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SYNTHESIS OF HUNNEMANINE

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Abstract—Starting from berberrubine (I), hunnemanine (VIIa) has been synthesized using Perkin's method. Protection of the phenolic group during several steps of the synthesis was afforded by benzylation.

HUNNEMANINE (VIIa) is the only known phenolic base of the protopine group of alkaloids, first isolated[1] from *Hunnemannia fumariaefolia* Sweet (Papaveraceae) and its presence in that species recently confirmed.[2] Its structure was determined[1] by transforming it into allocryptopine (VIIb) by methylation with diazomethane. The position of the phenolic group was determined by ethylation and degradation of the O-ethyl-hunnemanine (VIIc) to 3-ethoxy-4-methoxy-2-methylbenzonic acid, by applying the procedure employed by Perkin.[3]

In view of our synthetic work on protopine alkaloids,[4,5] it was of interest to synthesize hunnemanine (VIIa). Fortunately, berberrubine (I), the starting material, could be easily prepared from berberine.[6]

Catalytic hydrogenation of berberrubine (I) was the best method for preparing (±)-nandinine (II), which on treatment with methyl iodide afforded the α- and β-*methiodides* (IIIa); which were easily transformed into the α- and β-methochlorides (IIIb).

When the mixture of nandinine methiodides was submitted to the Hoffman reaction, the usual *vinylic* (IVa) and *cyclic* (Va) *methines* were obtained, which were differentiated by their UV and NMR spectra and the chemical characterization of the vinyl group.

Difficulties appeared when the preparation of the N-oxide of the cyclic methine (Va) was attempted by the usual methods. We did not succeed in preparing a pure sample of the N-oxide (VIa) but acidic isomerization of the impure product gave a small amount of a compound that in TLC behaved as hunnemanine. Several other substances giving a positive alkaloidal reaction were also present, and it proved to be very difficult to isolate and purify the product responsible for the hunnemanine-like spot.

As the presence of the sensitive phenolic OH could account for the difficulties, it was decided to protect this group. Benzylation of the mixture of α- and β-nandinine methiodides afforded the pure O-*benzylnandinine methiodide* (IIIc) which when

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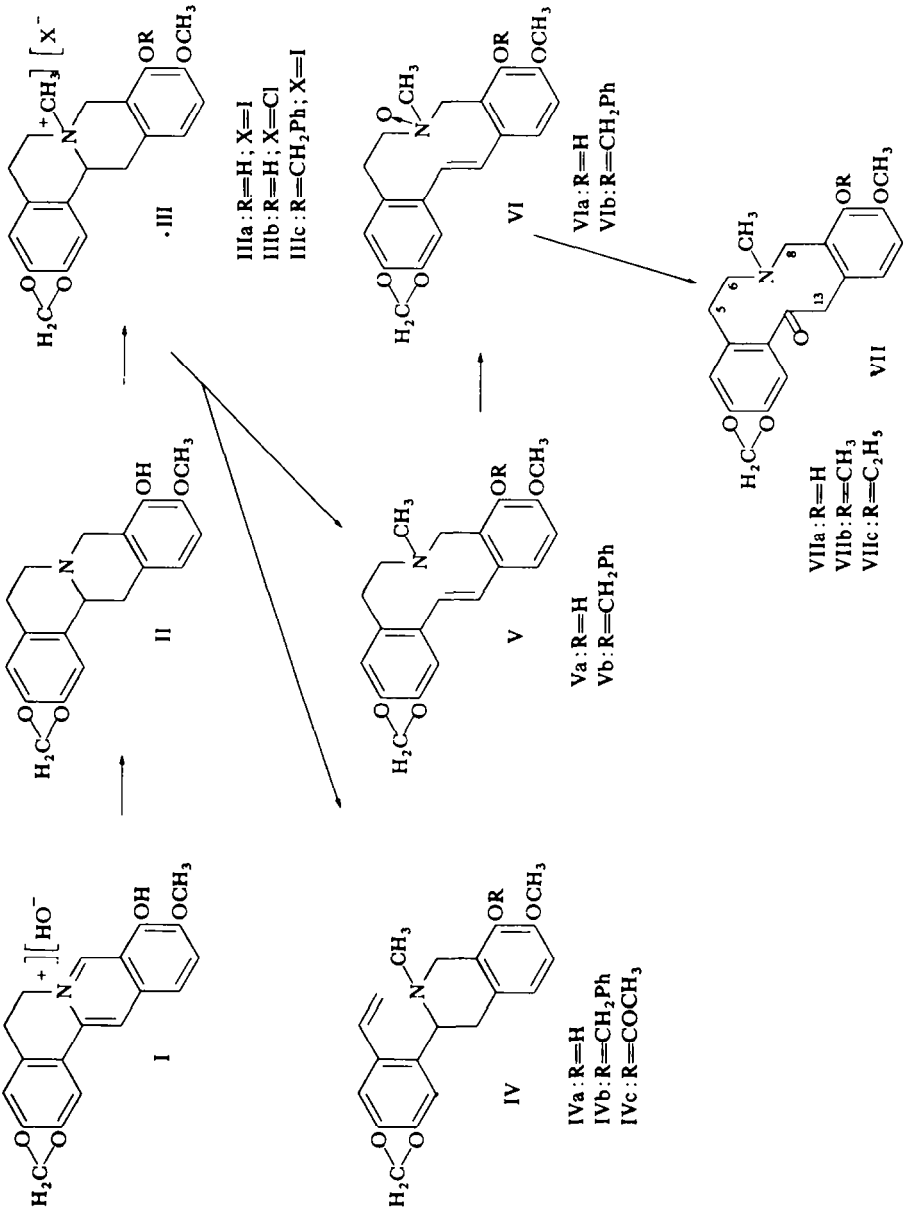
[2] L. Slavíková and J. Slavík, *Coll. Czech. Chem. Comm.* **31**, 1355 (1966).
[3] W. H. Perkin, *J. Chem. Soc.* 815 (1916).
[4] D. Giacopello, V. Deulofeu and J. Comin, *Tetrahedron* **20**, 2971 (1964).
[5] D. Giacopello and V. Deulofeu, *Tetrahedron Letters* 2859 (1966).
[6] G. Frerichs, *Arch. Pharm.* **248**, 276 (1910); E. Späth and G. Burger, *Ber. Dtsch. Chem. Ges.* **59**, 1486 (1926).


