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NOVEL REARRANGEMENT OF 6β,19-OXIDO-2,17-DIHYDROXYANDROSTA-1,4-DIEN-3-ONE

R. J. CHORVAT*, R. H. BIBLE, JR., and L. SWENTON
Department of Chemistry and Department of Analytical Resources and Methods, Searle Laboratories, A Division of G. D. Searle & Co., Skokie, Ill 60076, U.S.A.

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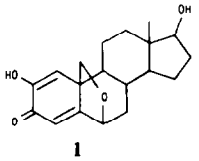
Abstract—Under benzilic acid rearrangement conditions and acidic work-up, 6β,19-oxido-2,17-dihydroxyandrosta-1,4-dien-3-one (**1**) underwent unusual, extensive rearrangement affording a furopyranone (**3**) in high yield. This product was the result of B-ring contraction, double bond isomerization and benzilic acid rearrangement of **1**, followed by acid catalyzed cyclization of the carboxy intermediate with the vinyl ether portion of the molecule. Alternatively, alkylation of the barium salt (**2**) of the reaction mixture with dimethyl sulfate in dimethyl formamide gave a carbomethoxy dihydrofuran derivative (**6**). Oxidation of the furopyranone (**3**) with Jones reagent produced a furanone derivative (**5**) formed *via* hydrolysis and oxidative-decarboxylation. The complex molecular structures of these rearrangement products were determined through extensive analysis of NMR spectra utilizing double resonance and Eu(FOD)$_3$ shift reagent. The structural assignments are supported by a proposed mechanism of formation.

6β,19 - Oxido - 2,17 - dihydroxyandrosta - 1,4 - dien - 3 - one (**1**) is an important intermediate in the synthesis of unsaturated 2-oxa- and 2-azasteroids due to its propensity to add ozone with a high degree of regioselectivity.[1] More recently we have discovered an anomalous reactivity of this α-diketone and we now wish to report the results of this study.

The benzilic acid rearrangement of steroidal diosphenols has provided an efficient synthesis of A-ring contracted steroids.[2] However, molecules possessing a 4,5-double bond conjugated to the 2,3-diketone moiety afford low yields of isolable products, apparently due to the inability of the conjugated double bond to withstand the stringent conditions necessary for ring contraction.[3] When the bridged α-diketone **1** was subjected to benzilic acid rearrangement conditions followed by acidic work-up, compound **3** was produced in high yield. This extremely unusual and totally unexpected structure, involving extensive rearrangement of **1**, has been firmly established through detailed spectroscopic studies (*vide infra*) and corroborated by X-ray crystallography.[4] This furopyranone (**3**) is the result of a reaction sequence wherein B-ring contraction preferentially occurs before the expected benzilic acid rearrangement contraction of the A-ring. In the following sections we will describe the spectral evidence which led to the structure of **3** and the chemical evidence that supports the mechanism of its formation.



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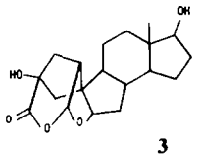

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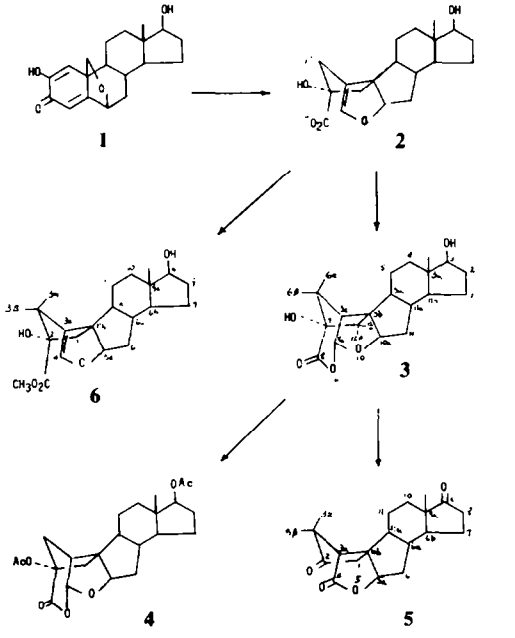
RESULTS AND DISCUSSION

