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A Novel Oxidation Stage in the Chemistry of Protoberberine Alkaloids. Synthesis of 7,8-dehydroberbines

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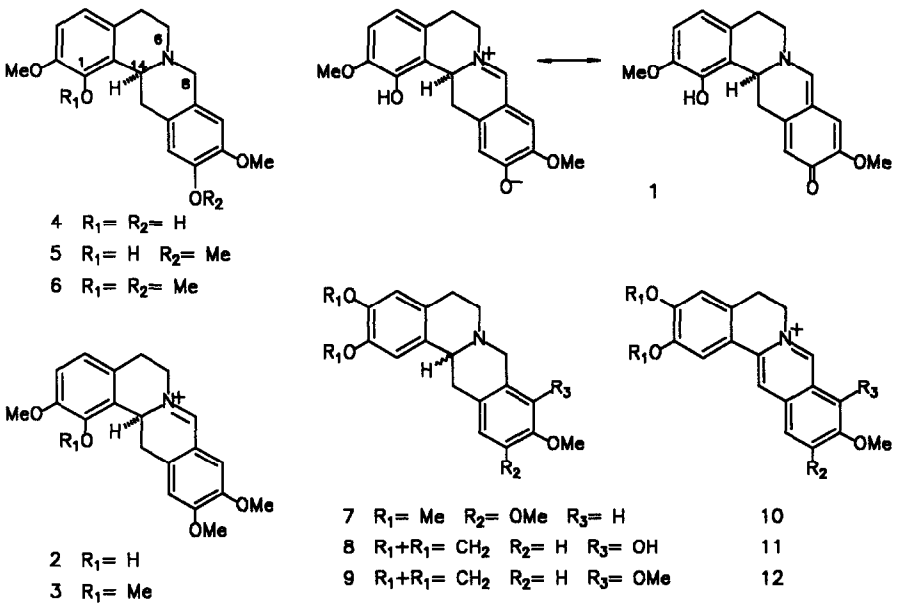
Abstract 1,2-substituted berbines, such as (-)-caseamine, (-)-caseadine and (-)-O-methylcaseadine, are partially oxidized by iodine to the 7,8-dehydroberbines, while the 2,3-substituted berbines are oxidized all the way to the protoberberinium salts This different behaviour is interpreted in terms of the preferred *cis* or *trans* B/C quinolizidine conformation of the starting berbines

Protoberberines constitute an important class of isoquinoline alkaloids due to their pharmacological properties and to their central role in the biosynthesis of several other types of alkaloids including protopines, spirobenzylisoquinolines and rhoeadines[1,2] From the biosynthetic point of view, there are two types of protoberberine alkaloids, those derived from the benzylisoquinoline, reticuline[3], which have oxygenated substituents at positions 2 and 3 of ring-A and those derived from the benzylisoquinoline, crassifoline, which are substituted at positions 1 and 2[4] For both natural and synthetic 2,3-substituted protoberberines, three oxidation stages are known, the berbines (tetrahydroprotoberberines), the 13,14-dehydroberbines, and the protoberberinium salts (protoberberines)[1,5] The 2,3-substituted berbines can be oxidized to the corresponding quaternary protoberberines with a variety of reagents such as iodine, mercuric acetate, or air Protoberberinium salts can easily be reduced all the way to berbines by Zn/HCl, catalytic hydrogenation or mixed hydrides in protic solvents, the reaction in dry aprotic solvents allows the isolation of 13,14-dehydroberbines[6]

Our interest in the synthesis and biosynthesis of crassifoline-derived alkaloids prompted us to investigate the oxidation of 1,2-substituted berbines, since neither the 1,2-substituted protoberberinium salts nor the related 1,2-substituted protopines, benzophenanthridines, phthalidoisoquinolines, rhoeadines or spirobenzylisoquinolines have been isolated from natural sources We report here the synthesis and properties of 7,8-dehydrocaseamine

(1) as well as its methyl ether derivatives **2** and **3**, which represent a novel oxidation stage in the chemistry of the protoberberine alkaloids



