SYNTHESIS OF LIMOUSAMINE, A 4-HYDROXYLATED CULARINE

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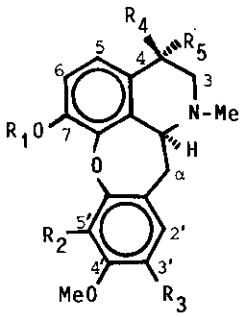
Abstract- LTA treatment of cularidine 1c as described by Umezawa afforded a 2:3 mixture of limousamine 1a and its 4-epimer 1g, whose stereochemistry is discussed. DDQ oxidation of the O-methyl derivative 1h gave the first 3,4-dioxocularine alkaloid 9.

INTRODUCCION

The isolation of the first two 4-hydroxylated cularines, limousamine 1a[1] and 4-hydroxysarcocapnine 1b[2] has recently been reported. The first total synthesis of 1b, based on the Ullmann condensation of a regioselectively 4-hydroxylated (acetoxylated) tetrahydrobenzylisoquinoline 2 has also been described[2]. However, this lead tetraacetate-mediated hydroxylation reaction gave a greater percentage (9:1) of the tetrahydrobenzylisoquinoline precursor of the non-natural epimer than of that of 1b. We would now like to describe the first synthesis of *limousamine 1a using a different hydroxylation approach.*



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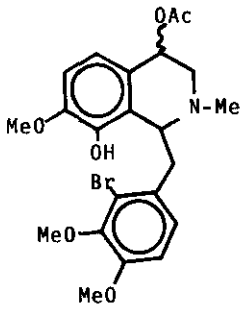

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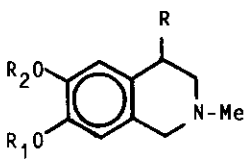
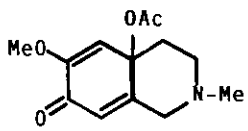
1a R_1=R_2=R_5=H, R_3=OMe, R_4=OH
1b R_1=Me, R_2=OMe, R_3=R_5=H, R_4=OH
1c R_1=R_2=R_4=R_5=H, R_3=OMe
1d R_1=Ac, R_2=R_5=H, R_3=OMe, R_4=OAc
1e R_1=Ac, R_2=R_4=H, R_3=OMe, R_5=OAc
1f R_1=Ac, R_2=R_4=R_5=H, R_3=OMe
1g R_1=R_2=R_4=H, R_3=OMe, R_5=OH
1h R_1=Me, R_2=R_5=H, R_3=OMe, R_4=OH
1i R_1=Me, R_2=R_4=R_5=H, R_3=OMe
1j R_1=Me, R_2=OMe, R_3=R_4=R_5=H

Due to the presence of the phenolic function at position C-7 of limousamine, which makes the synthesis of a precursor like 2 difficult, we turned our attention to the direct introduction of a hydroxy function at the C-4 position of the cularine nucleus. Direct hydroxylation at position C-4 of the tetrahydroisoquinoline nucleus has mainly relied on the use of lead tetraacetate (LTA)[3] or vanadium oxytrifluoride (VOF_3)[4]. The former requires the use of a guaiacol-type 1,2,3,4-tetrahydroisoquinoline[3]. 3a or 3b, oxidation of which gives a p-quinol 4 or o-quinol acetate 5, which rearranges to a 4-acetoxy derivative[5] (3c or 3d). LTA has found wide applicability in the aporphine[8] and tetrahydroprotoberberine[9] series, and has allowed the alkaloid cataline[10] 6d to be obtained starting from thaliporphine 6a via intermediate 6b, and compound 7b from tetrahydrojatrorrhizine 7a. The use of VOF_3 has been limited to the aporphine group, staring with nonphenolic compounds. Thus oxidation of glaucine 6c with the aid of VOF_3 in TFA is highly stereospecific, giving cataline 6d in 61% yield[4]. In view of these possibilities, we approached the synthesis of limousamine 1a by the hydroxylation of the parent compound cularidine 1c, which has also been isolated from Corydalis claviculata (L)D.C.





