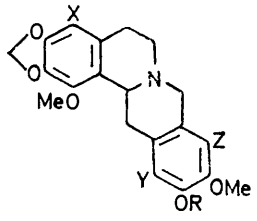
Total Synthesis of (±)-Mecambridine (1,10,11-Trimethoxy-2,3-methylenedioxyberbin-12-ylmethanol)

By **Tetsuji Kametani,* Akira Ujiie,** and **Keiichiro Fukumoto,** Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan

Hydroxymethylation of 1.10-dimethoxy-2.3-methylenedioxyberbin-11-ol (5). followed by *O*-methylation, gave (±)-mecambridine (2). thus confirming the suggested structure of the latter.

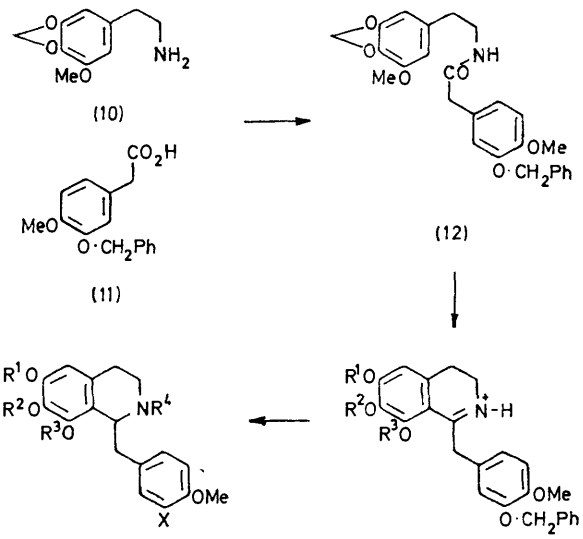
MECAMBRIDINE, an alkaloid isolated from *Meconopsis cambrica* by Slavík [1] and from *Papaver oreophilum* by Pfeifer,[2] was initially assigned structure (1) on the basis of spectral analysis and the results of chemical degradations.[3] Later, u.v. spectral analyses of the bismethine derivatives and of the product of dehydrogenation, and biogenetic considerations indicated that the structure (2) was more likely.[4-6] We report here the total synthesis of (±)-mecambridine, which confirms the structure (2).

Bischler–Napieralski cyclisation of the amide (12) [prepared by a fusion of 3-methoxy-4,5-methylenedioxyphenethylamine (10) [7] with 3-benzyloxy-4-methoxyphenylacetic acid (11) [8] at 180°] with phosphoryl chloride



	R	X	Y	Z
(1)	Me	H	H	CH_2·OH
(2)	Me	H	CH_2OH	H
(3)	CH_2Ph	H	H	H
(4)	CH_2Ph	CH_2OH	H	H
(5)	H	H	H	H
(6)	H	CH_2·OH	H	H
(7)a;	H	H	CH_2OH	H
b;	H	H	H	CH_2·OH
(8)	Ac	H	CH_2OAc	H
(9)	H	H	CHO	H

in refluxing dry benzene gave a mixture of 8-methoxy-6,7-methylenedioxy-3,4-dihydroisoquinoline hydrochloride (13a) and the 6-methoxy-7,8-methylenedioxy-isomer (13b) in the ratio 5 : 3 (by n.m.r. spectral analysis), which was separated by crystallisation of the hydrochlorides into needles (13b) and a syrup (13a). Bischler–Napieralski reactions of amides having three different



	R^1	R^2	R^3	R^4	X
(14)a;	CH_2		Me	H	O·CH_2Ph
b;	Me	CH_2		H	O·CH_2Ph
(15)	CH_2Ph	Me	Me	Me	H
(16)	Me	Me	H	Me	H

	R^1	R^2	R^3
(13)a;	CH_2		Me
b;	Me	CH_2	

alkoxy-groups are known to give mixtures of 3,4-dihydroisoquinolines.[9]

The reduction of both hydrochlorides with sodium borohydride gave the corresponding tetrahydroisoquinolines, which were characterised as their hydrochlorides (14a and b). Their structures were determined by n.m.r. spectral analysis: thus, the product (14a) showed MeO and O·CH_2·O signals at δ ($CDCl_3$) 3·98 and 5·83 as singlets, and the product (14b) revealed the corresponding resonances at δ 3·82 as a singlet and 5·92 as a distorted quartet. It has been reported that an 8-methoxy-group in 1-benzyl-1,2,3,4-tetrahydroisoquinolines is deshielded and resonates at *ca.* 3·95,[10,11] and that a methylenedioxy-function gives rise to two

