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SYNTHESIS OF C-18-FUNCTIONALIZED C-NOR-D-HOMOSTEROID BY HYPOIODITE REACTION (1)

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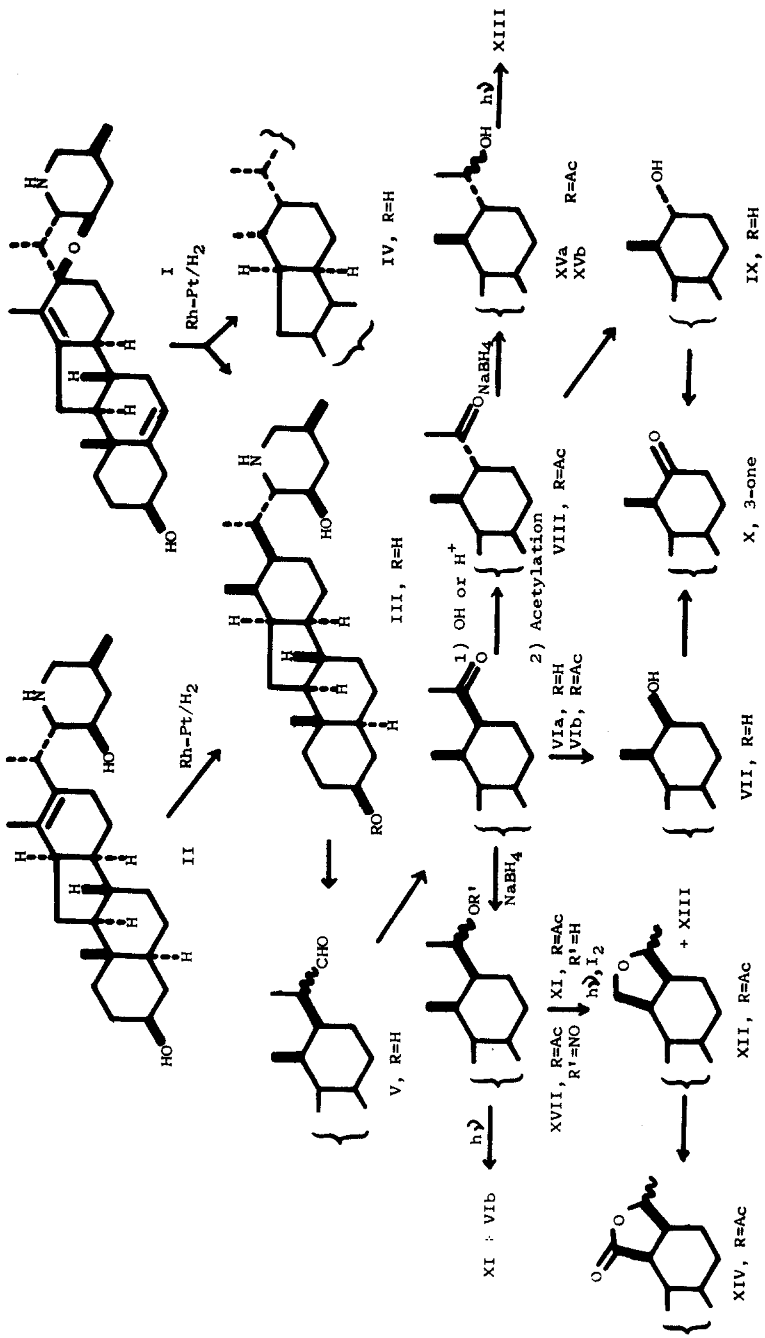
Compared with normal steroids little success has been noted on the functionalization of 18-methyl group in the field of C-nor-D-homosteroids. We report briefly the successful achievement of the synthesis of C-18-oxygenated C-nor-D-homosteroid XIV, which may be valuable as a relay compound in transforming jerveratrum alkaloids into the cevine nucleus.

11-Deoxojervine (I) (2) in acetic acid was hydrogenated in the presence of a mixed rhodium-platinum oxide catalyst (3). Two crystalline hexahydro derivatives III, m.p. 219-221° (36%) and IV, m.p. 178-180° (4%), were obtained. III is also obtained by hydrogenation of 11-deoxo-5,6,8,9-tetrahydroisojervine (II) (4) under comparable conditions. Franck-Johnson fragmentation (5) of III afforded an aldehyde V, m.p. 109-111°, in 95% yield (M^+, 332). V was subsequently transformed into a ketone VIa, m.p. 150-152°, (90%) and its acetate VIb, m.p. 116-118°, by the established procedure (5). VIa and VIb were identical with the compounds obtained by Johns and Laos from C-nor-D-homosapogenin (recorded m.ps. 154-156° and 131-133°, respectively) (6).