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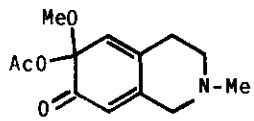

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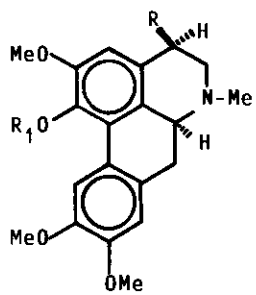
3a R_1=H, R_2=Me, R=H

3b R_1=Me, R_2=H, R=H

3c R_1=Ac, R_2=Me, R=OAc

3d R_1=Me, R_2=H, R=OAc

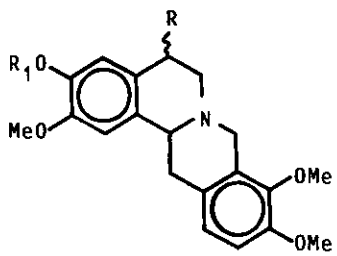


6a R_1=H, R=H

6b R_1=H, R=OAc

6c R_1=Me, R=H

6d R_1=Me, R=OH

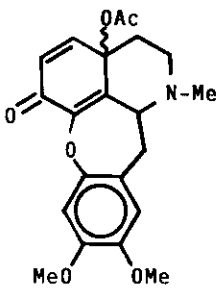


7a R_1=H, R=H

7b R_1=H, R=OAc (diastereomeric mixture)

RESULTS AND DISCUSSION

Oxidation of 1c with LTA in glacial acetic acid for 30 min and careful work-up[11] gave the oily p-quinol acetate 8, which after treatment with acetic anhydride/conc. sulfuric acid for 30 min[11] and column chromatography afforded a diastereomeric mixture of cularidine-4,7-diacetates 1d and 1e (38% yield) together with cularidine-7-acetate 1f (32% yield). The latter was identified by direct comparison with a synthetic sample obtained by acetylation (acetic anhydride/pyridine, rt; 24 h) of cularidine 1c, to which it was hydrolysed.



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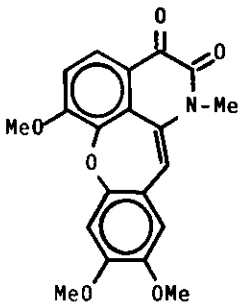

