinoline (1) [2a] hydrochloride (2 g), acetic anhydride (5 ml), and pyridine (5 ml) was heated on a water-bath for 3 h; the solution was then evaporated to dryness and the resulting solid was recrystallised from methanol to give (3) (1.9 g) as *needles*, m.p. 185—186° (Found: C, 72.8; H, 6.4; N, 2.9. $C_{28}H_{29}NO_5$ requires C, 73.2; H, 6.35; N, 3.05%), $\lambda_{max.}$(MeOH) 332 nm (log ε 4.63), δ($CDCl_3$) 1.73 (3 H, s, COMe), 3.83, 3.85, and 3.91 (each 3 H, s, 3 × OMe), 5.15 (2 H, s, O·CH_2Ph), 6.57—7.3 (6 H, m, 5 × ArH and :CH), and 7.35br (5 H, s, Ph).

(Z)-2-*Acetyl*-1-(4-*benzyloxy*-3-*methoxybenzylidene*)-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (4).—The 3,4-dihydroisoquinoline (2) [2b] hydrochloride (2 g) was similarly treated with acetic anhydride (5 ml) in pyridine (5 ml) to give (4) (1.8 g) as *prisms*, m.p. 203—204° (from ethanol) (Found: C, 72.8; H, 6.35; N, 2.85%), $\lambda_{max.}$(MeOH) 332 nm (log ε 4.55), δ($CDCl_3$) 1.73 (3 H, s, COMe), 3.84 (6 H) and 3.91 (3 H) (each s, 3 × OMe), 5.11 (2 H, s, O·CH_2Ph), 6.57, 6.65, 6.87, 6.92, 7.04, 7.07 (each 1 H, each s, 5 × ArH and :CH), and 7.32br (5 H, s, Ph).

11-*Benzyloxy*-5,6-*dihydro*-2,3,10-*trimethoxy*-8-*methyldibenzo*[a,g]*quinolizinylium Iodide* (5).—A mixture of the enamide (3) (1 g), methanol (400 ml), dioxan (350 ml), and hydriodic acid (0.3 ml) was irradiated under nitrogen with a 450 W Hanovia high-pressure mercury lamp enclosed in a Vycor well for 2 h. The resulting yellow crystals were collected to afford the 8-*methyldibenzoquinolizinylium iodide* (5) (700 mg), m.p. 251—253° (decomp.) (from methanol) (Found: C, 58.95; H, 5.25; N, 2.15. $C_{28}H_{28}INO_4$ requires C, 59.05; H, 4.95; N, 2.45%), $\lambda_{max.}$(MeOH) 383 (log ε 3.94), 339 (4.34), 308sh (4.56), 287 (4.72), and 266 nm (4.42).

10-*Benzyloxy*-5,6-*dihydro*-2,3,11-*trimethoxy*-8-*methyldibenzo*[a,g]*quinolizinylium Iodide* (6).—A mixture of the enamide (4) (1 g), methanol (400 ml), dioxan (350 ml), and hydriodic acid (0.3 ml) was irradiated similarly to give the 8-*methyldibenzoquinolizinylium iodide* (6) (700 mg), m.p. 255—256° (decomp.) (from methanol) (Found: C, 58.9; H, 5.0; N, 2.3%), $\lambda_{max.}$(MeOH) 383 (log ε 4.0), 339 (4.43), 308sh (4.54), 287 (4.8), and 266 nm (4.48).