[1] J. Slavík and L. Slavíková, *Coll. Czech. Chem. Comm.*, 1963, **28**, 1720.
[2] S. Pfeifer and I. Mann, *Pharmazie*, 1964, **19**, 786.
[3] S. Pfeifer, I. Mann, L. Dalejš, V. Hanus, and A. D. Cross, *Tetrahedron Letters*, 1967, 83.
[4] V. Preininger, V. Šimánek, and F. Šantavý, *Tetrahedron Letters*, 1969, 2109.
[5] V. Šimánek, V. Preininger, P. Sedemera, and F. Šantavý, *Coll. Czech. Chem. Comm.*, 1970, **35**, 1440.
[6] V. Preininger, L. Hruban, V. Šimánek, and F. Šantavý, *Coll. Czech. Chem. Comm.*, 1970, **35**, 124.
[7] K. Péter and B. Rezaö, *Magyar Kem. Folyóirat*, 1971, **77**, 655.
[8] W. W.-C. Chan and P. Maitland, *J. Chem. Soc.* (*C*), 1966, 753.
[9] T. Kametani, T. Kikuchi, and K. Fukumoto, *Chem. and Pharm. Bull.* (*Japan*), 1968, **16**, 1003.
[10] M. Tomita, T. Singu, K. Fujitani, and H. Furukawa, *Chem. and Pharm. Bull.* (*Japan*), 1965, **13**, 921.
[11] T. Kametani and K. Ohkubo, *Chem. and Pharm. Bull.* (*Japan*), 1968, **16**. 909.

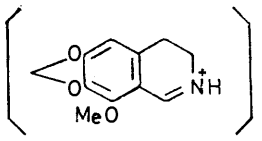
doublets (or a quartet) owing to a small difference in chemical shifts between the two non-equivalent protons when a bulky group is nearby.[12] Furthermore, the chemical shift of the methoxy-group in compound (14a) agrees well with that (δ 3·96) of the 8-methoxy-group in compound (15),[11] and the shift of the methoxy-group in compound (14b) corresponds to that (δ 3·81) of the 6-methoxy-group in compound (16).[13]

A Mannich reaction of the tetrahydroisoquinoline (14a) with 37% formalin and acetic acid at 100° for 2 h gave the berbine (3) [δ ($CDCl_3$) 6·27 (s, 4-H), 6·53br (2H, s, 9- and 12-H), which on hydroxymethylation with 37% formalin and formic acid[14,15] afforded the 4-hydroxymethylberbine (4), identified from its mass [*m/e* 475 (M^+), 240 (19), and 234 (18b)] and n.m.r. spectra [δ ($CDCl_3$–$(CD_3)_2SO$] 6·57 and 6·61 (9- and 12-H)]. Furthermore, a Mannich reaction of (14a) with the same reagents for a long time gave a mixture of the berbine (3) and its 4-hydroxymethyl derivative (4).

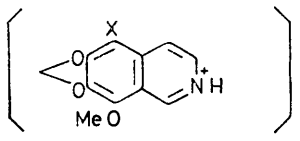
Debenzylation of the berbine (3) with ethanolic hydrochloric acid in the presence of zinc powder afforded the phenolic berbine (5) [$\nu_{max.}$ ($CHCl_3$) 3500 cm^{-1}, δ 6·29 (4-H), 6·49 (12-H), and 6·56 (9-H) (all singlets)]. Debenzylation in the absence of zinc powder gave (5) in poor yield. Hydroxymethylation of the phenol (5) with formalin and formic acid furnished a mixture of hydroxymethylberbines. The n.m.r. spectrum indicated that the main product was the 4-hydroxymethylberbine (6), but separation was not achieved.

It is known that the formation of the corresponding phenoxide anion enriches the electron density at the position *ortho* to a phenolic hydroxy-group, thus making electrophilic attack at this position more likely.[16] Therefore, hydroxymethylation of the phenol (5) in a strongly basic medium was examined; as expected, treatment with 37% formalin and N-sodium hydroxide[17] in methanol at room temperature for 24 h gave the 12-hydroxymethylberbine (7a). The mass spectrum of the product showed abundant ions at *m/e* 206 (17) and 204 (18a), which suggested the presence of a hydroxymethyl group in ring C or D and ruled out structure (6). The n.m.r. spectrum showed an aromatic proton signal at δ 6·46, shifted to 6·66 in the spectrum of the diacetyl compound (8). This difference (0·2 p.p.m.) is the same as that (0·19 p.p.m.) between the aromatic protons of 4-hydroxymethyldiscretine (20) (δ 6·67) and 4-acetoxymethyl-*O*-acetyldiscretine (21) (δ 6·86).