When **1** was refluxed overnight in pyridine with barium hydroxide octahydrate a single product was obtained in high yield (80–85%) after acidic work-up (Scheme 1). The NMR spectrum of this material immediately suggested than an unusual transformation has occurred since the characteristic signals of the ethereal 19-methylene bridge protons of the starting material were absent.* The other terminus of the oxido bridge appeared to be intact, as suggested by the presence of a doublet at 4·38 ppm (J = 5·6 Hz) similar in coupling and chemical shift to that of the C–6 proton of the starting material (4·75 ppm, J = 5 Hz). The spectrum also showed a one proton downfield doublet (J = 5 Hz) at 6·04 ppm, a two proton singlet at 2·23 ppm and a one proton triplet at 2·66 ppm. In



Scheme 1. Rearrangement products and their derivatives are numbered according to IUPAC rules of organic nomenclature and are as suggested by Chemical Abstracts Service, Nomenclature Division.

*Steroid numbering is utilized only with regard to compound **1**. The numbering used for the rearrangement products is shown in Scheme 1.

addition, the compound had no UV absorption above 220 nm and its infrared spectrum showed a single carbonyl-stretching band at 1745 cm^{-1}. The elemental analysis as well as the mass spectrum of the compound indicated an empirical formula which differed from the empirical formula of the starting material only by the addition of a molecule of water (*m/e* 334, M+).

Acetylation of **3** in acetic anhydride and pyridine gave the diacetate (**4**) (*m/e* 418, M+), whose NMR spectrum showed not only the typical resonance of the 17-acetate group at 2·05 ppm, but also that of an additional acetate methyl signal at 2·11 ppm. The fact that no concommittant downfield shift of a proton or protons had accompanied introduction of this latter group suggested that an unhindered, readily acylated tertiary hydroxyl group was present in the rearrangement product **3**. This was also indicated by the presence of an exchangeable one proton singlet in the NMR spectrum of **3** in DMSO (d_6).[5]

In an early attempt to gain information about the structure of **3**, the compound was oxidized with Jones reagent.[6] This reaction produced the diketolactone **5** whose initial structural assignment was equally perplexing. However, it revealed to us that since the 6·05 ppm proton signal of **3** was destroyed during the oxidation, it was not due to an olefinic proton. This then suggested that this signal was from a hemiacetal proton, an assignment which would be consistent with its chemical shift and its disappearance after the oxidation.

The structure of **5**, which was elucidated after our determination of the structure of **3**, further supports the latter's assignment. It is postulated that during the oxidation, **3** underwent hydrolysis of the lactone followed by oxidative-decarboxylation of the resultant α-hydroxy acid. Oxidation of the hemiacetal formed at the C-9a carbon atom would then yield product **5**.[7] The structural assignment is supported by infrared bands at 1775 cm^{-1} attributed to the γ-lactone carbonyl and at 1755 cm^{-1} attributed to the two cyclopentanone carbonyl groups. Furthermore, the mass spectrum of **5** corroborated the molecular weight of this molecule (*m/e* 302, M+) and its NMR spectrum is also consistent with this structure.

The isolation of the dihydroxyfurano ester (**6**) provided substantial evidence for our assignment of the structure of **3** and, in addition, lent considerable support to our proposed mechanism (*vide infra*). When the barium salt of the benzilic acid rearrangement reaction (**2**) was isolated, without acidic work-up, and then alkylated with dimethyl sulfate in DMF, compound **6** was produced. This carbomethoxy derivative exhibits a signal in its NMR spectrum at 6·19 ppm, ascribed to the vinyl ether proton of the dihydrofuran portion of structure **6**. Under acidic conditions, the β-olefinic carbon atom of the vinyl ether moiety would be readily susceptible to hydration *via* proton transfer.[8] Subsequent ring closure with the unesterified carboxy group would yield the lactone (**3**). Further elaboration of the NMR spectra of **6** follows in the spectroscopy discussion section.

