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LONG RANGE EFFECTS IN STEROIDS*

THE EFFECT OF A 9,11-DOUBLE BOND ON THE ENOLIZATION PROPERTIES OF Δ^4-3-OXO-STEROIDS

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Abstract- Thermodynamically controlled enol acetylation of 17β-acetoxy-2α-phenylandrosta-4,9(11)-dien-3-one (**3**) affords a mixture of 2α-phenylandrosta-3,5,9(11)-triene-3,17β-diol diacetate (**4**) and 2-phenylandrosta-2,4,9(11)-triene-3,17β-diol diacetate (**5**) in the ratio 43:57 respectively. This leads to a value of 0·20 kcal/mole for the free-energy difference between the isomers, and a value of 0·49 kcal/mole for the effect of the 9,11-double bond on the enolization properties of the Δ^4-3-oxo group in favor of the 2,4-dienol.

BARTON *et al.*[1-3] have demonstrated that the rate of base-catalyzed condensation of benzaldehyde with 3-oxo-5α-steroids and triterpenes can be affected by structural features far removed from the site of reaction. It was shown that the variations in reactivity are not due to the polarity of the remote substituents, but are caused by bond angle deformations which are accommodated by the whole molecule and transmitted through the fused ring system to the reaction site.[3-5] The term "conformational transmission" was introduced to describe this effect.[2] Subsequent work has confirmed and extended these results.[5-10]

As part of a program to examine the influence of remote substituents on the enolization properties of the Δ^4-3-oxo group found in many steroid hormones, we have been studying the acid-catalyzed enol acetylation of steroid ketones.[11-14] As a means of investigating long range effects we have employed the thermodynamically controlled[15] enol acetylation reaction. The ratio of the isomeric 2,4- and 3,5-dienol acetates at equilibrium, and hence the free-energy difference between them, reflects the relative stabilities of the enol acetates.[13, 14] Any change in the isomer ratio (and consequently also in the free-energy difference between them) induced by the introduction of remote substituents is a measure of the conformational transmission effect of that substituent on the relative stabilities of the enol acetates derived from the Δ^4-3-oxo group. Unsubstituted Δ^4-3-oxo-steroids enolize at equilibrium under the reaction conditions to produce exclusively the 3,5-dienol acetate.[13, 14] However, a convenient system in which to study the effects of remote substituents is provided by 2α-phenyl-Δ^4-3-oxo-steroids.[13, 14] Enol acetylation of 17β-acetoxy-2α-phenylandrost-4-en-3-one under thermodynamic control at 82° yields a mixture of 2α-phenylandrosta-3,5-diene-3,17β-diol diacetate (**8**) and 2-phenylandrosta-2,4-diene-3,17β-diol diacetate (**9**) in the ratio 60:40 respectively, i.e., the free-energy difference is 0·29

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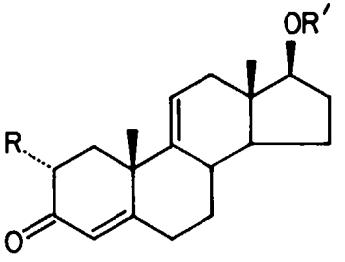
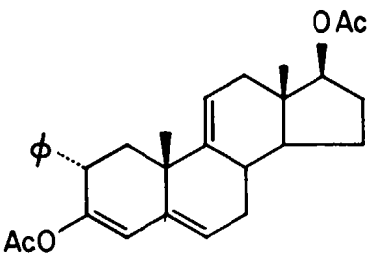


1 R=R′=H
2 R=ϕ, R′=H
3 R=ϕ, R′=Ac



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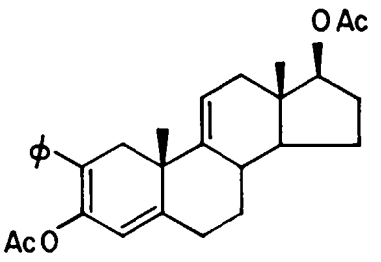

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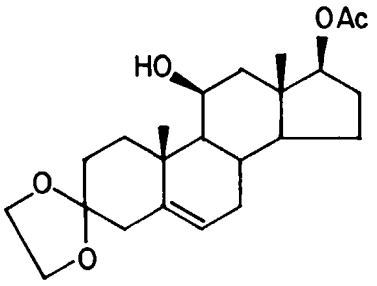

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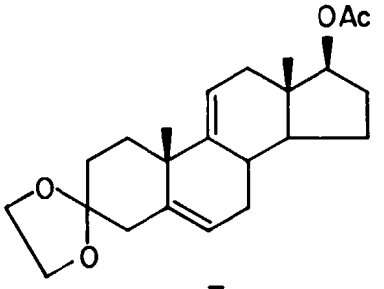

