# Studies on the Syntheses of Heterocyclic Compounds. Part CCCII.[1] Alternative Total Syntheses of (±)-Nandinine, (±)-Canadine, and Berberine Iodide

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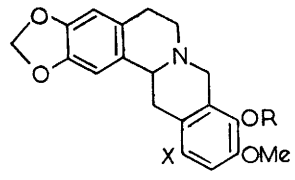
Mannich reaction of 1-(2-bromo-5-hydroxy-4-methoxybenzyl)-1;2,3,4-tetrahydro-6 7-methylenedioxyisoquinoline (IX) gave 12-bromonandinine (II) which was debrominated to afford (±)-nandinine (I). Methylation of (±)-nandinine with diazomethane gave (±)-canadine (III), dehydrogenation of which with iodine afforded berberine iodide (XI).

NANDININE (I), $C_{19}H_{19}NO_4$, and canadine (III), $C_{20}H_{21}NO_4$, have been isolated from *Nandina domestica* [2] and *Corydalis* [3] species, respectively. Their structures were elucidated from degradative evidence and by total synthesis.[4-6] We are investigating a modified Mannich reaction which selectively affords protoberberines cyclised *ortho* to the hydroxy group. This reaction has been




(I) X = H, R = H
(II) X = Br, R = H
(III) X = H, R = Me

used for the synthesis of a number of natural protoberberine alkaloids.[7-9] We now report alternative total syntheses of (±)-nandinine (I), (±)-canadine, and berberine iodide (XI) by this modified Mannich reaction.

Condensation of 3,4-methylenedioxyphenethylamine (IV) with methyl 5-benzyloxy-2-bromo-4-methoxyphenylacetate [9] (V) afforded the amide (VI), cyclisation of which with phosphoryl chloride gave the 3,4-dihydroisoquinoline (VII). Reduction of the hydrochloride of (VII) with sodium borohydride afforded the 1,2,3,4-tetrahydroisoquinoline (VIII), characterised as its oxalate. Debenzylation of (VIII) with concentrated hydrochloric acid in ethanol gave the expected phenolic base (IX), the structure of which was supported by micro-analysis and spectral determinations.

Mannich reaction of (IX) with formalin in the presence of hydrochloric acid afforded 12-bromonandinine (II), the i.r. spectrum of which showed Bohlmann bands at 2850—2700 $cm.^{-1}$. The n.m.r. spectrum of (II) showed a low-field singlet due to one aromatic proton adjacent

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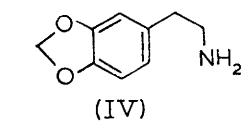
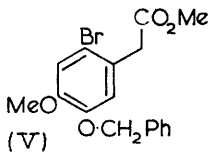
to bromine [δ 6·97 p.p.m.,[9] *cf.* δ 6·60 p.p.m. for the debrominated compound (I)].

Debromination of (II) with zinc powder in sodium hydroxide solution afforded (±)-nandinine (I) as colourless prisms,[2,4] m.p. 184—186°. Methylation of (I) with diazomethane gave (±)-canadine (III) quantitatively, identical (spectra and t.l.c.) with an authentic sample.

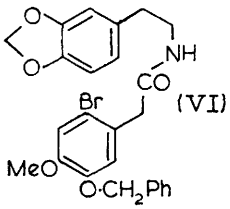
Dehydrogenation of (±)-canadine with iodine afforded berberine iodide (XI) in good yield; its i.r. spectrum (KBr) was identical with that of an authentic sample derived from berberine chloride (X) by treatment with potassium iodide solution.




(IV)




(V)

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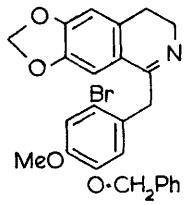
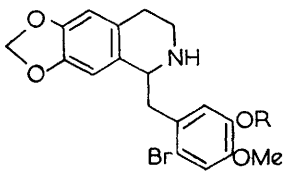
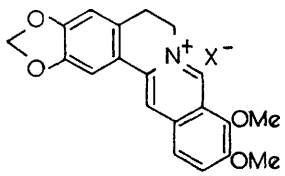



(VII)




(VIII) R = $CH_2Ph$
(IX) R = H




(X) X = Cl
(XI) X = I

## EXPERIMENTAL

N.m.r. spectra were determined with a Hitachi H-60 spectrometer for solutions in deuteriochloroform with tetramethylsilane as internal reference.

