# Studies on the Syntheses of Heterocyclic Compounds. Part CDXII.† Total Synthesis of Canadine

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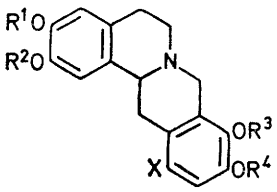
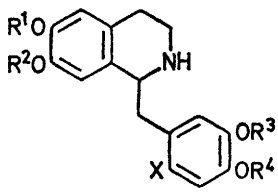
Canadine (4) has been synthesised by methylation of nandinine (3), prepared from 1,2,3,4-tetrahydro-1-(3-hydroxy-4-methoxybenzyl)-6,7-methylenedioxyisoquinoline (13) by a Mannich reaction. This Mannich reaction was studied under various conditions and the structure of an abnormal product, 9-hydroxy-12-hydroxymethyl-10-methoxy-2,3-methylenedioxyberbine, (7) has been elucidated.



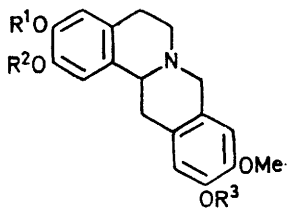
We have previously reported the total synthesis of scoulerine (1) by Mannich reaction of the diphenolic bromoisoquinoline (10) and debromination of the resulting berbine (2).[1,2] This method has also been applied to the total synthesis of the 9,10-dioxygenated berbine alkaloids nandinine (3),[3] canadine (4),[3] and palmatine (5),[1,2] which could not be synthesised by a Mannich reaction in the usual way.[4] Battersby[5] had earlier reported the synthesis of scoulerine (1) and coreximine (14) from norreticuline (11) by a Mannich reaction at pH 6·3; we used a similar method in the total synthesis of kikemanine (6).[6] The formation of a 'berbine bridge' in this type of reaction has also been achieved in neutral medium;[7] we have now investigated this reaction under a variety of pH conditions and have carried out total syntheses of nandinine (2) and canadine (4).



(1) $R^1 = R^4 = Me$, $R^2 = R^3 = X = H$
(2) $R^1 = R^4 = Me$, $R^2 = R^3 = H$, $X = Br$
(3) $R^1R^2 = CH_2$, $R^3 = X = H$, $R^4 = Me$
(4) $R^1R^2 = CH_2$, $R^3 = R^4 = Me$, $X = H$
(5) $R^1 = R^2 = R^3 = R^4 = Me$, $X = H$
(6) $R^1 = R^2 = R^3 = Me$, $R^4 = X = H$
(7) $R^1R^2 = CH_2$, $R^3 = H$, $R^4 = Me$, $X = CH_2{\cdot}OH$
(8) $R^1R^2 = CH_2$, $R^3 = Ac$, $R^4 = Me$, $X = CH_2{\cdot}OAc$
(9) $R^1R^2 = CH_2$, $R^3 = H$, $R^4 = Me$, $X = CHO$

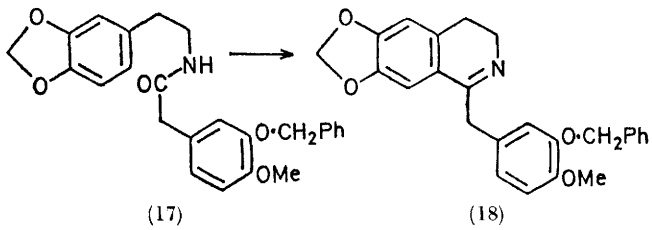


(10) $R^1 = R^4 = Me$, $R^2 = R^3 = H$, $X = Br$
(11) $R^1 = R^4 = Me$, $R^2 = R^3 = X = H$
(12) $R^1R^2 = CH_2$, $R^3 = CH_2Ph$, $R^4 = Me$, $X = H$
(13) $R^1R^2 = CH_2$, $R^3 = X = H$, $R^4 = Me$