The reaction of (-)-caseamine (**4**)[4] with iodine, when performed under standard conditions[7] (either I_2/EtOH or I_2/EtOH/NaOAc) afforded a yellow compound (55% yield) that was not the expected protoberberinium salt, since its mass spectrum indicated the loss of only two mass units from **4** The optical activity measured for the unknown compound invalidated the possibility that positions 13,14- or 7,14- had been oxidized and the five aromatic proton signals in the ^{1}H NMR spectrum excluded the presence of a 5,6- double bond Consequently it was assumed that oxidation took place at positions 7,8 and the betaine-quinonoid resonance structure **1** was proposed for this compound The high field NMR signal recorded for H-8 and the low field signal for C-11 suggested that **1** was largely in the quinoid form Protonation of **1** takes place on oxygen and signals for H-8 and C-11 reach their anticipated values (Table 1)

Table 1 Relevant NMR data for compounds **1**, **2**, **3** and **10** ($CDCl_3$)

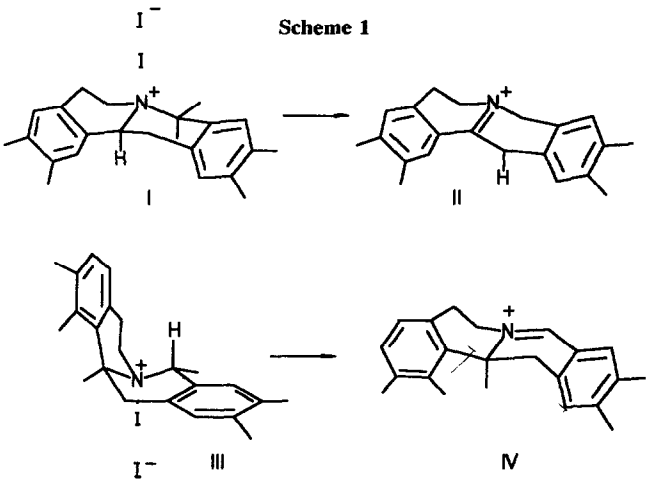
	H-8	H-6eq	H-14	H-9	H-12	C-11	C-13
1	7 82	3 90	4 95	6 60	6 32	174 3	32 5
1+TFA	9 18	4 53	5 18	7 25	6 80	156 1	31 3
2[a]	10 34	4 99	5 23	7 77	6 84	157 7	31 4
3[a]	10 26	4 92	5 29	7 76	6 79	157 4	32 8
10[a]	9 43	4 82	-	7 55	7 44	153 7	118 3

a) NMR spectra were not affected by TFA adition

This partial oxidation of the quinolizidine nucleus was attributed to the stabilization due to the betaine-quinonoid resonance which requires the presence of a phenolic group at C-11 of the starting berbine Contrary to our expectations the reaction of (-)-caseadine (**5**)[4] and iodine also resulted in partial oxidation, (-)-7,8-dehydro-caseadine iodide (**2**) was obtained in 52% yield Its identity was substantiated by analytical data (its FAB/Ms showing a molecular ion at *m/z* 340) and by comparison of UV and NMR data with those recorded for **1** in acid medium Analogous reaction of iodine with the non phenolic (-)-O-methylcaseadine (**6**)[4] gave an excellent yield (97%) of the 7,8-dehydro derivative **3** Under identical reaction conditions the 2,3-substituted berbines, (±)-xylopinine (**7**), (±)-nandinine (**8**) and (±)-canadine (**9**)[8] afforded the predicted protoberberinium iodides, pseudopalmatine (**10**), berberrubine (**11**) and berberine (**12**)(complementary spectroscopic data for **10**, and **11** are given in the experimental details)

The observed difference in behaviour of the 1,2- and 2,3- berbines in their reaction with iodine must be attributed to the substituent at C-1 and its influence on the conformation of the quinolizidine nucleus It is known that 2,3-substituted berbines exist in solution in the *trans* B/C quinolizidine conformation[6,9] (Scheme 1), and it is readily seen that the charge transfer complex **I** formed in the interaction between the axial nitrogen lone pair and the iodine molecule facilitate the *anti* H-14 elimination (the axial H-6 and the pseudoaxial H-8 are less likely to be eliminated from product stability and geometrical reasons) The generated 7,14-dehydro derivative **II** can tautomerize to 13,14-dehydro berbine, thus making feasible further oxidation to protoberberine

Scheme 1



In contrast, the C-1 berbines exist in solution mainly in a *cis* B/C quinolizidine conformation[4,10] so that H-8 is the proton *anti-periplanar* to the axial nitrogen lone pair-iodine complex **III** The elimination from the imonium ion **IV** does not allow any possibility of tautomerization, thus preventing further oxidation of the molecule Our results relating the *cis* conformation of 1,2-substituted berbines and the existence of 7,8-dehydroberbines suggest an alternative pathway to explain the biosynthesis of (-)-malacitanine[11], a 8-hydroxymethyl-caseamine, by alkylation of the electrophilic C-8 position Moreover, these partially oxidized berbines might be involved in the biosynthesis of 7,8-secoberbines (imonium hydrolysis) and 8,8a-secoberbines (Baeyer-Villiger type oxidation)[12], at least for those retaining the configuration at C-14, an assumption presently being investigated