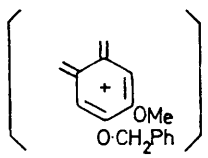
Oxidation of the hydroxymethyl derivative (7a) with manganese dioxide[16] gave the phenolic aromatic aldehyde (9), which showed phenolic hydroxy and carbonyl absorptions at 3420—3150 and 1635 cm^{-1}, respectively. This indicated that the phenolic hydroxy-function was *ortho* to the carbonyl group,[15] and this fact was confirmed by the observation of an aromatic proton n.m.r. signal at δ 6·46. Thus, the aromatic proton and hydroxymethyl group on ring D in the hydroxymethylation product (7a) are *meta* and *ortho* to the phenolic hydroxy-group, respectively, and structure (7b) is ruled out.



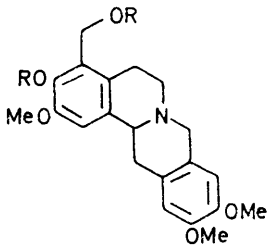
(17)



(18) a; X = H
b; X = CH_2OH



(19)



(20) R = H
(21) R = Ac

Methylation of (7a) with diazomethane gave (±)-mecambridine (2), identical [t.l.c. and i.r. ($CHCl_3$), mass, and n.m.r. ($CDCl_3$) spectra] with the natural base.

EXPERIMENTAL

M.p.s were determined with a Yanagimoto micro-apparatus. I.r. and u.v. spectra were taken with Hitachi 215 and Hitachi 124 recording spectrometers, respectively. Mass spectra were measured with a Hitachi RMU-7 spectrometer and n.m.r. spectra with a Hitachi R-20 spectrometer (for solution in deuteriochloroform with tetramethylsilane as internal standard).

2-(3-Benzyloxy-4-methoxyphenyl)-N-(3-methoxy-4,5-methylenedioxyphenylethyl)acetamide (12).—A mixture of 3-methoxy-4,5-methylenedioxyphenethylamine (10)[7] (9 g) and 3-benzyloxy-4-methoxyphenylacetic acid (9)[8] (12 g) was heated in an oil-bath at 180° for 1 h. The cooled mixture was recrystallised from benzene to give the *amide* (12) (14 g) as prisms, m.p. 126—127° (Found: C, 69·6; H, 6·25; N, 2·95. $C_{26}H_{27}NO_6$ requires C, 69·45; H, 6·05; N, 3·1%), $\nu_{max.}$ ($CHCl_3$) 3430 (NH) and 1660 cm^{-1} (C=O), δ ($CDCl_3$) 3·85 (3H) and 3·88 (3H) (each s, 2 × OCH_3), 5·09 (2H, s, O·C*H*$_2$Ph), 5·89 (2H, s, O·CH_2·O), 6·22 (2H) and 6·77br (3H) (each s, ArH), and 7·37 (5H, s, O·CH_2·C_6H_5).

8-Methoxy-6,7-methylenedioxy- (13a) *and 6-Methoxy-7,8-methylenedioxy-1-(3-benzyloxy-4-methoxybenzyl)-3,4-dihydroisoquinoline Hydrochloride* (13b).—A mixture of the amide (12) (10 g), phosphoryl chloride (10 ml), and dry benzene

[12] T. Kametani, H. Sugi, S. Shibuya, and K. Fukumoto, *Tetrahedron*, 1971, **27**, 5375.
[13] T. Kametani, K. Ohkubo, and I. Noguchi, *J. Chem. Soc.* (*C*), 1966, 715.
[14] T. Kametani, K. Fukumoto, T. Terui, K. Yamaki, and E. Taguchi. *J. Chem. Soc.* (*C*), 1971, 2709.
[15] T. Kametani, M. Takeshita, and S. Takano, *J.C.S. Perkin I*, 1972, 2834.
[16] N. Kornblum, R. Seltzer, and P. Haberfield, *J. Amer. Chem. Soc.*, 1963, **85**, 1148.
[17] O. Manasse, *Ber.*, 1894, **27**, 2409.

