SYNTHESIS OF (±)-STEPHOLIDINE*

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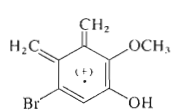
Received November 5th, 1976

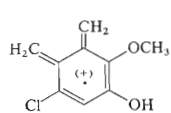
(±)-Stepholidine (*I*) and 2,10-dihydroxy-3,11-dimethoxyberbine (*IX*) were synthesized through the N-formyl derivative *VII* of 7-benzyloxy-1-(4-benzyloxy-6-bromo-5-methoxybenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (*VI*). The compounds *I* and *IX* were also prepared from 7-benzyloxy-1-(4-benzyloxy-3-hydroxybenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (*XIII*) by Mannich cyclization at pH 6·4, followed by methylation and debenzylation.

Cava and coworkers[1] isolated (−)-stepholidine, a tetrahydroprotoberberine alkaloid, from *Stephania glabra* tubers and assigned it structure *I* on the basis of degradative and oxidative studies. Later on, it was isolated[2] from *Menispermum dauricum* DC. and its structure was confirmed on the basis of IR, mass and ^{1}H-NMR spectral data. We report the synthesis of (±)-stepholidine by two different routes.

In the first route, 2-(4-benzyloxy-3-methoxyphenyl)ethylamine (*II*) was condensed with 4-benzyloxy-2-bromo-5-methoxyphenylacetic acid (*III*) to yield the amide *IV*, which was cyclized using $POCl_3$ in benzene to *V*. On sodium borohydride reduction, the compound *V* gave 7-benzyloxy-1-(4-benzyloxy-2-bromo-5-methoxybenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (*VI*). Treatment of *VI* with formic acid in the presence of triethylamine yielded the N-formyl derivative *VII*. Cyclization of *VII* using $POCl_3$ in benzene, followed by reduction ($NaBH_4$) and debenzylation (ethanol–HCl) gave products *VIII* and *IX* in the ratio of 1 : 2. On the basis of our earlier experiments[3] and also based on the spectral data, compound *VIII* was identified as a mixture of 12-bromo- and 12-chloro-2,10-dihydroxy-3,9-dimethoxyberberine. The IR

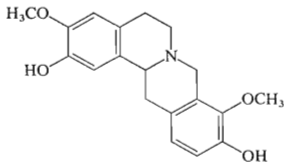


a

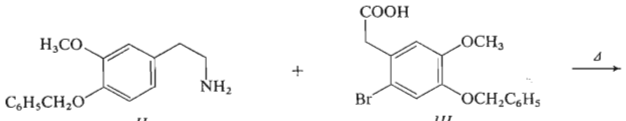


b

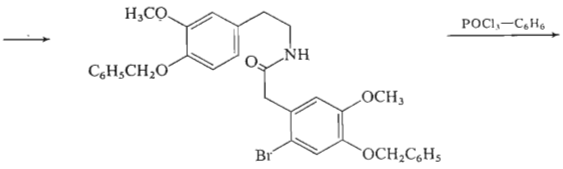
* Part VIII in the series Studies in Protoberberine Alkaloids. Heterocycles *3*, 811 (1975) can be considered as Part VI and this Journal *41*, 1219 (1976) as Part VII.



