SYNTHESIS OF TETRAHYDROGROENLANDICINE, A PROTOBERBERINE ALKALOID

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Dedicated to Professor F. Šantavý on the occasion of his 60th birthday.

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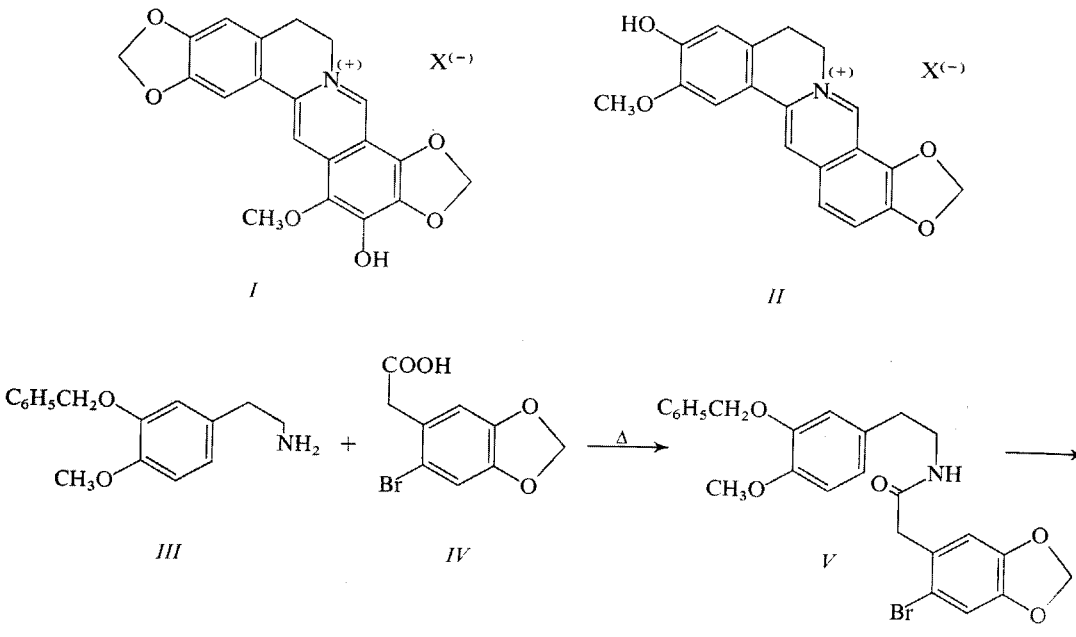
3-Hydroxy-2-methoxy-9,10-methylenedioxyberbine (*XII*) and 3-hydroxy-2-methoxy-10,11-methylenedioxyberbine (*X*) were synthesized through the N-formyl derivative *VIII* of 6-benzyloxy-1-(6-bromo-3,4-methylenedioxybenzyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline (*VII*). Compound *XII* was found to be identical with tetrahydrogroenlandicine.

Cooper, Mockle and Beliveau[1] reported the isolation of two alkaloids, besides berberine, from the rhizomes of *Coptis groenlandica* (OEDER) FERN. They named the alkaloids A and B. Alkaloid B was assigned structure *I* and later[2] revised to structure *II*. Structure *II* was independently proposed by Jewers and coworkers[3], on the basis of the reported ^{1}H-NMR spectral data and the alkaloid was given the trivial name groenlandicine.

