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ASSISTANCE BY VICINAL, CIS OXYGEN IN ACETYLENE-ALLENE REARRANGEMENT. ALLENYLSTEROIDS FROM OXIDES

R. Vitali and R. Gardi

Warner-Vister Steroid Research Institute - Casatenovo (Como), Italy

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Propargyl magnesium bromide has been reported by American and French workers [1,2] to undergo low temperature carbonation with partial acetylene-allene rearrangement giving rise to mixtures of acetylenic and allenic acids. On the contrary, only β-acetylenic carbinols are known to arise from the reaction of the same Grignard reagent with aldehydes and ketones [2,3]. As far as oxides are concerned, only steroid 5α,6α-oxides have been investigated and found to afford 5α-hydroxy-6β-propargyl derivatives alone [4].

In the study of the same reaction on steroid 4α,5α-oxides we observed examples of acetylene-allene rearrangement we will here refer about. In these cases, the rearrangement proved to be specifically controlled by the oxygenated function vicinal to the oxide.

The reaction of steroid 4α,5α-oxides with Grignard reagents to give 4β-alkyl-5α-hydroxy-steroids had been reported by Julia et al. [5]. In pursuing our research on steroid α-allenyl ketones and related compounds [6], we studied the reaction of 4α,5α-oxides with propargyl magnesium bromide as a route to 4-propargyl steroids.

The known 4α,5α-oxido-17,17-cycloethylenedioxyandrostan-3β-ol (IIa) [7], however, when allowed to react with propargyl magnesium bromide in ether at reflux, gave rise to a product, m.p.202-205°, $[\alpha]_D$ +22° [8], isolated in 70% yield and identified as 4β-allenyl-17,17-cycloethylenedioxyandrostane-3β,5α-diol (IIIa) on the basis of spectroscopic and chemical evidences.

The presence of the allenic group was suggested by the typical band at 1960 cm^{-1} in the IR. The structure of secondary-tertiary diol was in accordance with the formation of monoacetate IIIb, m.p.183-185°, $[\alpha]_D$ -7.5°, which, by treatment with thionyl chloride in pyridine, underwent dehydration to IV, m.p.129-131°, $[\alpha]_D$ -139°. The negative increment of the molecular rotation was consistent with the introduction of a 5,6 double bond, thus confirming the position of the tertiary hydroxyl. NMR spectrum of IIIb showed a two-proton multiplet centered at 4.61 ppm (=C=CH_2) and the signals of two overlapping one-proton multiplets

(-CH=C and axial C^3-H [9]) between 5.05 and 5.50 ppm. The pronounced downfield shift of the $C^{19}H_3$ to 1.03 ppm supported the stereochemistry of the substituent at C^4, suffering 1,3-diaxial interaction with the angular methyl group [10]. Furthermore, hydrogenation of IIIa over palladium on carbon absorbed 2 moles of hydrogen giving rise to the propyl analogue V, m.p. 213-215°, $[\alpha]_D$ +16.2°, which was converted by chromic oxidation into ketone VI, m.p. 198-200°, $[\alpha]_D$ +1.5°. Acid treatment of VI afforded the known 4-propylandrost-4-ene-3,17-dione (VII) [11].