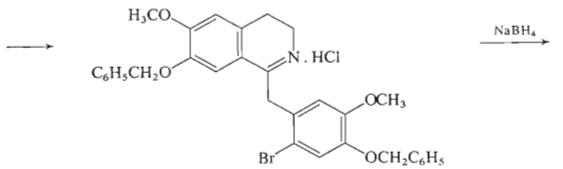
I



II *III*



IV



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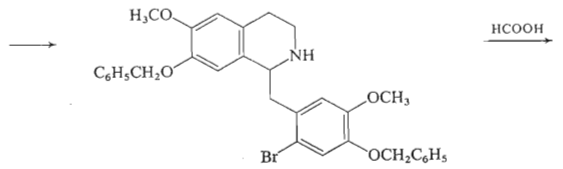
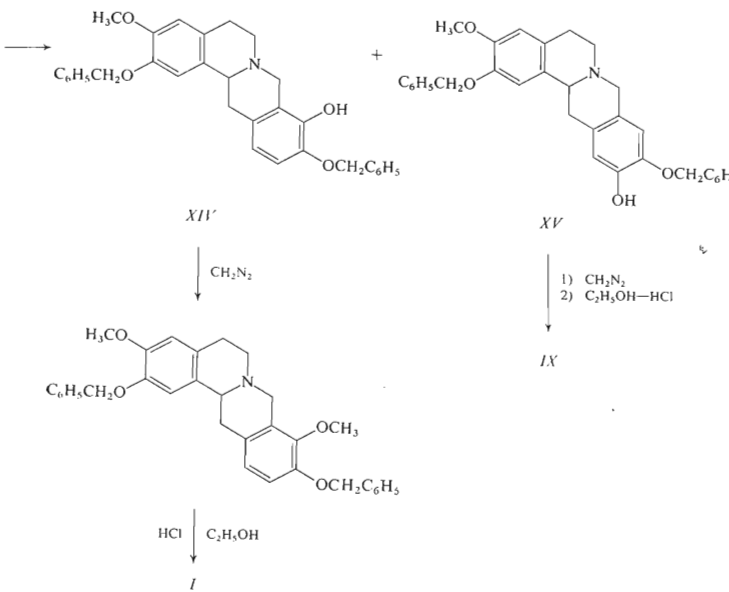


