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SYNTHESIS OF O,N-DIACETYL-3β-HYDROXY-5α,12α-JERVAN-11-ONE WITH 17-EPI-CONFIGURATION BY HYPOIODITE REACTION (1,2)

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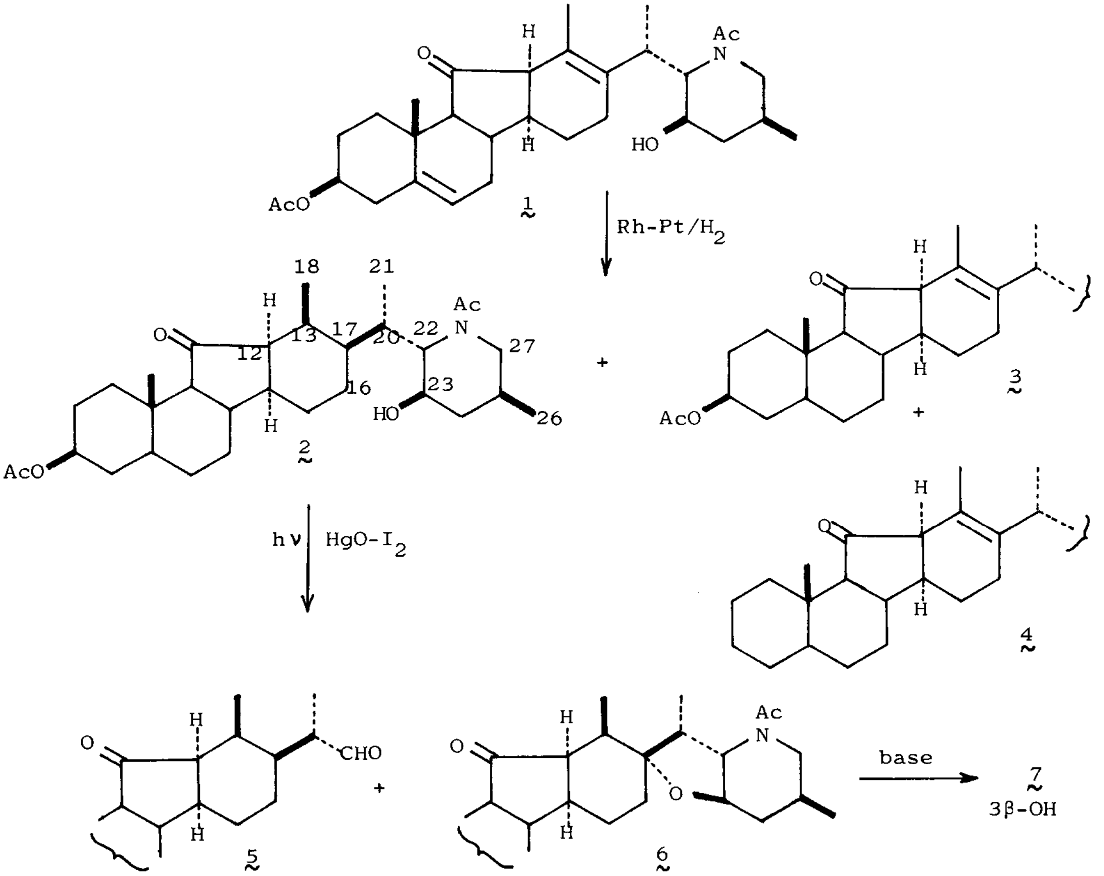
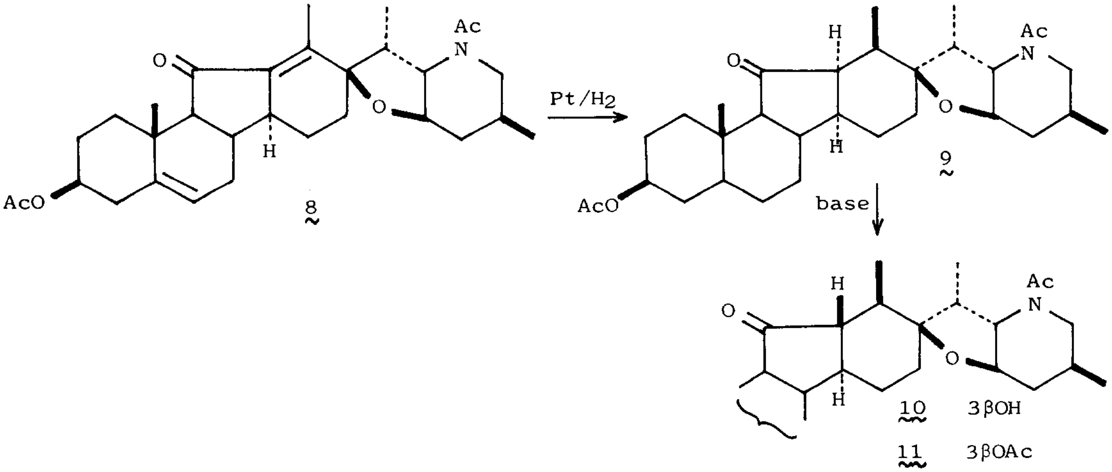
We wish to report the formation of the title jerveratrum alkaloid derivative 6 by the hypoiodite reaction. 6 is novel in having an unnatural configuration at the C-17.