We now report a synthesis of tetrahydrogroenlandicine according to the Scheme 1. 2-(3-Benzyloxy-4-methoxyphenyl)ethylamine (*III*) was condensed with 6-bromohomopiperonylic acid[4] (*IV*) to get the amide *V*, which was cyclised with $POCl_3$ and toluene to *VI* which on sodium borohydride reduction gave 6-benzyloxy-1-(6-bromo-3,4-methylenedioxybenzyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline (*VII*). *VII* was converted into its N-formyl derivative *VIII* by treating it with formic acid and triethylamine. Cyclisation of *VIII* with $POCl_3$ in benzene, followed by reduction and debenzylation (ethanol–HCl) gave products *IX* and *X* in the ratio of 1 : 3. Compound *IX* was found to be a 1 : 1 mixture of the 12-bromo- and 12-chlorotetrahydroprotoberberine derivatives, on the basis of spectral data. The IR spectrum in KBr showed Bohlmann bands[5] in the region 2820–2720 cm^{-1}. The molecular ion peaks *m/e* 405 and 403 (bromo compound) and *m/e* 361 and 359 (chloro compound) and also the peak *m/e* 324 (M^+-halogen) were present in its mass spectrum. ^{1}H-NMR spectrum in deuteriochloroform–hexadeuteriodimethyl sulphoxide showed two signals at δ 3·82 and 3·83 for one OCH_3, two signals at δ 6·10 and 6·12 for $-OCH_2O-$ and 6 signals at δ 6·57, 6·60, 6·67, 6·73, 6·90 and 7·13 for three isolated aromatic protons.



Compound *X* also showed Bohlmann bands in the region 2840–2760 cm^{-1}. Mass spectrum showed *m/e* 325 (M^+). ^{1}H-NMR spectrum in hexadeuteriodimethyl sulphoxide showed signals at δ 3·78 (3 H, s, OCH_3), 3·98 (2 H, bs, $C_{(8)}$—H), 5·92 (2 H, s, —OCH_2O—), 6·42–6·88 (4 H, aromatic), 8·68 (1 H, bs, OH). The peak at δ 8·68 was found to disappear on D_2O addition. The broad two proton singlet due to $C_{(8)}$ protons centred at δ 3·98 indicating the compound to be a 10,11-substituted tetrahydroprotoberberine derivative[6] and therefore compound *X* is 3-hydroxy-2-methoxy--10,11-methylenedioxyberbine.

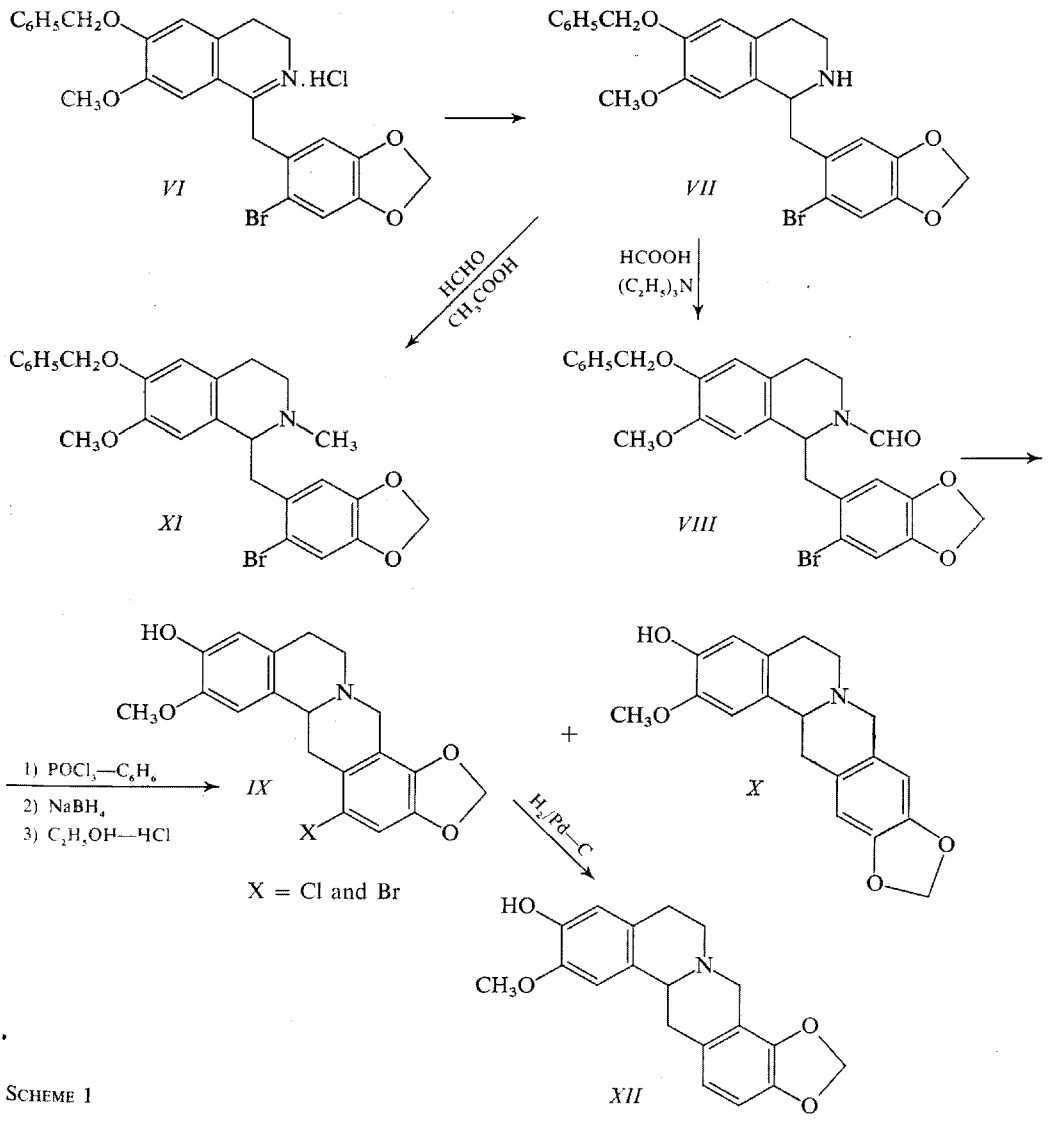
Reductive cleavage of halogen from *IX* was effected catalytically with 10% Pd—C catalyst in ethanol. This yielded tetrahydrogroenlandicine (*XII*). The IR spectrum of the synthetic tetrahydrogroenlandicine showed to be identical with the tetrahydro-derivative[2] of the alkaloid B from *Coptis groenlandica*. Mannich reaction of *VII* with formaldehyde and acetic acid did not give the expected product but only the corresponding N-methyl derivative *XI*.