Stereochemistry

Baeyer-Villiger oxidation of VIa followed by saponification yielded 12α-etiojervane-3β,17β-diol (VII) (7), m.p. 167-169°, in 34% yield, which was oxidized with Jones' reagent to yield the corresponding diketone X, m.p. 169-170°. X was identical with 12α-etiojervane-3,17-dione (X) derived from C-nor-D-homosapogenin by Johns and Laos (recorded m.p. 169-170°) (6). These transformations establish


I
Rh-Pt/H$_2$
II
Rh-Pt/H$_2$
III, R=H
IV, R=H
V, R=H
1) OH or H$^+$
2) Acetylation
VIa, R=H
VIb, R=Ac
VIII, R=Ac
NaBH$_4$
XVa
XVb
R=Ac
hν
XIII
VII, R=H
X, 3-one
IX, R=H
NaBH$_4$
XVII, R=Ac, R'=NO
XI, R=Ac, R'=H
hν, I$_2$
hν
XI + VIb
XII, R=Ac
+ XIII
XIV, R=Ac
HO
RO
OR'
CHO
OH
H
N

that the configurations of 18-methyl and C-12-hydrogen of III, V, VI and VII are β and α respectively, since Johns' assignments with regard to these configurations are acceptable. Configuration of the substituent at C-17 of VI, and hence that of III, was confirmed as follows: treatment of VIb with either acid or base followed by acetylation converts it into its C-17 epimer VIII, m.p. 88-90° (8). On Baeyer-Villiger oxidation, the deacetyl derivative of VIII affords diol IX, m.p. 179-179.5°, isomeric with VII at C-17, since VII and IX yield X by Jones' oxidation. The flexible D-ring of VIII can adopt four possible conformations, two chair and two boat forms. Whatever the conformation of the D-ring is, both the 18-methyl and an acetyl at C-17 of VIII should occupy more stable equatorial conformations. It follows then that 13β-CH_3 and respective substituents at C-17 of VI, and hence those of III and V, should be situated either in equatorial and β-axial conformations or vice versa, respectively, i.e., these substituents (most probably in the chair form) are oriented in cis. On the basis of these configurational assignments, the diols VII and IX are formulated as depicted, since the Baeyer-Villiger oxidation occurs with retention of configuration (9).

Functionalization of 18-methyl group

Reduction of VIb with $NaBH_4$ yields virtually a single reduction product XI, m.p. 126-129°. This 20ξ-ol (180 mg) and iodine (160 mg) in cyclohexane (18 ml) containing lead tetraacetate (600 mg) and sodium carbonate (200 mg) were irradiated for 30 min. by a 450 W high pressure Hg arc lamp (10). Two products were formed, one XIII in amorphous and another XII in crystalline, m.p. 76-79° (29 mg) (11). Nmr spectrum of XII reveals the signals due to 19 methyl, 21 methyl and O-acetyl at τ9.22, τ8.75 (doublet J=6.3) and τ7.98, respectively. C-18 methylene protons appeared from τ5.88 to τ6.91 as multiplet of AB part of ABX system. XII can be oxidized to the corresponding γ-lactone XIV, m.p. 89-90° (nmr spectrum; τ9.15, 19 methyl; τ7.97, O-acetyl; τ8.60 (doublet J=6.0), 21 methyl. ir spectrum; γ-lactone, 1752 cm^{-1}) with CrO_3 in acetic acid in 19% yield.

Reduction of VIII with $NaBH_4$ yields two diols XVa, m.p. 140-140.5° and X Vb, m.p. 187-189°, in the yield of 38% and 41% respectively. Hypoiodite reaction of a mixture of these diols led only to the formation of an amorphous compound having identical nmr spectrum with the compound XIII obtained from XI.

Finally, Barton reaction (12) of nitrite XVII, m.p. 102-106°, prepared from XI was attempted to functionalize 18-methyl group. However, we obtained only recovered XI and 20-ketone VIb from the reaction and failed to isolate desired oxime (13).

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References and footnotes

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(7) This was identical with the compound obtained by Johns and Laos and was assigned as 12α-etiojervane-3β,17α-diol (recorded m.p. 169-170°) (6).

(8) Curiously the nmr and ir spectra of VIa and deacetyl derivative of VIII are indistinguishable.

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