The substrate for the hypoiodite reaction, 3-O, N-diacetyl-22, 27-imino-11-oxo-5α,12α-jervane-3β,23β-diol 2, m.p. 204-6^{o} (Mass., M^{+} 515, ir., Nujol, 1734, 1722 and 1609 cm^{-1}, nmr., τ9.29, d, (J=6.0), 18-C-H, τ9.13, s, 19-C-H, τ 9.13, d, (J=5.4), 21-C-H, τ8.95, d, (J=6.0), 26-C-H, τ8.01, s, OAc, τ7.90, s, N-Ac) was prepared by the catalytic hydrogenation of 3-O,N-diacetyl-22,27-imino-11-oxo-12α-jerva-5,13 (17)-diene-3β-23β-diol 1 (25.0g) (3) with Rh-Pt catalyst (38.65g) (4) in acetic acid in the yield of 72%. The assigned configurations at the C-5, the C-13 and the C-17 of 2 are based on the principle of the well-established cis addition of hydrogens to the double bond from the less hindered side in the steroid molecules, as well as on the analogy with the results in the closely related compounds (4,6). Two minor products, amorphous 3 (ir., Nujol 1728, 1607 cm^{-1}, nmr., τ7.23, d, (J=9.0), 12-C-αH, τ8.14, s, 18-C-H, τ 9.21, s, 19-C-H, τ8.85, d, (J=6.3), 21-C-H, τ5.39, d, (J=11.0), 22-C-βH, τ5.95, s, 23-C-αH, τ8.99, d, (J=6.6), 26-C-H, τ 8.00, s, N-Ac) and crystalline 4, m.p. 218.5^{o}-219.5^{o} (Mass., M^{+}455, ir., Nujol, 1725, 1608 cm^{-1}, no band due to acetoxyl, nmr., τ5.38, 3-C-αH, τ7.24, d, (J=8.4), 12-C-αH, τ8.14, s, 18-C-H, τ9.23, s, 19-C-H, τ8.85, d, (J=6.3), 21-C-H, τ5.38, d, (J=11.1), 22-C-βH, τ5.95, s, 23-C-αH, τ8.98, d, (J=6.6), 26-C-H, τ7.98, s, N-Ac) were obtained and the structures were assigned as depicted in the Scheme.