EXPERIMENTAL

All mp's are uncorrected IR spectra were recorded with a Perkin-Elmer 883 spectrometer UV spectra were recorded with a HP-5482A spectrophotometer Optical rotations were measured at 18-20°C with a Perkin-Elmer mod 241 polarimeter Low resolution mass spectra in the electron impact (EIMS) mode were recorded with a HP-5988, high resolution spectra and fast atom bombardment (FABMS) were obtained with a Kratos MS 50 apparatus ^{1}H and ^{13}C-NMR spectra were recorded using a Bruker WP 200 SY spectrometer Proton chemical shifts are referenced to the residual chloroform signal (δ 7 24) and carbon chemical shifts to the solvent ($^{13}CDCl_3$ = 77ppm) The multiplicity of ^{13}C resonances was determined by INEPT experiments The 2D NMR and NOE data were analyzed using Bruker's microprograms TLC were performed on silicagel 60 F 254 plates

Compounds **4** and **5** were isolated from a natural source[4], and **6** was obtained by diazomethane methylation of **4**

(-)-7,8-Dehydrocaseamine (1)

(-)-Caseamine (**4**, 66 mg, 0 2 mmol) was dissolved in EtOH (16 ml) with stirring and iodine (152 mg, 0 6 mmol) was added The mixture was refluxed for 1 h, cooled to room temperature, and several drops of sat $Na_2S_2O_3$ added to reduce excess iodine The reaction mixture was evaporated and the residue was extracted with $CHCl_3$-MeOH (50 1) The soluble portion was purified by preparative TLC using CH_2Cl_2-MeOH (8 1) to give **1** (37 mg, 56%) as a yellow amorphous powder, mp 158-160°C, $[\alpha]_D$ -217 6 (c 0 07, MeOH), Uv λ_{max} nm MeOH (log ε) 204 (4 61), 222h (4 11), 276 (4 10), 320 (3 56), 412 (4 22), +NaOH 206 (4 77), 276 (4 15), 410 (4 43), +HCl 206 (4 52), 218h (4 20), 252 (4 24), 288 (3 83), 314 (3 99), 366 (4 02), IR ν_{max} 3040, 1620-1600 cm^{-1}, ^{1}H-nmr ($CDCl_3$ + CD_3OD) δ (ppm) 7 82 (s, 1H, H-8), 6 71 (d, 1H, J = 8 2 Hz, H-3), 6 60 (s, 1H, H-9), 6 59 (d, 1H, J = 8 2 Hz, H-4), 6 32 (s, 1H, H-12), 4 95 (dd, 1H, J = 16 4 and 4 3 Hz, H-14), 3 90 (broad d, 1H, J = 12 0 Hz, H-6eq), 3 78 (s, 3H, OCH_3 on C-2), 3 67 (s, 3H, OCH_3 on C-10), 3 60 (dd, 1H, J = 16 4 and 4 3 Hz, H-13eq), 3 5 (m, 1H, H-6ax), 2 98 (ddd, 1H, J = 15 5, 12 2 and 3 5 Hz, H-5ax), 2 80 (broad d, 1H, J = 15 5 Hz, H-5eq), 2 51 (t, 1H, J = 16 4 Hz, H-13ax) ^{1}H-nmr ($CDCl_3$ + TFA) δ (ppm) 9 18 (s, 1H, H-8), 7 25 (s, 1H, H-9), 6 82 (d, 1H, J = 8 3 Hz, H-3), 6 80 (s, 1H, H-12), 6 73 (d, 1H, J = 8 3 Hz, H-4), 5 18 (dd, 1H, J = 16 5 and 4 1 Hz, H-14), 4 53 (broad d, 1H, J = 12 0 Hz, H-6eq), 3 88 (s, 3H, OCH_3), 3 79 (s, 3H, OCH_3), 3 70 (dd, 1H, J = 16 5 and 4 1 Hz, H-13eq), 3 60 (m, 1H, H-6ax), 3 15 (ddd, 1H, J = 16 0, 12 7 and 3 5 Hz, H-5ax), 2 97 (broad d, 1H, J = 16 0 Hz, H-5eq), 2 67 (t, 1H, J = 16 5 Hz, H-13ax), ^{13}C-nmr ($CDCl_3$ + CD_3OD) δ (ppm) 174 3 (C-11), 154 5 (C-8), 151 2, 145 9, 142 9 (C-1, C-2, C-10), 138 7, 126 3, 120 1, 108 8 (C-4a, C-8a, C-12a, C-14a), 119 2, 112 1, 110 3 (C-3, C-4, C-9, C-12), 56 0, 55 3, 54 7 (C-14, 2xOCH_3), 52 5 (C-6), 32 5 (C-13), 29 9 (C-5) ^{13}C-nmr ($CDCl_3$ + TFA) δ (ppm) 164 9 (C-8), 156 1 (C-11), 147 1, 145 8, 142 4 (C-1, C-2, C-10), 135 8, 125 6, 117 7, 116 9 (C-4a, C-8a, C-12a, C-14a), 120 2, 115 2, 114 7, 110 0 (C-3, C-4, C-9, C-12), 56 6, 56 4, 56 1 (C-14, 2xOCH_3), 55 8 (C-6), 31 3 (C-13), 29 3 (C-5) HR-Ms m/z 325 1299 $[M]^+$ ($C_{19}H_{19}NO_4$ requires 325 13140) FAB-Ms m/z 326 $(M+1)^+$