(300 ml) was refluxed for 2 h. The solvent was evaporated off and the residue was washed with n-hexane to give a brown syrup. The mixture of hydrochlorides was crystallised from ethanol to afford 6-*methoxy*-3,4-*dihydroisoquinoline hydrochloride* (13b) (2·5 g) as yellow needles, m.p. 165—167° (decomp.) (Found: C, 64·5; H, 5·85; N, 2·5. $C_{26}H_{26}ClNO_5$,-H_2O requires C, 64·25; H, 5·8; N, 2·9%), $\nu_{max.}$ ($CHCl_3$) 1628 cm^{-1} ($C{=}N^+$), $\lambda_{max.}$ (MeOH) 318 nm (log ε 4·24), *m/e* 431 (M^+ — HCl) and 340 (base peak).

Material from the ethanolic mother liquor gave the 8-methoxy-3,4-dihydroisoquinoline hydrochloride (13a) (7 g) as a viscous syrup, $\nu_{max.}$ ($CHCl_3$) 1641 cm^{-1} ($C{=}N^+$), $\lambda_{max.}$ (MeOH) 325 nm, *m/e* 431 (M^+ — HCl) and 340 (base peak). The *picrate* gave yellow needles, m.p. 179—181° (from ethanol) (Found: C, 58·1; H, 4·6; N, 8·2. $C_{32}H_{28}N_4O_{12}$ requires C, 58·2; H, 4·25; N, 8·5%).

1-(3-*Benzyloxy*-4-*methoxybenzyl*)-1,2,3,4-*tetrahydro*-8-*methoxy*-6,7-*methylenedioxyisoquinoline* (14a).—To a solution of the 8-methoxy-3,4-dihydroisoquinoline hydrochloride (13a) (7 g) in methanol (200 ml) was added sodium borohydride (4 g) in small portions with stirring and cooling in ice, and the resultant mixture was stirred for 0·5 h at room temperature, then heated under reflux (0·5 h). The solvent was evaporated off 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 the 8-methoxy-1,2,3,4-tetrahydroisoquinoline (14a) as a viscous syrup, δ ($CDCl_3$) 3·85 (3H) and 3·98 (3H) (each s, 2 × OCH_3), 5·21 (2H, s, O·CH_2Ph), 5·83 (2H, s, O·CH_2·O), 6·27 (1H, s, 5-H), 6·75br (3H, s, 2′-, 3′- and 6′-H), and 7·35br (5H, O·CH_2·C_6H_5). The *hydrochloride* (5 g) formed cubes, m.p. 199—202° (decomp.) (from ethanol) (Found: C, 66·25; H, 6·05; N, 3·0. $C_{26}H_{28}ClNO_5$ requires C, 66·45; H, 6·0; N, 3·0%), $\lambda_{max.}$ (MeOH) 283 nm (log ε 3·69).

1-(3-*Benzyloxy*-4-*methoxybenzyl*)-1,2,3,4-*tetrahydro*-6-*methoxy*-7,8-*methylenedioxyisoquinoline* (14b).—The same procedure was applied to the 6-methoxy-3,4-dihydroisoquinoline hydrochloride (13b) (2 g), methanol (100 ml), and sodium borohydride (1 g) to afford the 6-methoxy-1,2,3,4-tetrahydroisoquinoline (14b) as a viscous syrup, δ ($CDCl_3$) 3·82 (6H, s, 2 × OCH_3), 5·07 (2H, s, O·CH_2Ph), 5·92 (2H, distorted q, *J* 1 Hz, O·CH_2·O), 6·22 (1H, s, 5-H), 6·76br (3H, 2′-, 5′-, and 6′-H), and 7·31br (5H, O·CH_2·C_6H_5). The *hydrochloride* (1·5 g) afforded cubes, m.p. 180—182° (decomp.) (from ethanol) (Found: C, 65·35; H, 6·1; N, 2·8. $C_{26}H_{28}ClNO_5$,0·5H_2O requires C, 65·2; H, 6·1; N, 2·9%), $\lambda_{max.}$ (MeOH) 281 nm (log ε 3·66).