EXPERIMENTAL

N-2-(3-Benzyloxy-4-methoxyphenethyl)-6-bromo-3,4-methylenedioxyphenylacetamide (*V*)

A mixture of 2-(3-benzyloxy-4-methoxyphenyl)ethylamine (7 g) and 6-bromohomopiperonylic acid (*IV*, 6 g) was heated at 180–190°C for 2 h. It was cooled to room temperature and extracted with chloroform. The chloroform extract was washed with dilute hydrochloric acid, water,

saturated sodium hydrogen carbonate solution and finally with water. It was dried (Na_2SO_4) and distilled to get the amide *V*, which was crystallised from chloroform–methanol (7 g), m.p. 178–180°C. For $C_{25}H_{24}BrNO_5$ (498·4) calculated: 60·15% C, 4·85% H, 2·80% N; found: 60·28% C, 5·07% H, 2·55% N. IR spectrum (KBr disc): ν(N—H) 3280, ν(C=O) 1640 cm^{-1}. Mass spectrum: *m/e* 499 and 497 (M^+), 418 (M^+—Br), 408 and 406 (M^+—$CH_2C_6H_5$).



SCHEME 1

6-Benzyloxy-1-(6-bromo-3,4-methylenedioxybenzyl)-7-methoxy-3,4-dihydroisoquinoline (*VI*)

The amide *V* (3 g) was refluxed with phosphorus oxychloride (7·5 ml) and toluene (30 ml) for 2 h. Excess solvent and reagent were removed *in vacuo*. Repeated crystallisation of the residue with methanol–ether gave dihydroisoquinoline hydrochloride *VI* (2·5 g), m.p. 210°C. For $C_{25}H_{23}$ . . $BrClNO_4.H_2O$ (534·8) calculated: 56·15% C, 4·71% H, 2·62% N; found: 55·82% C, 5·09% H, 2·65% N. UV spectrum (ethanol): λ_{max} 244, 302, 360 nm (log ε 4·31, 4·06, 3·99). UV spectrum (ethanol + 1M-NaOH): λ_{max} 281, 301 nm (log ε 4·01, 4·00).

