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AN UNUSUAL INTRAMOLECULAR HYDRIDE TRANSFER REACTION INVOLVING NONBONDED GROUPS

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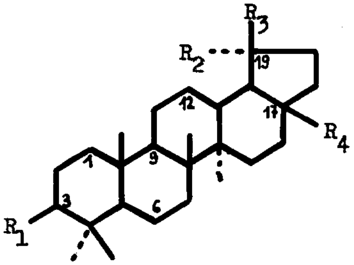
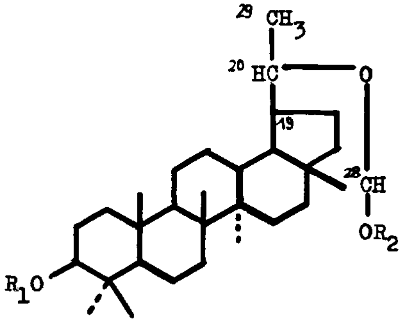
In considering the possibility of epimerisation at C-19 of certain nor-derivatives (I,II) involving the lupane skeleton III, it may be noted that, in the parent skeleton III, only the configuration 19β H is known in spite of appreciable steric interaction with C-12. The corresponding dinor-diacid IV is epimerised (1) to the 19αH diacid V via the corresponding anhydride. We therefore investigated the equilibration of the 30-nor-19β H-ketone I under the usual conditions (2,3). In contrast to, for example, pregnan-20-one and its derivatives (4-9), the configuration at C-19 of the norketone I does not change under the conditions of acid catalysis and, therefore, acid catalysed enol-acetylation (Ac_2O + TsOH or $\succ$—OAc + TsOH) stabilises only the 20(30)-enol form. The enol acetate VI thus formed had m.p. 143-144,5°,$/\alpha/_D$ -0,3°($CHCl_3$), $\nu^{CHCl_3}_{max}$ 1740, 1190, 1150 and 1655,900,875 cm^{-1}; NMR ($CDCl_3$) τ = 7.865 (C-20-OAc), doublets at 5.28 and 5.315 (CH_2= C$<$).

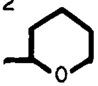
The influence of base on the 19β H-ketone I has not been described; the corresponding dihydroxyderivative VII was prepared (10) under non-basic conditions. With 5% KOH in boiling 95% MeOH the diacetoxynorketone I gives a mixture of products in which the most polar component, i.e. dihydroxynorketone VII preponderates. In 5% ethanolic sodium ethoxide the yield of the less polar component increases and it is the only product in butanolic t-butoxide (1 hour boiling). The dihydroxynorketone VII reacts with sodium t-butoxide in the same manner so that the formation of the less polar product is not connected with the hydrolysis of the C-28-OAc group.

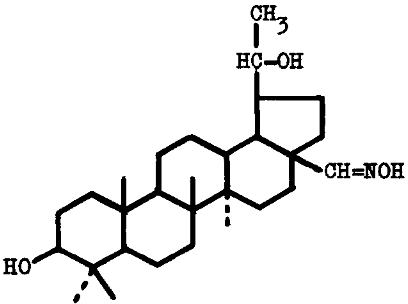
For the less polar substance ($C_{29}H_{48}O_3$, 2 act. H; m.p. 292-295°,$/\alpha/_D$ + 28°($CHCl_3$)) we propose the hydroxyhemiacetal structure IX since it has no infrared absorption for carbonyl or methylketone, but bands at 1060 and 3620 cm^{-1} for C-O-C and OH, respectively. Also the NMR spectrum contained signals (τ=4.74) for the proton of a secondary alcoholic group 28-CHOH (assignements were made on the basis of the spectrum in DMSO using DR-experiment and D_2O exchange) as well as a doublet at 8.93, J= 6.5 (29-Me) and a quartet at 6.035, J= 6.5(C-20-H). The acetylation of hydroxyhemiacetal IX gives a diacetate X ($C_{33}H_{52}O_5$, m.p.



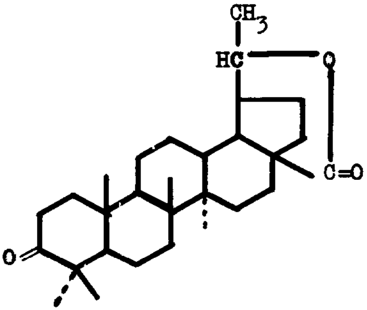


I R_1= OAc, R_2= Ac, R_3= H, R_4= CH_2OAc
II R_1= OAc, R_2= COOH, R_3= H, R_4= CH_2OAc
III R_1= H, R_2= $C(=CH_2)CH_3$, R_3= H, R_4= CH_3
IV R_1= OAc, R_2= COOH, R_3= H, R_4= COOH
V R_1= OAc, R_2= H, R_3= R_4= COOH
VI R_1= OAc, R_2= $C(=CH_2)OAc$, R_3= H, R_4= CH_2OAc
VII R_1= OH, R_2= Ac, R_3= H, R_4= CH_2OH
VIII R_1= OH, R_2= H, R_3= Ac, R_4= CH_2OH