(-)-7,8-Dehydrocaseadine iodide (2)

This compound was obtained from (-)-caseadine (**5**, 68 mg, 0 2 mmol) using the procedure described above Chromatographic purification afforded **2** (49 mg, 52%) as a yellow amorphous powder, mp 166-168°C, $[\alpha]_D$ -221 4 (c 0 06, MeOH), Uv λ_{max} nm MeOH (log ε) 204 (4 66), 218h (4 43), 248 (4 24), 288 (4 17), 312h

(3 98), 368 (3 88), +NaOH 206 (4 83), 224h (4 43), 250 (4 01), 2 88 (4 06), 312h (3 61), ^{1}H-nmr ($CDCl_3$) δ (ppm) 10 34 (s, 1H, H-8), 7 77 (s, 1H, H-9), 6 84 (s, 1H, H-12), 6 83 (d, 1H, J= 8 3 Hz, H-3), 6 75 (d, 1H, J= 8 3 Hz, H-4), 5 23 (dd, 1H, J= 16 8 and 4 3 Hz, H-14), 4 99 (broad d, 1H, J= 13 0 Hz, H-6eq), 4 0 (s, 3H, OCH_3), 3 93 (s, 3H, OCH_3), 3 90 (s, 3H, OCH_3), 4 1-3 8 (m, 2H, H-13eq, H-6ax), 3 26 (ddd, 1H, J= 16 5, 12 8 and 3 7 Hz, H-5ax), 2 99 (broad d, 1H, J= 16 5 Hz, H-5eq), 2 84 (t, 1H, J= 16 8 Hz, H-13ax) ^{13}C-nmr ($CDCl_3$) δ (ppm) 165 3 (C-8), 157 7 (C-11), 149 3, 145 7, 142 4 (C-1, C-2, C-10), 134 8, 125 8, 117 9, 117 4 (C-4a, C-8a, C-12a, C-14a), 120 0, 115 8, 110 8, 110 6 (C-3, C-4, C-9, C-12), 56 9, 56 8, 56 4, 55 9, 55 2 (C-14, C-6, 3xOCH_3), 31 4 (C-13), 29 2 (C-5) FAB-Ms ($C_{20}H_{22}NO_4$) m/z 340 (M^+)

(-)-7,8-Dehydro-O-methylcaseadine iodide (3)

