An Alternative Total Synthesis of (±)-Scoulerine and (±)-Tetrahydropalmatine [1]

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The total synthesis of (±)-scoulerine was accomplished by Mannich reaction of 1-(2-bromo-5-hydroxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxyisoquinoline, followed by debromination. Methylation of 12-bromoscoulerine and debromination of 12-bromotetrahydropalmatine afforded (±)-tetrahydropalmatine.

SCOULERINE (I) occurs as the (+)- and (−)-form in several *Corydalis* species, and as a partial racemate in both *Corydalis* and *Glaucium* plants.[2] This structure was elucidated by firm degradative evidence [3] and total synthesis.[4]

The purpose of this investigation was to study the Mannich reaction of the 1-benzyl-1,2,3,4-tetrahydroisoquinoline derivative (IX) in order to obtain the corresponding protoberberine (II) as a possible intermediate for the synthesis of (±)-scoulerine (I); the debromination of compound (II) was studied, leading eventually to a synthesis of (±)-scoulerine. Methylation of compound (II) gave the dimethoxy-compound (IV), which was debrominated to give (±)-tetrahydropalmatine (III).[5]

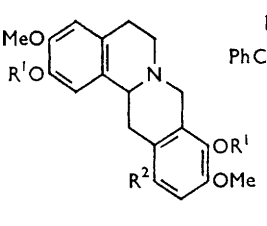
Cyclisation of the amide (V), which was obtained by the fusion of 4-benzoyloxy-3-methoxyphenethylamine with methyl 3-benzyloxy-4-methoxyphenylacetate, gave

[1] This Paper forms Part CLXXII of "Studies on the Syntheses of Heterocyclic Compounds," by T. Kametani.
[2] H.-G. Boit, "Ergebnisse der Alkaloid-Chemie bis 1960," Akademie-Verlag, Berlin, 1961, p. 334.
[3] E. Späth, E. Mossetig, and O. Tröthandl, *Ber.*, 1923, **56**, 875; R. H. F. Manske, *Canad. J. Res.*, 1940, *B*, **18**, 414.
[4] A. R. Battersby, R. Scouthgate, J. Staunton, and M. Hirst, *J. Chem. Soc.* (*C*), 1966, 1052.
[5] R. H. F. Manske, *Canad. J. Chem.*, 1956, **34**, 1; Roussel-UCLAF. Neth. Appl. 6,501,747 (*Chem. Abs.*, 1966, **64**, 2135).

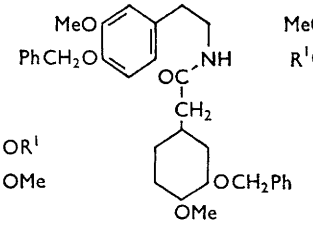
the corresponding 3,4-dihydroisoquinoline (VI). Reduction of the hydrochloride of (VI) with sodium borohydride gave the 1,2,3,4-tetrahydroisoquinoline (VII),[6] which was converted into 7-benzyloxy-1-(5-benzyloxy-2-bromo-4-methoxybenzyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline (VIII) by bromination. Debenzylation of the above bromide (VIII), followed by methylation with diazomethane, gave the 2′-bromo-compound which was identical with 2′-bromonorlaudanosine[7] (XI) obtained by bromination of norlaudanosine (X). This fact proves that the 2′-position of (VII) is selectively brominated.

Mannich reaction of compound (IX) with formalin in the presence of hydrochloric acid afforded 12-bromoscoulerine (II), whose debromination with lithium aluminium hydride in tetrahydrofuran gave the expected scoulerine (I). The i.r. spectrum (in $CHCl_3$) of compound (I) was superimposable on that of natural (−)-scoulerine donated by Dr. R. H. F. Manske. Furthermore, methylation of compound (II) with diazomethane gave the 12-bromotetrahydropalmatine (IV), whose debromination with zinc in 10% sodium hydroxide solution gave (±)-tetrahydropalmatine (III), which was also identical with an authentic sample.

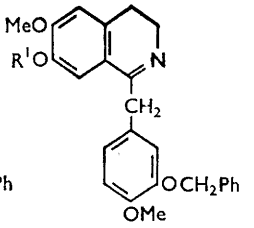
Thus the alternative total syntheses of (±)-scoulerine and (±)-tetrahydropalmatine have been accomplished.