VI

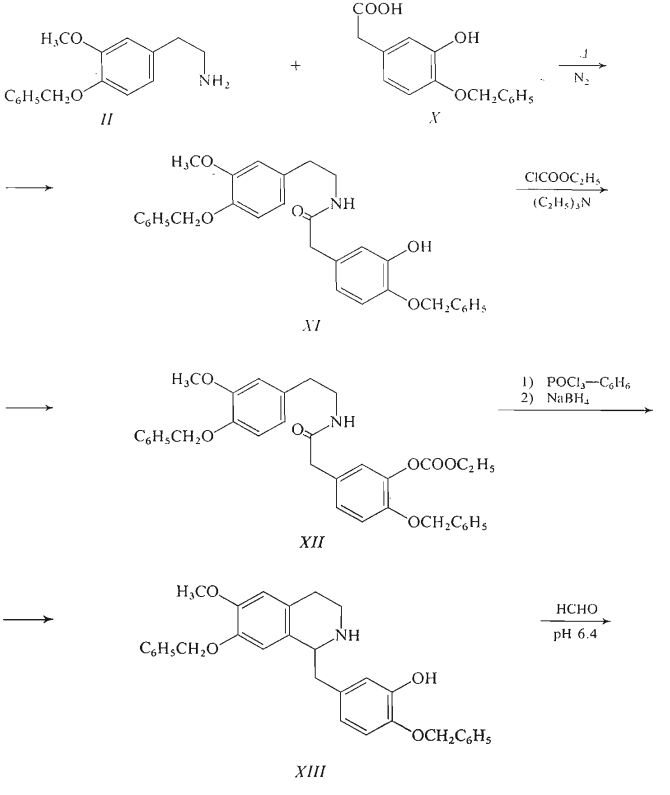


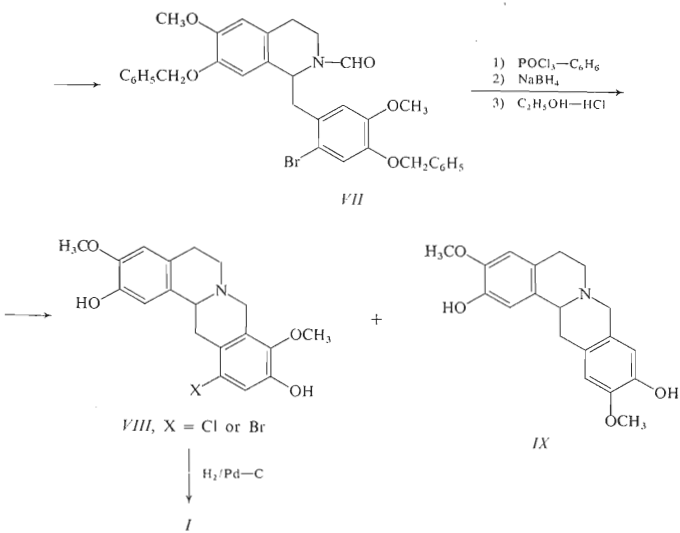
SCHEME 1

spectrum in KBr showed Bohlmann bands[4] in the region 2840–2750 cm^{-1}. Mass spectrum showed the molecular ion peaks at *m/e* 407 and 405 (bromo compound) and at *m/e* 363 and 361 (chloro compound). The other major peaks were *m/e* 326 (M^+ – halogen), *m/e* 230 and 228 (fragment *a*) and *m/e* 186 and 184 (fragment *b*). ^{1}H-NMR spectrum in hexadeuteriodimethyl sulphoxide showed two signals at δ 3·80 and 3·83 for the methoxyl groups and many signals for three isolated aromatic protons. Compound *IX* also showed Bohlmann bands in the region 2850–2700 cm^{-1}. Mass spectrum showed *m/e* 327 (M^+). The broad two-proton singlet, observed at δ 3·97 ($C_{(8)}$-protons), in its ^{1}H-NMR spectrum taken in hexadeuteriodimethyl sulphoxide, indicated that the compound could be a 10,11-substituted tetrahydroprotoberberine derivative[5] and hence compound *IX* is 2,10-dihydroxy-3,11-dimethoxyberberine. Reductive cleavage of halogen from *VIII* was effected catalytically with 10% Pd-C catalyst in ethanol to yield (±)-stepholidine (*I*). The IR spectrum in KBr of *I* was identical with that of natural stepholidine. The ^{1}H-NMR spectral

data and mass spectral fragmentation pattern were consistent with the values reported for the natural alkaloid[2,6].

In the second route, the amine *II* was condensed with 4-benzyloxy-3-hydroxyphenylacetic acid[7] (*X*), at 130–140°C in an atmosphere of nitrogen, to give the phenolic amide *XI*. The O-ethoxycarbonyl derivative *XII* of *XI*, on cyclization with OCl_3 in benzene, followed by reduction with sodium borohydride, yielded





SCHEME 2

7-benzyloxy-1-(4-benzyloxy-3-hydroxybenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (*XIII*). Mannich cyclization of *XIII* with formaldehyde (37%) at pH 6·4 gave two tetrahydroprotoberberine derivatives *XIV* and *XV*. The major product *XIV* was the required 2,10-dibenzyloxy-9-hydroxy-3-methoxyberbine. IR spectrum in dichloromethane showed Bohlmann bands in the region 2820 – 2740 cm^{-1}. Mass spectrum showed *m/e* 493 (M^+), 268 and 228. ^{1}H-NMR spectrum in deuteriochloroform showed a singlet at δ 3·87 for one OCH_3, two singlets each at δ 6·68 and 6·80 for two aromatic protons at $C_{(4)}$ and $C_{(1)}$, and a quartet centered at δ 6·72 (J_{AB} = 8 Hz) for the two aromatic protons at $C_{(11)}$ and $C_{(12)}$. The presence of a doublet at δ 4·28 (J_{AB} = 16 Hz) due to one of the $C_{(8)}$ protons confirmed its structure. Compound *XV*, which was obtained as a gum, on methylation followed by debenzylation, yielded a product, which was identical with compound *IX* obtained earlier and therefore compound *XV* is 2,10-dibenzyloxy-11-hydroxy-3-methoxyberbine. Methylation of *XIV* with diazomethane yielded the non-phenolic base *XVI*. Mass spectrum showed *m/e* 507 (M^+) and 476 ($M^+ - OCH_3$). The latter peak was cha-

racteristic of a 9-methoxytetrahydroprotoberberine[6,7]. ^{1}H-NMR spectrum in deuteriochloroform showed signals confirming the structure of *XVI* to be 2,10-dibenzyloxy--3,9-dimethoxyberbine. Debenzylation of *XVI* with ethanol–HCl gave a diphenolic base found to be identical with (±)-stepholidine (*I*) obtained earlier.

These two routes resemble each other and both of them require the separation of the positionally isomeric intermediates in the final steps of the synthesis. The second route gives, however, rise to an intermediary product whose substituents on the ring D are correctly localized in a more favourable ratio. Thus, it appears that the latter route (*II* – *XI* – *XII* – *XIII* – *XIV* – *XVI* – *I*) is more profitable.