(±)-11-*Benzyloxy*-2,3,10-*trimethoxy*-8α-*methyl*-13aα*H*-*berbine* [rac-(7)] *and its* 8β-*Methyl Isomer* [rac-(12)].—To a stirred suspension of the salt (5) (500 mg) in methanol (150 ml) sodium borohydride (500 mg) was added in small portions with cooling, and the mixture was stirred for 24 h. The solvent was then removed and the residue was diluted with water and extracted with chloroform. The extract was washed with water, dried (K_2CO_3), and evaporated to leave a syrup; recrystallisation from methanol gave the 8β-methyl isomer [*rac*-(12)] (150 mg). The methanolic mother liquor was evaporated and the residue subjected to preparative t.l.c. on silica gel (Kieselgel HF_{254}) in ethyl acetate–n-hexane (1 : 1) (two developments). The zone of lower R_F value was extracted with chloroform–methanol (9 : 1) to give a syrup; purification from chloroform–n-hexane gave the 8α-*methyl isomer* [rac-(7)] (85 mg), m.p. 122—126° (Found: C, 74.1; H, 7.2; N, 3.25. $C_{28}H_{31}NO_4$,0.5H_2O requires C, 74.0; H, 7.1; N, 3.1%), δ($CDCl_3$) 1.40 (3 H, d, *J* 6.5 Hz, 8-Me), 3.87 (9 H, s, 3 × OMe), 4.07 (1 H, q, *J* 6.5 Hz, 8-H), 4.11 (1 H, dd, *J* 4 and 10 Hz, 13a-H), 5.13 (2 H, s, O·CH_2Ph), 6.62 (3 H) and 6.67 (1 H) (each s, 4 × ArH), and 7.37br (5 H, s, Ph). The zone of higher R_F value was extracted with chloroform–methanol (9 : 1) to give the 8β-*methyl isomer* [rac-(12)] (100 mg) (total yield 250 mg) as needles, m.p. 126—127° (from methanol) (Found: C, 75.35; H, 7.1; N, 3.4. $C_{28}H_{31}NO_4$ requires C, 75.5; H, 7.0; N, 3.15%), $\nu_{max.}$($CHCl_3$) 2 800—2 700 cm^{-1} (*trans*-quinolizidine), δ($CDCl_3$) 1.54 (3 H, d, *J* 6.5 Hz, 8-Me), 3.86 (9 H, s, 3 × OMe), 5.13 (2 H, s, O·CH_2Ph), 6.60 (1 H), 6.68 (1 H), and 6.70 (2 H) (each s, 4 × ArH), and 7.35br (5 H, s, Ph).

(±)-10-*Benzyloxy*-2,3,11-*trimethoxy*-8α-*methyl*-13aα*H*-*berbine* [rac-(9)] *and its* 8β-*Methyl Isomer* [rac-(14)].—The salt (6) (500 mg) was reduced with sodium borohydride (500 mg) in methanol (150 mg) for 24 h at room temperature and the product was worked up as above to leave a syrup. Recrystallisation from methanol gave the 8β-methyl isomer [rac-(14)] (140 mg). The methanolic mother liquor was evaporated and the residue subjected to preparative t.l.c. on silica gel (Kieselger HF_{254}) in ethyl acetate–n-hexane (1 : 1) (two developments). The zone of lower R_F value gave the 8α-*methyl isomer* [rac-(9)] (90 mg) as prisms, m.p. 158—159° (from methanol) (Found: C, 75.2; H, 7.05; N, 2.9%), δ($CDCl_3$) 1.30 (3 H, d, *J* 6.5 Hz, 8-Me), 3.87 (6 H), and 3.89 (3 H) (each s, 3 × OMe), 4.06 (1 H, q, *J* 6.5 Hz, 8-H), 4.22 (1 H, dd, *J* 4 and 10 Hz, 13a-H), 5.14 (2 H, s, O·CH_2Ph), 6.63 (3 H) and 6.71 (1 H) (each s, 4 × ArH), and 7.4br (5 H, s, Ph). The zone of the higher R_F value afforded the 8β-*methyl isomer* [rac-(14)] (100 mg) (total yield 240 mg) as needles, m.p. 139—140° (from methanol) (Found: C, 75.2; H, 7.1; N, 2.9%), $\nu_{max.}$($CHCl_3$) 2 800—2 700 cm^{-1} (*trans*-quinolizidine), δ($CDCl_3$) 1.43 (3 H, d, *J* 6.5 Hz, 8-Me), 3.83 (9 H, s, 3 × OMe), 5.10 (2 H, s, O·CH_2Ph), 6.58, 6.65, 6.67, and 6.71 (each 1 H, each s, 4 × ArH), and 7.36br (5 H, s, Ph).

