SYNTHESIS OF HYPECORINE AND HYPECORININE ANALOGS FROM 3,4-DIHYDRO-PAPAVERINE[1]

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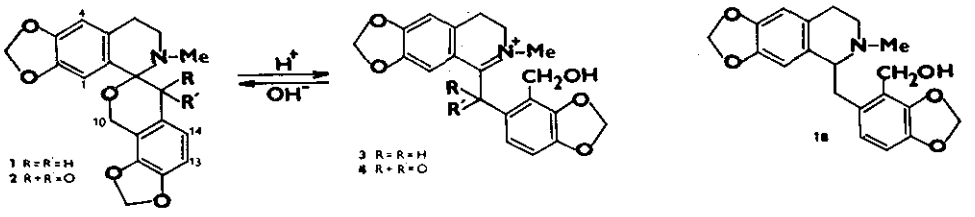
Reaction of 2'-hydroxymethyl-2-methyl-3,4-dihydropapaverinium (10) and ∝-oxo-2'-hydroxymethyl-2-methyl-3,4-dihydropapaverinium salts (11) with hydroxide ions gives cyclic pseudobases 12 and 13, analogs of the alkaloids hypecorine (1) and hypecorinine (2). Derivatives of 2-methylpapaverinium salts form pseudobases by addition of hydroxide ions to immonium bond. Biogenetic conclusions are given.

A new type of isoquinoline alkaloids hypecorine (1) and hypeco-

rinine (2), the latter also known as corydalispirone, have been recently isolated from Hypecoum erectum L.[2,3] and Corydalis incisa Pers.[4] (Papaveraceae). It seems likely that they are derived from the corresponding quaternary salts 3 and 4. They arise by addition of hydroxide ions to the immonium bond in alkaline medium and following rapid cyclization with 2'-hydroxymethyl group[5].



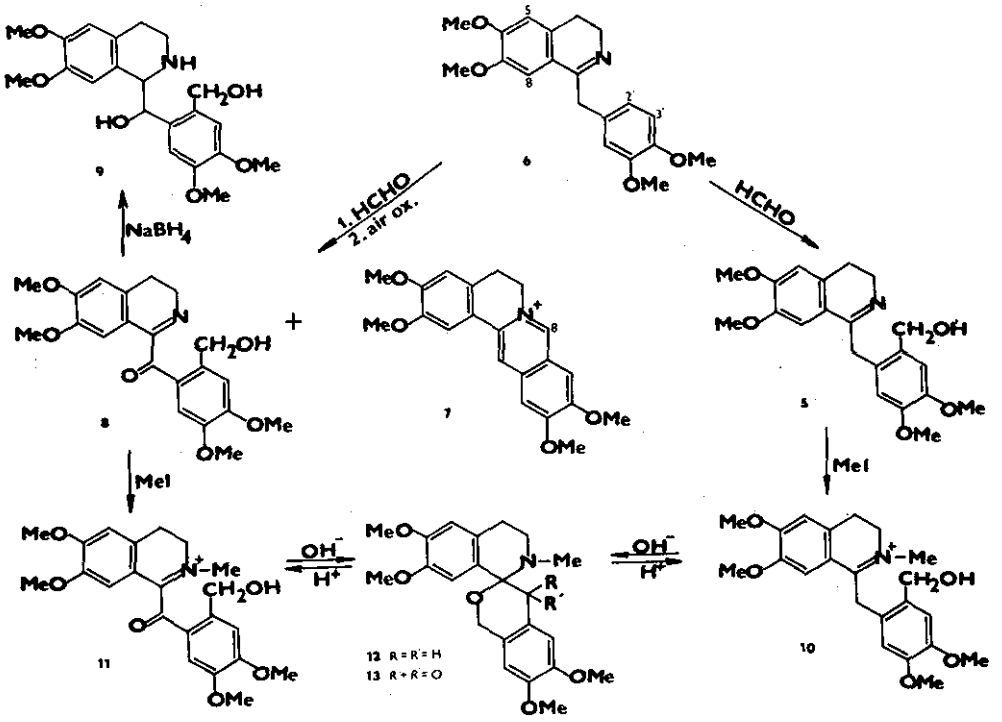
Within the scope of systematic studies of pseudobase formation from isoquinolinium cations, we now report the formation of 2,3,12,13-tetramethoxy analogs of alkaloids 1 and 2 (Scheme 1). The initial 1-(2-hydroxymethyl-4,5-dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (5) was prepared from 3,4-dihydropapaverine (6) as previously described for 2'-hydroxymethylpapaverine.[6] Compound 5, viscous oil, UV (EtOH) λ_{max} 235, 283 and 318 nm (log ε 4.40, 4.13 and 3.92), ^{1}H-NMR ($CDCl_3$) δ 2.60t (Ar-CH_2-CH_2-N), 3.63t (Ar-CH_2-CH_2-N), 3.80s (OMe), 3.86s (OMe), 3.93s (2xOMe), 4.10s (Ar-CH_2-), 4.60s (Ar-CH_2-OH), 4.76bs (Ar-CH_2-OH), 6.66s (Ar-H), 6.70s (Ar-H), 6.93s (Ar-H), 7.28s (Ar-H) in 58% yield; 5.HCl, mp 126-129° (water).[7] The minor product was identified as pseudopalmatinium chloride (7) (UV, IR spectra). Crystallization of the compound 5 from ethanol gave the imino ketone 8, mp 160-162°