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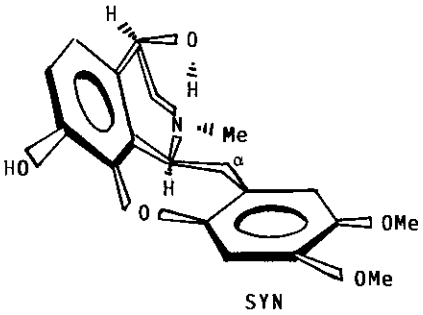
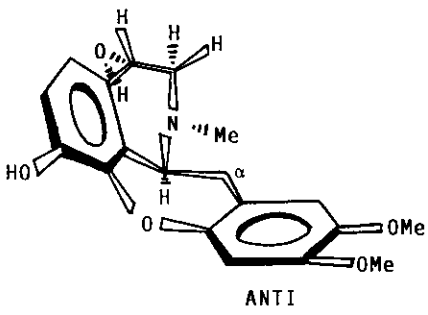
The PMR spectrum of the inseparable mixture of 1d and 1e (2:3 ratio) clearly showed the incorporation of an oxygen substituent at C-4 indicated by the broad triplets appearing at 5.92 (J=3.3 Hz) and 5.97 (J=5.0 Hz) ppm, and a widely separated signal for H_1 4.33(dd, $J_{1-\alpha\alpha}$=3.5 Hz, $J_{1-\alpha\beta}$=11.47 Hz) and 4.65(dd, $J_{1-\alpha\alpha}$ =3.4 Hz, $J_{1-\alpha\beta}$=12.09 Hz) respectively. This mixture was hydrolyzed in a basic medium (THF/2% Na_2CO_3, rt, 2 h) to afford in 85% yield a 2:3 mixture of epimeric alcohols 1a and 1g which were totally separated by careful repeated t.l.c. The former was identified as limousamine 1a by comparison of its spectroscopic data with those published[1] for the alkaloid. We have previously shown by PMR experiments[2] that limousamine 1a, with H_1 at 4.08 ppm, must have syn stereochemistry betwenn H_1 and H_4, as originally suggested[1] on the basis of a comparison between the H_4 chemical shift and that observed in the aporphine and berberine series. Epi-limousamine 1g must therefore possess anti-stereochemistry, with H_1 appearing at 4.52 ppm. These values can serve as a configurational diagnostic for 4-hydroxylated cularines. The fact that H_4 exhibits the same signal at the same position in both epimers (1a: 4.59 ppm; 1g: 4.56 ppm) must be due to ring B having a different conformation in each, making the hydroxyl group pseudoaxial in both. This may be attributed to the great flexibility of the cularine skeleton, together with a small peri-effect between a pseudoequatorial -OH at C-4 and H_5 and a stabilizing intramolecular hydrogen bond between the -OH and the nitrogen lone pair. By contrast, in the aporphine series the natural cataline 6d has a pseudoaxial hydroxyl group[10] which in the epimer is pseudoequatorial.

The synthesis of 4-hydroxycularines allows access to other oxidized members of this group, the dioxocularines and the aristocularines[12]. Thus, DDQ oxidation (2.5 mol equiv., 80ºC, 2 h) of the described compound O-methyllimousamine 1h (obtained by diazomethane methylation of limousamine 1a)[1] gave the 3,4-dioxo-



SYN

1a



ANTI

1g

cularine 9 in 40% yield. This highly colored compound has recently been isolated in very minor quantities in Corydalis claviculata (L)D.C.[13] and its structure is now confirmed by the above synthesis.

Finally, in connection with the hydroxylation step, it is noteworthy that direct oxidation of the non-phenolic cularines (cularine 1i and sarcocapnine 1j) with VOF_3[4] afforded mainly unchanged starting material, together with minor components with tetrahydrobenzylisoquinoline structure, in strong contrast with what occurs when VOF_3 is used in the aporphine series[4].

EXPERIMENTAL

Materials and techniques

Melting points were determined with a Büchi apparatus and are uncorrected. Infrared spectra were taken in KBr pellets with a Pye Unicam spectrometer. Ultraviolet-visible spectra were determined in ethanol solution on a Pye Unicam SP-1700 spectrophotometer. NMR spectra were recorded on either a Varian CFT-20 or a Bruker WM-250 spectrometer; chemical shifts are reported in parts per million (ppm) downfield (δ) from internal tetramethylsilane; the solvent for both ^{1}H-nmr and ^{13}C-nmr spectra was deuteriochloroform unless otherwise stated. Routine mass spectra were obtained using a Kratos MS-25 instrument operating at 70 eV. Combustion analyses were performed with a Perkin-Elmer model 240 B at the Inorganic Chemistry Department.

All reactions were monitored by thin-layer chromatography (tlc) carried out on 0.2-mm silica gel 60 GF-254 (Merck) plates using UV light and iodine vapour as the developing agent. Preparative-layer chromatography was performed on 0.5 mm x 20 mm x 20 mm silica gel 60 GF-254 (Merck) plates. Column chromatography was conducted with silica gel 60 (Merck) or neutral aluminium oxide Activity grade I (Woelm).

Reactions sensitive to air or moisture were conducted in ovendried glassware under an atmosphere of dry nitrogen or argon using dry freshly distilled solvents. Benzene was dried and distilled under nitrogen from sodium benzophenone

ketyl.