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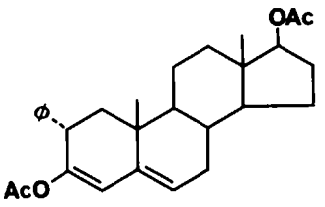

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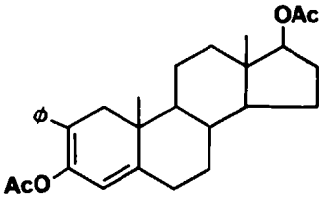

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kcal/mole.[13, 14] The influence of a 9,11-double bond on this equilibrium was investigated.

For this purpose we required 17β-acetoxy-2α-phenylandrosta-4,9(11)-dien-3-one (**3**), which was synthesized as follows. 3,3-Ethylenedioxyandrost-5-en-11β,17β-diol 17-acetate (**6**) obtained from cortisol[9] was converted into the 11β-trifluoracetate and the latter was treated with base to generate the $\Delta^{9,11}$-compound **7**, essentially by the method of Elks and Phillipps.[16] Deketalization and hydrolysis afforded 17β-hydroxyandrosta-4,9(11)-dien-3-one (**1**), which was phenylated[17] at C-2 to yield 17β-hydroxy-2α-phenylandrosta-4,9(11)-dien-3-one (**2**). Acetylation of the latter gave the desired starting material **3**.

Treatment of **3** with acetic anhydride-hydrobromic acid[13] gave a mixture consisting of a small quantity of starting material **3**, and two major products: 2α-phenylandrosta-3,5,9(11)-triene-3,17β-diol diacetate (**4**) and 2-phenylandrosta-2,4,9(11)-triene-3,17β-diol diacetate (**5**) separated on Florisil impregnated with silver nitrate. The structure of the former (**4**) was established on the basis of the IR spectrum which has bands for the acetate and enol acetate groups, and the UV spectrum (242 mμ) which is characteristic for a heteroannular diene.[12, 18] Confirmation was provided by the NMR spectrum which has signals due to the three olefinic hydrogens at C-4, C-6, and C-11. The structure of **5** was also deduced from the IR spectrum which has bands for the acetate and enol acetate, and the UV spectrum which has maximum absorption at 299 mμ, characteristic for the 2-phenyl-2,4-diene structure.[13, 14] The NMR spectrum has signals due to the two olefinic hydrogens at C-4 and C-11. The occurrence of signals in the NMR spectra of **4** and **5** due to the olefinic hydrogen at C-11 also proves that the 9,11-double bond had not migrated during the reaction to the presumably more stable 8,9- or 8,14- positions.

Treatment of compounds **3**, **4**, or **5**, individually under thermodynamically controlled[15] enol acetylation conditions[13, 14] produced the same equilibrium mixture of products in each case, namely **3** (5%), **4** (41%), and **5** (54%). The equilibrium ratio of **4**:**5** is 43:57 at 82°. This leads to a value for ΔG°_{82} of −0·20 kcal/mole for the isomerization **4** ⇌ **5**, i.e., the 2,4-diene **5** is more stable than the 3,5-diene **4** by 0·20 kcal/mole. In the analogous 9,11-saturated system the corresponding isomerization reaction is **8** ⇌ **9** and the equilibrium ratio is 60:40, respectively, leading to a value for ΔG°_{82} of +0·29 kcal/mole. The introduction of a 9,11-double bond, therefore, produces distortions in the steroid nucleus which alter the relative stabilities of the 2,4-diene and 3,5-diene structures by 0·49 kcal/mole in favor of the former.

The replacement of the enolic H atom by an acetyl group which occurs on enol acetylation should not introduce any significant additional steric interaction with the remainder of the molecule, since the major interaction in the A ring occurs between the phenyl group and the lone-pairs of electrons on the oxygen at C-3, which will be identical in both the enol and the enol acetate. Consequently, the equilibrium ratio of the isomeric dienol acetates reflects the equilibrium ratio of the free dienols, i.e., the enolization properties of the parent ketones. The $\Delta\Delta G$ value of 0·49 kcal/mole, therefore, represents the conformational transmission effect of the 9,11-double bond on the enolization properties of the Δ^4-3-oxo group.

In their study of the rate of condensation of benzaldehyde at C-2 in 3-oxo-5α-steroids, Barton *et al.*[3] found that the introduction of a 9,11-double bond increased the rate of condensation by a factor of 1·24. However, Orr *et al.*[7] found that the rates

of formation and hydrolysis of thiosemicarbazones of Δ^4-3-oxo-steroids were unaffected by the presence of a 9,11-double bond.

