1,2-Dehydroreticuline: Conversion of Iminium Salts Into Enamines

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J. Nat. Prod., **1993**, 56 (6), 973-975• DOI:
10.1021/np50096a029 • Publication Date (Web): 01 July 2004

Journal of Natural Products
Vol. 56, No. 6, pp. 973-975, June 1993

1,2-DEHYDRORETICULINE: CONVERSION OF IMINIUM SALTS INTO ENAMINES[1]

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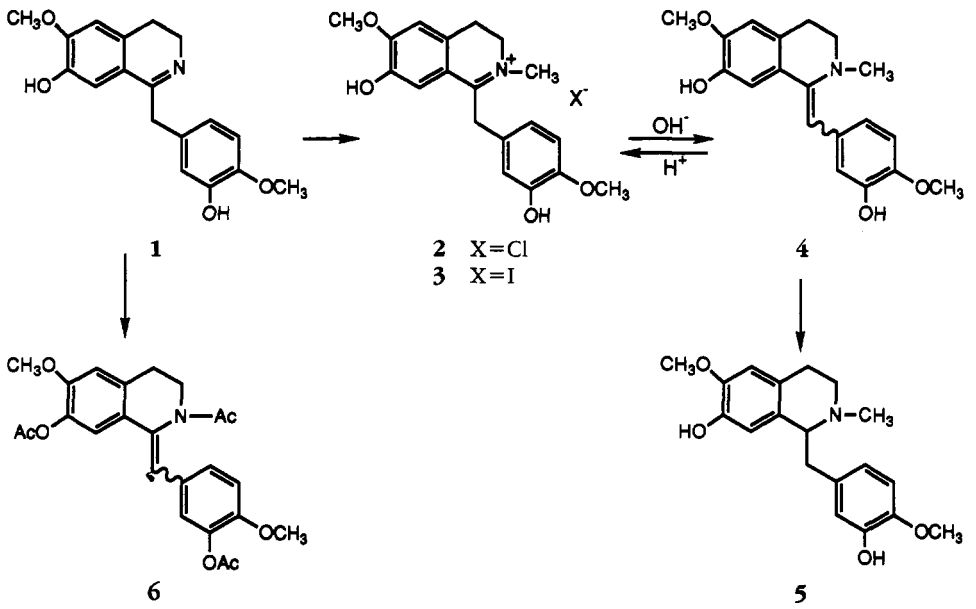
ABSTRACT.—1,2-Dehydroreticulinium iodide [**3**] is converted at pH 8 and above into the enamine **4**. It is suggested that the cytosolic $NADPH_2$-dependent enzyme which converts 1,2-dehydroreticulinium salts at alkaline pH 7.8 may be operating on the enamine, rather than a quaternary iminium salt.

The biosynthesis of morphine alkaloids from (*S*)-reticuline requires conversion of the *S* into the *R* enantiomer which also is a natural alkaloid (1,2). It is assumed that this transformation proceeds via a 1,2-dehydroreticulinium salt (3) since the chloride **2** was found to occur naturally (4). A cytosolic and $NADPH_2$-dependent enzyme, found in Berberidaceae plants and operating at pH 7.8, was reported to control this reaction (5). It is well established that quaternary 1-benzyl-substituted 3,4-dihydroisoquinolines exist in alkaline milieu as enamines (6), and that *N*-acylated analogues undergo in the presence of chiral catalysts a highly stereospecific reduction (7). It seemed prudent, in light of these reports, to explore whether quaternary 1,2-dehydroreticulinium salts were stable under the basic conditions used in their enzymatic reduction or whether they existed in the form of enamines. We now present evidence that 1,2-dehydroreticulinium iodide [**3**], prepared by a published procedure (8), is present at pH 8 and above in considerable amounts as the enamine **4**.