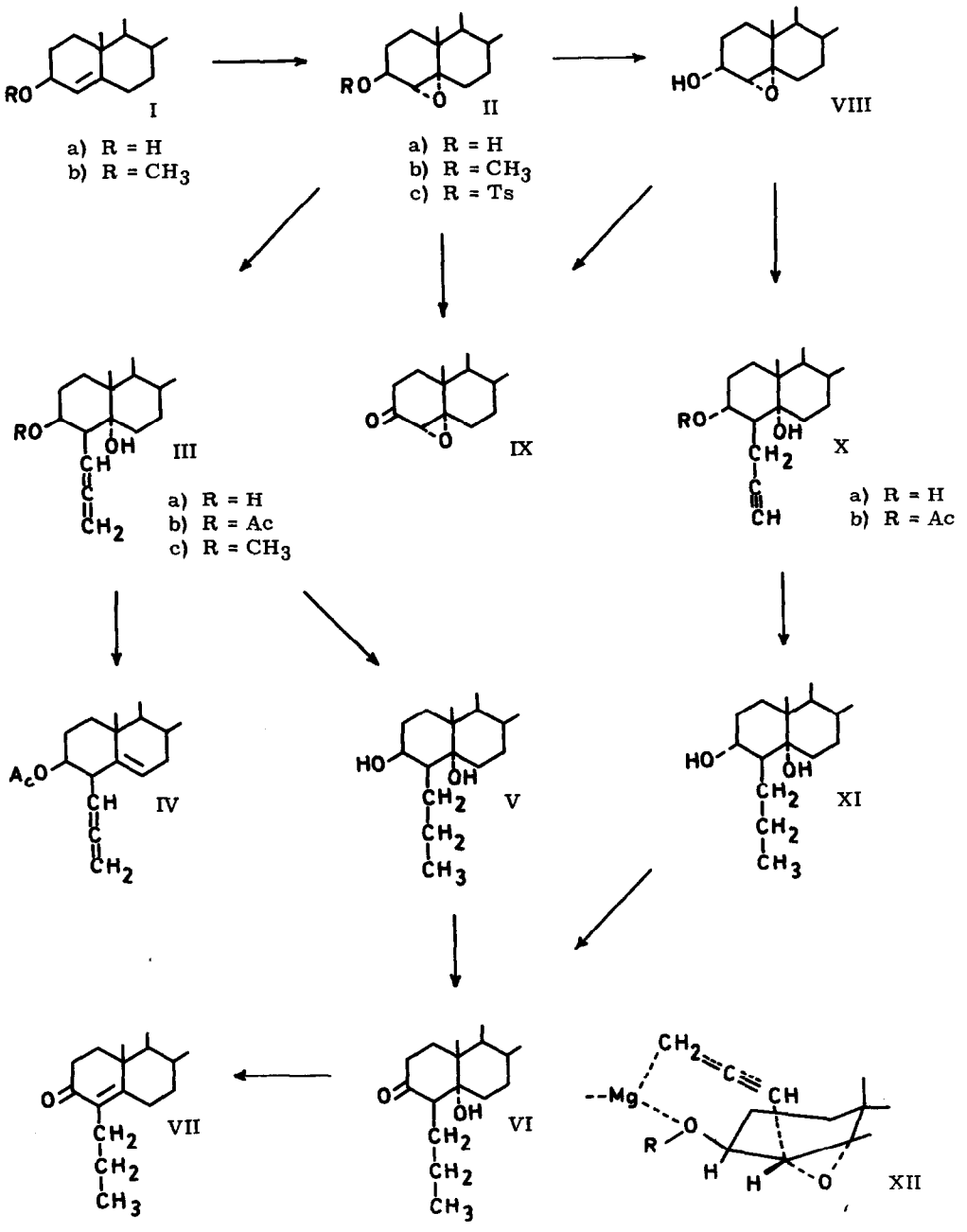
In order to establish whether an ether group plays the same role as the free hydroxyl in this kind of acetylene-allene rearrangement, the Grignard reaction was investigated on 3β-methoxy-4α,5α-oxide IIb, m.p. 155-157°, $[\alpha]_D$ +14.5°, prepared from Ia [7] by methylation with methyl iodide-potassium tert. butoxide to Ib, m.p. 128-130°, $[\alpha]_D$ -1°, and monoperphtalic acid oxidation of the latter. Actually, reaction of IIb with propargyl magnesium bromide gave rise to the rearrangement product, 3β-methoxy-4β-allenyl-17,17-cycloethylenedioxyandrostan-5α-ol (IIIc), m.p. 174-176°, $[\alpha]_D$ -10.5°, ν_{max} 1950 cm^{-1} (-C=C=C). The NMR spectrum revealed signals at 5.22 ppm (-CH=C), 4.68 ppm (=C=CH_2), 3.32 ppm (CH_3O), and 1.02 ppm ($C^{19}H_3$).

The possible dependence of the acetylene-allene rearrangement on the configuration of the neighbouring hydroxyl was then investigated.

To this purpose, tosylate IIc, m.p. 141-143°, $[\alpha]_D$ +1°, after refluxing in DMF in the presence of litium carbonate [12] and subsequent alkaline hydrolysis of the resulting formyloxy derivative, was converted in 50% yield into 4α,5α-oxido-17,17-cycloethylenedioxyandrostan-3α-ol (VIII), m.p. 193-196°, $[\alpha]_D$ +63° [13]. Chromic oxidation of both IIa and VIII gave rise to ketone IX, m.p. 205-206°, $[\alpha]_D$ -76°.