EXPERIMENTAL

General. M.ps were determined on an Electrothermal apparatus by the capillary method and are corrected. Rotations were measured in chloroform soln. The IR spectra were recorded on a Perkin–Elmer Model 237B double beam spectrophotometer. The UV spectra were determined in EtOH soln using a Bausch and Lomb Spectronic 502 recording spectrophotometer. The NMR spectra were determined on a Varian A-60 A spectrometer in $CDCl_3$ with TMS as an internal standard. Gas chromatography was carried out on a Model 810 F and M gas chromatograph equipped with dual flame detectors and a Kipp and Zonen BC1 electronic integrator. The columns were 5% OV-210 (trifluoropropyl silicone) on 60–80 mesh Diatoport S, 8 ft by 4 mm ID. The carrier gas was helium at a flow rate of 60 ml/min and the column temp was 230°. Microanalyses were performed by Alfred Bernhardt, Germany.

3,3-*Ethylenedioxyandrosta*-5,9(11)-*dien*-17β-*ol acetate* (**7**). Compound **6**[9] (6·9 g) in pyridine (50 ml) was treated with trifluoroacetic anhydride (10 ml) at room temp for 30 min. The soln was diluted with ether and washed with 3 N HCl, water and brine, and dried (Na_2SO_4). Evaporation gave crude 3,3-ethylenedioxy-androst-5-en-11β,17β-diol 17-acetate, 11-trifluoroacetate, which was dissolved in DMF (50 ml) and treated with powdered $CaCO_3$ (7 g). The stirred suspension was refluxed for 30 min, and poured into excess dil HCl aq. The product was extracted with CH_2Cl_2 and crystallized from acetone–hexane to yield: **7** (4·3 g), m.p. 181–182°; $[\alpha]_D^{26}$ −34° (*c* 1·0); IR (CCl_4) 1735 and 1245 (-OAc), 1355, and 1090 and 1040 cm^{-1} (ketal); NMR δ 0·79 (s, 3, 18-H), 1·24 (s, 3, 19-H), 2·08 (s, 3, 17-OAc), 3·95 (s, 4, ketal-H), 4·72 (t, 1, J = 8 Hz, 17-H), and 5·45 (m, 2, 6-H and 11-H). (Found: C, 73·97; H, 8·74. Calcd. for $C_{23}H_{32}O_4$: C, 74·16; H, 8·66%).

17β-*Hydroxyandrosta*-4,9(11)-*dien*-3-*one* (**1**). Compound **7** (17 g) was hydrolyzed with ethanolic KOH aq and the product was deketalized using 75% AcOH. Crystallization from acetone hexane afforded **1** (11 g), m.p. 152–153°; $[\alpha]_D^{25}$ +92° (*c* 1·0) (lit[19] m.p. 153–155°; $[\alpha]_D^{23}$ +89°).

17β-*Hydroxy*-2-*hydroxymethyleneandrosta*-4,9(11)-*dien*-3-*one*. Compound **1** (11·0 g) in anhyd benzene (300 ml) was treated with redistilled ethyl formate (16 ml) and NaH (50% oil dispersion, 8·5 g), and the slurry was stirred under N_2 at room temp overnight (18 hr). MeOH (50 ml) was added to decompose residual NaH, and the mixture was diluted with water (400 ml). The aqueous layer was separated, washed with ether, and was then acidified with 3 N HCl. The liberated steroid was isolated with ether to yield the oily product (8·1 g) which was used directly without further purification.

17β-*Acetoxy*-2α-*phenylandrosta*-4,9(11)-*dien*-3-*one* (**3**). 17β-Hydroxy-2-hydroxymethyleneandrosta-4,9(11)-dien-3-one (8·0 g) was added to a soln of K (1·25 g) in dry t-BuOH (250 ml). Diphenyliodonium chloride (10·5 g) was added and the stirred suspension was refluxed for 24 hr. The solvent was partially removed by evaporation *in vacuo*, and the mixture was diluted with water, and extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), and evaporated. The residue was dissolved in MeOH (350 ml) and treated with Na (3·0 g) in MeOH (75 ml), and the soln was refluxed for 4 hr. The cooled soln was neutralized with AcOH and the solvent was partially evaporated. Water was added and the mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), and the solvent was evaporated. The residue was chromatographed on Florisil with benzene as eluant. The product, **2** (3·2 g), failed to crystallize and was therefore acetylated with Ac_2O and pyridine in the usual way to yield **3** (3·0 g), which crystallized from acetone–hexane, m.p. 172–173°; $[\alpha]_D^{28}$ +74° (*c* 1·0); UV max 240 mμ (ε 17,240); IR (CCl_4) 1740 and 1240 (acetate), 1680 (C=C—C=O), 1620 (C=C), 1050, and 1025 cm^{-1}; NMR δ 0·79 (s, 3, 18-H), 1·43 (s, 3, 19-H), 2·03 (s, 3, 17-OAc), 3·71 (dd, 1, J = 12 Hz, J = 7 Hz, 2-H), 4·71 (t, 1, J = 8 Hz, 17-H), 5·49 (t, 1, J = 3·5 Hz, 11-H), 5·86 (d, 1, J = 1 Hz, 4-H), and 7·25 (s, 5, 2-Ph). (Found: C, 79·99; H, 7·90. Calcd. for $C_{23}H_{32}O_4$: C, 80·16; H, 7·97%).