The enamine **4** was extracted from an aqueous suspension of the quaternary iodide **3** after the addition of $NaHCO_3$ (pH 8.5), or from an aqueous suspension of **3** in a buffered solution at pH 8. It was found from the ^{1}H-nmr spectra that the enamine **4** in pH 8.5 solution contained 18% of the quarternary salt, while at pH 8 it contained 60% of the quarternary salt. The enamine **4** was very polar on tlc [Si gel, $CHCl_3$-MeOH (4:1)] but clearly separated from the much less polar reticuline [**5**] which was used for reference (9) and from the more polar **3**. Amorphous **4** showed a molecular ion in the ms at *m/z* 328, and its ^{1}H-nmr spectrum showed an allylic proton at 5.79 ppm which was absent in **5**. The uv spectrum of **4** in MeOH showed maxima at 270 and 326 nm. On addition of acid to the alcoholic solution of **4** the uv maxima displayed a bathochromic shift and became identical with the uv spectrum of **3**, which showed maxima at 253, 311, and 370 nm. Reduction of **4** with $NaBH_4$ in MeOH and catalytic reduction of **4** in MeOH over Pt-catalyst afforded **5**, which was isolated as its perchlorate salt and identical with a reference sample (9) (Scheme 1).

The structure of the amorphous enamine **4** is supported by its *m/z* of 328, by the presence of a vinylogous proton at 5.79 ppm, which is present in the triacetate **6** at 6.37 ppm, and by its uv spectrum showing maxima at 270 and 326 nm. Presence of the OH group in the

[1]This paper is dedicated to Hans Heine, Director of Licensing and Product Planning at Madaus AG., Cologne, Germany, who died on June 5, 1992.



SCHEME 1

benzylidene moiety as a clearly separated doublet at 8.75 ppm suggests that **4** is a mixture of geometrical isomers as present in *N*-formylated (10) and *N*-ethoxycarbonylated analogues (11).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mp (uncorrected) Thomas Hoover capillary mp apparatus; uv spectra (λ max in nm, measured in MeOH) Hewlett-Packard-8450-A UV/VIS spectrophotometer; ^{1}H nmr spectra Varian-XL-300 (300 Hz) spectrometer, δ values in ppm relative to internal TMS, coupling constants (*J*) in Hz; cims (NH_3) Finnigan-1015D; hrms Hitachi-Perkin-Elmer RMU-6E instrument; tlc Si gel plates from Analtech Inc.; solvent system A,$CHCl_3$-MeOH-NH_4OH (90:9:1), B, $CHCl_3$-MeOH (4:1); pH 8.00 buffer solution from Chemical Manufacturing Division, Fisher Scientific, Fair Lawn, NJ.

3,4-Dihydro-1-(3′-hydroxy-4′-methoxybenzyl)-6-methoxyisoquinolin-7-ol [**1**].—This compound was synthesized as described by Teitel and Brossi (8).

3,4-Dihydro-1-(3′-hydroxy-4′-methoxybenzyl)-6-methoxy-2-methylisoquinolin-7-ol iodide [**3**].—Compound **3** was synthesized as described in Teitel and Brossi (8): uv λ max 250, 311, 368; ^{1}H nmr (DMSO-d_6) δ 3.06 (t, 2H, *J*=7.5 Hz, 4-CH_2), 3.74–3.70 (d, 6H, OMe), 3.90 (s, 3H, NMe), 4.04 (t, 2H, *J*=7.5 Hz, 3-CH_2), 4.40 (s, 2H, CH_2-Ar), 6.48 (d, 1H, *J*=9 Hz, H-6′), 6.70 (d, 1H, *J*=9 Hz, H-5′), 6.86 (s, 1H, H-2′), 7.07 (s, 1H, H-8), 7.36 (s, 1H, H-5), 9.06 (s, 1H, OH), 9.59 (s, 1H, OH).

