# STUDIES OF THE SLOWING OF THE DIENONE-PHENOL REARRANGEMENT OF A STEROIDAL 1,4-DIEN-3-ONE BY THE INTRODUCTION OF AN 11-KETO GROUP

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ABSTRACT

It has been shown previously that steroidal 11-keto-1,4-dien-3-ones undergo dienone-phenol rearrangement significantly more slowly than their 11-deoxy-, or 11β-hydroxy- and 11-acetoxy analogs. We have tested the explanations suggested for this, and are able to reject most of them. There remains the probability that the 11-keto group reduces the migrating ability of the adjacent atom, C-9, which frequently migrates in steroidal rearrangements.

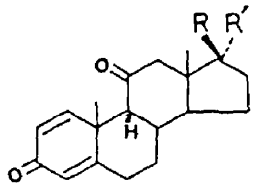
## INTRODUCTION

Steroidal 1,4-dien-3-ones containing an 11-keto group undergo dienone-phenol rearrangement with greater difficulty than their 11-deoxy analogs. Attempts to rearrange the 11-keto steroids (I) under normal conditions failed (1), or only marginally succeeded (2). However, rearrangement of compounds of type (I) can occur, with dilute perchloric acid in acetic anhydride as the reagent, to give initially the products (II) (3). The 11-keto dienone, prednisone acetate (III), rearranges much more slowly than its 11β-acetoxy analog, prednisolone acetate, and cholesta-1,4-dien-3-one under these conditions (3). We have examined the explanations previously suggested for this deactivating effect.

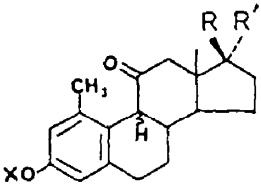
Dienone-phenol rearrangement of steroidal 1,4-dien-3-ones follows two paths (Scheme I), whose relative importance depends

on the substituents on rings A, B, and C, and the reaction conditions (4–7, and references therein). A more complex path which occurs with their bicyclic analogs (6,8–10) has not been found for steroids themselves (11).

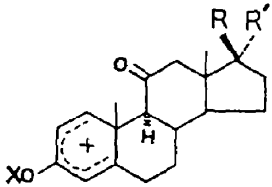
An 11-keto group could influence the rearrangement in a number of ways. First, it may reduce the basicity of the dienone function by destabilizing the cation (IV) relative to dienone. This would reduce the amount of the reactive cation at a given acidity and slow all rearrangement paths. The effect would apply only at acidities too low to give complete protonation of the dienone function, which would include the conditions used by the Glaxo group (3). The basicity can be studied directly and, together with the inherent reactivity of the dienone-cations should be reflected in plots of rearrangement rate against acidity (12). The 11-keto group may also modify the charge distribution in the cation (IV) by a through-space interaction with C-1 [(V)-(VI)] (3), or by an inductive (I) interaction with C-1 and C-5. We tested for these effects using proton nuclear magnetic resonance (NMR) chemical shifts, which correlate with charge densities in benzenonium ions (13) and in the cations of cyclohexadienones (14), and using $^{13}C$-NMR spectra. A further explanation is that the electron-attracting 11-keto group may reduce the migrating ability of C-9, which would slow Path B relative to Path A. There is evidence (15) from a simpler



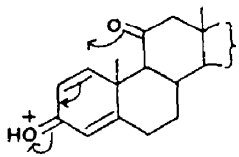
(I)
(Ia) R,R' = O
(III) R' = $CO.CH_2OAc$,
R' = OH



