Chemical Conversion of Lycotonine into an Aconitine Alkaloid, 7-Deoxylycoctonine

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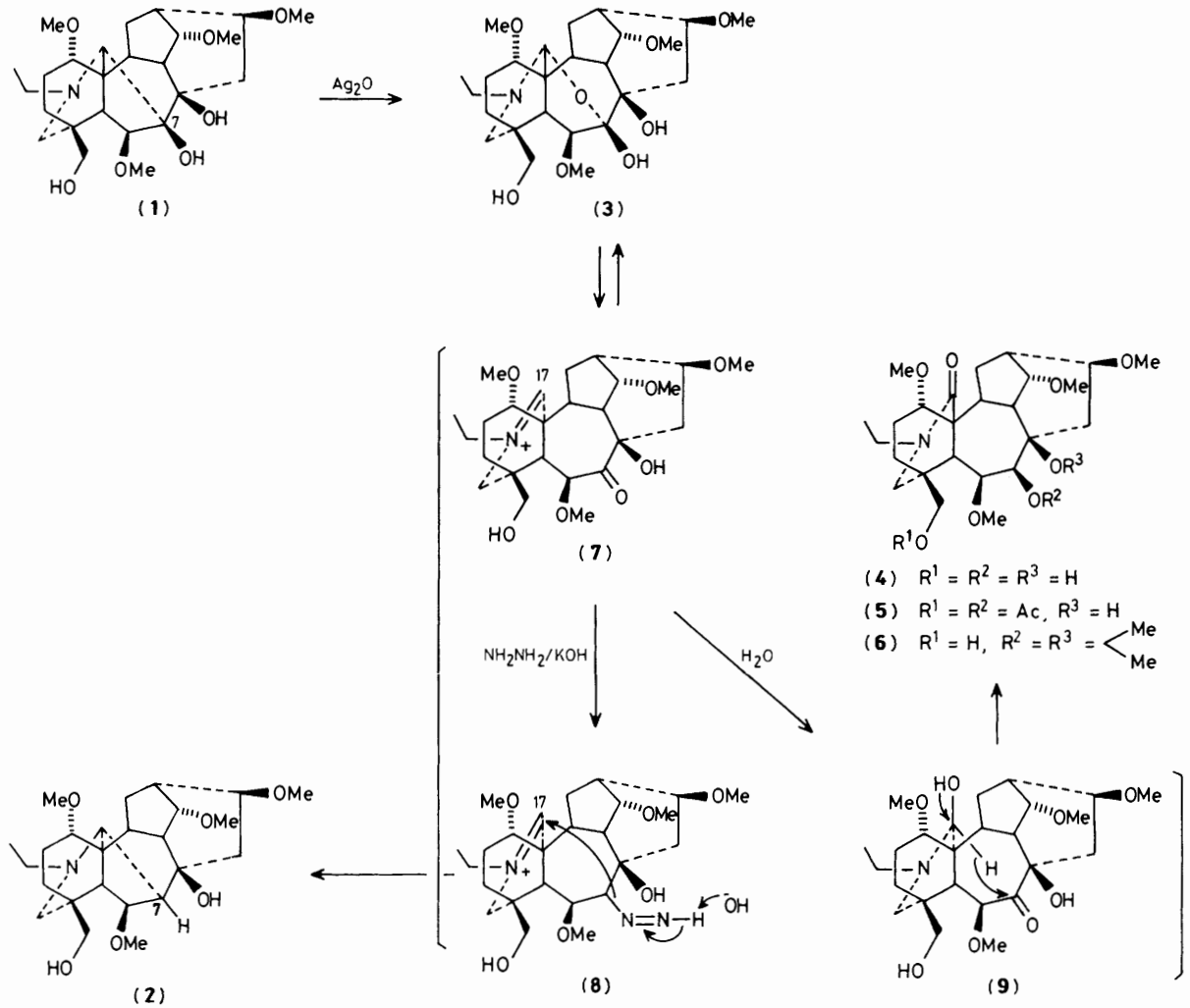
The first chemical correlation of a lycoctonine with an aconitine alkaloid has been achieved by selective removal of the hydroxy group at C-7 in lycoctonine (**1**) utilizing Huang-Minlon reduction of hydroxylycoctonine (**3**); the crystal structure of the aconotine alkaloid (**2**) has been determined.

Over 160 C_{19}-diterpenoid alkaloids have been isolated from plants of the *Aconitum* and *Delphinium* species to date. Most of these may be classified into two groups, aconitine and lycoctonine, which are defined by a simple difference in structure. Thus, lycoctonine alkaloids always possess an oxygen function at C-7, while aconitine alkaloids lack a substituent at C-7.[1] However, there is no report on the chemical correlation between these two groups. In this communication we describe the first chemical conversion of a lycoctonine into an aconitine alkaloid, 7-deoxylycoctonine (**2**), by selective removal of the hydroxy group at C-7 in lycoctonine (**1**). In our synthetic plan, the crucial step was