*5-Benzyloxy-2-bromo-4-methoxyphenyl*-N-(*3,4-methylenedioxyphenethyl*)*acetamide* (VI).—A mixture of 3,4-methylenedioxyphenethylamine (IV) (4·5 g.) and methyl 5-benzyloxy-2-bromo-4-methoxyphenylacetate[9] (V) (7·0 g.) was heated at 170—180° for 4 hr. The mixture was then extracted with chloroform. The extract was washed with 10% hydrochloric acid solution and water, dried ($K_2CO_3$), and evaporated to give a brownish gum, which gave the *amide* (VI) as pale yellow prisms (6·5 g.), m.p. 138—140° (from ether) (Found: C, 60·2; H, 4·9; N, 3·3. $C_{25}H_{24}BrNO_5$ requires C, 60·15; H, 4·85; N, 2·8%), $\nu_{max.}$ ($CHCl_3$) 1670 cm.$^{-1}$ (C=O).

1-(*5-Benzyloxy-2-bromo-4-methoxybenzyl*)-1,2,3,4-*tetrahydro-6,7-methylenedioxyisoquinoline* (VIII).—A mixture of the amide (VI) (5·5 g.), phosphoryl chloride (15 ml.), and dry benzene (200 ml.) was heated under reflux for 2 hr., and an excess of n-hexane was then added. The mixture was set aside at room temperature for 5 hr., then the syrup precipitated was separated by decantation and washed with n-hexane.

To a stirred solution of this 3,4-dihydroisoquinoline (VII) hydrochloride in methanol (500 ml.) was added sodium borohydride (3·0 g.), and the mixture was heated under reflux for 1 hr. Removal of the solvent left a residue which was extracted with benzene. The extract was washed with water, dried ($K_2CO_3$), and evaporated to afford a pale yellow gum (4·0 g.), $\nu_{max.}$ ($CHCl_3$) 3350 cm.$^{-1}$ (NH), δ 7·34br (5H, s, Ph), 7·07 (1H, s, 3′-H), 6·74 (2H, 8- and 6′-H), 6·52 (1H, s, 5-H), 5·86 (2H, s, O·$CH_2$·O), 5·09 (2H, s, O·$CH_2$Ph), and 3·83 (3H, s, OMe) p.p.m., which formed an *oxalate*, as colourless prisms, m.p. 198—200° (from ethanol) (Found: C, 56·8; H, 5·0; N, 2·6. $C_{27}H_{26}BrNO_8$ requires C, 56·6; H, 4·55; N, 2·45%).

1-(*2-Bromo-5-hydroxy-4-methoxybenzyl*)-1,2,3,4-*tetrahydro-6,7-methylenedioxyisoquinoline* (IX).—To a solution of (VIII) (1·0 g.) in ethanol (40 ml.) was added concentrated hydrochloric acid (40 ml.). The mixture was heated under reflux for 3 hr. Removal of the solvent left a brownish powder (0·6 g.), which was washed with ether and recrystallised from methanol–ether to afford the *hydrochloride* of (IX) as colourless prisms, m.p. 174—176° (decomp.) (Found: C, 49·9; H, 4·8; N, 2·95. $C_{18}H_{18}BrNO_4$,HCl requires C, 50·4; H, 4·45; N, 3·25%).

12-*Bromo*-5,6,13,13a-*tetrahydro*-9-*hydroxy*-10-*methoxy*-2,3-*methylenedioxy*-8H-*dibenzo*[a,g]*quinolizine* (II).—To a solution of the phenolic base (IX) hydrochloride (0·5 g.) in methanol (20 ml.) were added 37% formalin (20 ml.) and concentrated hydrochloric acid (3 drops), and the mixture was heated under reflux for 3 hr. After cooling, it was basified with ammonia and extracted with chloroform. The extract was washed with water, dried ($Na_2SO_4$), and evaporated to give a brownish gum, which afforded the *bromoprotoberberine* (II) (0·3 g.) as colourless prisms, m.p. 132—134° (from ether–n-hexane) (Found: C, 56·6; H, 4·4; N, 3·4. $C_{19}H_{18}BrNO_4$ requires C, 56·45; H, 4·5; N, 3·45%), $\nu_{max.}$ ($CHCl_3$) 3450 (OH), 2850—2700 (*trans*-quinolizidine), and 935 (O·$CH_2$·O) cm.$^{-1}$, δ 6·97 (1H, s, 11-H), 6·79 (1H, s, 1-H), 6·59 (1H, s, 3-H), 5·91 (2H, s, O·$CH_2$·O), and 3·85 (3H, s, OMe) p.p.m.