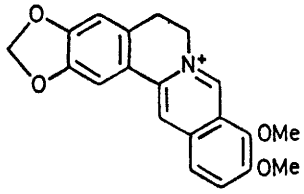


(14) $R^1 = Me$, $R^2 = R^3 = H$
(15) $R^1R^2 = CH_2$, $R^3 = CH_2Ph$
(16) $R^1R^2 = CH_2$, $R^3 = H$

Cyclisation of 3-benzyloxy-4-methoxyphenyl-*N*-(3,4-methylenedioxyphenethyl)acetamide (17)[8] with phosphoryl chloride in boiling benzene gave the 3,4-dihydroisoquinoline (18) hydrochloride, which was reduced with sodium borohydride to afford the 1,2,3,4-tetrahydroisoquinoline (12), characterised as its hydrochloride.



(17) (18)



(19)

Debenzylation of this hydrochloride with ethanolic hydrochloric acid gave the phenolic isoquinoline (13), which was also characterised as the hydrochloride.

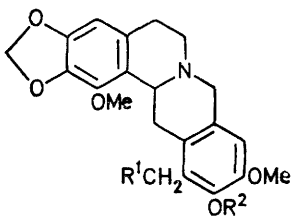
A Mannich reaction of compound (12) with formalin in acetic acid gave the 10,11-dioxygenated berbine (15),

† Part CDXI, T. Kametani, S. Shibuya, and M. Shio, *J. Heterocyclic Chem.*, in the press.

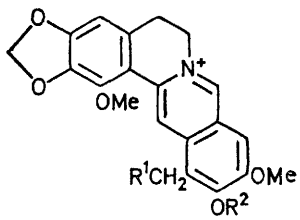
[1] T. Kametani and M. Ihara, *J. Chem. Soc.* (*C*), 1967, 530.
[2] T. Kametani and M. Ihara, *J. Chem. Soc.* (*C*), 1968, 1305.
[3] T. Kametani, I. Noguchi, K. Saito, and S. Kaneda, *J. Chem. Soc.* (*C*), 1969, 2036.
[4] W. M. Whaley and T. R. Govindachari, *Org. Reactions*, 1951, **6**, 151.
[5] A. R. Battersby, R. Southgate, J. Staunton, and M. Hirst, *J. Chem. Soc.* (*C*), 1966, 1052.
[6] T. Kametani, T. Honda, and M. Ihara, *Chem. Comm.*, 1970, 1254.
[7] T. Kametani, T. Terui, T. Ogino, and K. Fukumoto, *J. Chem. Soc.* (*C*), 1969, 874.
[8] T. R. Govindachari, S. Rajadurai, and C. V. Ramadas, *J. Sci. Ind. Res., India*, 1959, **18***B*, 533 (*Chem. Abs.*, 1960, **54**, 21,169).

debenzylation of which afforded 11-hydroxy-10-methoxy-2,3-methylenedioxyberbine (16), whose structure was confirmed by the n.m.r. spectrum of its acetyl derivative [δ 6·51, 6·59, 6·62, and 6·74 p.p.m. (each s, ArH)]. On the other hand a Mannich reaction of compound (13) in methanol at pH 1·2 furnished two products, which were separated by silica gel column chromatography. The i.r. spectrum of the first, m.p. 184—185° (71% yield), showed Bohlmann bands, indicating the presence of a berbine system, as also shown by its n.m.r. spectrum which revealed typical AB doublets at 4·2 and 3·42 p.p.m. (C-8 protons with geminal coupling). The second product, m.p. 243—245° (18% yield), was identical with compound (16), thus the first was probably nandinine (3). This conclusion was verified as follows. The n.m.r. spectrum revealed a pair of doublets ($J$ 9 Hz) at 6·73 and 6·44 p.p.m., which showed the product to be a 9,10-dioxygenated berbine. Methylation with diazomethane gave an *O*-methyl ether, m.p. 165—166°, identical with canadine (4) prepared from berberine (19).

