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FRONT SIDE NEIGHBOURING GROUP PARTICIPATION IN 16-HYDROXYMETHYL-17-HYDROXYSTEROIDS.

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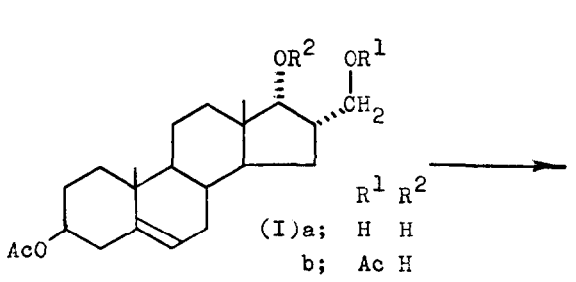
GOLDING and associates recently found that cis- and trans-derivatives of vicinal diols show high stereospecificity in reacting with hydrogen bromide in acetic acid /1/. Thus, cis-cyclohexane-1,2-diol is converted in good yield to trans-1-acetoxy-2-bromocyclohexane, while trans-cyclohexane--1,2-diol gives trans-1,2-diacetoxy-cyclohexane. The mechanism of this process is knownas "front side neighbouring group participation", elucidated by BOSCHAN and WINSTEIN /2/.

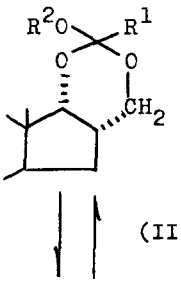
More recently we found that the stereospecificity of 1,2-diols with hydrogen bromide in acetic acid can be extended to 1,3-diols fused to the steroid skeleton. For example, 3β-acetoxy-16α-hydroxymethylandrost-5-en--17α-ol (I a), containing cis-functions on the D ring, reacts with hydrogen bromide in acetic acid (2 mol. equivalent of HBr per mol. equivalent of steroid) at room temperature to yield 16α-bromomethylandrost-5-ene-3β, 17α-diacetate (IV); m.p. 186-87°; $/\alpha/_D$ -25 ± 5° (c=o.5 $CHCl_3$).

Under similar conditions, 3β-acetoxy-16β-hydroxymethylandrost-5-en--17α-ol (V a), containing trans functions, gives exclusively the triacetate (V b); m.p. 126-28°; $/\alpha/_D$ -45 ± 4° (c=o.5 $CHCl_3$).

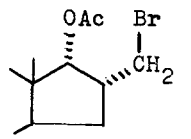
We assume that the first step of the stereospecific transformation of (I a) is the formation of 3β-acetoxy-16α-acetoxymethylandrost-5-en-17α-



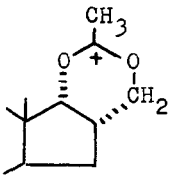
(I)a; R^1 H, R^2 H
b; R^1 Ac, R^2 H



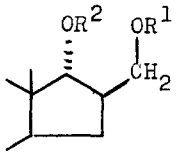
(II)(a; R^1 CH_3, R^2 H)
b; R^1 CH_3, R^2 C_2H_5



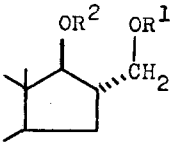
(IV)



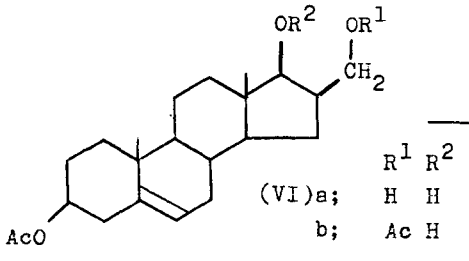
(III)



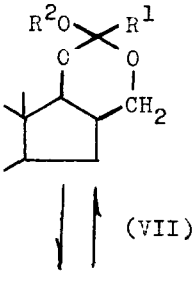
(V)a; R^1 H, R^2 H
b; R^1 Ac, R^2 Ac



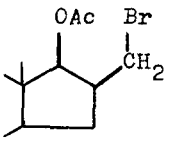
(X)a; R^1 H, R^2 H
b; R^1 Ac, R^2 Ac



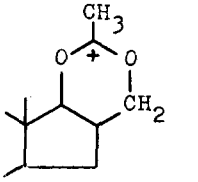
(VI)a; R^1 H, R^2 H
b; R^1 Ac, R^2 H



(VII)(a; R^1 CH_3, R^2 H)
b; R^1 CH_3, R^2 C_2H_5



(IX)



(VIII)

-ol (I b). This compound is cyclised in acidic medium to the orthoester (II a), which is converted by HBr to the ambident 1,3-dioxene-2-ylium ion (III) and stabilized in the form of 3β-acetoxy-16α-bromomethylandrost--5-en-17α-acetate (IV).

To prove this reaction mechanism, we prepared 3β-acetoxy-16α--acetoxymethylandrost-5-en-17α-ol (I b) /3/, and by transesterification of (I a) with triethyl orthoacetate the cyclic orthoester (II b); m.p. 152-56°; $/\alpha/_D$ -72 ± 4° (c=o.5 $CHCl_3$).

Both compounds were transformed by HBr in acetic acid to the corresponding 16α-bromomethyl derivative (IV) in very good yield. In this process the configuration did nor change, as the opening of the ring of the ambident cation (III) occurs at the sterically-favoured symmetric methylene group.

On the other hand, (V a) cannot form an orthoester or ambident cation and thus, under the experimental conditions applied, this compound gives only the triacetate of (V b) via proton-catalysed acetylation.

Quite similarly, 3β-acetoxy-16β-hydroxymethylandrost-5-en-17β-ol (VI a), containing functions in the β position, is transformed by HBr in acetic acid to 16β-bromomethylandrost-5-en-3β,17β-diacetate (IX); m.p. 132-36°; $/\alpha/_D$ -46 ± 3° (c=o.5 $CHCl_3$). Under similar experimental conditions 3β-acetoxy-16β-acetoxymethylandrost-5-en-17β-ol (VI b) /3/, the assumed intermediate, and the cyclic orthoester (VII b) (m.p. 13o-32°; $/\alpha/_D$ -74 ± 4°; c=o.5 $CHCl_3$) also give the corresponding bromomethyl derivative (IX).

3β-Acetoxy-16α-hydroxymethylandrost-5-en-17β-ol (X a), with <u>trans</u> substituents on the D ring, can not form an ambident cation and thus, under the above experimental conditions, results in the triacetate (X b); m.p. 1o8-1o°; $/\alpha/_D$ -1o7 ± 4°.

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