Free-energy Differences Between Isomeric Dienol Acetates by Thermodynamically Controlled Enol Acetylation of Δ^4-3-Oxo-steroids

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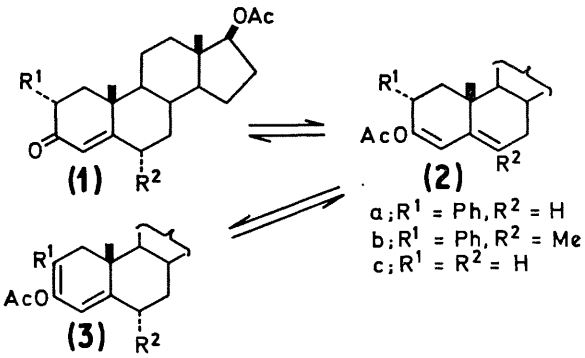
Summary Hydrobromic acid–acetic anhydride yields thermodynamically controlled mixtures of enol acetates from steroidal ketones.

EQUILIBRIUM mixtures of liquid enol acetates have been produced by prolonged heating of the reactants in sealed tubes with toluene-*p*-sulphonic acid as catalyst.[1] The most convenient method available at present to study the enolisation of steroid ketones by a thermodynamically controlled[2] enol acetylation reaction† uses acetic anhydride and perchloric acid.[3,4] With this reagent 17β-acetoxy-5β-androstan-3-one gives a mixture consisting of starting material, 5β-androst-2- and -3-ene-3,17β-diol diacetates in a constant ratio. When either enol acetate is subjected to the acetylating conditions the same equilibrium mixture is regenerated.[4] When the acetylating reagent is used with conjugated ketones the reaction leads to mixtures of *O*-acylated and *C*-acylated compounds[5] and enone–phenol transformation products,[6] the last two being secondary products formed from the intermediate dienol acetates. *C*-Acylated secondary products also result if boron trifluoride is employed as the acid catalyst.[7]

We report the use of a new reagent which produces equilibrium mixtures of enol acetates of both saturated and conjugated ketones without the disadvantage of secondary reactions. When 17β-acetoxy-2α-phenylandrost-4-en-3-one (**1a**) (1 g) {m.p. 168—170°; $[\alpha]_D^{28}$ + 70·9° (*c* 0·5, $CHCl_3$)} was heated under reflux in dry benzene (100 ml) with acetic anhydride (40 ml) and 48% hydrobromic acid (1 ml) for 1 hr., the equilibrium mixture was established. G.l.c. analysis showed that the reaction mixture consisted of (**1a**)



(10·5%), (**2a**) (53·8%) {m.p. 156—158°; $[\alpha]_D^{29}$ +37° (*c* 1·0, $CHCl_3$); λ_{max} (EtOH) 239 nm (ϵ 25,290)}, and (**3a**) (35·7%) {m.p. 168—171°; $[\alpha]_D^{29}$ + 20·4° (*c* 1·0, $CHCl_3$), λ_{max} (EtOH) 297 (ϵ 13,390) and 220 nm (ϵ 8500)}. Proof that equilibrium had been achieved was obtained by subjecting pure (**2a**) and (**3a**) separately to the acetylating conditions; in each case the

† Enol acetylation of steroid ketones with sulphuric acid or toluene-*p*-sulphonic acid catalyst and acetic anhydride or isopropenyl acetate leads to kinetically controlled[2] mixtures; J. Libman and Y. Mazur, *Tetrahedron*, 1969, **25**, 1699, and the references cited therein.

same ratio of products was observed‡. The equilibrium ratio of (**2a**) to (**3a**) at the reflux temperature (82°) is thus 60·1 : 39·9. 17β-Acetoxy-6α-methyl-2α-phenylandrost-4-en-3-one (**1b**) was also treated with acetic anhydride–hydrobromic acid reagent, and generated an equilibrium mixture consisting of (**1b**) (8·5%), (**2b**) (84·4%), and (**3b**) (7·1%). The equilibrium ratio of (**2b**) to (**3b**) at the reflux temperature is therefore 92·2 : 7·8. Since the replacement of the enolic hydrogen atom by an acetyl group should have no additional steric interaction with the remainder of the molecule, these ratios of isomers reflect the enolisation properties of the parent ketones.

The difference in free energy between the isomeric pairs of dienol acetates was calculated from the equilibrium constant. The free-energy difference which corresponds to an equilibrium ratio of 60·1% of (**2a**) and 39·9% of (**3a**) is 0·285 kcal./mole. Similarly, (**2b**) is more stable than its isomer (**3b**) by 1·738 kcal./mole at the same temperature (82°). These analogues, (**2a**/**3a**) and (**2b**/**3b**), differ by only a 6-methyl group. The extra stability conferred by the 6-methyl group can be deduced from the difference between the relative free energies, and equals 1·45 kcal./mole. This is in good agreement with the accepted value of 1·5 kcal./mole[8] for the stabilisation energy due to the conjugation of a single methyl group with a C=C bond.

Testosterone acetate (**1c**) on treatment with the new reagent, gave a mixture consisting of starting material and the 3,5-dienol acetate (**2c**); no 2,4-dienol acetate was detected.

In the acetylation of phenols with acetyl bromide catalysed by hydrobromic acid, Satchell[9] has suggested the participation of the acetylium ion and the ion pairs $MeCO^+Br^-$ and $MeCO^+HBr_2^-$. It has been suggested that the extensive *C*-acylation which occurs during the enol acetylation of Δ^4-3-oxo-steroids catalysed by perchloric acid or boron trifluoride proceeds *via* the attack of acetylium ion on the intermediate dienol acetates.[5a,6,7] In our system, ion pairs such as $MeCO^+Br^-$ and $MeCO^+HBr_2^-$ are probably involved in the enol acetylation with a minimum participation of free acetylium ion, since no *C*-acylated products were formed.

Satisfactory physical data were obtained for all new compounds.

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‡ The equilibrium ratio of 5β-androst-2-ene-3,17β-diol diacetate and 5β-androst-3-ene-3,17β-diol diacetate is known,[4] and the ability of this reagent to generate the same ratio of enol acetates was verified.

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