11-*Benzyloxy*-5,6,13,13a-*tetrahydro*-1,10-*dimethoxy*-2,3-*methylenedioxy*-8H-*dibenzo*[a,g]*quinolizine* (11-*Benzyloxy*-1,10-*dimethoxy*-2,3-*methylenedioxyberbine*) (3).—A mixture of the 8-methoxy-1,2,3,4-tetrahydroisoquinoline (14a) hydrochloride (1 g), 37% formalin (10 ml), and 99% acetic acid (10 ml) was heated on a water-bath for 2 h, cooled, basified with 10% sodium hydroxide, and extracted with chloroform. The extract was washed with water, dried (K_2CO_3), and evaporated to give the 1-*methoxyberbine* (3) (700 mg) as prisms, m.p. 145—146° (from ethanol) (Found: C, 72·55; H, 6·05; N, 3·15. $C_{27}H_{27}NO_5$ requires C, 72·8; H, 6·1; N, 3·15%), δ ($CDCl_3$) 3·80 (3H) and 3·92 (3H) (each s, 2 × OCH_3), 5·02 (2H, s, O·CH_2Ph), 5·79 (2H, s, O·CH_2·O), 6·27 (1H, s, 4-H), 6·53br (2H, s, 9- and 12-H), and 7·3br (5H, O·CH_2·C_6H_5).

Hydroxymethylation of the 1-*Methoxyberbine* (3).—A mixture of the 1-methoxyberbine (3) (20 mg), 37% formalin (1·5 ml), and 98% formic acid (1·5 ml) was heated on a water-bath for 4 h, cooled, basified with aqueous sodium hydrogen carbonate, and extracted with chloroform. The extract was washed with water, dried (K_2CO_3), and evaporated to afford the 4-hydroxymethyl-1-methoxyberbine (4) (10 mg) as a viscous syrup, δ [$CDCl_3$–$(CD_3)_2SO$] 3·74 (3H), and 3·92 (3H) (each s, 2 × OCH_3), 4·40br (2H, s, CH_2·OH) 4·97 (2H, s, O·CH_2Ph), 5·87 (2H, s, O·CH_2·O), 6·57 (1H) and 6·61 (1H) (each s, 9- and 12-H), and 7·32 (5H, s, O·CH_2·C_6H_5), *m/e* 475 (M^+), 240 (19), and 234 (18b).

5,6,13,13a-*Tetrahydro*-1,10-*dimethoxy*-2,3-*methylenedioxy*-8H-*dibenzo*[a,g]*quinolizin*-11-*ol* (5).—A mixture of the 1-methoxyberbine (3) (500 mg), concentrated hydrochloric acid (50 ml), zinc powder (50 mg), and ethanol (50 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 (K_2CO_3), and evaporated to afford the 1-*methoxyberbin*-11-*ol* (5) (270 mg) as needles m.p. 204—206° (from ethanol) (Found: C, 67·2; H, 6·0; N, 4·2. $C_{20}H_{21}NO_5$ requires C, 67·6; H, 5·95; N. 3·95%), $\nu_{max.}$ ($CHCl_3$) 3550 cm^{-1} (OH), δ ($CDCl_3$) 3·81 (3H) and 3·96 (3H) (each s, 2 × OCH_3), 5·83 (2H, s, O·CH_2·O), 6·29 (1H, s, 4-H), and 6·49 (1H) and 6·56 (1H) (each s, 9- and 12-H).

5,6,13,13a-*Tetrahydro*-11-*hydroxy*-1,10-*dimethoxy*-2,3-*methylenedioxy*-8H-*dibenzo*[a,g]*quinolizin*-12-*ylmethanol* (7a).—A mixture of the 1-methoxyberbin-11-ol (5) (50 mg), methanolic N-sodium hydroxide (5 ml), and 37% formalin (7·5 ml) was stirred at room temperature for 24 h, acidified with 10% hydrochloric acid, and then basified with 10% ammonia. The methanol was removed under reduced pressure and the aqueous residue was diluted with water and extracted with chloroform. The extract was washed with water, dried (K_2SO_3), and evaporated to leave a yellow syrup, which was subjected to thick-layer chromatography on silica gel (Wakogel B-5) in benzene–ethyl acetate–methanol (5 : 4 : 1 v/v). Material of R_F 0·23 was extracted with chloroform–methanol (9 : 1) to afford the *berbin*-12-*ylmethanol* (7a) (40 mg) as a pale yellow gum (Found: C, 65·3; H, 5·85; N, 3·75. $C_{21}H_{23}NO_6$ requires C, 65·45; H, 6·0; N, 3·65%), $\nu_{max.}$ ($CHCl_3$) 3550 cm^{-1} (OH), δ ($CDCl_3$) 3·80 (3H) and 3·95 (3H) (each s, 2 × OCH_3), 4·64 (2H, s, CH_2·OH), 5·85 (2H, s, O·CH_2·O), 6·31 (1H, s, 4-H), and 6·46 (1H, s, 9-H), *m/e* 385 (M^+), 206 (17), 204 (18a), and 164.