Similar treatment of compound (13) at pH 6·2 and 7·2 gave nandinine (3) and the 10,11-dioxygenated berbine (16), but the reaction at pH 7·8 afforded only the latter (16) (see Table). An abnormal product, m.p. 201—202°, was obtained in the reactions at pH 6·0, 7·2, and 7·8. It was assigned structure (7) as follows. The mass spectrum and microanalysis suggested the molecular formula $C_{20}H_{21}NO_5$ and the i.r. spectrum revealed the presence of a berbine system. The mass spectrum also showed a 6,7-methylenedioxyisoquinoline fragment at *m/e* 175 and an ion ($C_{10}H_{12}O_3$) attributable to the cleaved CD ring at *m/e* 180. The n.m.r. spectrum showed the presence of a hydroxymethylene group on the aromatic ring [δ 4·40 p.p.m. (s)], shifted downfield (to 5·10 p.p.m.) in the spectrum of the acetyl derivative (8). An aromatic proton signal at 6·83 p.p.m. was shifted to 6·96 p.p.m. in the spectrum of the acetyl compound (8); thus this aromatic proton was *meta* to a phenolic hydroxy-group. Oxidation of the compound with manganese dioxide gave an aromatic aldehyde, which showed the phenolic hydroxy- and carbonyl absorptions at 3555 and 1676 $cm^{-1}$, respectively. This indicated that the hydroxy- and carbonyl groups were not vicinal, and this fact was supported by an aromatic proton signal at 7·30 p.p.m. The aldehyde was thus identified as 12-formyl-9-hydroxy-10-methoxy-2,3-methylenedioxyberbine (9), and the abnormal product as the 12-hydroxymethyl derivative (7). The formation of the compound of the latter type by a Mannich reaction at the appropriate pH could well provide a method of synthesising mecambridine (oreophiline) (20),[9] orientalidine (bractavine) (21),[9] alkaloid PO-4 (22),[9] and alkaloid PO-5 (alborine) (23)[9] from *Papaver* species.




(20) $R^1$ = OH, $R^2$ = Me
(21) $R^1R^2$ = O·$CH_2$




(22) $R^1R^2$ = O·$CH_2$
(23) $R^1$ = OH, $R^2$ = Me

Products of the Mannich reaction of compound (13) at various pH values

| pH | (3) (%) | (16) (%) | (7) (%) |
|---|---|---|---|
| 1·2 | 71·0 | 18·0 | |
| 6·0 | 5·1 | 18·3 | 2·0 |
| 7·2 | 3·3 | 17·5 | 11·2 |
| 7·8 | | 11·4 | 8·5 |

## EXPERIMENTAL

I.r. spectra were taken for solutions in chloroform with a Hitachi 215 recording spectrometer and mass spectra with a Hitachi RMU-7 spectrometer. N.m.r. spectra were measured with a Hitachi R-20 instrument for solutions in deuteriochloroform with tetramethylsilane as internal standard.

1-(3-*Benzyloxy*-4-*methoxybenzyl*)-1,2,3,4-*tetrahydro*-6,7-*methylenedioxyisoquinoline* (12).—A mixture of 3-benzyloxy-4-methoxyphenyl-*N*-(3,4-methylenedioxyphenethyl)acetamide (17)[8] (11·9 g), phosphoryl chloride (25 ml), and dry benzene (300 ml) was refluxed for 2 h, and the solvent and reagent were distilled off *in vacuo* to leave the 3,4-dihydroisoquinoline (18) hydrochloride. To a solution of this hydrochloride in methanol (300 ml) sodium borohydride (8·5 g) was added in small portions with stirring, and the mixture was refluxed for 1 h. Evaporation left a residue, which was decomposed with water and extracted with chloroform. The extract was washed with water, dried ($K_2CO_3$), and evaporated to leave the 1,2,3,4-tetrahydroisoquinoline (12) (12 g) as a yellowish-brown syrup, which was characterised as the *hydrochloride*, needles, m.p. 225—226° (from methanol–ether) (Found: C, 68·05; H, 5·9; N, 3·15. $C_{25}H_{25}NO_4$,HCl requires C, 68·25; H, 5·95; N, 3·2%), δ ($CF_3$·$CO_2H$), 7·28 (5H, s, O·$CH_2$·$C_6H_5$), 6·40—6·95 (5H, m, ArH), 5·86 (2H, s, O·$CH_2$·O), 5·04 (2H, s, O·$CH_2$Ph), and 3·88 p.p.m. (3H, s, OMe).