All the starting materials and reagents used in this work were either commercially available with 98% or higher purity and used without further purification, or were prepared by standard literature procedures.

LTA treatment of cularidine 1c

To a solution of 0.4 g (1.22 mmol) of cularidine 1c in 5 ml of glacial acetic acid 0.58 g (1.46 mmol, 1.2 mol equiv.) of 90% $Pb(OAc)_4$ was added in one portion at room temperature, with magnetic stirring maintained for 30 min. The mixture was poured into ice-water, neutralized with $NaHCO_3$ and extracted with CH_2Cl_2 (5x40 ml). The organic layer was washed with brine, dried (Na_2SO_4) and evaporated to dryness (T<40ºC) to give an unstable residue of the p-quinol acetate 8, which was used immediately. IR(KBr) ν_{max}: 1685(CO), 1740(-OAc). PMR($CDCl_3$, 250MHz, δ): 6.61 and 6.14(AB_q, J=9.9Hz, H_6 and H_5), 6.59 and 6.48(2s, 2H, H_2, and H_5,), 3.85 and 3.77(2s, 6H, 2xOMe), 3.40-2.80(m, 4H, $-CH_2-$), 2.47(s, 3H, N-Me), 2.17(s, 3H, OAc).

To the above residue dissolved in 3 ml of acetic anhydride, a mixture of 0.18 g of conc. H_2SO_4 and 0.4 ml of acetic anhydride, was added dropwise at room temperature with stirring continued for 30 min. The mixture was poured into ice-water and worked up as described above to give a residue which was further purified by column chromatography. In subsequent TLC, the higher R_f spot afforded a mixture of the epimeric 4,7-diacetoxycularidines 1d and 1e (0.2 g, 38% yield); PMR(250MHz, δ): *the underlined signals below belong to the main epimer*, 7.30-6.50(m, ArH), 5.97(t, J=5.0Hz, H_4), 5.92(broad t, J=3.3Hz, H_4), 4.65(dd, $J_{1-\alpha\alpha}$=3.4Hz, $J_{1-\alpha\beta}$=12.09Hz, H_1), 4.33(dd, $J_{1-\alpha\alpha}$=3.5Hz, $J_{1-\alpha\beta}$=11.47Hz, H_1), 3.86, 3.85, 3.81 and 3.80(4s, OMe), 2.65(s, NMe), 2.62(s, NMe), 2.42(s, 7-OAc), 2.41(s, 7-OAc), 2.13(s, 4-OAc), 2.08(s, 4-OAc). MS m/e(%): 427(M^+, 36), 412(12), 352(22), 310(67), 308(19), 262(55), 220(54), 178(46), 86(42), 84(67), 60(100).

The lower R_f spot afforded, 0.145 g (32% yield) of 7-acetoxycularidine 1f (cularidine acetate) as a syrup which was crystallized as its hydrochloride, mp 250-252ºC (decomp.) (Lit. 250-252ºC)[14]. PMR (250 MHz, $CDCl_3$, δ): 6.92 and 6.88(AB_q, J=8.3Hz H_5 and H_6), 6.56 and 6.50(2s, 2H, H_2, and H_5,), 4.35(dd, $J_{1-\alpha\alpha}$=3.5Hz, $J_{1-\alpha\beta}$=11.7Hz H_1), 3.84 and 3.79(2s, 6H, 2xOMe), 3.30-2.70(m, 6H, $-CH_2-$ alif), 2.57(s, 3H, NMe), 2.39(s, 3H, OAc). MS m/z(%): 369(M^+, 57), 354(100), 312(91), 69(82).

Hydrolysis of 4,7-diacetoxycularidines 1d and 1e. Synthesis of limousamine 1a and 4-epilimousamine 1g.

