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AN UNUSUAL OXIDATION OF AN N-CH_3 GROUP TO AN N-CHO GROUP BY OSMIUM TETROXIDE

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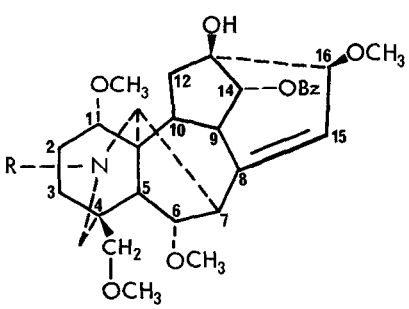
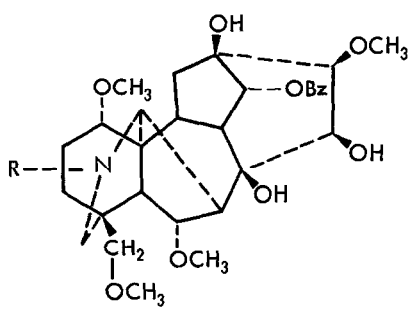
Treatment of pyrodelphinine (1) with osmium tetroxide afforded a mixture of the cis-hydroxylation product 2 and an unexpected product 3 in the ratio of 4:1, respectively. Similarly, oxidation of delphinine (5) afforded α-oxodelphinine (6; 75%) and oxidation of mesaconitine (8) furnished oxonitine (9; 92%). Thus a very selective oxidation of the N-methyl group of delphinine and mesaconitine is effected by osmium tetroxide.

We wish to report an unusual oxidation of an N-CH_3 group to an N-CHO group during treatment of pyrodelphinine (1) with osmium tetroxide. During synthetic work on C_{19}-diterpenoid alkaloids, we used osmium tetroxide for the hydroxylation of the C(8)-C(15) double bond of pyrodelphinine. The reaction afforded the cis hydroxylation product **2** and a minor polar compound **3** in the ratio of 4:1, respectively. The structure of the minor product **3** was determined by a single-crystal X-ray analysis and subsequently compound **3** was synthesized from α-oxopyrodelphinine (4).

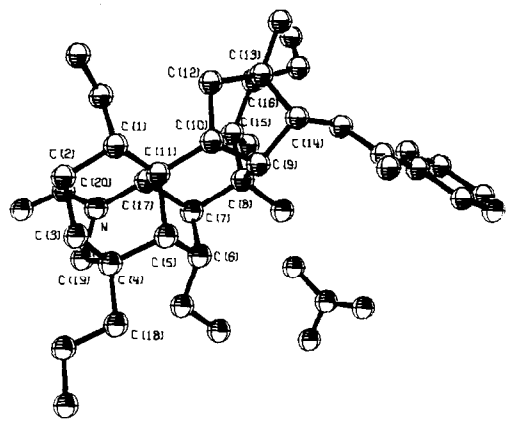


1 R = CH_3
4 R = CHO



2 R = CH_3
3 R = CHO

To a solution of pyrodelphinine (135 mg) in dry pyridine (2.5 ml), osmium tetroxide (87 mg) in dioxane (2 ml) was added and the mixture was stirred at room temperature for 1.5 hrs. A solution of sodium bisulphite (150 mg) in water (2.5 ml) and pyridine (3.8 ml) was then added and after 15-20 minutes the clear orange solution was extracted with dichloromethane (3x30 ml). Evaporation of the dried (anhydrous Na_2SO_4) extract gave a brownish gum (125 mg) consisting of two compounds. These were separated by chromatography on a small column of Al_2O_3 (Act. III). Compound **2**, mp. 241.5-243°C, was eluted first from the column. Alkaline hydrolysis of compound **2** afforded 15-epihypaconine.[1] The second compound (**3**) crystallized from acetone as plates, mp. 246-248°C; $[\alpha]_D^{25}$ - 24.8° (c 1, MeOH); $C_{31}H_{41}NO_{10}$. 1/2 CH_3COCH_3 (ms, elemental analysis); IR ($CHCl_3$):ν max 3443 (hydroxyl), 1697 (N-CHO), 1655 (carbonyl), 1600 (aromatic), and 1110 (ether) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.26, 3.36, 3.40 and 3.56 (each 3H, s, OCH_3), 4.96 (1H, d, C(14)-β-H), 7.53-8.20 (aromatic protons) and 8.16 (1H, bs, N-CHO); ^{13}C NMR ($CDCl_3$): 169.1, 162.6, 133.4, 129.9, 128.6, 86.2, 83.2, 81.9, 80.5, 79.3, 77.1, 71.7, 67.1, 63.3, 60.3, 59.4, 58.2, 57.2, 55.7, 49.3, 46.1, 42.6, 37.9, 36.6, 34.4, and 28.4 ppm. These spectral data are consistant with structure **3** for the minor product. This structure was confirmed by X-ray analysis. Compound **3** was also prepared from α-oxopyrodelphinine (**4**)[2] by osmylation using conditions similar to those described above.



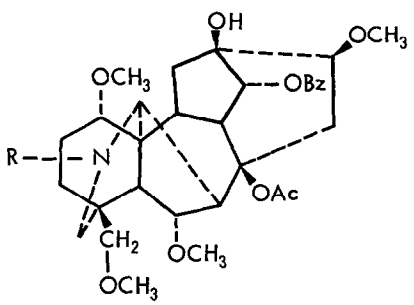
ORTEP DRAWING OF COMPOUND 3.