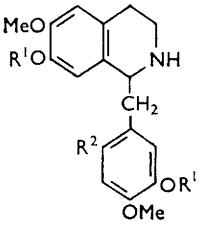
(I: $R^1 = H$; $R^2 = H$)
(II: $R^1 = H$; $R^2 = Br$)
(III: $R^1 = Me$; $R^2 = H$)
(IV: $R^1 = Me$; $R^2 = Br$)



(V)



(VI)



(VII: $R^1 = CH_2Ph$; $R^2 = H$)
(VIII: $R^1 = CH_2Ph$; $R^2 = Br$)
(IX: $R^1 = H$; $R^2 = Br$)
(X: $R^1 = Me$; $R^2 = H$)
(XI: $R^1 = Me$; $R^2 = Br$)

EXPERIMENTAL

Infrared and nuclear magnetic resonance spectra were measured on a type EPI-3 Hitachi recording spectrophotometer and a Varian A-60 spectrophotometer with deuteriochloroform as solvent and tetramethylsilane as internal reference. M. p.s were uncorrected.

7-Benzyloxy-1-(5-benzyloxy-2-bromo-4-methoxybenzyl-1,2,3,4-tetrahydro-6-methoxyisoquinoline (VIII).— To a stirred solution of 7-benzyloxy-1-(3-benzyloxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline[6] (VII) (5 g.) in 8% acetic acid (230 ml.) was added a mixture of glacial acetic acid (14 g.) and bromine (1·6 g.) at 5° with cooling within 30 min. After the addition, a yellow precipitate was deposited and the mixture was stirred at room temperature for a further 1 hr. The reaction mixture was basified with 10% sodium hydroxide solution and extracted with ether. The extract was washed with water, dried (K_2CO_3), and distilled to give a powder. Recrystallisation from methanol gave the *bromo-compound* (VIII) as needles (5·2 g.), m. p. 90—90·5°; n.m.r. (τ in $CDCl_3$): 2·95 (1H), 3·27 (2H), 3·42 (1H) (aromatic protons), 4·29 (4H, OCH_2Ph), 6·17 (6H, OCH_3), and 8·29 (1H, N*H*) (Found: C, 67·2; H, 5·8; N, 2·45. $C_{32}H_{32}BrNO_4$ requires C, 66·9; H, 5·6; N, 2·45%).

Recrystallisation of the *hydrochloride* of compound (VIII) from methanol gave needles, m. p. 251—252° (Found: C, 63·0; H, 5·65; N, 2·35. $C_{32}H_{32}BrNO_4$,HCl requires C, 62·9; H, 5·45; N, 2·3%).

1-(2-Bromo-5-hydroxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxyisoquinoline (IX).—A mixture of the preceding bromo-derivative (VIII) (2 g.) and 20% ethanolic HCl (230 ml.) was heated under reflux for 3 hr. After the reaction, removal of the solvent gave a powder (1·2 g.), which was washed with ether and dissolved in water. The resultant acidic aqueous solution was basified with 10% ammonium hydroxide solution and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and distilled to give a powder, which on recrystallisation from methanol had m. p. 225° (Found: C, 55·1; H, 5·3; N, 3·45. $C_{18}H_{20}BrNO_4$ requires C, 54·85; H, 5·1; N, 3·55%).

1-(2-Bromo-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (XI).—(*a*) To a stirred and cooled solution of norlaudanosine (X) (150 mg.) in 10% acetic acid solution (10 ml.) was added dropwise a solution of bromine (75 mg.) in glacial acetic acid (5 ml.), and the mixture was stirred at room temperature for 1 hr. The resultant yellowish solution was basified with 10% sodium hydroxide solution and extracted with ether. The extract was washed with water, dried (K_2CO_3), and distilled. Recrystallisation of the residue from dilute ethanol gave a powder[6] (140 mg.), m. p. 111°; n.m.r. (τ in $CDCl_3$): 3·07, 3·32, 3·40, 3·56 (4H, aromatic protons), 6·22 (3H), 6·28 (6H), 6·30 (3H, OCH_3), and 8·52 (1H, N*H*) (Found: C, 57·15; H, 6·0; N, 3·25. $C_{20}H_{24}BrNO_4$ requires C, 56·85; H, 5·75; N, 3·3%).

(*b*) To a solution of the preceding base (IX) (100 mg.) in methanol was added an ethereal solution of diazomethane, and the mixture was set aside at room temperature for 24 hr. Removal of the solvent gave a residue, and recrystallisation from dilute ethanol afforded a powder (60 mg.), m. p. 110—111°, which was identical (mixed m. p. and i.r. spectrum) with the sample prepared by method (*a*).

[6] T. Kametani and M. Ihara, *J. Chem. Soc.* (*C*), 1966, 2010.
[7] E. Späth and N. Lang, 1921, *B*, **54**, 3064.