1,2,3,4-*Tetrahydro*-1-(3-*hydroxy*-4-*methoxybenzyl*)-6,7-*methylenedioxyisoquinoline* (13).—A mixture of the tetrahydroisoquinoline (12) hydrochloride (8 g), concentrated hydrochloric acid (60 ml), and ethanol (180 ml) was refluxed for 5 h, and hydrochloric acid and ethanol were distilled off *in vacuo* to give the *phenolic isoquinoline* (13) *hydrochloride* (5·4 g) as prisms, m.p. 166—167° (decomp.) (from ethanol–ether) (Found: C, 62·05; H, 6·25; N, 4·45. $C_{18}H_{19}NO_4$,HCl requires C, 61·8; H, 5·75; N, 4·0%). The free base was recrystallised from benzene to give *needles*, m.p. 186—187° (Found: C, 69·3; H, 6·0; N, 4·4. $C_{18}H_{19}NO_4$ requires C, 69·0; H, 6·1; N, 4·5%), $\nu_{max.}$ 3575 $cm^{-1}$ (OH).

*Mannich Reaction of the Benzylisoquinoline* (12).—A solution of the tetrahydroisoquinoline (12) (200 mg) and 37% formalin (10 ml) in acetic acid (30 ml) was heated on a water bath for 2 h and the mixture was then poured into water (150 ml). The separated oil was extracted with chloroform, and the extract was washed with aqueous sodium hydrogen carbonate and water, dried ($Na_2SO_4$), and evaporated *in vacuo* to give 11-*benzyloxy*-10-*methoxy*-2,3-*methylenedioxyberbine* (150 mg) (15) as pale yellow needles, m.p. 216—220° (decomp.) (from benzene) (Found:

[9] V. Simanek, V. Preininger, P. Sedmere, and F. Santavy, *Coll. Czech. Chem. Comm.*, 1970, **35**, 1440.

C, 74·85; H, 5·85; N, 3·5. $C_{26}H_{25}NO_4$ requires C, 75·15; H, 6·05; N, 3·4%), $\nu_{max.}$ 2850—2750 $cm^{-1}$ (*trans*-quinolizidine), δ 7·28br (5H, s, O·$CH_2$·$C_6H_5$), 6·59 (1H, s, ArH), 6·57 (11H, s, ArH), 6·50 (2H, s, ArH), 5·81 (2H, s, O·$CH_2$·O), 5·05 (2H, s, O·C$H_2$Ph), and 3·80 p.p.m. (3H, s, OMe).

*Debenzylation of the Berbine* (15).—A mixture of compound (15) (100 mg), concentrated hydrochloric acid (10 ml), and ethanol (30 ml) was refluxed for 3·5 h, and hydrochloric acid and ethanol were distilled off under reduced pressure. 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 11-hydroxy-10-methoxy-2,3-methylenedioxyberbine (60 mg) (16) as pale yellow plates, m.p. 243—245° (from chloroform–ethanol), identical with the sample prepared from compound (13) by a Mannich reaction as described later.

*Acetylation of the Berbine* (16).—A mixture of the 11-hydroxyberbine (16) (40 mg), acetic anhydride (2 ml), and pyridine (3 drops) was stirred for 24 h at room temperature, then poured into water (20 ml). The separated solid was extracted with chloroform, and the extract was washed with water, aqueous sodium hydrogen carbonate, and water, dried ($Na_2SO_4$), and evaporated to leave a brown syrup, which was chromatographed on silica gel (2 g.) Elution with chloroform afforded the acetoxyberbine (31 mg) as a pale yellow viscous syrup, $\nu_{max.}$ 1755 $cm^{-1}$ (OAc), δ 6·74 (1H, s, 12-H), 6·51 (1H, s, 9-H), 6·62 (1H, s, 1- or 4-H), 6·58 (1H, s, 4- or 1-H), 5·84 (2H, s, O·$CH_2$·O), 3·75 (3H, s, OMe), and 2·28 p.p.m. (3H, s, OAc).