To a stirred solution of 0.2 g (0.468 mmol) of epimeric 4,7-diacetoxycularidines 1d and 1e in 20 ml of THF was added an equal volume of aqueous 2% Na_2CO_3 solution and stirring was maintained for 2 h. Solvent was evaporated to a small volume and water (25 ml) was added to the residue, which was extracted with CH_2Cl_2 (3 x 40 ml). The organic extracts were dried (Na_2SO_4) and evaporated to dryness. The residue obtained was subjected to silica gel preparative separation using 2% $MeOH/CH_2Cl_2$ as eluent.

The fast-moving component (0.081 g, 50.5% yield) was identified as 4-epilimousamine 1g, mp 120°C (ethanol). PMR(250 MHz, $CDCl_3$, δ): 7.13 and 6.87(AB_q, J=8.3Hz, H_5 and H_6), 6.73 and 6.52(2s, 2H, $H_{2'}$ and $H_{5'}$), 4.56(broad t, J=2.9 Hz, H_4), 4.52, 3.20 and 2.90(ABx, H_1, $H_{\alpha\alpha}$ and $H_{\alpha\beta}$ respectively, $J_{1-\alpha\alpha}$=3.3Hz, $J_{1-\alpha\beta}$=12.1Hz, $J_{\alpha\alpha-\alpha\beta}$=15.2Hz), 3.14(dd, $H_{3\alpha}$, $J_{3\alpha-4}$=2.8Hz, $J_{3\alpha-3\beta}$=11.0Hz), 2.84(dd, $H_{3\beta}$, $J_{3\beta-4}$=3.0Hz, $J_{3\beta-3\alpha}$=11.0Hz), 3.86 and 3.80(2s, 6H, 2xOMe), 2.64(s, 3H, NMe). MS m/e(%): 343(M^+, 9), 342(48), 327(100), 325(22), 322(26), 310(25), 308(26). Anal.Calcd for $C_{19}H_{21}NO_5$: C, 66.47; H, 6.12; N, 4.08. Found: C, 66.82; H, 6.00; N, 4.41. The slower moving epimer proved to be the natural limousamine 1a (0.054 g, 34% yield), identified by comparison of its spectroscopic data with those published[1] for the alkaloid. This product was subjected to O-methylation by diazomethane to give the known[1] O-methyllimousamine 1h.

DDQ oxidation of O-methyllimousamine 1h. Synthesis of 4,5-dioxocularine 9.

To a deoxygenated solution of 1h (0.14 g, 0.392 mmol) in dry benzene (40 ml), 0.23 g (0.98 mmol, 2.5 mol equiv.) of DDQ were added in one portion and the mixture was refluxed with stirring under inert gas for 2 h. The residue after evaporation of solvent was passed through a basic Al_2O_3 (Act III) column using CH_2Cl_2 as eluent, to afford 0.057 g (40% yield) of a red solid which crystallized from EtOH, mp 212-214°C. PMR(250 MHz, $CDCl_3$, δ): 8.05 and 7.20(AB_q, J=8.7Hz, H_5 and H_6), 6.92, 6.69 and 6.65(3s, 3H, ArH), 4.07, 3.94 and 3.87(3s, 9H, 3xOMe), 3.68(s, 3H, NMe). ^{13}CMR($CDCl_3$, 62.89MHz, δ): 175.30(CO), 156.89(CO), 156.86(s), 151.36(s), 148.92(s), 146.85(s), 141.41(s), 134.33(s), 129.57(s), 126.72(d), 121.90(s), 119.96(s), 118.12(d), 113.91(d), 111.62(d), 105.24(d), 56.65(q), 56.38(q), 56.28(q) and 32.83(q). MS m/e(%): 367(M^+, 100), 339(38), 324(45), 296(57), 238(38), 210(26). Anal.Calcd for $C_{20}H_{17}NO_6$: C, 65.39; H, 4.63; N, 3.81. Found: C, 65.26; H, 4.84; N, 4.07.

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