Reaction of VIII with propargyl magnesium bromide afforded in 75% yield 4β-propargyl-17,17-cycloethylenedioxyandrostane-3α,5α-diol (Xa) [14,15], which on acetylation gave monoacetate Xb, m.p. 155-157°, $[\alpha]_D$ -16.9°. IR (3250 cm^{-1}, C≡C-H) and NMR spectra of Xb showing signals at 5.41 ppm ($Wh/_2$ 5.5 Hz, equatorial C^3-H) [9], 3.28 ppm (OH), 2.43 ppm (C≡C-H), 0.92 ($C^{19}H_3$), supported the identification. Catalytic hydrogenation of Xa to XI, m.p. 189-191°, $[\alpha]_D$ +21.1°, and chromic oxidation of the latter, afforded the same 4β-propyl-5α-hydroxy-3-ketone V obtained from allene IIIa.

According to the above results, the acetylene-allene rearrangements occurring in the reaction of steroid 4α,5α-oxides with propargylic Grignard are determined by the presence of an oxygenated function at C^3, trans to the oxide group and cis to the entering group, through the assistance by one of the unshared electron pairs of the oxygen. In this connection, we may envisage an attack at C^4 on the β-side of the steroid skeleton by a molecule of Grignard reagent coordinated to the 3β-oxygen through the acidic magnesium. This coordination would favour the rearrangement of the nucleophilic agent and shield C^4 from attack by


RO
I
a) R = H
b) R = CH3
RO
O
II
a) R = H
b) R = CH3
c) R = Ts
HO
O
VIII
RO
OH
CH
C
CH2
III
a) R = H
b) R = Ac
c) R = CH3
O
O
IX
RO
OH
CH2
C
CH
X
a) R = H
b) R = Ac
AcO
CH
C
CH2
IV
HO
OH
CH2
CH2
CH3
V
HO
OH
CH2
CH2
CH3
XI
O
CH2
CH2
CH3
VII
O
OH
CH2
CH2
CH3
VI
--Mg
CH2
C
CH
O
R
H
H
O
XII

uncoordinated propargyl magnesium bromide. By considering an extremely simplified picture of the actual propargylic Grignard reactant, a cyclic transition state like XII may be supposed.

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References and Footnotes

1. J.H. Wotiz, J.S. Matthews and J.A. Lieb, J. Am. Chem. Soc. 73, 5503 (1951). See also J.H. Wotiz, ibid. 72, 1639 (1950); J.H. Wotiz and R.J. Palchak, ibid. 73, 1971 (1951).

2. C. Prévost, M. Gaudemar and J. Honigsberg, Compt. rend. 230, 1186 (1950); M. Gaudemar, Ann. Chim. (Paris) 1, 161 (1956).

3. M. Gaudemar, Compt. rend. 233, 64 (1951).

4. D. Burn, G. Cooley, V. Petrow and G.O. Weston, J. Chem. Soc. 3808 (1959).

5. S. Julia, B. Decouvelaere, J.-P. Lavaux, C. Moutonnier and P. Simon, Bull. Soc. Chim. 1221 (1963).

6. R. Gardi, R. Vitali and P.P. Castelli, Tetrahedron Letters 3203 (1966).

7. S. Julia and J.-P. Lavaux, Bull. Soc. Chim. 1223 (1963).

8. Rotations are in dioxane. IR spectra were recorded in Nujol mull. NMR spectra ($CDCl_3$) were recorded on a Varian A-60 spectrometer employing TMS as an internal reference. All new compounds gave spectral and analytical data in accord with the assigned structures. We are indebted to Dr. C. Pedrali for IR spectra.

9. D.H. Williams and N.S. Bhacca, J. Am. Chem. Soc. 86, 2742 (1964).

10. G. Slomp and B.R. McGarvey, J. Am. Chem. Soc. 81, 2200 (1959). See also A.I. Cohen and S. Rock, Steroids 3, 243 (1964).

11. R. Gardi and P.P. Castelli, Gazz. Chim. Ital. 93, 1681 (1963).

12. Cf. G.E. Selter and K.D. McMichael, J. Org. Chem. 32, 2546 (1967).

13. In the cholestane series, this reaction has been recently reported to give low recoveries of identifiable products. See J.M. Coxon, R.P. Garland, M.P. Hartshorn and G.A. Lane, Tetrahedron 26, 1533 (1970).

14. An allenic by-product was detected in trace amount by chromatography of mother liquors on silvered silica gel.

15. It is noteworthy that reaction of 3α-acetoxy-4α,5α-oxidocholestane with methyl magnesium bromide fails to afford the expected 4β-methyl-3α,5α-diol. See N.D. Hall and G. Just, Steroids 6, 111 (1965).