3,4-Dihydro-1-(3′-hydroxy-4′-methoxybenzylidene)-6-methoxy-2-methyl isoquinolin-7-ol [**4**].—A. Compound **3** (100 mg, 0.22 mmol) was dissolved in 5 ml of saturated $NaHCO_3$ solution (pH 8.5) and extracted with CH_2Cl_2 (25 ml×6). The alkaline aqueous solution was evaporated in vacuo and the residue washed with CH_2Cl_2 (50 ml). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated in vacuo to give an orange-colored amorphous solid: uv λ max 270, 326; cims $[MH]^+$ 328; hrms $[M]^+$ 327.1479 ($C_{19}H_{21}NO_4^+$ requires 327.1471); ^{1}H nmr (DMSO-d_6) δ 2.60 (s, 3H, NMe), 2.67–3.06 (dt, 4H, *J*=6 Hz, 3,4-CH_2), 3.74 (s, 3H, OMe), 3.77 (s, 3H, OMe), 5.79 (s, 1H, CH-Ar), 6.70-7.11 (m, 5H, Ar-H), 8.31 (s, 1H, OH), 8.75 (d, 1H, OH).

B. Compound **3** (250 mg, 0.55 mmol) was dissolved in 10 ml of a pH 8.0 buffer solution ($NaOH+KH_2PO_4$) and extracted with CH_2Cl_2 to give a pale yellow solid (114 mg, 0.35 mmol, 63.6%). The ^{1}H-nmr spectra with an intensity ratio of the peaks at 3.91 (=NMe, intensity 98.5) and 2.61 (-NMe, intensity 65.0) established that 60% of the quaternary salt and 40% of the enamine **4** were present.

1,2,3,4-Tetrahydro-1-(3′-hydroxy-4′-methoxybenzyl)-6-methoxy-2-methyl isoquinolin-7-ol perchlorate (reticuline perchlorate; **5**·*HClO$_4$*).—A. Compound **4** (50 mg, 0.15 mmol) was dissolved in 5 ml of MeOH, and 10 mg of $NaBH_4$ was added. The mixture was stirred at room temperature for 1.5 h and evaporated in vacuo to give a light brown oil which was dissolved in $CHCl_3/H_2O$ (10 ml/10 ml). The H_2O layer was extracted with $CHCl_3$ (10 ml×2). The combined $CHCl_3$ layers were washed

with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo to give a colorless oil. This was converted in boiling iPrOH on addition of 60% $HClO_4$ into the perchlorate salt as off-white crystals (42.7 mg, 0.1 mmol, 66.3%): mp 173–174° [lit. (8) mp 128–130°; lit. (12) mp 144–145°]; ms, ^{1}H nmr, and tlc identical with those of reticuline (9). The mp's of **5**·$HClO_4$ given in the literature vary considerably.

B. Compound **4** (59 mg, 0.18 mmol) was dissolved in 5 ml of MeOH, and 10 mg of PtO_2 was added. The mixture was stirred at room temperature under H_2 until the tlc indicated the reaction to be complete. The reaction mixture was filtered through celite, and the filtrate was evaporated in vacuo to give a light brown oil which was treated in the same way as in method A to give the perchlorate salt as off-white crystals (28 mg, 0.065 mmol, 36.1%): ms, ^{1}H nmr, and the tlc were identical with those of an authentic sample of reticuline (9).

3,4-Dihydro-1-(3'-acetoxy-4'-methoxybenzylidene)-7-acetoxy-6-methoxy-2-acetylisoquinoline [**6**].—Dihydroisoquinoline **1** (20 mg) was dissolved in 2 ml of Ac_2O, and a little DMAP (4-dimethylaminopyridine) was added. The reaction mixture was stirred at room temperature overnight and then evaporated in vacuo. The residue was dissolved in $CHCl_3$, and the solution was washed with saturated $NaHCO_3$, 2 N HCl, and brine and dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo to give a yellow oil which was purified by preparative tlc [Si gel, $CHCl_3$-MeOH (100:2), eluted twice] to give **6** as a colorless oil as a mixture of rotamers (24 mg, 85% yield): cims $[MH]^+$ 440; ^{1}H nmr ($CDCl_3$) δ 2.23 (s, 6H, OAc), 2.28 (s, 3H, NAc), 2.94 (t, 2H, J=6.6 Hz, 4-CH_2), 3.83 (s, 6H, OMe), 3.94 (t, 2H, J=6.6 Hz, 3-CH_2), 6.37 (brs, 1H, CH-Ar), 6.76–7.23 (m, 5H, Ar-H).

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Received 6 November 1992