EXPERIMENTAL

4-Benzyloxy-2-bromo-5-methoxyphenylacetic Acid (*III*)

Bromine (1 ml) was added to 4-benzyloxy-3-methoxyphenylacetic acid[8] (5 g) in glacial acetic acid (50 ml) containing sodium acetate (1 g) and the mixture was stirred for 30 min. Water (100 ml) was added and the precipitated bromo acid was collected and crystallized from methanol to yield *III* (5·5 g), m.p. 191–192°C. For $C_{16}H_{15}BrO_4$ (351·2) calculated: 54·73% C, 4·31% H; found: 54·96% C, 4·40% H.

N-2-(4-Benzyloxy-3-methoxyphenethyl)-4-benzyloxy-2-bromo-5-methoxyphenylacetamide (*IV*)

A mixture of 2-(4-benzyloxy-3-methoxyphenyl)ethylamine (5·2 g) and 4-benzyloxy-2-bromo--5-methoxyphenylacetic acid (*III*, 7 g) was heated at 180–185°C for 2 h. The mixture was cooled to room temperature and the solid was extracted with chloroform. The chloroform extract was washed with dilute hydrochloric acid, water, saturated sodium hydrogen carbonate solution and with water, dried (Na_2SO_4) and the solvent distilled off to get the amide *IV*, which was crystallized from benzene (8·5 g), m.p. 126°C. For $C_{32}H_{32}BrNO_5$ (590·5) calculated: 65·08% C, 5·46% H, 2·37% N; found: 65·37% C, 5·65% H, 2·46% N. IR spectrum (CH_2Cl_2): ν(N—H) 3440, ν(C=O) 1640 cm^{-1}. Mass spectrum: *m/e* 591·5 and 589·5 (M^+). ^{1}H-NMR spectrum ($CDCl_3$): δ 3·83, 6 H, s, 2 OCH_3; 5·10, 4 H, s, 2 $OCH_2C_6H_5$; 5·55, 1 H, NH; 6·60–6·81, 4 H, aromatic; 7·08, 1 H, s, aromatic; 7·40, 10 H, aromatic. Peak at δ 5·55 disappears on D_2O addition.

7-Benzyloxy-1-(4-benzyloxy-2-bromo-5-methoxybenzyl)-6-methoxy-3,4-dihydroisoquinoline (*V*)

The above amide (3 g) was refluxed with freshly distilled phosphorus oxychloride (7·5 ml) and benzene (30 ml) for 2 h. n-Hexane was added to the resulting solution and kept overnight. The residue was repeatedly washed with n-hexane and the hexane layer was discarded. The crude product was crystallized from methanol–ether to give the hydrochloride of *V* (3 g), m.p. 189 to 190°C. For $C_{32}H_{31}BrClNO_4$ (608·9) calculated: 63·13% C, 5·13% H, 2·30% N; found: 63·81% C, 5·42% H, 2·34% N. UV spectrum (ethanol): λ_{max} 304, 360 nm (log ε 3·97, 3·87). UV spectrum (ethanol + 1M-NaOH): λ_{max} 280, 310 nm (log ε 4·04, 3·87).

7-Benzyloxy-1-(4-benzyloxy-2-bromo-5-methoxybenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (*VI*)

Hydrochloride of *V* (2 g) was dissolved in methanol (100 ml) and sodium borohydride (1·2 g) was added in portions. After 15 min at room temperature, the mixture was refluxed for 30 min and the solvent was distilled off. The residue was treated with water and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4) and distilled to leave a residue which was crystallized from benzene–light petroleum (b.p. 40–60°C) (1·7 g), m.p. 133°C. For $C_{32}H_{32}BrNO_4$ (574·5) calculated: 66·90% C, 5·61% H, 2·44% N; found: 67·04% C, 5·81% H, 2·19% N. UV spectrum (ethanol): λ_{max} 232 (sh), 280 nm (log ε 4·35, 3·93). ^{1}H-NMR spectrum ($CDCl_3$): δ 1·95, 1 H, s, NH; 3·74, 3·80, 6 H, 2 s, 2 OCH_3; 5·05, 4 H, s, 2 $OCH_2C_6H_5$; 6·60, 1 H, s, aromatic; 6·75, 2 H, s, aromatic; 7·10, 1 H, s, aromatic; 7·35, 10 H, aromatic. Peak at δ 1·95 disappears on D_2O addition.