Scheme 1

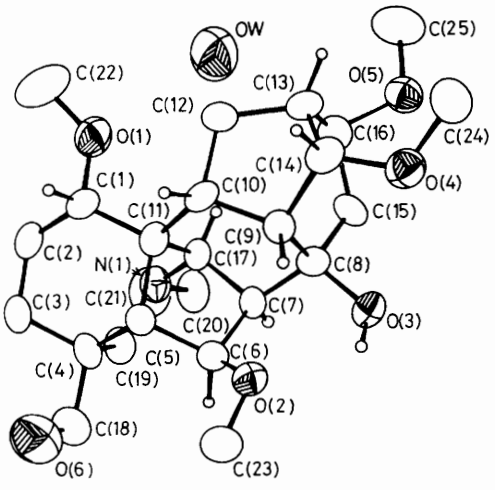


Figure 1. ORTEP drawing of the *X*-ray crystal structure of (**2**).

intramolecular C–C bond formation between the iminium carbon and the carbanion at C-7 produced by the Huang-Minlon reduction of hydroxylycoctonine (**3**).

Oxidation of lycoctonine (**1**), a major component of *Aconitum gigas* Lev et Van.,[2] with Ag_2O afforded hydroxylycoctonine (**3**)[3] in 82% yield. Treatment of (**3**) by the Huang-Minlon method[4] (NH_2NH_2, KOH, triethylene glycol at 160—175 °C, 1.5 h, then 200—220 °C, 3 h) under azeotropic conditions gave two isolable products. The major product (**2**) (37% yield, m.p. 118—121 °C) has the molecular formula $C_{25}H_{41}NO_6$, *i.e.* one oxygen less than that of (**1**). Comparison of the ^{13}C n.m.r. spectrum of (**2**)† with that of (**1**)[5] afforded

† ^{13}C N.m.r. data for (**2**): δ 83.2(C-1), 26.2(C-2), 31.8(C-3), 38.6 (C-4), 44.4(C-5), 84.8(C-6), 51.5(C-7), 74.6(C-8), 49.5(C-9), 37.8 (C-10), 48.6(C-11), 29.2(C-12), 46.4(C-13), 84.2(C-14), 39.4(C-15), 82.1(C-16), 63.4(C-17), 67.7(C-18), 53.9(C-19), 49.4(N–CH_2), 13.4(Me), 56.1, 57.5, 57.7, 56.1(4OMe). The C-7 resonance in (**2**) is shifted 36.9 p.p.m. upfield of that of (**1**). The observed downfield shift of the C-15 signal of (**2**) by 5.8 p.p.m. compared with the corresponding signal for (**1**) is caused by a 1,3-hydrogen–hydrogen interaction[8] between C-7–H and C-15–α-H.

evidence for the absence of the hydroxy group at C-7. Furthermore the major product was confirmed by *X*-ray analysis (Figure 1) as the desired 7-deoxylycoctonine (**2**).‡ The minor product of the Huang-Minlon reduction, obtained as an amorphous powder [(**4**), $C_{25}H_{41}NO_8$, 12%] after chromatographic separation, has a six-membered lactam ring (i.r. ν 1630 cm^{-1}). Spectroscopic analysis of (**4**) and its diacetate (**5**) [^{1}H n.m.r. δ 4.72 s,C-7–H)] and acetonide (**6**) [m.p. 106—108 °C, ^{1}H n.m.r. δ 4.08 (s,C-7–H); 4.18 (d, *J* 10.2 Hz, C-6–H); 3.16 (d, *J* 10.2 Hz, C-5–H)] demonstrates the generation of a secondary hydroxy group at C-7. By Dreiding model analysis, the dihedral angle between C-7–H and C-6–H is *ca.* 90° and that between C-6–H and C-5–H is *ca.* 180°; consequently these protons appear as singlet, doublet, and doublet, respectively. Compound (**4**) was also obtained in 80% yield by alkaline treatment of (**3**) (KOH, H_2O, 120 °C, 3 h).[6]

The most plausible mechanism for the formation of (**2**) and (**4**) is that shown in Scheme 1. In alkaline solution, (**3**) would be equivalent to the keto-iminium intermediate (**7**). The carbanion at C-7 generated under the Huang-Minlon conditions attacks the iminium carbon (intramolecular Mannich reaction) to produce 7-deoxylycoctonine (**2**). On the other hand, hydride transfer *via* (**9**) to the carbonyl function from the α-side (intramolecular Cannizzaro reaction) yields lactam (**4**) having a β-hydroxy group at C-7.

The successful transformation of lycoctonine (**1**) into an aconitine alkaloid utilizes a novel reaction between C-7 and C-17 positions in the diterpene alkaloid skeleton and is an important stage in the study of the biosynthesis of aconite alkaloids.[7]

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‡ *Crystal data* for (**2**): $C_{25}H_{41}NO_6 \cdot H_2O$ (from ethyl acetate–methanol), monoclinic, space group $P2_1$, a = 10.776(2), b = 8.077(1), c = 14.634(3) Å, β = 103.67(2)°, Z = 2, U = 1237.6 Å^3, D_c = 1.26 g cm^{-3}, Mo-K_α-radiation, λ = 0.71069 Å. The structure was solved by direct methods (MULTAN 74) and refined by block diagonal least squares to R = 0.082 for 2474 unique reflections with $|F_o| > 3\sigma(|F_o|)$, $3 < 2\theta < 55°$, measured on a Rigaku AFC-5 diffractometer. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

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