*Mannich Reaction of the Benzylisoquinoline* (13).—(a) *At pH* 1·2. A mixture (pH 1·2) of the phenolic isoquinoline (13) hydrochloride (500 mg), 37% formalin (25 ml), concentrated hydrochloric acid (3 drops), and methanol (25 ml) was refluxed for 1 h, and methanol was distilled off. The residue was basified with 10% ammonia and extracted with chloroform. The extract was washed with water, dried ($Na_2SO_4$), and evaporated *in vacuo* to leave a solid, which was chromatographed on silica gel (8 g). Elution with benzene–chloroform (1 : 1 v/v) gave 9-hydroxy-10-methoxy-2,3-methylenedioxyberbine (nandinine) (330 mg) (3) as needles, m.p. 184—185° (from benzene) (lit.,[13] 183—185°) (Found: C, 70·05; H, 5·7; N, 4·55. Calc. for $C_{19}H_{19}NO_4$: C, 70·15; H, 5·9; N, 4·3%), $\nu_{max.}$ 3575 (OH) and 2750—2850 $cm^{-1}$ (*trans*-quinolizidine), δ 6·73 (1H, d, *J* 9 Hz, 12-H), 6·61 (2H, s, 1- and 4-H), 6·44 (1H, d, *J* 9 Hz, 11-H), 5·84 (2H, s, O·$CH_2$·O), 4·2 (1H, d, $J_{gem}$ 16 Hz, 8-H), 3·79 (3H, s, OMe), and 3·43 p.p.m. (1H, d, $J_{gem}$ 16 Hz, 8-H). Elution with chloroform afforded 11-*hydroxy*-10-*methoxy*-2,3-*methylenedioxyberbine* (84 mg) (16) as pale yellow plates, m.p. 243—245° (from chloroform–ethanol), identical with the sample prepared from compound (12) (Found: C, 69·7; H, 5·6; N, 4·3. $C_{19}H_{19}NO_4$ requires C, 70·15; H, 5·9; N, 4·3%), $\nu_{max.}$ 3565 (OH) and 2750—2850 $cm^{-1}$ (*trans*-quinolizidine), δ ($CF_3$·$CO_2H$) 6·88 (1H, s, 9-H), 6·78 (1H, s, 12-H), 6·69 (2H, s, 1- and 4-H), 5·98 (2H, s, O·$CH_2$·O), and 3·92 p.p.m. (3H, s, OMe).

(b) *At pH* 6·0. To a Clark–Lubs buffer (15 ml) adjusted to pH 6·2 was added a mixture of the phenolic isoquinoline (13) hydrochloride (300 mg), 37% formalin (15 ml), and methanol (20 ml), and the resulting solution (pH 6·0) was heated under reflux for 1 h. Methanol was evaporated off; the residue was made basic with 10% ammonia and extracted with chloroform. The extract was worked up as before and chromatographed on silica gel (4 g). Elution with benzene–chloroform (1 : 1 v/v) gave nandinine (3) (15 mg), and elution with chloroform afforded compound (16) (51 mg). Elution with chloroform–methanol (99 : 1 v/v) then yielded 9-*hydroxy*-12-*hydroxymethyl*-10-*methoxy*-2,3-*methylenedioxyberbine* (7) (5 mg) as needles, m.p. 201—202° (from ethanol) (Found: C, 67·35; H, 5·85; N, 4·0%; $M^+$, 355. $C_{20}H_{21}NO_5$ requires C, 67·6; H, 5·95; N, 3·95%; *M*, 355), $\nu_{max.}$ (KBr) 2850—2750 $cm^{-1}$ (*trans*-quinolizidine), δ [$(CD_3)_2SO$] 6·90 (1H, s, 1- or 4-H), 6·83 (1H, s, 11-H), 6·60 (1H, s, 4- or 1-H), 5·91 (2H, s, O·$CH_2$·O), 4·40br (2H, s, C$H_2$·OH), and 3·74 (3H, s, OMe), *m/e* 180, 176, 175, 174, and 149.