7-Benzyloxy-1-(4-benzyloxy-2-bromo-5-methoxybenzyl)-2-formyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (*VII*)

Distilled formic acid (3·3 g) was added to triethylamine (1·7 g) at 0°C. To this was added *VI* (3 g) and the mixture was refluxed at 145–150°C for 3 h. The solution was cooled, poured into water and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4) and distilled to yield a gum which was crystallized from benzene–n-hexane (2·75 g), m.p. 144 to 145°C. For $C_{33}H_{32}BrNO_5$ (602·5) calculated: 65·78% C, 5·35% H, 2·32% N; found: 65·98% C, 5·51% H, 2·40% N. IR spectrum (CH_2Cl_2): ν(C=O) 1 680 cm^{-1}. ^{1}H-NMR spectrum ($CDCl_3$): δ 3·78; 3·85, 6 H, 2 OCH_3; 5·10, 5·13, 4 H, 2 $OCH_2C_6H_5$; 6·48, 6·65, 6·76, 7·10, 4 H, aromatic; 7·36, 10 H, aromatic.

12-Bromo(chloro)-2,10-dihydroxy-3,9-dimethoxyberbine (*VIII*) and 2,10-Dihydroxy-3-11-dimethoxyberbine (*IX*)

A mixture of *VII* (2 g), phosphorus oxychloride (4 ml) and benzene (20 ml) was refluxed for 15 min, when the chloride started separating out. It was cooled and the excess solvent and the reagent were removed *in vacuo*. The residue was suspended in methanol (250 ml) and sodium borohydride (1·4 g) was added in portions, stirring the mixture during addition. After leaving it overnight, the solvent was distilled off and the residue was treated with water. It was extracted with chloroform, the extract was washed with water and dried (Na_2SO_4). Distillation of the solvent left a gum (1·6 g) which was refluxed with ethanol (100 ml) and concentrated hydrochloric acid (100 ml) for 3 h and left overnight. Excess solvent and reagent were removed *in vacuo*, the residue basified with 10% ammonia and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4) and distilled. The resulting gum (1·17 g) was chromatographed over silica gel (15 g) using chloroform as eluant and 20 ml fractions were collected. Fractions 6–9 were combined and crystallized from chloroform–methanol to yield *VIII* (185 mg), m.p. 192–200°C. IR spectrum (KBr disc): ν (*trans*-quinolizidine band) 2840–2720 cm^{-1}. Mass spectrum: *m/e* 407 and 405 (M^+) bromo compound, 363 and 362 (M^+) chloro compound, 326 ($M^+ - X$; X = Br or Cl), 230, 228, 186, 184. ^{1}H-NMR spectrum (hexadeuteriodimethyl sulphoxide): δ 3·80, 3·83, 6 H, 2 OCH_3; 6·60, 6·83, 7·40, 3 H, aromatic.

Fractions 11–20 were combined and crystallized from chloroform–methanol to give *IX* (345 mg), m. 220–224°C (lit.[8,9] m.p. 207–210°C). For $C_{19}H_{21}NO_4$ (327·4) calculated: 69·70% C, 6·47% H, 4·28% N; found: 69·61% C, 6·78% H, 3·89% N. IR spectrum (KBr disc): ν(OH) 3 540, ν (*trans*-quinolizidine band) 2820–2740 cm^{-1}. UV spectrum (ethanol): λ_{max} 225, 287 nm

(log ε 4·20, 4·10). UV spectrum (ethanol + 1M-NaOH): λ_{max} 245, 302 nm (log ε 4·21, 4·15). ^{1}H-NMR spectrum (hexadeuteriodimethyl sulphoxide): δ 3·80, 6 H, s, 2 OCH_3; 3·97, 2 H, bs, $C_{(8)}$—H; 6·55, 2 H, s, aromatic; 6·76, 2 H, s, aromatic.

