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REVISION OF THE C_{12} CONFIGURATION OF DIHYDROJERVINE (1)

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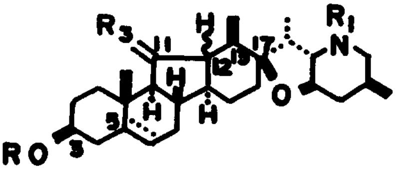
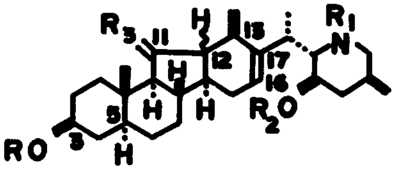
An argument (2) has recently been advanced in support of assignment of the α-hydrogen configuration to C_{12} and C_{13} of dihydrojervine (I) and tetrahydrojervine (II) (3). We now present evidence that the β-configurational assignment to the hydrogen at C_{12} is preferred for these compounds, as shown by formulas I and II (12βH, 13αH).



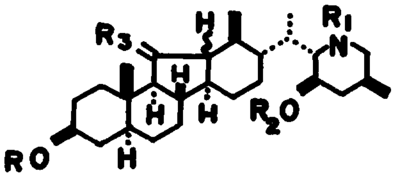


I Δ^5, 12βH, $R=R_1=H$, $R_3=O$
Ia Δ^5, 12βH, $R=R_1=Ac$, $R_3=O$
II 5αH, 12βH, $R=R_1=H$, $R_3=O$
IIa 5αH, 12βH, $R=R_1=Ac$, $R_3=O$
V 5αH, 12βH, $R=R_1=Ac$, $R_3=H_2$
VIII Δ^5, 12αH, $R=R_1=H$, $R_3=O$

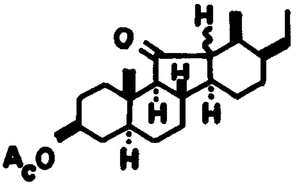
III 12βH, $R=R_1=R_2=Ac$ $R_3=O$
IV 12αH, $R=R_1=R_2=Ac$, $R_3=O$
VI 12βH, $R=R_1=R_2=Ac$, $R_3=H_2$

(i) 3-O,N-Diacetyltetrahydrojervine (IIa) is transformed to a compound (III), assigned as 3-O,23-O,N-triacetyl-22,27-iminojerv-16-ene-3β,23β-diol-11-one (4), by acetolysis (2), in which epimerization at C_{13} is improbable. The configurational change at C_{12}, located adjacent to the 11-ketonic group, is also improbable during the acetolysis, because the reactant II is essentially stable to alkali and the product III is a less stable isomer as compared with the corresponding 12-epimer (IV) (2,4).

(ii) In the previous paper (5) we reported on the formation of an 11-deoxo compound (V) by a modification of the Wolff-Kishner reduction of I followed by acetylation and hydrogenation. In the present study, compound V was treated under the same conditions as the afore-mentioned acetolysis to give a Δ^{16}-compound (VI) (6), m.p. 200-202°, in 35% yield. Hydrogenation of VI produced the 16,17-dihydro derivative (VIIa), m.p. 214-215°, which was identified as a 3-O,23-O,N-triacetyl derivative of 22,27-iminojervane-3β,23β-diol-11-one (VII) (compound XII in the preceding communication 4). The transformation from V to VIIa involves no possibility of epimerization at C_{12} and, therefore, the configuration in question of V must be assigned as β. Since compound I has been recovered unchanged (95%) after treatment with alkali (5), I would have to possess the same configuration (β) at C_{12} as V, as shown by formula I.

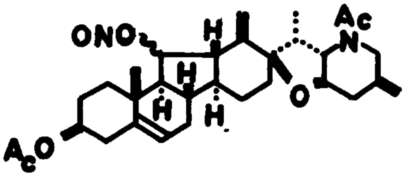


VII 12βH, $R=R_1=R_2=H$, $R_3=H_2$
VIIa 12βH, $R=R_1=R_2=Ac$, $R_3=H_2$
IX 12βH, $R=R_1=R_2=Ac$, $R_3=O$
X 12αH, $R=R_1=R_2=Ac$, $R_3=O$



XI 12βH
XII 12αH

(iii) Treatment of dihydrojervine I with alkali (15% KOH) in refluxing ethanol for 2 hr resulted in recovery of the starting material in a yield over 75% after recrystallization of the product from acetone. Further recrystallization of the mother liquor followed by preparative TLC (Wakogel B-5) led to isolation of a 12-epimer (VIII), amorphous, in 1% yield, showing a single spot on TLC, which was readily reconverted into I in a yield over 90% by treatment with alkali (10% KOH in refluxing methanol) or with acid (chloroform containing HCl). The epimer VIII displayed a singlet due to 19-methyl protons at τ 8.94 in the NMR spectrum (deuterochloroform) and also a negative Cotton effect with amplitude of -92° in the ORD curve (dioxane). These values are consistent with the assigned structure VIII, as compared with the corresponding (τ 8.98 and -164°) of I: chemical shifts (τ) of 19-methyl protons, III and IV, 9.14 and 9.12; 16,17α-dihydro derivatives (IX and X) of III and IV, 9.17 and 9.14; O-acetyl-17β-ethyletiojervan-3β-ol (XI), m.p. 115.5-116.5°, (7,8) and its 12-epimer (XII), m.p. 121-123°, (8), 9.16 and 9.12 (9); amplitudes (a) of ORD curves, III and IV, -172° and -82°; IX and X, -169° and -96°; XI and XII, -170° and -96° (4).



XIII 11β-nitrite
XIV 11α-nitrite

(iv) The proton at C_{11} of 3-O,N-diacetyl-22,27-imino-17β,23β-oxido-jerv-5-ene-3β,11β-diol 11-nitrite (XIII) (10) appeared at τ 3.95 as a clear triplet with coupling constant (J) of 7.3 c/s in the NMR spectrum and that of the 11-epimer (XIV) (10) at τ 4.08 as a poorly resolved quartet with J of ca. 4.0 and 5.6 c/s. Examination of the Dreiding model reveals that, if the C/D ring is cis-fused (12αH) and the flexible D-ring adopts a half-chair form with the β-methyl group at C_{13} equatorial, a conformation considered to be the most stable, dihedral angles between hydrogens at (C_{11} and C_{12}) become ca. 40° and 160° for XIII and XIV, which give J of 4.6 and 10.1 c/s, respectively, using Conroy's graph. When both the compounds XIII and XIV possess the assigned structures (12βH), coupling constants calculated from the angles between hydrogens at (C_{11} and C_{12}) and at (C_{11} and C_9) are 7.7 (ca. 140°) and 7.6 c/s (ca. 10°) for XIII and 6.6 (ca. 25°) and 6.1 c/s (ca. 130°) for XIV. This finding supports the trans-fused C/D linkage in compound I and, accordingly, II.

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8 The stereochemistry of XI and XII will be described in a detailed paper.

9 The observed chemical shifts of 19-methyl protons in a number of 22,27-iminojervane and etiojervane derivatives, having a 13β-methyl group and a saturated 17-carbon atom, are in good agreement (within 0.02 ppm), with few exceptions, with the calculated values, using the shielding effects of various functional groups on the A, B and C rings applied to 22,27-imino-17β,23β-oxidojervane derivatives (5) and assuming the reference chemical shift to be *τ 9.26* (cf., ref. 5) for the C/D trans-fused compounds and that *τ 9.21* for the C/D cis-fused; T. Masamune et al., unpublished observations.

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