Acetylation of the 12-*Hydroxymethylberbine* (7a).—A mixture of compound (7a) (20 mg), acetic anhydride (0·2 ml), and pyridine (5 drops) was set aside overnight, poured into water, and basified with aqueous sodium hydrogen carbonate. The separated oil was extracted with chloroform and the extract was washed with water, dried (K_2CO_3), and evaporated to afford the *OO*-diacetyl derivative (8) as a brown syrup, $\nu_{max.}$ ($CHCl_3$) 1760 and 1735 cm^{-1}, δ ($CDCl_3$) 1·99 (3H) and 2·30 (3H) (each s, 2 × CH_3·CO), 3·78 (3H) and 3·97 (3H) (each s, 2 × OCH_3), 5·04 (2H, s, CH_2·OAc), 5·84 (2H, s, O·CH_2·O), 6·31 (1H, s, 4-H), and 6·66 (1H, s, 9-H).

Oxidation of the 12-*Hydroxymethylberbine* (7a).—A suspension of compound (7a) (100 mg) and manganese dioxide (400 mg) in chloroform (100 ml) was refluxed with stirring for 24 h, then filtered. The filtrate was washed with water, dried (K_2CO_3), and evaporated to give a brown solid, which was chromatographed on silica gel (5 g). Elution with chloroform–methanol (9 : 1 v/v) gave the 11-hydroxyberbine-12-carbaldehyde (9) (10 mg) as a brown syrup, $\nu_{max.}$ ($CHCl_3$) 1635 (CHO) and 3420—3150 cm^{-1} (hydrogen bond), δ ($CDCl_3$) 3·87 (3H), and 3·99 (3H) (each s, 2 × OCH_3), 5·88 (2H, s

O·CH_2·O), 6·35 (1H, s, 4-H), 6·75 (1H, s, 9-H), and 10·27 (1H, s, CHO).

(±)-*Mecambridine* (2).—To a solution of the berbin-12-ylmethanol (7a) (25 mg) in methanol (30 ml) was added ethereal diazomethane [prepared from *N*-methyl-*N*-nitroso-toluene-*p*-sulphonamide (5 g)]. The mixture was set aside overnight at room temperature. Removal of the solvent left a pale yellow syrup, which was subjected to thick-layer chromatography on silica gel (Wakogel B-5) developed with benzene–ethyl acetate–methanol (5 : 4 : 1 v/v). Material of R_F 0·4 was extracted with chloroform–methanol (10 : 1) to give (±)-mecambridine (2) as prisms, m.p. 158—160° (from ethyl acetate) (lit.,[6] 175—177°; lit.,[18] 177°; lit.,[19] 189—192°) (Found: C, 66·05; H, 6·15; N, 3·55. $C_{22}H_{25}NO_6$ requires C, 66·15; H, 6·3; N, 3·5%), whose i.r. ($CHCl_3$), n.m.r. [δ ($CDCl_3$) 3·81 (6H, s 2 × OCH_3), 3·97 (3H, s, OCH_3), 4·63 (2H, s, CH_2·OH), 5·83 (2H, s, O·CH_2·O), 6·30 (1H, s, 4-H) and 6·56 (1H, s, 9-H)] and mass [3] [*m/e* 399 (M^+), 206, 204, 194, and 179] spectra and t.l.c. behaviour [R_F 0·28 ($CHCl_3$–MeOH 20 : 1); 0·45 ($CHCl_3$–MeOH, 10 : 1); 0·64 ($CHCl_3$–MeOH, 5 : 1), 0·72 ($CHCl_3$–Me_2CO–MeOH, 5 : 4 : 1)] on silica gel were identical with those of natural mecambridine.

We thank Professor F. Šantavý, Chemical Institute, Medical Faculty, Palacký University, Olomouc, Czechoslovakia, for a gift of natural mecambridine, and Dr. K. Okui, Research Laboratories, Chugai Pharmaceutical Co. Ltd., for microanalyses. We also thank Mr. T. Ohuchi, Miss A. Ujie, Mrs. H. Hori, Mrs. A. Sato, Mrs. C. Koyanagi, Miss R. Kato, and Miss C. Yoshida for microanalyses and spectral measurements.

[4/608 *Received*, 25*th March*, 1974]

[18] S. Pfeifer and D. Thomas, *Pharmazie*, 1966, **21**, 701.
[19] V. Novak and J. Slavík, *Coll. Czech. Chem. Comm.*, 1974. **39**, 883.