(±)-Stepholidine (*I*)

The compound *VIII* (200 mg) in ethanol (200 ml) was shaken with hydrogen at 2·5—3 atm in the presence of palladized-charcoal catalyst (10%, 100 mg) in a Paar reduction apparatus for 15 h. The solution was filtered off from the catalyst and the solvent was removed *in vacuo*. The residue was basified with 10% ammonia and extracted with chloroform. The chloroform extract was washed with water, dried (Na_2SO_4) and distilled to leave a solid, which was crystallized from chloroform–methanol to obtain *I* (85 mg), m.p. 148°C. IR spectrum (KBR disc) of this compound was identical with that of (−)-stepholidine. For $C_{19}H_{21}NO_4.H_2O$ (345·4) calculated: 66·08% C, 6·71% H; found: 66·07% C, 7·05% H, UV spectrum (ethanol): λ_{max} 225, 284 nm (log ε 4·20, 3·80). UV spectrum (ethanol + 1M-NaOH): λ_{max} 245, 298 nm (log ε 4·09, 3·80). Mass spectrum: *m/e* 327 (M^+), 326 (M − 1)$^+$, 296 (M − OCH_3)$^+$, 178, 176, 150, 149. ^{1}H-NMR spectrum (hexadeuteriodimethyl sulphoxide): δ 3·80, 6 H, s, 2 OCH_3; 4·13, 1 H, d, J_{AB} = 16 Hz, $C_{(8)}$—H; 6·65, 6·75, 4 H, 2 s, aromatic.

N-2-(4-Benzyloxy-3-methoxyphenethyl)-4-benzyloxy-3-hydroxyphenylacetamide (*XI*)

A mixture of 2-(4-benzyloxy-3-methoxyphenyl)ethylamine (12·9 g) and 4-benzyloxy-3-hydroxyphenylacetic acid (*X*, 4·5 g) was heated at 130°C for 4 h under nitrogen. The product was dissolved in chloroform, washed with 5% hydrochloric acid, diluted sodium hydrogen carbonate, water and dried (Na_2SO_4). After removal of the solvent *in vacuo*, the residue was crystallized from benzene to yield the amide *XI* (9 g), m.p. 112—114°C. For $C_{31}H_{31}NO_5$ (497·5) calculated: 74·83% C, 6·28% H, 2·82% N; found: 75·06% C, 6·52% H, 2·52% N. IR spectrum (CH_2Cl_2): ν(OH, NH) 3 560, 3 450, ν(C=O) 1 630 cm^{-1}. Mass spectrum: *m/e* 497 (M^+). ^{1}H-NMR spectrum ($CDCl_3$): δ 3·80, 3 H, s, OCH_3, 5·08, 4 H, s, 2 $OCH_2C_6H_5$; 5·58, 2 H, bs, NH, OH; 6·45—6·90, 6 H, aromatic; 7·36, 10 H, aromatic. Peak at δ 5·58 disappears on D_2O addition.

N-2-(4-Benzyloxy-3-methoxyphenethyl)-4-benzyloxy-3-ethoxycarbonylphenylacetamide (*XII*)

To a stirred solution of the amide *XI* (6 g) and triethylamine (2·5 g) in benzene (400 ml), ethyl chloroformate (3·4 g) was added dropwise at 4—9°C. The mixture was stirred for 1·5 h at room temperature. The benzene solution was washed with water, 5% hydrochloric acid, again with water and dried (Na_2SO_4). Evaporation of the solvent gave a gum which was crystallized from ethanol to yield *XII* (7 g), m.p. 78—80°C. For $C_{34}H_{35}NO_7$ (569·6) calculated: 71·69% C, 6·19% H, 2·46% N; found: 71·70% C, 6·51% H, 2·52% N. IR spectrum (CH_2Cl_2): ν(NH) 3 450, ν(C=O) 1 780, 1 680 cm^{-1}. Mass spectrum: *m/e* 569 (M^+). ^{1}H-NMR spectrum ($CDCl_3$): δ 1·30, 3 H, *t*, *J* = 7 Hz, $COOCH_2CH_3$; 4·29, 2 H, q, *J* = 7 Hz, CH_2CH_3; 3·83, 3 H, s, OCH_3; 5·10, 4 H, s, $OCH_2C_6H_5$; 5·55, 1 H, bs, NH; 6·40—7·00, 6 H, aromatic; 7·38, 10 H, aromatic. Peak at δ 5·55 disappears on D_2O addition.