(±)-2,3,10-*Trimethoxy*-8α-*methyl*-13aα*H*-*berbin*-11-*ol* [(±)-*Corytenchirine*] [rac-(8)].—A mixture of the benzyl ether (7) (50 mg) and concentrated hydrochloric acid (5 ml) in ethanol (5 ml) was refluxed on a water-bath for 3 h. The solvent was removed under reduced pressure and the residue was basified with 10% ammonia and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to afford (±)-*corytenchirine* [rac-(8)] (35 mg) as prisms, m.p. 203—205° (from methanol) (Found: C, 70.75; H, 7.15; N, 3.85. $C_{21}H_{25}NO_4$ requires C, 70.95; H, 7.1; N, 3.95%), whose i.r. [$\nu_{max.}$($CHCl_3$) 3 550 cm^{-1} (OH)] and n.m.r. [δ($CDCl_3$) 1.40 (3 H, d, *J* 6.5 Hz, 8-Me), 3.87 (6 H) and 3.89 (3 H) (each s, 3 × OMe), 4.06 (1 H, q, *J* 6.5 Hz, 8-H), 4.21 (1 H, dd, *J* 4 and 10 Hz, 13a-H), and 6.53, 6.59, 6.63, and 6.67 (each 1 H, each s, 4 × ArH)] spectra, and chromatographic behaviour (t.l.c.

and h.p.l.c.) were identical with those of natural corytenchirine.

(±)-2,3,11-*Trimethoxy*-8α-*methyl*-13aαH-*berbin*-10-*ol* [rac-(10)].—The benzyloxyberbine (9) (50 mg) was debenzylated with concentrated hydrochloric acid (5 ml) in ethanol (5 ml) and the product worked up as above to give the 8α-*methylberbin*-10-*ol* [rac-(10)] (35 mg) as prisms, m.p. 231—233° (from methanol) (Found: C, 70.85; H, 7.3; N, 3.75. $C_{21}H_{25}NO_4$ requires C, 70.95; H, 7.1; N, 3.95%), $\nu_{max.}$($CHCl_3$) 3 550 cm^{-1} (OH), δ($CDCl_3$) 1.40 (3 H, d, *J* 6.5 Hz, 8-Me), 3.88, 3.91, and 3.92 (each 3 H, each s, 3 × OMe), 4.09 (1 H, q, *J* 6.5 Hz, 8-H), 4.24 (1 H, dd, *J* 4 and 10 Hz, 13a-H), and 6.59, 6.64, 6.68, and 6.72 (each 1 H, each s, 4 × ArH).

(±)-2,3,10-*Trimethoxy*-8β-*methyl*-13aαH-*berbin*-11-*ol* [rac-(13)].—The berbine [*rac*-(12)] (50 mg) was debenzylated as above to afford the 8β-*methylberbin*-11-*ol* [rac-(13)] (32 mg) as prisms, m.p. 164—166° (from ethanol) (Found: C, 70.7; H, 7.0; N, 3.85%), $\nu_{max.}$($CHCl_3$) 3 550 (OH) and 2 800—2 700 cm^{-1} (*trans*-quinolizidine), δ($CDCl_3$) 1.53 (3 H, d, *J* 6.5 Hz, 8-Me), 3.85 (3 H) and 3.87 (6 H) (each s, 3 × OMe), and 6.60, 6.64, 6.68, and 6.71 (each 1 H, each s, 4 × ArH).

(±)-2,3,11-*Trimethoxy*-8β-*methyl*-13aαH-*berbin*-10-*ol* [rac-(15)].—Debenzylation of the berbine [*rac*-(14)] (50 mg) as above gave the 8β-*methylberbin*-10-*ol* [rac-(15)] (30 mg) as needles, m.p. 119—121° (from methanol) (Found: C, 69.3; H, 7.4; N, 3.35. $C_{21}H_{25}NO_4$,0.5H_2O requires C, 69.2; H, 7.2; N, 3.85%), $\nu_{max.}$($CHCl_3$) 3 550 (OH) and 2 800—2 700 cm^{-1} (*trans*-quinolizidine), δ($CDCl_3$) 1.50 (3 H, d, *J* 6.5 Hz, 8-Me), 3.85 (9 H, s, 3 × OMe), and 6.60 (2 H) and 6.72 (2 H) (each s, 4 × ArH).