I
II
III
IIIa : R=H ; X=I
IIIb : R=H ; X=Cl
IIIc : R=CH2Ph ; X=I
IV
IVa : R=H
IVb : R=CH2Ph
IVc : R=COCH3
V
Va : R=H
Vb : R=CH2Ph
VI
VIa : R=H
VIb : R=CH2Ph
VII
VIIa : R=H
VIIb : R=CH3
VIIc : R=C2H5

submitted to the Hoffman reaction gave also the two usual methines (IVb and Vb).

The cyclic methine (Vb) was obtained in good yield and transformed into a crystalline N-*oxide* (VIb), which when boiled with a mixture of acetic and hydrochloric acids, was isomerized and simultaneously debenzylated, affording as a main product, a base identical with natural hunnemanine (VIIa).

EXPERIMENTAL

M.ps are uncorrected. UV spectra were recorded in 95% EtOH and IR spectra in $CHCl_3$, except as indicated. The NMR spectra were taken in a Varian A-60 spectrophotometer, employing TMS as internal reference. TLC was carried out on "Avicel" cellulose[7] employing n-butanol saturated with water: AcOH (95·5:0·5) as solvent; spots were developed with the modified Dragendorff reagent[8] and iodoplatinic acid.[9] All evaporations were done *in vacuo* and at the lowest possible temp. Organic sols were dried with Na_2SO_4.

Berberrubine (I). An adaptation of the method of Frerichs[6] gave a purer product in an increased yield. Berberinium chloride (25 g) and urea (50 g) were fused for 30 min in an oil bath (200°) with constant stirring. The resulting red mass was dissolved in water (200 ml) and continuously extracted with $CHCl_3$ for 24 hr. The dried $CHCl_3$ extracts, on evaporation, yielded 20 g of a red solid residue which was chromatographed on 600 g neutral alumina (Woelm, grade III).

The column was washed with benzene: MeOH (99:1) which eluted a yellow solid which was discarded. Benzene: MeOH (95:5) was then used, when berberrubine was eluted. The fractions containing that base were evaporated to dryness and the residue, on recrystallization from FtOH, gave 10 g red needles (44%), m.p. 297; R_f 0·21, Frerichs[6] gave m.p. 285°. UV maxima at: 214 (log ε 4·37), 240(4·42), 279(4·31), 327(3·92), 394(4·01), 516(3·67) mμ.