7-Benzyloxy-1-(4-benzyloxy-3-hydroxybenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (*XIII*)

A solution of the amide *XII* (4·5 g) in benzene (45 ml) was refluxed with phosphorus oxychloride (18 ml) for 2 h. After adding n-hexane (300 ml), the mixture was allowed to stand at room temperature overnight and the supernatant liquid was removed by decantation. The syrupy residue was

washed repeatedly with n-hexane and was concentrated to dryness *in vacuo*. The residue was crystallized from methanol (4·5 g), m.p. 175–176°C. UV spectrum (ethanol): λ_{max} 304, 355 nm (log ε 4·10, 4·11). UV spectrum (ethanol + 1M-NaOH): λ_{max} 275 nm (log ε 4·14). This was dissolved in methanol (225 ml), sodium borohydride (5·67 g) was added at room temperature and the solution was refluxed for 2 h. After removal of the solvent *in vacuo*, water was added and the resulting precipitate was dissolved in chloroform. The chloroform layer was washed with water and dried (Na_2SO_4). Distillation of the solvent *in vacuo* left a residue which was crystallized from methanol to yield *XIII* (3·1 g), m.p. 153–154°C. For $C_{31}H_{31}NO_4$ (481·6) calculated: 77·31% C, 6·49% H, 2·91% N; found: 77·17% C, 6·64% H, 2·73% N. UV spectrum (ethanol): λ_{max} 283 nm (log ε 3·97). UV spectrum (ethanol + 1M-NaOH): λ_{max} 290 nm (log ε 4·02). ^{1}H-NMR spectrum ($CDCl_3$): δ 3·90, 3 H, s, OCH_3; 5·10, 4 H, s, $OCH_2C_6H_5$; 6·60–6·95, 5 H, aromatic; 7·34, 10 H, aromatic.

Mannich Cyclization of *XIII*

To a solution of the hydrochloride of *XIII* (0·7 g) in a mixture of methanol (100 ml) and water (60 ml), whose pH was adjusted to 6·4 with 5% aqueous sodium hydrogen carbonate solution (5–7 ml), was added dropwise 37% formaldehyde (15 ml) with stirring and the pH was adjusted once again to 6·4 with 5% aqueous sodium hydrogen carbonate solution. The mixture was stirred overnight at room temperature and the resulting precipitate was collected, dissolved in chloroform, washed with aqueous sodium hydrogen carbonate solution, water, and dried (Na_2SO_4). After removal of the solvent *in vacuo*, the residue was crystallized from chloroform–methanol to yield 2,10-dibenzyloxy-9-hydroxy-3-methoxyberberine (*XIV*), (350 mg), m.p. 77–78°C. For $C_{32}H_{31}NO_4$ (493·6) calculated: 77·86% C, 6·33% H, 2·84% N; found: 77·94% C, 6·49% H, 3·06% N. IR spectrum (CH_2Cl_2): ν(OH) 3540, ν *trans*-quinolizidine band: 2840 to 2720 cm^{-1}. UV spectrum (ethanol): λ_{max} 282 nm (log ε 3·96). UV spectrum (ethanol + 1M-NaOH): λ_{max} 289 nm (log ε 4·02). Mass spectrum: *m/e* 493 (M^+), 268, 225. ^{1}H-NMR spectrum ($CDCl_3$): δ 3·87, 3 H, s, OCH_3; 4·29, 1 H, d, J_{AB} = 16 Hz, $C_{(8)}$—H; 5·07, 5·15, 4 H, 2 s, 2 $OCH_2C_6H_5$; 6·68, 1 H, s, $C_{(4)}$—H; 6·80, 1 H, s, $C_{(1)}$—H; 6·72; 2 H, q, J = 8 Hz, $C_{(11)}$ and $C_{(12)}$—H; 7·35, 10 H, aromatic.