6-Benzyloxy-1-(6-bromo-3,4-methylenedioxybenzyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline (*VII*)

Hydrochloride *VI* (2 g) was dissolved in methanol (100 ml) and sodium borohydride (1·2 g) was added in portions. 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 evaporated. The residue was crystallised from benzene–light petroleum (b.p. 40—60°C) (1·7 g), m.p. 130°C. For $C_{25}H_{24}BrNO_4$ (482·4) calculated: 62·24% C, 5·01% H, 2·90% N; found: 62·33% C, 5·31% H, 2·61% N. UV spectrum (ethanol): λ_{max} 230 (sh), 290 nm (log ε 4·02, 3·87). Mass spectrum: *m/e* 483 and 481 (M^+), 400, 269, 268, 215, 213, 177, 176. ^{1}H-NMR spectrum ($CDCl_3$): δ 1·92 (1 H, NH), 3·82 (3 H, s, OCH_3), 4·00—4·37 (1 H, m, $C_{(1)}$—H), 5·01 (2 H, s, $OCH_2C_6H_5$), 5·92 (2 H, s, OCH_2O), 6·63 (1 H, s, aromatic), 6·77 (2 H, s, aromatic), 7·03 (1 H, s, aromatic), 7·35 (5 H, C_6H_5). Peak at δ 1·92 disappears on D_2O addition.

Mannich Reaction on Compound *VII*

A mixture of *VII* (500 mg), 37% formaldehyde (5 ml) and glacial acetic acid (5 ml) was refluxed for 2 h and the reagents were removed by distillation *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 evaporated to get a gum which on crystallisation from benzene–n-hexane gave 6-benzyloxy-1-(6-bromo-3,4-methylenedioxybenzyl)-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (*XI*) (150 mg), m.p. 110°C. For $C_{26}H_{26}BrNO_4$ (496·4) calculated: 62·90% C, 5·28% H, 2·82% N; found: 63·00% C, 5·30% H, 2·72% N. UV spectrum (ethanol): λ_{max} 235 (sh), 290 nm (log ε 4·14, 3·87). ^{1}H-NMR spectrum ($CDCl_3$): δ 2·50 (3 H, s, N—CH_3), 3·67 (3 H, s, OCH_3) 3·77—3·98 (1 H m, $C_{(1)}$—H), 5·01 (2 H, s, $OCH_2C_6H_5$), 5·92 (2 H, s, OCH_2O), 6·23 (1 H, s, aromatic), 6·62 (2 H, s, aromatic), 7·02 (1 H, s, aromatic), 7·20—7·58 (5 H, C_6H_5).

6-Benzyloxy-1-(6-bromo-3,4-methylenedioxybenzyl)-2-formyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline (*VIII*)

Anhydrous formic acid (3·3 g) was added to triethylamine (1·7 g) at 0°C. To this was added *VII* (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 chloroform extract was washed with water, dried (Na_2SO_4) and distilled to yield a gum which was crystallised from benzene–n-hexane to yield *VIII* (2·5 g), m.p. 148—150°C. For $C_{26}H_{24}BrNO_5$ (510·4) calculated: 61·19% C, 4·74% H, 2·75% N; found: 61·69% C, 5·08% H, 2·95% N. IR spectrum (KBr disc): ν(C=O) 1695 cm^{-1}. ^{1}H-NMR spectrum ($CDCl_3$): δ 5·01 (2 H, $OCH_2C_6H_5$), 5·93 (2 H, OCH_2O), 7·37 (5 H, C_6H_5). Two signals at δ 3·77 and 3·85 (3 H, OCH_3) and many signals in the aromatic region show that the compound exists as two isomers arising due to the restricted rotation around N—CHO bond.