2 (13.5g) in dry benzene (700 ml) in the presence of HgO (27.0g) and I_2


1
Rh-Pt/H$_2$
2
3
4
hν HgO-I$_2$
5
6
base
7
3β-OH
AcO
HO
Ac
N
CHO
18
21
12
13
17
20
22
23
16
26
27


8
Pt/H2
9
base
10 3βOH
11 3βOAc
AcO
Ac
N
O
H

(33.8g) was irradiated by a 100-W high pressure Hg arc lamp while argon was bubbled. The analysis of the product indicated, besides a large amount of an expected aldehyde 5 (5) due to β-cleavage, the presence of a small amount of a more polar compound. Column chromatography on Mallinckrodt SiO_2 afforded the aldehyde 5, m.p. 134-5^{o} (63% in a crude form, 43% as crystals) {Mass., M^{+} 388, ir., Nujol, 1732 cm^{-1}, nmr., τ9.26, d, (J=6.9), C-18-H, τ9.10, s, C-19-H, τ8.98, d, (J=7.2), C-21-H, τ7.98, OAc, τ0.45, d, (J=4.5), CHO} and a new compound 6, $C_{31}H_{47}O_5N$ (elemental analysis and mass M^{+} 513), m.p. 219-220^{o} in 3% yield.

It was apparent from its molecular formula that 6 was a cyclic ether due to an intramolecular hydrogen abstraction by the 23β-O-radical, and ir of 6 revealed the absence of OH band and the presence of a series of bands at 1733 cm^{-1} (3β-$OCOCH_3$ and C-11-carbonyl) and 1671 cm^{-1}($NCOCH_3$).

Judging from the Dreiding model of 2 the hydrogens available for the intramolecular abstraction would be those at C-16-H, C-17-H, and C-21-H and the cyclic transition states of these reactions would be 6, 7, and 6-membered (7).

^{1}H nmr of 6 revealed a 3-proton doublets at τ9.21 (J=6.0), τ9.08 (J=6.0) and τ9.01 (J=6.6) assignable to three secondary methyls (C-18-H, C-21-H, C-26-H), as well as three-proton singlet at τ9.12, τ7.99 and τ7.92, assignable to C-19-H, OAc and NAc respectively. This result excludes the structure of 6 based on the hydrogen abstraction from either C-18-H or C-21-H hydrogens, leaving only two possible structures formed via hydrogen abstraction from either C-16-H or C-17-H.

The ^{13}C FT nmr spectrum (8) of 6 (25.1 MHz, $CDCl_3$, TMS) shows the C-11, the OAc (or NAc) and the NAc (or OAc) carbon atoms appearing at 220.36 ppm, 172.91 ppm and 170.36 ppm and a signal due to quarternary carbon atom at 86.64 ppm. This signal is not present in the starting 2 and the shift is consistent with the value for the oxygen bearing quarternary carbon (9). ^{1}H off-resonance decoupling confirmed this quarternary nature.

On the basis of this ^{13}C nmr spectrum, the position of the attachment of the C-23-oxygen is confirmed to be the 17-position. In agreement with this assignment ^{13}C FT nmr of O,N-diacetyl-3β-hydroxy-5α-jervan-11-one 11 (vide infra) revealed the signal due to the C-17 at 86.52 ppm. Moreover, since the direct comparison of 6 with O,N-diacetyl-3β-hydroxy-5α,12α-22,27-imino-jervan-11-one 9

(6), prepared by the catalytic hydrogenation of O,N-diacetyljervine 8, disclosed the 6 and 9 are not identical, oxygen at the C-17 should be α-oriented.

It is interesting to note that, while the treatment of 9 with a base causes an epimerization at the C-12 to afford 10 (4), no isomerization was observed and 6 afforded simply 7 when 6 was treated under the comparable condition.

Mechanistically 6 would be formed via the direct combination between C-17 radical or carbonium ion and 23-Oxygen moiety, rather than the ethereal ring formation through iodohydrin intermediate since the combination of iodine atom with the C-17 radical or charged species of 2 from the β-side would be severely hindered by the 13β-methyl group.

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7) The model of 2 indicates that the most stable conformation of the D-ring of 2 may be a chair form with the C-13 axial and the C-17 equatorial substituents. Based on this conformation of 2, the C-18-H and the C-13-H satisfy the distant requirements of the hydrogen abstraction as well. However, the possibilities of abstraction of these hydrogens are rather safely eliminated since the models indicate the presence of 1,3-diaxial-like interactions between the C-13 methyl and the C-20 methyl in the transition states of abstraction of these hydrogens.

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