A crystal of compound **3** approximately 0.5 x 0.4 x 0.2 mm., was mounted on a glass fiber. Preliminary examination and data collection were performed on an Enraf-Nonius CAD-4 diffractometer using CuKα radiation (λ = 1.5418Å). The crystals were monoclinic, space group = $P2_1$, a = 12.503(7), b = 8.410(4), c = 15.697(7)Å, β = 101.55(5)°, and $d_{calcd.}$ = 1.26 g cm^{-3} for two molecules of $C_{31}H_{41}NO_{10}$ and one molecule of acetone in the unit cell. A total of 2585 reflections with $\theta \leq 60°$

were measured with ω -2 θ scans of width (1.2 + 0.14 tanθ)°, and 1807 of these were observed at the 2σ level of significance after Lorentz and polarization corrections had been applied.

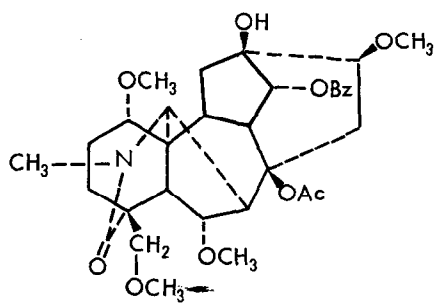
Direct methods[3] were, at first, unsuccessful in solving the structure, but when the known C_{19}-diterpenoid alkaloid skeleton was utilized during E calculation, direct phasing of the data proceeded smoothly. An E synthesis revealed 41 of the 42 atoms in the alkaloid molecule. Refinement[4] of these atoms and subsequent difference syntheses revealed the remaining atom, plus a disordered solvent molecule, and most of the hydrogen atoms. All hydrogen atoms not located on difference maps, except those of the solvent molecule, were placed in idealized positions. All nonhydrogen atoms in the molecule were refined anisotropically, while the solvent molecule, and all but the methyl hydrogens, were isotropically refined. The quantity minimized in least-square refinement was $\underline{w}(\Delta \underline{F})^2$, where the weight of a reflection $\underline{w} = (1.0+((|\underline{F}|-9.0/10.0)^2)^{-1}$. The final $\underline{R}$ factor was 0.058 and $\underline{R}_w$=0.067 for the observed reflections.[5]

Because of the small size of the electron density peaks for the solvent atoms, and the presence of short contacts between the solvent molecule and its symmetry related partner, we concluded that only one molecule of acetone crystallized per unit cell. A disordered model for the acetone molecule was used, but was not entirely satisfactory as evidenced by several peaks of approximately 0.25eÅ^{-3} in its vicinity on a difference map calculated at the conclusion of refinement. The oxygen was identified by its lower temperature factor and by its short distance from H(8OH): 2.30(10)Å. Other hydrogen bonds in the crystal structure include an intramoecular bond between O(15) and O(8): H(15-OH)-O(8)=2.30(7)Å; and an intermolecular bond between O(13) and O(1): O(1)-H(13-OH)'= 2.30(8)Å, (x,y,z)'=1.0-x,1/2+y, -z.



5 R = CH_3

6 R = CHO



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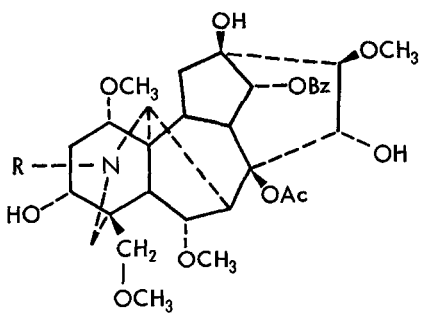
To explore this reaction further, we treated delphinine (5), the parent compound of pyrodelphinine, with OsO_4 under similar reaction conditions. α -Oxodelphinine (6) was produced in good yield (75%) with the oxidation occurring selectively at the N-CH_3 group. By contrast, treatment of delphinine with potassium permanganate[2] afforded a mixture of α -oxodelphinine (6) and

β-oxodelphinine (7). In a similar reaction of OsO_4 with mesaconitine (8), oxonitine (9) was formed in almost quantitative yield (92%). In both the above reactions the products were carefully purified and identified by comparison (mp, $[\alpha]_D$, ir, ^1H and ^{13}C nmr, ms) with authentic samples prepared by known procedures.[2,6]

Recent work [7,8] indicates that osmium tetroxide reacts with tertiary amine type alkaloids under non-reducing conditions to give $OsO_4.L$ adducts (L=tertiary amine). Schroder further indicates that the $OsO_4.L$ adduct probably forms an internal oxo-osmium (VI) ester via an inter- or intra- molecular reaction with the double bond. As far as we are aware ours is the first report of the oxidation of an N-CH_3 group to an N-CHO group by osmium tetroxide. Formation of compounds **3** and **6** from pyrodelphinine and delphinine, respectively, and compound **9** from mesaconitine (8) by oxidation with OsO_4 is very unusual and systematic study is in progress to determine the generality of this oxidation among other tertiary amine type alkaloids.



8 R = CH_3

9 R = CHO

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5. Tables (7 pp) of atomic coordinates, bond distances, bond angles and thermal parameters, all with standard deviations, are available on request from the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lenfield Road, Cambridge CB2 1EW, England.
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