(c) *At pH* 7·2. To a Clark–Lubs buffer (15 ml) adjusted to pH 7·5 were added the hydrochloride of compound (13) (300 mg), 37% formalin (15 ml), and methanol (20 ml). The resulting solution (pH 7·2) was refluxed for 1 h, and worked up as before to give compounds (3) (9 mg), (16) (48 mg), and (7) (30 mg).

(d) *At pH* 7·8. To a Clark–Lubs buffer (15 ml) adjusted to pH 8·0 were added the phenolic isoquinoline (13) hydrochloride (300 mg), 37% formalin (15 ml), and methanol (20 ml). The solution (pH 7·8) was heated under reflux for 1 h and worked up as before to afford compounds (16) (32 mg) and (7) (23 mg).

*Canadine* (4).—To a solution of nandinine (100 mg) in methanol (60 ml) was added diazomethane in ether [prepared from *N*-methyl-*N*-nitrosotoluene-*p*-sulphonamide (15 g)], and the mixture was set aside for 38 h at room temperature. The solvent was distilled off to give canadine (4) (74 mg) as prisms, m.p. 165—166° (lit.,[3] 165°) (from methanol) (Found: C, 70·6; H, 5·95; N, 4·25. $C_{20}H_{21}NO_4$ requires C, 70·8; H, 6·25; N, 4·15%), identical (i.r. and n.m.r. spectra) with an authentic sample prepared from berberine.

*Acetylation of the Berbine* (7).—A mixture of compound (7) (30 mg), acetic anhydride (10 ml), and dry pyridine (1 ml) was stirred for 24 h at room temperature, and then poured into water (30 ml). The separated oil was extracted with chloroform, and the extract was washed with water, aqueous sodium hydrogen carbonate, and water, dried ($Na_2SO_4$), and evaporated to leave a brown syrup, which was chromatographed on silica gel (1 g). Elution with chloroform gave the acetate (8) (12 mg) as a yellow viscous syrup, $\nu_{max.}$ 1735 and 1770 $cm^{-1}$, δ [$(CD_3)_2SO$] 6·96 (1H, s, 11-H), 6·90 (1H, s, 1- or 4-H), 6·59 (1H, s, 4- or 1-H), 5·92 (2H, s, O·$CH_2$·O), 5·10 (2H, s, ArC$H_2$·OAc), 3·74 (3H, s, OMe), 2·27 (3H, s, OAc), and 2·03 p.p.m. (3H, s, OAc).

*Oxidation of the Berbine* (7).—Manganese dioxide (800 mg) was added to a suspension of the hydroxymethylberbine (7) (200 mg) in chloroform (100 ml). The mixture was refluxed for 6 h, filtered, and concentrated to dryness, and the residue was chromatographed on silica gel (8 g). Elution with chloroform gave the *aldehyde* (9) (24 mg) as pale brown needles, m.p. 242—245° (decomp.) (from ethanol) (Found: C, 67·65; H, 5·45; N, 3·95. $C_{20}H_{19}NO_5$ requires C, 68·0; H, 5·4; N, 3·95%), $\nu_{max.}$ 3550 (OH), 2850—2750 (*trans*-quinolizidine), and 1676 $cm^{-1}$ (CHO), δ [$(CD_3)_2SO$] 10·07 (1H, s, CHO), 7·30 (1H, s, 11-H), 6·94 (1H, s, 1-H or 4-H), 6·64 (1H, s, 4-H or 1-H), 5·93 (2H, s, O·$CH_2$·O), and 3·85 p.p.m. (3H, s, OMe).

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