Tetrahydroberberrubine. (±)-nandinine. (II). To a soln of 1·5 g I in 200 ml EtOH, 150 mg PtO_2 was added and the mixture hydrogenated for 24 hr at room temp (45 lbs). After filtering the catalyst and evaporating the filtrate, a colorless oil was obtained, which was recrystallized from n-propanol, giving colorless prisms of II (1·1 g; 76%) m.p. 185–186°; R_f 0·51. UV maxima at: 287 (log ε 3·79) mμ. IR bands at 3450 cm^{-1} (OH). Lit.[10] m.p. 186°.

Reduction of I with NaBHy also gave II, but the product obtained always contained small amounts of the original base which could only be eliminated by chromatography.

(±)-Nandinine α- and β-methiodides. (IIIa). (±)-Nandinine (1·5 g) was boiled for 30 min with MeI (10 ml) when a yellow solid separated out from the soln. The excess MeI was evaporated to dryness, yielding a white residue (1·80 g, m.p. 265–270°). TLC showed that it was a mixture of two products, R_f 0·15 and 0·33. It was suspended in 18 ml MeOH at 25° and the suspension shaken for 30 min. The insoluble material was then filtered off (1·0 g, 45%) m.p. 266–267°, R_f 0·15, and on recrystallization from MeOH, long needles of pure IIIa were obtained, m.p. 280–281°. UV maxima at: 287 (log ε 3·75) mμ. (Found: C, 51·57; H, 4·75; I, 26·82 $C_{20}H_{22}O_4NI$ requires: C, 51·40; H, 4·75; I, 27·18%).

The filtrate from the separation of the crude β-isomer was cooled at 0° for 2 hr. Small prisms of the α-isomer separated (0·4 g; 18%), m.p. 167°, which were recrystallized from EtOH, m.p. 172°, R_f 0·33. UV maxima at: 287 (log ε 3·76) mμ. (Found: C, 51·20; H, 5·18; I, 26·93. $C_{20}H_{22}O_4NI$ requires: C, 51·20; H, 4·75; I, 27·18%).

(±)-Nandinine α-and β-methochlorides. (IIIb). The original mixture of methiodides (2·40 g, m.p. 265–270°) was suspended in MeOH (110 ml) and HCl was passed through the suspension until complete dissolution.[11]

It was then boiled until nitrous acid gave a negative test for I_2 (40 min) and then the solvent removed. The residue, dissolved in warm water (13 ml), gave needles (1·70 g, 88%) m.p. 249°, which on further recrystallization from MeOH produced the pure β-isomer of IIIb, m.p. 267–270°, R_f 0·20 UV maxima at: 236 (log ε 3·95), 286 (3·83) mμ. (Found: C, 64·10; H, 5·80; Cl, 9·84. $C_{20}H_{22}O_4NCl$ requires: C, 63·91; H, 5·90; Cl, 9·44%).

[7] D. Giacopello, *J. Chromatog.* **19**, 172 (1965).
[8] R. Munier and M. Macheboeuf, *Bull. Soc. Chim. Biol.* **38**, 846 (1951).
[9] L. R. Goldbaum and L. Kazyak, *Analyt. Chem.* **28**, 1989 (1956).
[10] T. R. Govindachari, S. Rajadurain and C. V. Ramadas, *J. Sci. and Ind. Res. India* **18B**, 533 (1959).
[11] A. P. Phillips and R. Baltzly, *J. Am. Chem. Soc.* **74**, 5231 (1952).

The aqueous mother liquors were evaporated to dryness and the solid residue recrystallized several times from water yielding the pure α-isomer of IIIb (0·18 g; 9·5%), m.p. 237–238°, R_f 0·46, UV maxima at: 237 (log ε 3·97), 287(3·83) mμ. (Found: Cl, 9·68. $C_{20}H_{22}O_4NCl$ requires: Cl, 9·44%).

Hoffman reaction with the (±)-nandinine methiodides. The crude solid mixture of the methiodides (1·20 g, m.p. 265–270°) was suspended in 20% methanolic NaOH (100 ml) and boiled for 30 min, when a reddish clear soln was obtained. It was then diluted with water, freed from MeOH by partial evaporation and the new extracts were evaporated to dryness giving a brown–reddish oil which contained 2 bases (R_f 0·57 and 0·84).

The oily residue was passed through a column of 40 g silica gel (200 mesh), eluting with acetone. The base with R_f 0·84 was eluted first (440 mg) and latter identified as IVa; and afterwards the second base, R_f 0·57, was collected (250 mg) and characterized as Va.