Mannich Reaction of 1,2,3,4-*Tetrahydro*-1-(3-*hydroxy*-4-*methoxybenzyl*)-6,7-*dimethoxyisoquinoline* (18).—A mixture of the phenolic tetrahydroisoquinoline (18) hydrochloride (100 mg) and 90% acetaldehyde (5 ml) in 99% acetic acid (10 ml) was refluxed at 100 °C for 3 h. The acetic acid was evaporated off and the residue was basified with ammonia and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to leave a gum. Preparative t.l.c. on silica gel (Kieselgel HF_{254}; ethyl acetate) gave four compounds, positive to Gibbs reagent. The zone of R_F 0.3 was extracted with chloroform–methanol (9 : 1) to give (±)-corytenchirine [*rac*-(8)] (45 mg) as prisms, m.p. 203—205° (from methanol), identical (i.r. and n.m.r. spectra) with the sample prepared by the above method. The zone of R_F 0.45 similarly furnished the 8β-methylberbin-11-ol [*rac*-(13)] (10 mg) as prisms, m.p. 164—166° (from ethanol), identical with the sample prepared by the above method. The zone of R_F 0.6 afforded the 8α-*methylberbin*-9-*ol* [rac-(20)] (15 mg) as prisms, m.p. 154—155° (from ethanol) (Found: C, 70.7; H, 7.35; N, 3.7. $C_{21}H_{25}NO_4$ requires C, 70.95; H, 7.1; N, 3.95%), $\nu_{max.}$($CHCl_3$) 3 540 cm^{-1}, δ($CDCl_3$) 1.40 (3 H, d, *J* 6.5 Hz, 8-Me), 3.85 (6 H) and 3.87 (3 H) (each s, 3 × OMe), 4.23 (1 H, dd, *J* 6 and 10 Hz, 13a-H), 4.37 (1 H, q, *J* 6.5 Hz, 8-H), and 6.62 (1 H), 6.66 (1 H), and 6.71 (2 H) (each s, 4 × ArH). The zone of R_F 0.7 gave 8β-*methylberbin*-9-*ol* [rac-(21)] (3 mg) as prisms, m.p. 191—192° (from ethanol), $\nu_{max.}$($CHCl_3$) 3 540 (OH) and 2 800—2 700 cm^{-1} (*trans*-quinolizidine), δ($CDCl_3$) 1.55 (3 H, d, *J* 6.5 Hz, 8-Me), 3.83 (9 H, s, 3 × OMe), and 6.58 (1 H), 6.67 (2 H), and 6.75 (1 H) (each s, 4 × ArH), *m/e* 355 (M^+), 340, 192, and 164.

Separation of Base D.—A methanolic solution of base D [1] (200 μl portions) was introduced to the h.p.l.c. instrument [column (1 ft × 1/4 in) packed with μ-Bondapak C_{18}]. Elution was carried out with methanol–water (3 : 1 v/v) at 1.5 ml min^{-1}. The faster running eluate (retention time 5.5 min) gave corytenchine (17), m.p. 257—258° (from methanol) (lit.,[1] 257—258°), identical [i.r. ($CHCl_3$) and n.m.r. ($CDCl_3$) spectra] with those of authentic material. The slower running eluate (retention time 12.0 min) afforded *corytenchirine* (8), m.p. 233—234° (from methanol) (Found: M^+, 355.1787. $C_{21}H_{25}NO_4$ requires *M*, 355.1784), identical [i.r. ($CHCl_3$) and n.m.r. ($CDCl_3$) spectra and chromatographic behaviour] with the synthetic compound [*rac*-(8)].

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