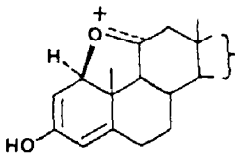
(II)
(IIa) R,R' = O



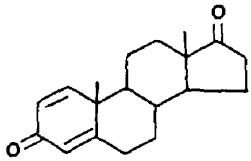
(IV)
(IVa) R,R' = O



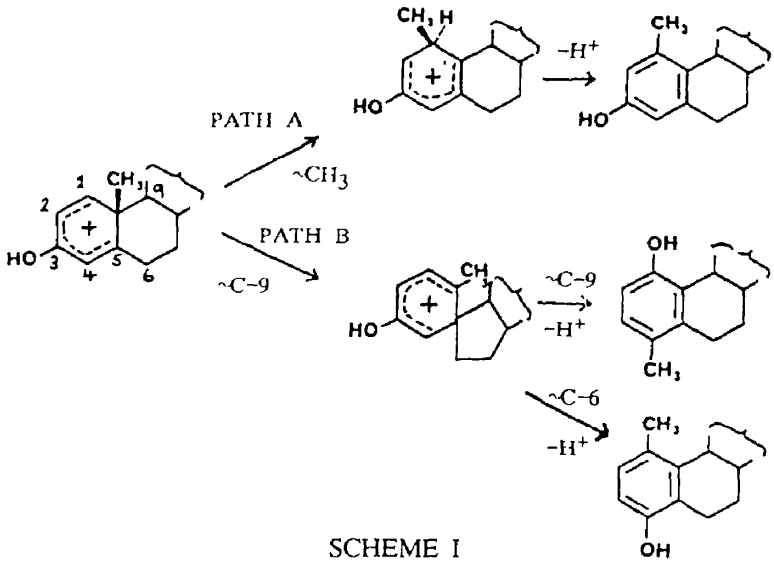
(V)



(VI)



(VII)




SCHEME I

compound that the $-CH_2\overset{|}{C}=O$ group has a lower migrating ability than does $-CH_2CH_2-$. If the 11-keto group is also appreciably protonated at the acidities used, the interaction (V)-(VI) should be reduced, but the effect on the migrating ability of C-9 magnified.

We studied androsta-1,4-diene-3,11,17-trione (Ia) as the 11-keto steroid, and compared it with androsta-1,4-diene-3,17-dione (VII) which we investigated previously (16). Aqueous sulfuric acid was used for basicity measurements. It, and aqueous perchloric acid, which should give faster rearrangements (16,17), were used for kinetic studies. Aqueous acids give a relatively high proportion of Path A products from steroidal 1,4-dien-3-ones (18) and their bicyclic analogs (16). The same has been found for reaction in anhydrous hydrogen fluoride/antimony pentafluoride (19). In contrast, mineral acids in acetic anhydride usually give a high proportion of Path B products (6,8,16 and references therein). We confirmed the report (3) that the trione (Ia) with perchloric acid in acetic anhydride reacts more slowly than (VII), and that it is unusual in giving the Path A product.

## EXPERIMENTAL

Spectroscopic and kinetic measurements were made as before (20). Equation 1 was used in basicity determinations (see Table 1).

For a base, B, with cation $BH^+$, which follows the Hammett acidity function, $H_0$, Equation 1 applies:

$$\log_{10}[BH^+]/[B] = m_0[(H_0)_{1/2}-H_0] \qquad \text{Equation (1)}$$

For amide bases, $H_0$ is replaced by $H_A$ and $m_0$ by $m_A$.

Values of the Hammett acidity function, $H_0$, and amide acidity function, $H_A$, for sulfuric acid are from references 21 and 22, respectively, and the $H_A$ function for perchloric acid from reference 23. The amide acidity scale for sulfuric acid has been redetermined and re-anchored by Edward and Wong (24), but the values used here allow direct comparison with our earlier results (16). Acid strengths expressed as percentages are weight/weight, determined from the densities using data in reference 25.

Proton NMR data are given in Table 2. The 13-C-NMR data are as follows, for the trione (Ia) then for its cation (IVa; X=H), followed by the shift due to protonation (in parentheses), expressed as an increase in the $\delta$-value: C-1, 154.3, 176.0 (21.7); C-2, 127.7, 123.3 (-4.4); C-3, 185.6, 194.1 or 190.5 (8.5 or 4.9); C-4, 124.8, 120.9 (-3.9); C-5, 165.3, 190.5 or 194.1 (25.2 or 28.8); C-9, 60.9, 60.9 (0.0); C-10, 42.2, 48.8 (6.6); C-11, 207.4,213.8 (6.4); C-17, 216.3, 228.2 (11.9). The assignments for the neutral trione match published data (26). The 13-C-NMR data for the dione (VII), then for its cation (produced by protonation of the 3-keto group), followed by the shift due to protonation (in parentheses), expressed as an increase in the $\delta$-value, are as follows: C-1, 155.2, 178.7 (23.4); C-2, 127.6, 122.6 (-5.0); C-3, 186.0, 199.1 or 189.5 (13.1 or 3.5); C-4, 124.0, 119.9 (-4.1); C-5, 168.2, 189.5 or 199.1 (21.3 or 30.9); C-9, 52.3, 54.7 (2.4); C-10, 43.4, 50.1 (6.7); C-17, 219.6, 234.6 (15.0). The protonation shifts for the two cyclohexadienone functions are considered to be very similar, and to show no evidence of an inter-ring interaction as shown in (V)-(VI).