IX R_1= R_2= H
X R_1= R_2= Ac
XI R_1= Ac, R_2= H
XII R_1= R_2= 



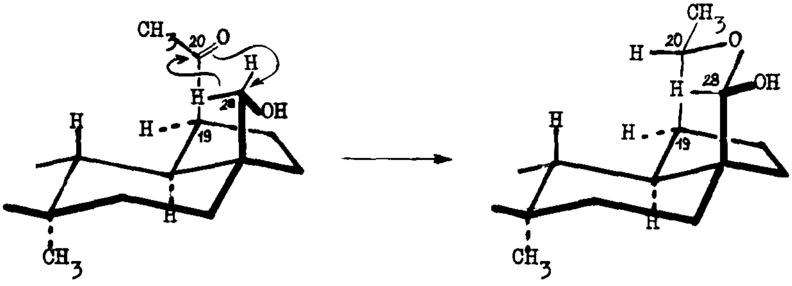
XIII



XIV

207-209°, $/\alpha/_D$ +33,2°($CHCl_3$), $\nu_{max}^{CHCl_3}$ 1732, 1265, 1035, 985 cm^{-1}, NMR($CDCl_3$) τ= 8.915, doublet, J= 6.5 (29-Me), 7.98 (3β-OAc), 7.93 (28-OAc), 5.975, quartet, J= 6.5 (C-20-H), 3.73 (C-28-H)). Solvolysis (95% MeOH) of the diacetate X affords the monoacetate XI ($C_{31}H_{50}O_4$, 1 act.H , m.p. 260-263°, $/\alpha/_D$ +32°($CHCl_3$), $\nu_{max}^{CHCl_3}$ 3600, 1724, 1037 cm^{-1}, NMR ($CDCl_3$) τ= 8.935, doublet, J= 6.5 (29-Me), 6.045, quartet, J= 6.5 (C-20-H), 4.74, doublet, J= 7.5 (C-28-H)). In accordance with the hemiacetal formulation, an oxime XIII ($C_{29}H_{49}NO_3$, m.p. 277-281°, ν_{max}^{nujol} 3620, 3480, 1695 cm^{-1}) could be prepared. Oxidation with the Jones reagent under very mild conditions gives the ketolactone XIV ($C_{29}H_{44}O_3$, m.p. 328°(subl.), $/\alpha/_D$ +41°($CHCl_3$), $\nu_{max}^{CHCl_3}$ 1725, 1706, 1240, 1178, 1120, 1090, 1051 cm^{-1}) . The signals (τ= 8.94, 8.99 and 9.02) of the methyl groups 23-25 in the NMR spectrum ($CDCl_3$) are characteristically shifted (11) by the 3-oxo group. Other signals were at τ= 8.73, doublet, J= 6.5 (29-Me) and 5.41, quartet, J= 6.5 (C-20-H)).

Under the influence of alcoholate, oxidative-reductive exchange between the C-20 carbonyl and the C-28 alcoholic group takes place in addition to the epimerisation at C-19 (i.e. an intramolecular Meerwein-Pondorff-Oppenauer reaction). To learn more of the course of this reaction, the dihydroxynorketone VII was transformed to the 3,28-bis-(α-tetrahydropyranyl)-ether (amorphous, $\nu_{max}^{CHCl_3}$ 1713, 1145, 1130, 1084 and 1038 cm^{-1}, no OH absorption), which is quantitatively changed by sodium t-butoxide into the less polar isomer XII (amorphous, no IR band for CH_3CO-). With acetic anhydride and 0,016 M HCl in chloroform, the ether XII gave the diacetate X, which was hydrolysed to the monoacetate XI. Therefore, the oxidation-reduction exchange must take place by direct transfer of a hydride ion from C-28 to C-20 with simultaneous oxygen bond shift from C-20 to C-28. Four diastereoisomers can be expected, but only one was proved. It is very probable, therefore, that only the preferred rotamers of the dihydroxy-19αH-ketone VIII take part in the reaction leading to a stable conformation of the resulting 2′,6′-disubstituted tetrahydropyran ring. Using models it can be shown that the rotamer XV is that most favorable for conversion into the hemiacetal XVI, where the C-28-OH and C-20-Me groups are equatorial. Any other arrangement must have appreciable nonbonding interaction of both substituents. The proposed configuration at C-20 is further supported by the shape of the signal for C-20-H in the NMR spectrum, the interaction of which with C-19-H is very near to zero; the dihedral angle of C-19-H and C-20-H in the formula XVI is near to 90°.



XV XVI

References

1. Guider J.M., Halsall T.G., Jones E.R.H.: J.Chem.Soc. 1953, 3024
2. Moffett R.B., Hoehn W.M.: J.Am.Chem. Soc. 66, 2098 (1944)
3. Biellmann J.P., Kucan D., Ourisson G.: Bull.Soc.Cim.France 1962, 337
4. Chamberlain E.M., Chemerda J.M.: J.Am.Chem.Soc. 77, 1221 (1955)
5. Bernstein S., Heller M., Stolar S.M.: J.Am.Chem.Soc. 77, 5327 (1955)
6. Engel Ch.R., Hoegerle R.M., Deghenghi R.: Can.J.Chem. 38, 1199 (1960)
7. Barton D.H.R., Evans R.M.,Hamlet J.C., Jones P.G., Walker T.: J.Chem.Soc. 1954, 747
8. Moffett R.B., Weisblat D.I.: J.Am.Chem.Soc. 74, 2183 (1952)
9. Djerassi C., Grossman J., Thomas G.H.: J.Am.Chem.Soc. 77, 3826 (1955)
10. Ruzicka L., Brenner M.: Helv. Chim. Acta 23, 1325 (1940)
11. Tursch B., Savoir R., Ottiger R.,Chiordoglu G.: Tetrahedron Letters 1967, 539.