(-)-O-Methylcaseadine (**6**, 71 mg, 0 2 mmol) was dissolved in EtOH (15 ml) with stirring and iodine (152 mg, 0 6 mmol) was added The mixture was refluxed for 1 h, cooled to room temperature, and several drops of sat $Na_2S_2O_3$ added to reduce excess iodine The reaction mixture was evaporated and the residue was extracted with $CHCl_3$, dried and the solvent evaporated to give **3** (93 mg, 97%) Yellow amorphous powder, mp 92-96°C, $[\alpha]_D$ -206 1 (c 0 06, MeOH), Uv λ_{max} nm MeOH (log ε) 204 (4 67), 218h (4 49), 250 (4 24), 288 (4 00), 312 (3 99), 366 (3 91), +NaOH 206 (4 85), 224h (4 48), 286 (3 99), ^{1}H-nmr ($CDCl_3$) δ (ppm) 10 26 (s, 1H, H-8), 7 76 (s, 1H, H-9), 6 94 (d, 1H, J= 8 7 Hz, H-3), 6 87 (d, 1H, J= 8 7 Hz, H-4), 6 79 (s, 1H, H-12), 5 29 (dd, 1H, J= 16 8 and 5 1 Hz, H-14), 4 92 (broad d, 1H, J= 12 5 Hz, H-6eq), 3 99 (s, 3H, OCH_3), 3 91 (s, 3H, OCH_3), 3 89 (s, 3H, OCH_3), 3 85 (s, 3H, OCH_3), 4 1-3 8 (m, 1H, H-6ax), 3 67 (dd, 1H, J= 16 8 and 5 1 Hz, H-13eq), 3 25 (ddd, 1H, J=16 2, 12 5 and 3 7, H-5ax), 3 0 (broad d, 1H, J= 16 2 Hz, H-5eq), 2 85 (t, 1H, J= 16 8 Hz, H-13ax) ^{13}C-NMR ($CDCl_3$) δ (ppm) 164 9 (C-8), 157 4 (C-11), 151 3, 149 2, 145 8 (C-1, C-2, C-10), 134 8, 125 7, 125 2, 117 5 (C-4a, C-8a, C-12a, C-14a), 124 1, 115 7, 113 0, 110 4 (C-3, C-4, C-9, C-12), 61 1 (C-14), 56 8, 56 7, 56 5, 56 0, 55 3 (C-6, 4xOCH_3), 32 8 (C-13), 29 1 (C-5) FAB-Ms ($C_{21}H_{24}NO_4$) m/z 354 (M^+)

Anal Calcd for $C_{21}H_{24}NO_4I$ ½H_2O C, 51 43, H, 5 10, N, 2 86 Found C, 51 25, H, 5 00, N, 2 72

Pseudopalmatine iodide (10)

(±)-Xylopinine (**7**, 355 mg, 1 mmol) was dissolved in EtOH (24 ml) with stirring and iodine (762 mg, 3 mmol) was added The mixture was refluxed for 1 h, cooled to room temperature, and several drops of sat $Na_2S_2O_3$ added to reduce excess iodine A yellow precipitate had formed which was filtered and dried, to give a quantitative yield of **10** Mp 244°C (dec)[lit[13] 245°C (dec)] ^{1}H-nmr ($CDCl_3$ + TFA) δ (ppm) 9 43 (s, 1H, H-8), 8 39 (s, 1H, H-13), 7 55 (s, 1H, H-9), 7 44 (s, 1H, H-12), 7 41 (s, 1H, H-1), 6 81 (s, 1H, H-4), 4 82 (t, 2H, J= 6 4 Hz, H-6,6'), 4 10 (s, 3H, OCH_3 on C-9), 4 04, 4 03 (two s, 3H each, 2xOCH_3), 3 95 (s, 3H, OCH_3 on C-4), 3 20 (t, 2H, J= 6 4 Hz, H-5,5') ^{13}C-nmr ($CDCl_3$ + TFA) δ (ppm) 153 7 (C-11), 152 6, 149 2, 139 5 (C-2, C-3, C-10), 144 1 (C-8), 138 0 (C-14), 129 2, 123 2, 123 1, 119 3 (C-4a, C-8a, C-12a, C-14a), 118 3 (C-13), 111 6, 109 3, 106 4 (C-4, C-9, C-12), 105 1 (C-1), 57 1, 56 9, 56 8, 56 3, 55 8 (C-6, 4xOCH_3), 27 2 (C-5)

Berberrubine iodide (11)[14] was prepared from (±)-nandinine (**8**) using the procedure described above Mp 238°C (dec) ^{13}C-nmr ($CDCl_3$ + TFA) δ (ppm) 151 2, 149 0, 145 4, 143 2 (C-2, C-3, C-9, C-10), 144 4 (C-8), 137 6 (C-14), 132 7, 129 6, 117 1 (C-4a, C-8a, C-12a, C-14a), 125 0, 120 1, 119 1 (C-11, C-12, C-13), 108 6 (C-4), 105 1 (C-1), 102 4 (O-CH_2-O), 57 1 (OMe), 56 3 (C-6), 27 5 (C-5)

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