2α-*Phenylandrosta*-3,5,9(11)-*triene*-3,17β-*diol diacetate* (**4**) *and* 2-*phenylandrosta*-2,4,9(11)-*triene*-3,17β-*diol diacetate* (**5**). Compound **3** (1·10 g) in dry benzene (110 ml) was treated with Ac_2O (25 ml) and 45% HBr in AcOH (3 ml), and the soln was refluxed for 1 hr. GLC analysis of an aliquot indicated that the reaction was complete and that three compounds were formed. The cooled soln was diluted with ether and washed with $NaHCO_3$ aq and brine, and dried (Na_2SO_4). The solvent was evaporated and the residue was taken up in benzene and adsorbed on to a column of Florisil impregnated with 10% $AgNO_3$. Elution with benzene afforded **4** (210 mg) free from the $\Delta^{2,4}$-isomer, which crystallized from aqueous MeOH containing 1% pyridine, m.p. 164–167°; $[\alpha]_D^{26}$ +2·8° (*c* 1·0); UV max 242 mμ (ε 20,400); IR (KBr) 1755 and 1215 (enol

Ac), 1740 and 1250 (-OAc), 1665 (C=C), 1640 (C=C), 1605 (C=C), 1130, 1026, and 925 cm^{-1}; NMR δ 0·80 (s, 3, 18-H), 1·36 (s, 3, 19-H), 1·75 (s, 3, 3-OAc), 2·03 (s, 3, 17-OAc), 4·02 (m, 1, 2-H), 4·71 (t, 1, J = 8 Hz, 17-H), 5·48 (m, 2, 6-H and 11-H), 5·90 (d, 1, J = 2·5 Hz, 4-H), and 7·22 (s, 5, 2-Ph). (Found: C, 77·79; H, 7·60. Calcd. for $C_{29}H_{34}O_4$: C, 78·00; H, 7·67%).

Further elution with benzene gave a mixture of compounds **4** and **5** (390 mg) in approximately a 1:1 ratio.

Further elution with benzene afforded **5** (350 mg) free from the $\Delta^{5,5}$-isomer, which crystallized from acetone–hexane, m.p. 153–155°; $[\alpha]_D^{26}$ −23·1° (*c* 1·0); UV max 299 (ε 10,500) and 220 mμ (ε 7,800); IR (CCl_4) 1760 and 1210 (enol Ac), 1740 and 1245 (OAc), 1365, and 1095 cm^{-1}; NMR δ 0·79 (s, 3, 18-H), 1·25 (s, 3, 19-H), 2·04 (s, 6, 3-OAc and 17-OAc), 4·72 (t, 1, J = 8 Hz, 17-H), and 5·47 (m, 2, 4-H and 11-H). (Found: C, 77·72, H, 7·56. Calc for $C_{29}H_{34}O_4$: C, 78·00; H, 7·67%).

Further elution with benzene–ether (19:1) afforded **3** (53 mg) which crystallized from acetone–hexane, m.p. 172–173°. The mixture m.p. with authentic compound was undepressed, and the IR spectra of the two compounds were identical.

Equilibration with acetic anhydride hydrobromic acid reagent

Reaction conditions. The steroid (10 mg) in dry benzene (4 ml) was treated with Ac_2O (1 ml) and 45% HBr in AcOH (0·1 ml), and the mixture was refluxed (82°) with stirring for 24 hr. Aliquots were withdrawn periodically and analyzed by gas chromatography. Peak identities were confirmed by enhancement with authentic compounds.

(a) Compound **3** produced an equilibrium mixture consisting of **4** (41%), **5** (54%), and **3** (5%), i.e., the ratio of **4**:**5** is 43:57.

(b) Compound **4** generated the same equilibrium mixture as in (a).

(c) Compound **5** generated the same equilibrium mixture as in (a).

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