Rearrangement of the trione (Ia) in acetic anhydride. The trione (0.5 g) was rearranged in acetic anhydride / perchloric acid, during 3 h at room temperature. Longer reaction led to a number of side products. Column chromatography on silica, eluting with toluene, and mixtures of toluene and ethyl acetate (up to 50:50) gave the acetate (IIa; X=$COCH_3$; 9α-H), m.p. 196-204°C [lit. (3) 203-208°C]. The 1-H-NMR spectrum included peaks at $\delta$ 6.70 and 6.76 (s, aryl 2- and 4-H), 3.62 (d, J 11.4 Hz, 9α-H), 2.27 (s, acetate), 1.96 (s, 1-Me), 0.93 (s, 13-Me).

Hydrolysis of acetate (IIa; X=$COCH_3$). The foregoing acetate was hydrolyzed with methanolic potassium hydroxide, and worked up as in reference 3. The crude mixture had 1-H-NMR peaks at $\delta$ 6.50 and 6.42 (s, aryl 2- and 4-H), 3.60 (d, J 11.2 Hz, 9α-H), 3.98 (smaller d, J 8.4 Hz, 9β-H), 1.91 (s, 1-Me), 1.26 (s, 13-Me of the 9β-isomer), 0.94 (s, 13-Me of the 9α-isomer) of the phenols (IIa; X=H). The shift differences between the aryl

TABLE 1

Basicity data for androsta-1,4-diene-3,11,17-trione (Ia) and androsta-1,4-diene-3,17-dione (VII)

| Cmpd | $\lambda$ /nm[a] | $-(H_0)_{1/2}$[b,c] | $m_0$[c] | $-(H_A)_{1/2}$[d,e] | $m_A$ | $-pK$[f] |
|---|---|---|---|---|---|---|
| (Ia) | 242 *† | 2.9 ± 0.1 | 0.70 ± 0.04 | 2.4 ± 0.05 | 1.00 ± 0.03 | |
| | 258 †¶ | 2.5 ± 0.2 | 0.60 ± 0.03 | 2.0 ± 0.1 | 1.02 ± 0.03 | 2.2 ± 0.2 |
| | 242 *§ | 2.9 ± 0.1 | 0.80 ± 0.04 | 2.16 ± 0.04 | 1.40 ± 0.05 | |
| | 258 ¶§ | 2.5 ± 0.2 | 0.58 ± 0.04 | 2.02 ± 0.08 | 0.83 ± 0.05 | |
| | 242/258 ** | 3.05 ± 0.05 | 0.63 ± 0.03 | 2.34 ± 0.01 | 0.97 ± 0.01 | 2.27 ± 0.03 |
| (VII)[g] | 250, 300 * | 2.31 ± 0.18 | 0.82 ± 0.07 | 1.92 ± 0.08 | 1.30 ± 0.05 | 2.1 ± 0.2 |

[a] Wavelengths used for the measurements. [b] Half-protonation acidity on the Hammett acidity function, $H_0$, using the scale of reference 21. [c] Values in Equation 1. [d] Half-protonation acidity on the amide acidity function, $H_A$, using the scale of reference 22. [e] Values in Equation 1, with $H_A$ and $m_A$ instead of $H_0$ and $m_0$. [f] Best estimate of thermodynamic pK, taken to be $m_A(H_A)_{1/2}$: see Eq. 1. The values quoted are weighted means. [g] Data from reference 16.

* Moderately strong medium effect at this wavelength. † Calculated by the method of Katritzky AR, Waring AJ, and Yates K (1963). TETRAHEDRON 19:465-469. ¶ About 25% change in absorbance at this wavelength due to protonation. § From unweighted least squares treatments of linear plots according to Eq. 1. ** Calculated by the method of reference 28.