The filtrate obtained after removal of *XIV*, was extracted with chloroform, washed with 5% aqueous sodium hydrogen carbonate solution, water and dried (Na_2SO_4). Evaporation of the solvent gave a gum (180 mg) which was combined with the mother liquor of crystallization of *XIV*. The mixture was chromatographed over silica gel (7 g; 1 × 10 cm) and eluted with chloroform–methanol (99 : 1 v/v). Fractions 3–11 gave 2,10-dibenzyloxy-11-hydroxy-3-methoxyberbine (*XV*) as a gum (100 mg) which was methylated with diazomethane. The product obtained was refluxed with concentrated hydrochloric acid (20 ml) and ethanol (20 ml) for 3 h. After removal of the solvent and the reagent *in vacuo*, the residue was basified with ammonia and extracted with chloroform. The chloform extract was washed with water, dried (Na_2SO_4) and distilled. The residue on crystallization from chloroform–methanol yielded 2,10-dihydroxy-3,11-dimethoxyberberine (*IX*), (25 mg), m.p. 223°C, identical (IR, Mass, ^{1}H-NMR spectra and TLC) with compound *IX* obtained in Scheme 1.

2,10-Dibenzyloxy-3,9-dimethoxyberbine (*XVI*)

To a solution of *XIV* (500 mg) in methanol (100 ml) an ethereal solution of diazomethane was added and allowed to stand overnight. After evaporation of the solvent the residue was crystallized from methanol to give *XVI* (350 mg), m.p. 93–94°C. For $C_{33}H_{33}NO_4$ (507·6) calculated: 78·08% C, 6·55% H, 2·77% N; found: 77·97% C, 6·73% H, 3·00% N. UV spectrum (ethanol):

λ_{max} 282 nm (log ε 3·97). Mass spectrum: *m/e* 507 (M^+), 493, 476 ($M^+ - OCH_3$), 268, 240. ^{1}H-NMR spectrum ($CDCl_3$): δ 3·87, 3·90, 6 H, 2 s, 2 OCH_3; 4·28, 1 H, d, $J_{AB} = 16$ Hz, $C_{(8)}$—H; 5·10, 5·15, 4 H, 2 s, 2 $OCH_2C_6H_5$; 6·65—6·80, 4 H, aromatic; 7·38, 10 H, aromatic.

(±)-Stepholidine (*I*)

O,O-Dibenzylstepholidine (*XVI*, 350 mg) was refluxed with ethanol (35 ml) and concentrated hydrochloric acid (35 ml) for 5 h. The solution was evaporated *in vacuo*. The residue was basified with ammonia and extracted with chloroform. The chloroform layer was washed with saturated solution of sodium chloride, dried (Na_2SO_4) and evaporated. The residue gum was crystallized from chloroform–methanol to yield (±)-stepholidine (*I*, 150 mg), m.p. 148°C, identical with that obtained in route 1 (m.p., mixed m.p., TLC, and IR spectrum).

We are grateful to Professor T. R. Govindachari and Dr K. Nagarajan for their constant encouragement. We thank Dr Selvavinayakam and his staff for the analyses and spectral data and Professor M. P. Cava and Dr M. V. Lakshmikantham for a gift of natural stepholidine for comparison. We express our sincere thanks to the CSIR, New Delhi, for a post doctoral fellowship (to H. S.) and to the Director of Tamil Nadu Forensic Science Laboratory, Madras, for permitting S. R. to complete this work. We are deeply indebted to Professor F. Šantavý, Olomouc, for his interest in this work.

REFERENCES

1. Cava M. P., Nomura K., Talapatra S. K., Mitchell M. J., Schlessinger R. H., Buck K. T., Beal J. L., Douglas B., Raffauf R. F., Weisbach J. A.: J. Org. Chem. *33*, 2785 (1968).
2. Okamoto Y., Tanaka S., Kitayama K., Isomoto M., Masaishi M., Yanagawa H., Kunitomo J.: J. Pharm. Soc., Jap. *91*, 684 (1971).
3. Suguna H., Pai B. R.: This Journal *41*, 1219 (1976).
4. Bohlmann F.: Angew. Chem. *69*, 641 (1957); Ber. Deut. Chem. *91*, 2157 (1958).
5. Chen. C.-Y., MacLean D. B.: Can. J. Chem. *46*, 2501 (1968).
6. Richter W. J., Brockmann-Hanssen E.: Helv. Chim. Acta *58*, 203 (1975).
7. Kametani T., Ihara M., Honda T.: J. Chem. Soc., C. *1971*, 3320.
8. Kametani T., Kano S.: J. Pharm. Soc., Jap. *72*, 1081 (1952).
9. Kametani T., Satoh M.: J. Pharm. Soc., Jap. *87*, 180 (1967).