(ethanol), MS (m/e) M^+ 385 (0.15, $C_{21}H_{23}NO_6$), 194 (73, $C_{10}H_{10}O_4$), 191 (69, $C_{11}H_{13}NO_2$), 176 (50, $C_{10}H_{10}NO_2$), 165 (100, $C_9H_9O_3$); UV (EtOH) λ_{max} 234, 283 and 316 nm (logε 4.10, 3.97 and 3.78); ^{1}H-NMR ($CDCl_3$) δ 2.20-3.65m (Ar-CH_2-CH_2-N), 3.73s, 3.83s, 3.90s, 3.93s (4xOMe), 4.65 and 5.32 ABq, J=15.0 Hz (Ar-$C\underline{H}_2$-OH), 6.56s (2 Ar-H), 6.60s (Ar-H), 7.46s (Ar-H), IR ($CHCl_3$) 1655 cm^{-1} (ν C=O). Air oxidation is typical for 1-benzyl-3,4-dihydroisoquinoline.[8] Preparative TLC of 2'-hydroxymethyl-3,4-dihydropapaverine (5) (system cyclohexane-diethyl amine 8:2) gave the imino ketone 8 and pseudopalmatine (7).

Sodium borohydride reduction of the compound 8 in 50% aqueous methanol yielded the corresponding amino alcohol 9, mp 183-185° (acetone), MS (m/e) no M^+, 192 ($C_{11}H_{14}NO_2$); UV (EtOH) λ_{max} 235 and 285 nm (logε 4.21 and 3.80); ^{1}H-NMR ($CDCl_3$) δ 2.40-3.20m (Ar-CH_2-CH_2-N), 3.76s (OMe), 3.83s (3xOMe), 4.23 and 4.62 ABq, J=12.0 Hz (Ar-$C\underline{H}_2$-OH), 4.95d, J=6.0 Hz (Ar-$C\underline{H}$-O), 6.50s (Ar-H), 6.72s (Ar-H), 7.03s (Ar-H), 7.22s (Ar-H).

The compounds 5 and 8 were quaternized with methyl iodide in acetonitrile to salts 10 and 11. Compound 10, mp 192-195° (acetone), UV (EtOH) λ_{max} 245, 290, 314 and 368 nm (logε 4.23, 3.77, 3.83 and 3.87); ^{1}H-NMR (DMSO-d_6) δ 3.18t (Ar-$C\underline{H}_2$-CH_2-N^+), 3.63s (N^+-Me), 3.66s (OMe), 3.76s (2xOMe), 3.92s (OMe), 4.13t (Ar-CH_2-$C\underline{H}_2$-N^+), 4.56s (Ar-CH_2-), 4.66s (Ar-$C\underline{H}_2$-OH), 6.40s (Ar-H), 7.00s (Ar-H), 7.13s (Ar-H), 7.36s (Ar-H); pK_{ROH} = 9.66 $\pm$ 0.08.[9] Compound 11, mp 169-171° (acetone), UV (EtOH) λ_{max} 241, 292 and 333 (logε 4.34, 4.12 and 3.95); IR (KBr) 1670 cm^{-1} (ν C=O); ^{1}H-NMR (DMSO-d_6) δ