Cyclisation of *VIII*

A mixture of *VIII* (2 g), phosphorus oxychloride (4 ml) and benzene (25 ml) was refluxed for 10 min till the chloride started separating out. It was cooled and the excess solvent and reagent were removed *in vacuo*. The residue was suspended in methanol (300 ml) and sodium borohydride (1·5 g) was added in portions, stirring the reaction mixture during addition. It was left overnight, the solvent was distilled off and the residue was treated with water. Then it was extracted with chloroform, the chloroform layer washed with water and dried (Na_2SO_4). Evaporation of the solvent left a gum (1·5 g) which was refluxed with ethanol (50 ml) and concentrated hydrochloric acid (50 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 chloroform extract was washed with water, dried (Na_2SO_4) and distilled. The resulting gum (1 g) was chromatographed over silica gel (15 g) using chloroform as eluant and 20 ml fractions were collected. Fractions 2—9 were combined and the crude solid which separated was crystallised from chloroform–methanol to get compound *IX* (120 mg), m.p. 184—191°C. IR spectrum (KBr disc): ν(OH) 3540, ν(*trans*-quinolizidine band) 2820—2720, $\nu(OCH_2O)$ 940 cm^{-1}. Mass spectrum: *m/e* 405 and 403 (M^+) bromo compound, 361 and 359 (M^+) chloro compound, 324 (M^+—X; X = = Br or Cl). ^{1}H-NMR spectrum (deuteriochloroform–hexadeuteriodimethyl sulphoxide): ν 3·82, 3·83 (3 H, OCH_3), 6·10, 6·12 (2 H, OCH_2O), 6·57, 6·60, 6·67, 6·73, 6·90, 7·13 (3 H, aromatic).

Fractions 13—30 were combined and crystallised from chloroform–methanol to give 3-hydroxy-2-methoxy-10,11-methylenedioxyberbine (*X*) (350 mg), m.p. 165—166°C. For $C_{19}H_{19}NO_4 \cdot H_2O$ (343·4) calculated: 66·56% C, 6·18% H, 4·09% N; found: 67·01% C, 6·39% H, 3·76% N. IR spectrum (KBr disc): ν(OH) 3600, ν(*trans*-quinolizidine band) 2840—2740, $\nu(OCH_2O)$ 930 cm^{-1}. UV spectrum (ethanol): λ_{max} 230 (sh), 290 nm (log ε 4·03, 3·92). UV spectrum (ethanol–1M-NaOH): λ_{max} 238—242 (sh), 296 nm) log ε 4·00, 4·01). Mass spectrum: *m/e* 325 (M^+). ^{1}H-NMR spectrum (hexadeuteriodimethyl sulphoxide): δ 3·78 (3 H, s, OCH_3), 5·98 (2 H, s, OCH_2O), 6·42—6·88) (4 H, aromatic), 8·68 (1 H, bs, OH). Peak at δ 8·68 disappears on D_2O addition.

Tetrahydrogroenlandicine (*XII*)

The compound *IX* (120 mg) in ethanol (200 ml) was shaken with hydrogen at 2·5—3 atm in the presence of palladised-charcoal catalyst (10%, 80 mg) in a Parr 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 evaporated to get *XII* which was crystallised from chloroform–methanol (55 mg), m.p. 202°C. IR spectrum of the isolated compound is identical with that of tetrahydrogroenlandicine[2]. For $C_{19}H_{19}NO_4 \cdot H_2O$ (343·4) calculated: 66·56% C, 6·18% H; found: 66·74% C, 6·26% H. UV spectrum (ethanol): λ_{max} 230 (sh), 287 nm (log ε 3·99, 3·83). UV spectrum (ethanol–1M-NaOH): λ_{max} 245, 292 nm (log ε 4·07, 3·84). Mass spectrum: *m/e* 325 (M^+), 176, 148. ^{1}H-NMR spectrum (deuteriochloroform–hexadeuteriodimethyl sulphoxide): δ 3·83 (3 H, s, OCH_3), 4·04 (1 H, d, J = 16 Hz, $C_{(8)}$—H), 5·97 (2 H, s, OCH_2O), 6·60 (1 H, s, aromatic), 6·68 (2 H, s, aromatic), 6·77 (1 H, s, aromatic), 8·50 (1 H, bs, OH). Peak at δ 8·50 disappears on D_2O addition.

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