TABLE 2

$^1$H NMR and UV data for dienones and their cations[a]

| Compound | H-1 | H-2 | H-4 | H-19 | Coupling constants J/Hz H(1)-H(2) | H(2)-H(4) | Solvent for UV | $\lambda_{max}$ | $\log_{10}$[c] |
|---|---|---|---|---|---|---|---|---|---|
| Trione (Ia) | 7.65 | 6.19 | 6.10 | 1.48 | 10.0 | 2.0 | 95% EtOH | 238 | 4.19 |
| | | | | | | | 0.5M $H_2SO_4$ | 239 | 4.17 |
| Cation of trione (Ia) = (IVa; X=H) | 8.78[b] | 7.10 | 7.03 | 1.60 | 10.0 | 1.6 | 70% $H_2SO_4$ | 256 | 4.14 |
| | | | | | | | | 299 | 3.77 |
| Dione (VII)[c] | 6.94 | 6.09 | 5.94 | 1.24 | 10.2 | 1.7 | $H_2O$[d] | 239 | 4.21 |
| Cation of (VII)[c] | 8.31 | 7.04 | 6.99 | 1.44 | 9.0 | 1.7 | 69% $H_2SO_4$ | 261 | 4.06 |
| | | | | | | | | 301 | 3.86 |

[a] δ Values; dienones in $CCl_4$ with $Me_4Si$ as internal standard; cations in 74% $H_2SO_4$ (for trione), or 72% $H_2SO_4$ (for dione), with tetramethylammonium chloride as internal standard, δ 3.16 (Levy GC, Cargioli JD, and Racela W. J AM CHEM SOC 92:6238-6246). [b] This value differs from δ 7.25 given by Jones HA (1971) [J CHEM SOC (B):99-101]. [c] NMR data from reference 14. [d] UV data from reference 16.

protons of the acetate and the phenols are in accordance with expectation for a structure having both protons ortho to the hydroxyl function (27).

## RESULTS AND DISCUSSION

Basicity comparisons. The protonation of the trione (Ia) was measured in aqueous sulfuric acid at 25 °C, using UV spectrophotometry and acidity function methods (16). The existence of medium effects and slight variations in absorbances measured at high acidities reduced the precision of results based on any single wavelength. However, the use of the ratios of absorbances at pairs of wavelengths (28) gave improved results. The results (Table 1) show that protonation of the 11-keto steroid (Ia) follows closely the amide acidity function, $H_A$. The difference between the basicity values for (I) and (VII) is small but real. If the dienone-cations were equally reactive the rate for the trione would be reduced by an amount which would vary with acidity (12), but should never fall below two-thirds of the rate for the dione. We can also predict the pK of androsta-1,4-diene-3,11,17-trione as $-(2.1 \pm 0.1)$. The empirical rules (29) which correlate the pK values of cyclohexa-2,5-dienones with those of cyclohex-2-enones can be applied to androst-1-ene-3,11,17-trione, an $H_A$ base having pK $-(3.60 \pm 0.04)$ for protonation of the 3-keto group (30).

Kinetic studies. Reaction of the 11-keto steroid (Ia) was followed by UV spectrophotometry at 25 °C, in aqueous sulfuric

acid. However, loss of dienone was too slow to measure [and significantly slower than reaction of (VII)], even in the most concentrated acid used (ca. 72% w/w). The solutions darkened and phenolic products could not be isolated. We therefore also attempted to measure kinetics in aqueous perchloric acid, in which the dione (VII) reacts about 14 times faster than in sulfuric acid of the same acidity ($H_A$ value). The trione was still consumed very slowly, and less than one-sixth as fast as the dione in perchloric acid of a given acidity. We could not isolate phenolic products from the trione, although the reaction mixture showed small $^1$H-NMR peaks for the phenol (IIa; X=H). Because of this, and the fact that darkening of the solutions occurs, we believe our kinetic data to have no quantitative significance, and do not present them here. Presumably the initially formed phenol, having a 9α-H, easily equilibrates with its 9β-H isomer (3,19): further reactions must account for their destruction and for darkening of the solutions. The Glaxo group (3) noted a similar lack of cleanness in their reactions. We prepared a comparison sample of (IIa; X=H) from the trione (Ia) in perchloric acid/acetic anhydride, via the acetate (IIa; X=$COCH_3$; 9α-H) (3). Alkaline hydrolysis was reported to give results suggestive of epimerization at C-9, and "with difficulty a relatively pure specimen of the presumed 9β - compound (IIa; X=H; 9β-H)" could be isolated (3). The crude product of

hydrolysis of our acetate (IIa; X=$COCH_3$; 9α-H) had $^1H$-NMR peaks consistent with the structure (IIa; X=H), but showed three methyl peaks and two sets of doublets which we assign to the 9-proton. The chemical shifts and coupling constants suggest that it is a mixture of the 9α- and 9β - isomers of (IIa; X=H). Comparable data for closely related pairs of 11-keto steroids have been discussed by Reusch and his co-workers (31).