3.53s (N^+-Me), 3.80s (OMe), 3.83s (2xOMe), 3.93s (OMe), 5.20 and 5.60 ABq, J=15.0 Hz (Ar-CH_2-OH), 6.50s (Ar-H), 6.96s (Ar-H), 7.12s (Ar-H), 7.38s (Ar-H); pK_{ROH} = 11.9 ± 0.1. A decrease in the acidity of 11 as compared with 10 is caused by cross conjugation of the immonium bond with oxo group. Alkalization of the salt 10 by aqueous sodium hydroxide afforded an analog of hypecorine 12,



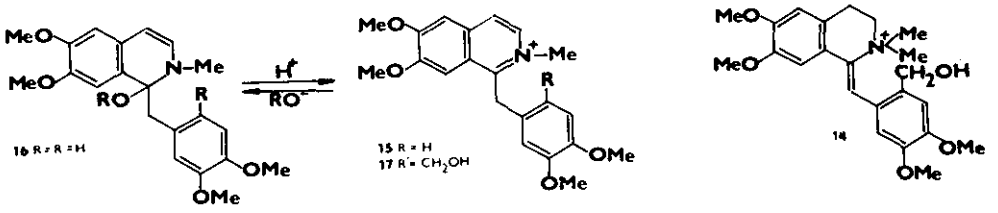
Scheme 1

mp 140-142° (ether), UV (EtOH) λ_{max} 286 nm (logε 3.92); MS (m/e) M^+ 385.1879 (1.4, $C_{22}H_{27}NO_5$), 370 (1.9, $C_{21}H_{24}NO_5$), 206 (100, $C_{12}H_{16}NO_2$), 191 (5.2, $C_{11}H_{13}NO_2$), 190 (9.3, $C_{11}H_{12}NO_2$), 164 (24, $C_{10}H_{12}O_2$); ^{1}H-NMR ($CDCl_3$) δ 2.40s (N-Me), 2.60-3.60m (Ar-CH_2--CH_2-N, Ar-CH_2-), 3.70s (OMe), 3.85s (3xOMe), 4.66 and 4.90 ABq, J=15.0 Hz (Ar-CH_2-O), 6.56s (Ar-H), 6.60s (2 Ar-H), 6.76s (Ar-H). Under the same conditions the salt 11 gave the compound 13, mp 184-186° (acetone), UV (EtOH) λ_{max} 238, 285 and 312 (logε 4.35, 4.14 and 3.85); MS (m/e) M^+ 399.1693 (3.9, $C_{22}H_{25}NO_6$), 206 (38, $C_{12}H_{16}NO_2$), 178 (100, $C_{10}H_{10}O_3$), 150 (6.4, $C_9H_{10}O_2$); ^{1}H-NMR ($CDCl_3$) δ 2.36s (N-Me), 2.40-3.60m (Ar-CH_2-CH_2-N), 3.66s (OMe), 3.83s (OMe), 3.93s (2xOMe), 4.71 and 5.15 ABq, J=15.0 Hz (Ar-CH_2-O), 6.48s (Ar-H), 6.58s (2 Ar-H), 7.53s (Ar-H); IR ($CHCl_3$) 1685 cm^{-1} (ν C=O).

The reaction of the compound 12 with methyl iodide in acetonitrile or benzene led to the quaternary salt 14, mp 192-194° (acetone), UV (EtOH) λ_{max} 218 and 325 nm (logε 4.68 and 4.26); ^{1}H-NMR ($CDCl_3$) δ 2.81s (ax N^+-Me), 3.31s (eq N^+-Me), 3.85s (3xOMe), 3.88s (OMe), 5.11s (Ar-$\underline{CH_2}$-OH), 5.95s (Ar-CH=), 6.58bs (2 Ar-H), 6.85s (Ar-H), 6.88s (Ar-H).