12-*Bromoscoulerine* (II).—A mixture of the hydrochloride (1·1 g.) of the preceding base (IX), water (25 ml.), and 28% formalin (25 ml.) was heated on a water-bath for 3 hr. The mixture was then basified with ammonia and extracted three times with ethyl acetate. The extract was washed with water, dried (K_2CO_3), and distilled to give a powder (0·95 g.), whose recrystallisation gave prisms, m. p. 136—138°; n.m.r. (τ in CF_3CO_2H): 2·70, 2·88, 3·12 (3H, aromatic protons), 5·91 (3H), and 6·00 (3H, OCH_3); i.r. (in $CHCl_3$): 2650—2820 cm.$^{-1}$ (*trans*-quinolizidine band) (Found: C, 56·2; H, 5·05; N, 3·1. $C_{19}H_{20}BrNO_4$ requires C, 56·2; H, 4·95; N, 3·45%).

(±)-*Scoulerine* (I).—The preceding bromo-derivative (II) (200 mg.) in dry tetrahydrofuran (10 ml.) was gradually added to a stirred suspension of lithium aluminium hydride (500 mg.) in tetrahydrofuran (40 ml.) at 55°. After the addition, the mixture was stirred at 55° for a further 3 hr., cooled, and the excess of reagent was decomposed by dropwise addition of water (2 ml.). After removal of the solvent by distillation, the residue was mixed with water, made alkaline by adding ammonium chloride, and extracted with ethyl acetate. The extract was washed with water, dried (K_2CO_3), and distilled to give a powder (90 mg.). Recrystallisation from methanol yielded plates, m. p. 183—185° (lit.,[4] m. p. 183—185°); i.r. ($CHCl_3$): 2710—2820 cm.$^{-1}$ (*trans*-quinolizidine band).

Recrystallisation of the picrate from the ethanol gave a yellow powder, m. p. 205—206° (decomp.) (lit.,[4] m. p. 205—207° (decomp.) (Found: C, 54·15; H, 4·35; N, 9·9. $C_{19}H_{21}NO_4,C_6H_3N_3O_7$ requires C, 53·95; H, 4·35; N, 10·1%).

12-*Bromotetrahydropalmatine* (IV).—To a solution of the preceding compound (II) (0·7 g.) in tetrahydrofuran (80 ml.) and methanol (40 ml.) was added an ethereal solution of diazomethane, and the mixture was set aside at room temperature for 2 days. Removal of the solvent by distillation gave a powder, which was recrystallised from methanol to give scales (0·71 g.), 161—162° (lit.,[5] m. p. 162°); n.m.r. (τ in $CDCl_3$): 3·01, 3·25, 3·42 (3H, aromatic protons), 6·13 (3H), 6·80 (3H), and 6·21 (6H, OCH_3); i.r. ($CHCl_3$): 2700—2800 cm.$^{-1}$ (*trans*-quinolizidine band) (Found: C, 58·35; H, 5·35; N, 3·1. $C_{21}H_{24}BrNO_4$ requires C, 58·1; H, 5·55; N, 3·25%).

(±)-*Tetrahydropalmatine* (III).—A mixture of the preceding base (IV) (100 mg.), ethanol (5 ml.), 40% aqueous sodium hydroxide (0·6 ml.), and zinc powder (900 mg.) was heated under reflux on a water-bath for 2 hr. After the reaction mixture had been cooled and filtered, the solvent was removed by distillation, and the residue extracted with benzene. The extract was washed with water, dried (K_2CO_3), and distilled to give a pale yellow powder, which was recrystallised from methanol to give colourless scales (60 mg.), m. p. 151—151·5° (lit.,[5] m. p. 151°); n.m.r. (τ in $CDCl_3$): 3·18 (2H), 3·24 (1H), 3·38 (1H, aromatic protons), 6·13 (3H), 6·15 (6H), and 6·16 (3H, OCH_3); i.r. ($CHCl_3$): 2700—2830 cm.$^{-1}$ (*trans*-quinolizidine band) (Found: C, 70·95; H, 7·15; N, 3·6. $C_{21}H_{25}NO_4$ requires C, 70·95; H, 7·1; N, 3·95%).

The i.r. spectrum of synthetic (±)-tetrahydropalmatine was superimposable on that of natural racemic compound [8] (III) donated by Professor S. Sugasawa and Dr. M. Kawanishi.

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[8] M. Kawanishi and S. Sugasawa, *Chem. and Pharm. Bull. (Japan)*, 1965, **13**, 522.