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STEREOCHEMICAL STUDY ON THE REARRANGEMENTS OF 3β-HYDROXY 4,4-DIALKYL-5α-STEROIDS AND THEIR p-TOLUENESULFONATES

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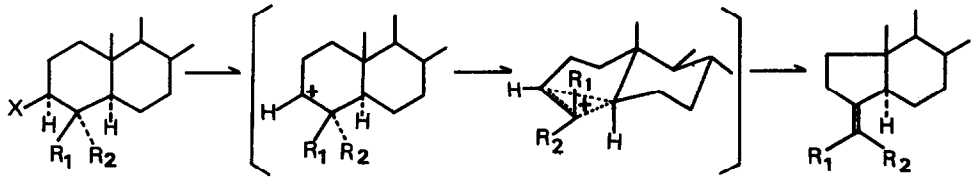
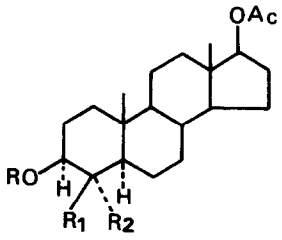
The appropriate 3β-substituted derivatives of 4,4-dimethyl-5α-steroids undergo solvolysis to give A-nor-steroids, and the kinetics of this reaction as well as the intermediate cations have been studied. Schoppee[1] pointed out that the reaction contains two stages of intermediate cations: a) an electron deficient center at C_3 (A) produced by an initial bond fission, and b) a non-classical cation (B) stabilized with the C_4-C_5σ-bond participation as the product determination step. According to this mechanism *via* intermediate B, this



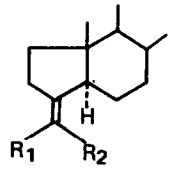
1 A B *2*

Figure 1

rearrangement should undergo stereospecifically to give A-nor-steroid *2* in which exo-methyl group is to be derived from 4β-methyl in compound *1*. In order to substantiate this argument 4,4-dimethyl-5α-androsta-3β,17β-diol 17-acetate *3a* and corresponding 4β-deuteratedmethyl compound *3b* were prepared according principally to the procedure by H. J. Ringold[2]. For the preparation of *3b*, stepwise methylations by deuterated methyl iodide and methyl iodide were required[3]. Compound *3a* has the nmr signals at δ0.80 and 0.96 assigned to 4β- and 4α-methyls respectively[4]. The nmr spectrum of *3b* indicates that 4β-methyl group is deuterated in 70.0 %, this is supported also in the mass spectrum which shows 69.0 % of the total deuterium incorporation (d_3=49.3 %, d_2=11.3 %, d_1=36.6 %, d_0=2.8 %). The direct dehydration of *3a*



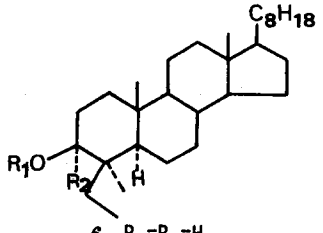
3a $R_1=R_2=CH_3$, R=H
3b $R_1=CD_3$, $R_2=CH_3$, R=H
3c $R_1=R_2=CD_3$, R=H
4a $R_1=R_2=CH_3$, R=Ts
4b $R_1=CD_3$, $R_2=CH_3$, R=Ts



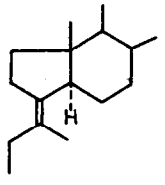
5a $R_1=R_2=CH_3$
5b $R_1=CD_3$, $R_2=CH_3$

occurred readily with phosphorous pentachloride in refluxing n-hexane and afforded 3-isopropylidene-A-nor-androst-3(4)-en-17β-ol acetate *5a* in 70 % yield. A solvolysis of the tosylate *4a* at 90-100° in acetic acid with the presence of sodium acetate proceeded analogously in 2 hours affording the same product in 91 % yield. The nmr chart of *5a* shows two singlets at δ1.58 and 1.70 due to the isopropylidene methyls. The deuterated derivatives *3b* and *4b* were also converted to the corresponding A-nor compound *5b* under the same conditions as for *3a* and *4a* with 71 % and 84 % of respective yields. The nmr spectrum of *5b* demonstrated the 71.2 % of decrease in the signal integration at δ1.58 but no decrease at δ1.70 indicating the complete stereo specificity of the rearrangement. Since the endo-methyl signal would be expected to appear in a lower magnetic field (δ1.70) because of the anisotropic effect of the steroid nucleus, disappearance of the signal at 1.58 in *5b* would suggest that the β-methyl group in the starting compounds should be oriented to exo in the product. This assignment accords with mechanistic scheme shown in Figure 1.