It is assumed that 2-methyl-1-benzylisoquinolinium salts exist in the enamine form in alkaline solution.[10] Reaction of 2-methylpapaverinium iodide (15) with aqueous sodium hydroxide gave the so-called 2-methylisopapaverine, which on the basis of ^{1}H-NMR ($CDCl_3$) δ 3.16s (N-Me), 3.33s (OMe), 3.76s (OMe), 3.86s (2xOMe), 3.96s (Ar-CH_2), 5.35bs (-O$\underline{H}$), 5.60d, J=6.5 Hz (H-3), 6.43d,

J=6.5 Hz (H-4), 6.50s (Ar-H), 6.80s (3 Ar-H), 7.03s (Ar-H) can be ascribed structure 16. The ^{1}H-NMR spectrum of 15 (DMSO-d_6), after its alkalization in situ with sodium methoxide, showed only the 1-methoxide adduct δ 3.10s (N-Me), 3.16s (OMe), 3.61s (OMe), 3.68s (OMe), 3.70s (2xOMe), 5.58d, J=6.5 Hz (H-4), 6.30-7.10m (H-3, 5 Ar-H). In 2'-hydroxymethyl-2-methylpapaverinium (17) and 2-methyl-3,4-dihydropapaverinium iodides (6.MeI) it also comes to addition of hydroxide or methoxide ions to the C-1 atom, ^{1}H-NMR (DMSO-d_6, 0.1M CD_3ONa) of 17 δ 3.03s (N-Me), 3.08s (OMe), 3.53s (OMe), 3.65s (OMe), 3.66s (OMe), 5.50d, J=6.5 Hz (H-4), 6.50s (Ar-H), 6.53d, J=6.5 Hz (H-3), 6.56s (2 Ar-H), 6.98s (Ar-H), 6.MeI, pK_{ROH} = 8.53 $\pm$ 0.1, ^{1}H-NMR (DMSO-d_6, 0.1M CD_3ONa) δ 2.25s (N-Me), 2.60-3.30m (Ar-CH_2-CH_2-N), 3.46s (OMe), 3.58s (OMe), 3.68s (2xOMe), 6.35s (H-5), 6.73s (H-8), 6.76d, J=8.4 Hz (H-3'), 7.30d, J=2.0 Hz (H-6'), 7.51dd, J=8.4, 2.0 Hz (H-2'). Formation of enamine could not be proved.



The presence of corydalisol (18) and hypecorinine (s. corydalispirone) (2) in C. incisa[4] indicates their close genetic relationship. Corydalisol (18) appears to be a precursor of quaternary

1-(2-hydroxymethylbenzyl)-3,4-dihydroisoquinoline alkaloids. Corydalisol (18) is not a precursor of rhoeadine alkaloids.[11] The values of the equilibrium constants of pseudobase formation (pK_{ROH}) of the two analogs 12, 13 indicate that hypecorine (1) and hypecorinine (2) are secondary artifacts. In plants they exist in form of quaternary salts 3 and 4. They arise during isolation from the corresponding quaternary salts. The formation of artifacts from quaternary salts was discussed in connection with narceine alkaloids.[12] We assume that in plants the existence of isoquinoline alkaloids in form of quaternary salts is a common phenomenon.

REFERENCES

1 This paper constitutes Part LXXIV on Isolation and Chemistry of Alkaloids from some Plants of the Family Papaveraceae. (Part LXXIII: V. Preininger, J. Novák, V. Šimánek, and F. Šantavý, Planta Medica, 1978, 33.

2 L.D. Yakhontova, M.N. Komarova, M.E. Perel'son, K.F. Blinova, and O.N. Tolkachev, Khim. Prirod. Soedin., 1972, 624.

3 L.D. Yakhontova, M.N. Komarova, O.N. Tolkachev, and M.E. Perel'son, Khim. Prirod. Soedin., 1976, 491.

4 G. Nonaka and I. Nishioka, Chem. Pharm. Bull., 1975, 23, 294.

5 V. Šimánek and V. Preininger, Heterocycles, 1977, 6, 475.

6 W. Wiegrebe, V. Krüger, H. Reinhart, and L. Faber, Arch. Pharm., 1968, 301, 50.

7 The compound gave satisfactory elemental analysis for the formula given.

8 J.A. Weisbach, J.L. Kirkpatrick, E. Macko, and B. Douglas, J. Med. Chem., 1968, 11, 752.

9 The equilibrium constants K_{ROH} for pseudobase formation were measured spectrophotometrically in 50% w/w aqueous ethanol.

10 S. Ruchirawat, U. Borvornvinyanant, K. Hantawong, and Y. Thebtaranonth, Heterocycles, 1977, 6, 1119.

11 H. Rönsch, Phytochemistry, 1977, 16, 691.

12 V. Preininger, J. Veselý, O. Gašić, V. Šimánek, and L. Dolejš, Collection Czechoslov. Chem. Commun., 1975, 40, 669.

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