(a) N-*Methylanhydrotetrahydroberberrubine A* (Va). The fractions containing the second base, R_f 0·57, yielded on evaporation to dryness an oily product (250 mg, 28%), which crystallized on scratching. It was then recrystallized from AcOEt, giving plates, m.p. 113–115°. UV maxima at: 288 (log ε 3·80) mμ. IR bands at: 3600 cm^{-1} (OH) (Found: C, 68·24; H, 6·96; O, 21·00; N, 4·04. $C_{20}H_{21}O_4N$. 0·5 H_2O requires: C, 68·95; H, 6·37; O, 20·67; N, 4·02%). It gives a negative Lemieux[12] reaction and on boiling with EtOH–water was quaternized, and after adding NaI IIIa, m.p. 280–281° (mixed m.p. 280°) was obtained.

(b) N-*Methylanhydrotetrahydroberberrubine* B (IVa) *hydrochloride.* The dried residue (440 mg, 45%) of the fractions containing the base, R_f 0·84, was dissolved in 5 ml EtOH and on adding a few drops of conc HCl, the hydrochloride crystallized out. It was purified by recrystallization from EtOH, giving prisms, m.p. 238°. UV maxima at: 265 (log ε 3·91), 292(3·59) mμ. IR bands at: 3600 (OH), 990 and 920 (vinyl group) cm^{-1}. (Found: C, 63·87; H, 5·76; Cl, 9·30. $C_{20}H_{21}O_4N$.HCl requires: C, 63·91; H, 5·90; Cl, 9·44%). The IR and UV spectra are typical of the vinyl base B (IVa) and this was confirmed because the free base gave a strong positive Lemieux[12] reaction.

Acetylation of the crude IVa with pyridine–AcOH in the usual way gave IVc, which was recrystallized from EtOH to give small prisms, m.p. 183°, R_f 0·91. UV maxima at: 263 (log ε 3·98), 301(3·60) mμ. IR bands at: 1780 (CO), 1200 (acetate band), 990 and 920 (vinyl group) cm^{-1}. The Lemieux reaction[12] was positive. (Found: C, 69·50; H, 6·18; N, 3·63. $C_{22}H_{23}O_5N$ requires: C, 69·28; H, 6·08; N, 3·68%).

O-benzyl-nandinine-β-methiodide (IIIc). A soln of 2·5 g (±)-nandinine methiodides (m.p. 265–270°) in 100 ml EtOH was mixed with 100 ml 10% Na_2CO_3aq, and then 20 ml benzyl chloride added. The 2-phase mixture, which became homogenous on warming, was refluxed for 3 hr. It was then evaporated to dryness, 120 ml water added and the soln again evaporated, repeating this procedure until all the benzyl chloride was eliminated. The yellow solid residue was suspended in 100 ml cold water and filtered; the ppt, dissolved in 60 ml warm 80% EtOH, gave on cooling plates of IIIc m.p. 247° (2·0 g; 60%), R_f 0·65 (2-propanol:water; 3:1). The m.p. did not change on recrystallization from EtOH. (Found: I, 23·28. $C_{27}H_{28}O_4NI$ requires: I, 23·26%).

Hoffman reaction with O-benzyl-β-nandinine methiodide. The crude O-benzyl-nandinine methiodide (1·0 g; m.p. 247°) was dissolved in 300 ml warm water, previously freed of CO_2; moist Ag_2O (from 800 mg $AgNO_3$) was added and the suspension shaken for 20 min. It was filtered off and the clear soln evaporated to dryness avoiding carbonation during the operation. The yellow solid residue on heating to 95–100° *in vacuo* for 15 min was transformed into an oil. Ether was then added (40 ml), a small insoluble fraction was filtered off and well washed with the same solvent. The filtrate on evaporation to dryness gave 700 mg of a solid residue, m.p. 100–105°, which by TLC contained 2 bases (R_f 0·56 and 0·93).

(a) *O-benzyl-N-methylanhidrotetrahydroberberrubine A* (Vb). The solid residue (700 mg, m.p. 100–105°) was refluxed with 25 ml pet ether (b.p. 69–71°), an insoluble fraction filtered off, and the filtrate on cooling gave 510 mg (66%) of Vb, m.p. 114–119° which recrystallized from the same solvent as needles, m.p. 117–119°, R_f 0·56. UV maxima at: 229 (log ε 4·18), 284(3·87) mμ. (Found: C, 75·63; H, 6·39; O, 14·74; N, 3·21. $C_{27}H_{27}O_4N$ requires: C, 75·50; H, 6·34; O, 14·90; N, 3·26%). It gave a negative test for vinyl group and on boiling with EtOH–water was quaternized and when adding NaI, O-benzyl-nandinine-β-methiodide crystallized out, m.p. 246–247° (mixed m.p. 246°).