Our NMR and UV experiments show that the trione (Ia) reacts very slowly, and we cannot be sure that it gives predominantly phenols. We can say that the dienone-phenol reactions of the trione are less than one-sixth as fast as the dione's, and that this is not due to significant reduction of the dienone group's basicity by the 11-keto group. To examine the other explanations given in the Introduction we measured the $^{13}C$-NMR spectra of the trione-cation and dione-cation in acid in which the 3-keto group is more than 98% protonated. The neutral trione has its peaks for C-1, C-2, C-3, and C-4 within 1 ppm of those in the dione. On protonation, the chemical shift changes of C-1, C-2, and C-4 are the same, within 2 ppm, for the two compounds, and may be for C-3 also. These data give no evidence of the interaction shown in (VI). This type of interaction was used to explain the carboxylation at C-2 of the 9(11)-enolate anion of a steroidal 11-keto-1,4-dien-3-one (32), and the formation of a novel lumiproduct from prednisone acetate (33). Furthermore, the

proton NMR spectra of the cations of the dione and trione have virtually identical peak positions and protonation shifts for 2-H and 4-H, and very similar ones for the 19-methyl protons. However, 1-H in the trione cation ( $\delta$ 8.78) and the neutral trione ( $\delta$ 7.65) appears significantly downfield of that in the dione cation at $\delta$ 8.31 and the neutral dione ( $\delta$ 6.94). The protonation shifts for the trione and dione (1.13 and 1.37 ppm, respectively, downfield) are clearly, but not greatly different. This may reflect small conformational changes in the effect of the 11-keto group's diamagnetic anisotropy, or partial protonation of the 11-keto group, or a minor contribution from the structure (VI). However, the $^{13}$C-NMR data persuade us that the through-space interaction (V)-(VI) cannot adequately explain the slow rearrangements of the trione.

The extreme slowness of the trione's reaction, and uncertainties in the rate constants prevent an analysis of its rate/acidity profile (12), and we are unable to study the variation in the degree of protonation of the 11-keto group. However, such protonation does not seem to explain the trione's slow reaction, either in the aqueous acids or in dilute perchloric acid/acetic anhydride mixtures, although it should be significant at high acidities. Previous attempts (34) to use $^{13}$C-NMR spectroscopy to measure the basicity of the three ketone functions in androst-4-ene-3,11,17-trione were

unsuccessful. Studies of simple cyclic ketones (34) suggest that the 11-keto group should be the least basic center of the trione (Ia). At the highest acidity used for our kinetic measurements the dienone carbonyl group of (Ia) is essentially completely protonated, but the $^{13}$C-NMR shift data suggest the 11-keto group to be less than one-third protonated.

We thus believe that most of the explanations offered for the retarding effect of the 11-keto group on the dienone-phenol rearrangement are not supported. The one which remains is that the 11-keto group reduces significantly the migrating ability of the attached carbon atom, C-9. Support for this is given by the yields reported from rearrangements of 11-deoxy steroidal 1,4-dienones in acetic anhydride/mineral acids (4,5,35), and especially of 4-[$^{13}$C]cholesta-1,4-diene-3-one, which proved the rate ratio of Paths B/A to exceed 3/1 (36), and for the dione (VII) whose Path B/A rate ratio must exceed 2.33 (37). In contrast, the 11-keto steroid (Ia) must have a rate ratio of Path A/B of at least 2.22. The introduction of the 11-keto group must therefore reduce the rate of Path B relative to Path A to less than one-fifth. If, as seems probable, the 11-keto group retards migration of the methyl group by Path A, then it must retard even more strongly the migration of C-9 by Path B. Studies are in progress to determine the migratory aptitudes of ketoalkyl groups in other cation rearrangements.

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