An attempt to extend this rearrangement to 4β-ethyl-4α-methyl-cholest-3β-ol *6* and its p-toluene sulfonate *7a* was carried out[5]. *6* was prepared from cholestenone in 48 % yield by



6 $R_1=R_2=H$
7a $R_1=Ts$, $R_2=H$
7b $R_1=Ts$, $R_2=D$



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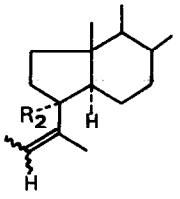
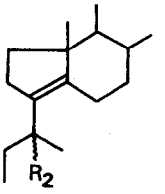
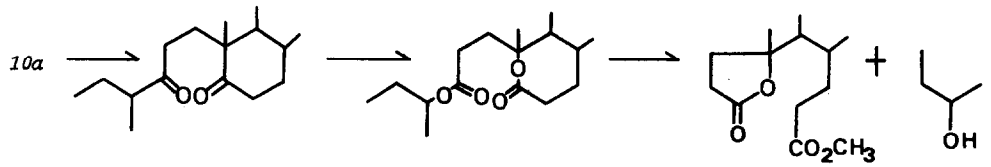


9a $R_2=H$
9b $R_2=D$



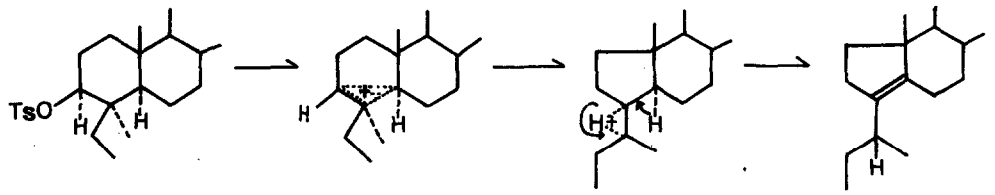
10a $R_2=H$
10b $R_2=D$

mono-ethylation with ethyl iodide followed by reductive methylation to give 4β-ethyl-4α-methyl-5α-cholest-3-one and by a subsequent lithium alminium hydride reduction. *6* was affected with phosphorous pentachloride in boiling n-hexane for 30 minutes and afforded three isomeric products 48 % *8*, 22 % *9a* and a few % *10a* (M^+=412). On the other hand, the solvolysis of the tosylate *7a* with the presence of sodium acetate gave *10a* almost exclusively either in refluxing aqueous aceton (95 %) or in acetic acid at 90-100° (90 %). *8* showed a methyl singlet at δ1.70 in the nmr spectrum and yielded, on ozonolysis, a keto compound (M^+=382) with five membered ring ketone (1735 cm^{-1}). It should be noted that the methyl signal appear at the same chemical shift as the methyl signal of isopropylidene moiety in compound *5b* and that the operation of the same stereochemical control would be suggested in the formation of *5b* and *8*. The structure of *9a* was elucidated from the nmr spectrum which exhibits the presence of an isobutenyl group, a methyl singlet at δ1.70 (3H), a methyl doublet at δ1.67 (3H, J=8 cps) and a qualtet at δ5.31 (1H, J=8 cps). Configurational assignment of this double bond was not achieved. The structure determination of *10a* was accomplished as follows, ozonolysis of *10a* gave a diketone *11*:M^+=444, IR 1710 cm^{-1}, which was converted to an ester-lactone *12*: M^+=476



11 *12* *13* *14*

IR 1720, 1735 cm^{-1} by Baeyer-Villiger oxidation with m-chloro perbenzoic acid. Base hydrolysis of *12* followed by acidification and methylation with diazo methane afforded a lactone ester *13*: M^+=434 IR 1740, 1770 cm^{-1} and isobutanol, trapped as the benzoate. For the formation of *10a* two mechanisms are quite probable: a) double bond migration from *8*, and b) 1,2 hydrogen shift from C_3 to C_4 after ring contraction and following C_5-hydrogen elimination (Figure 2). In order to differentiate these two mechanisms, a deuterated compound *7b* was prepared by a deuterated lithium alminium hydride ($LiAlD_4$) reduction of 3-keto group and subsequent tosylation. *7b* was subjected to the solvolysis with the presence of sodium acetate in acetic acid at 90-100° or in boiling aqueous acetone. The compound *7b* was apparently more stable than *7a* under these conditions and the solvolysis afforded three products *8*(20 %), *9b* (10 %) and *10b* (a few %)



7a *10a*

Figure 2

with considerable differences from the case of *7a* in product yields . This observations might be regarded as a primary isotope effect. The product *10b* was isolated and its mass spectrum showed 82.3 % of d_1 incorporation, while the starting compound *7b* contained 86.5 % d_1. The fact indicates that C_3-hydrogen of starting tosylate is retained almost completely in the product, hence the mechanism b (Figure 2) would be supported.

REFERENCES AND FOOTNOTES

1. C. W. Schoppee and G. R. A. Johnston, *J. Chem. Soc.*, 3261 (1961).
2. H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, 22 602 (1957).
3. Since the methylations at C_4 should occur by α-side attack, the deuterated methyl group should have β-configuration. G. Just and K. St. C. Richardson, *Can. J. Chem.*, 42 456 (1964).
4. The methyl signals were assigned by an inspection of nmr spectra of *3a*, *3b* and *3c*.
5. Solvolysis of 4-ethyl-4-methyl-Δ^5-cholesten-3β-ol 3-mesylate: G. Just, N. D. Hall and K. St. C. Richardson, *Can. J. Chem.*, 45 2521 (1967).