5,6,13,13a-*Tetrahydro*-9-*hydroxy*-10-*methoxy*-2,3-*methylenedioxy*-8H-*dibenzo*[a,g]*quinolizine* (I) [(±)-*Nandinine*] (±)-*Tetrahydroberberrubine*.—To a solution of the bromo-compound (II) (30 mg.) in 40% sodium hydroxide (10 ml.) and ethanol (10 ml.) was gradually added zinc powder (0·9 g.); the mixture was heated under reflux for 2 hr. The excess of reagent was removed by decantation and the resulting solution was saturated with solid ammonium chloride. The crystals precipitated were extracted with chloroform. The extract was washed with water, dried ($Na_2SO_4$), and evaporated to give a colourless gum, which gave (±)-nandinine (16 mg.) (I) as colourless needles, m.p. 183—185° (from ethanol) (lit.,[5] 186—187°), $\nu_{max.}$ 3500 (OH) and 935 (O·$CH_2$·O) cm.$^{-1}$, δ 6·76 (1H, d, *J* 6·5 c./sec., 12-H), 6·68 (1H, s, 1-H), 6·60 (1H, d, *J* 6·5 c./sec., 11-H), 6·57 (1H, s, 3-H), 5·90 (2H, s, O·$CH_2$·O), 5·06 (1H, m, OH), and 3·84 (3H, s, OMe) p.p.m.

5,6,13,13a-*Tetrahydro*-9,10-*dimethoxy*-2,3-*methylenedioxy*-8H-*dibenzo*[a,g]*quinolizine* (III) [(±)-*Canadine*].—To a solution of (±)-nandinine (I) (11 mg.) in methanol (20 ml.) was added an ethereal solution of diazomethane, and the mixture was kept at room temperature for 2 days. Distillation left a yellowish gum, which gave (±)-canadine (III) (7 mg.) as colourless prisms, m.p. 165° (from methanol)

(lit.,[2] m.p. 168°), $\nu_{max.}$ ($CHCl_3$) 2800—2700 (*trans*-quinolizidine) and 940 ($O{\cdot}CH_2{\cdot}O$) $cm.^{-1}$, δ 6·79br (2H, s, 11- and 12-H), 6·69 (1H, s, 1-H), 6·55 (1H, s, 3-H), 5·89 (2H, s, $O{\cdot}CH_2{\cdot}O$), and 3·83 (6H, s, 9- and 10-OMe) p.p.m., $R_F$ 0·75 [Wakogel B-5 activated at 100° for 4 hr.; chloroform–methanol (5 : 1) as solvent; detected with iodine].

The i.r. and n.m.r. spectra of synthetic (±)-canadine were identical with those of an authentic sample derived from berberine chloride (X).[10]

*Berberine Iodide* (XI).—(*a*) A solution of berberine chloride (X) (150 mg.) in ethanol (100 ml.) was mixed with 20% aqueous potassium iodide and set aside for 5 hr. The crystals precipitated gave berberine iodide (XI) (86 mg.) as yellow needles, m.p. 250° (decomp.) (from ethanol) (lit.,[11] 260°) (Found: C, 52·15; H, 4·25; N, 2·9. $C_{20}H_{18}INO_4$ requires C, 51·75; H, 3·9; N, 3·0%), $\nu_{max.}$ (KBr) 1735 and 1620 (C=C and $C{=}\overset{+}{N}$) and 935 ($O{\cdot}CH_2{\cdot}O$) $cm.^{-1}$.

(*b*) To a solution of (±)-canadine (III) (6 mg.) in ethanol (40 ml.) was added iodine (20 mg.), and the mixture was heated under reflux for 1 hr. The excess of iodine was decomposed by dropwise addition of 10% sodium thiosulphate, and an insoluble substance was filtered off. The product gave berberine iodide (XI) (4 mg.) (from ethanol), identical with an authentic sample (i.r. spectrum).

[9/553 *Received, March* 31*st*, 1969]

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