(b)-*benzyl-N-methylanhydrotetrahydroberberrubine B* (IVb) *hydrochloride.* The former pet ether filtrate from the isolation of the crude Vb was evaporated to dryness giving 217 mg of a yellow oil which was homogenous on TLC (R_f 0·93). It was dissolved in 5 ml warm EtOH, filtered from a small amount of impurities and to the clear filtrate 0·3 ml conc HCl were added. On cooling the hydrochloride crystallized

[12] R. W. Lemieux and E. von Rudloff, *Canad. J. Chem.* 33, 1701 (1955).

out (130 mg, 15%), m.p. 195–198° which recrystallized from the same solvent as prisms, m.p. 198–200°, R_f 0·93. UV maxima at: 262 (log ε 3·87), 297(3·49) mμ. (Found: C, 69·39; H, 6·02. $C_{27}H_{27}O_4N \cdot HCl$ requires: C, 69·59; H, 6·06%). It gives a positive Lemieux reaction[12] for vinyl groups.

O-*benzyl*-N-*methylanhydrotetrahydroberberrubine A* N-*oxide* (VIb). To a soln of 200 mg Vb in 20 ml ether cooled at 0°, 120 mg perbenzoic acid in 2 ml ether at the same temp was slowly added. The resulting suspension was left for 15 hr at −5° when a solid ppt was formed. It was then shaken with 10 ml 2N NaOH, the white solid filtered off and washed with water. After recrystallization from MeOH–water it gave needles (170 mg; 82%) of VIb m.p. 109–110°, R_f 0·77. UV maxima at 216 (log ε 4·53), 301(4·22) mμ. For analysis it was dried for 24 hr at 30°, turning yellow at higher temp. (Found: C, 70·44; H, 6·59; O, 18·96. $C_{27}H_{27}O_5N \cdot H_2O$ requires: C, 69·95; H, 6·31; O, 20·71%).

Hunnemanine (VIIa). To 120 mg VIb in 5 ml AcOH, 5 ml conc HCl were added and the soln refluxed for 30 min. TLC analysis of the reaction mixture, showed that it contained 3 substances giving alkaloidal reactions, with R_f 0·19, 0·49 and 0·83.

The soln was then evaporated to dryness and the residue chromatographed on 12 g cellulose and eluted with water satured n-butanol: AcOH (99·5:0·5). Fractions of 1 ml were collected and the bases eluted in the expected order. The substances with R_f 0·83 and 0·19 were present in small amount and discarded. The middle fractions (R_f 0·49) containing VIIa were evaporated to dryness and gave 91 mg of an amorphous residue. It was dissolved in 7 ml water, 5% $NaHCO_3$ soln added to pH 8 and the soln extracted with $CHCl_3$. On evaporation of the extracts 75 mg (65%) were obtained as an oil which crystallized by adding a few drops of 2-propanol and scratching. The crystals, m.p. 203–204° on recrystallization from the same solvent gave prisms m.p. 207–208°. UV maxima at 233 (log ε 4·11), 285(3·92) mμ. IR bands at 3510 (OH), 1650(CO of protopine alkaloids[13]) cm^{-1}. NMR signals at 1·88 ppm (3H, singlet, N-Me), 2·60 (2H, multiplet, C_6-methylene), 2·92 (2H, multiplet, C_5-methylene), 3·73 (4H, singlet, C_8- and C_{13}-methylene superimposed), 3·88 (3H, singlet, OMe), 5·98 (2H, singlet, methylenedioxy), 6·65–6·98 (4H, multiplet, aromatic protons).

The synthetic product showed no depression of the m.p. when mixed with a sample of natural hunnemanine, m.p. 207–208°, R_f values, UV znd IR spectra were identical for both samples and also with the spectra recorded by Slavíková and Slavík.[2]

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[13] F. A. L. Anet, A. S. Bailey and Sir Robert Robinson, *Chem. & Ind.* 944 (1953). F. A. L. Anet and L. Marion, *Canad. J. Chem.* 32, 452 (1954).