SPECTROSCOPY DISCUSSION SECTION

The structure of **3** was elucidated by careful study of its NMR spectrum and the NMR spectrum of its more chloroform-soluble diacetoxy derivative **4**. The NMR spectrum of **4** is shown in Fig. 1. Incremental additions of $Eu(FOD)_3$ to the deuterochloroform solution of this diacetate together with double irradiation experiments were used to analyze the coupling patterns. The apparent singlet at 2·18 ppm (FG of Figure 2) is actually the two-spin portion of a three-spin pattern. Proton G is coupled only with proton F, but proton F is coupled (by approximately 1·5 Hz) to proton D, the doublet at

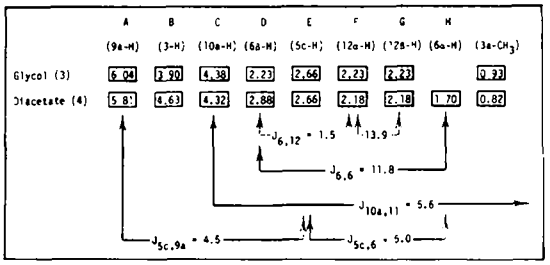


Fig. 2. NMR data for the glycol (**3**) in deuteropyridine and the diacetate (**4**) in deuterochloroform. Chemical shifts in ppm are indicated in boxes and coupling constants in Hz are indicated by arrows. Numbers in parenthesis correspond to the IUPAC numbering as indicated in Scheme 1.

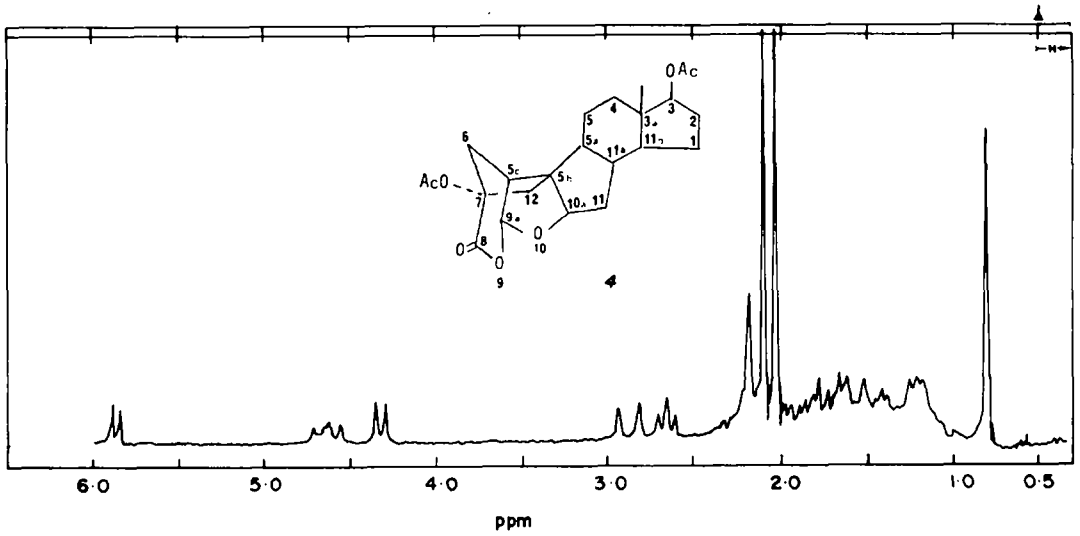


Fig. 1. 100 MHz NMR spectrum of the diacetate (**4**) in $CDCl_3$.

2·88 ppm. Further double irradiation experiments established the other relationships shown in Fig. 2.

Utilizing the information gained through these double resonance experiments, we eventually arrived at structure **3**, which does indeed account for all of the spectral features observed and is in accord with our proposed mechanism. The long range coupling observed for protons F (C–12αH) and D (C–6βH) is consistent with the "W" planar arrangement for these protons in the molecular model. The dihedral angles between proton E (C–5H) and one of the D protons (C–6βH) and between proton C and the 11α-proton are essentially 90°, thus accounting for the absence of appreciable vicinal coupling. The magnitudes of the geminal couplings of the D and H protons (11·8 Hz) and G and F protons (13·9 Hz) are in the expected range.

The chemical shifts observed in the study of the diacetate (**4**) with $Eu(FOD)_3$ are plotted in Fig. 3 as a function of the molar ratio of $Eu(FOD)_3$ to diacetate. The largest shifts with addition of $Eu(FOD)_3$ were for the signals due to protons in the vicinity of the 3-acetate group. The next largest shifts observed were for the signals due to proton D and the methyl protons of the tertiary acetate.

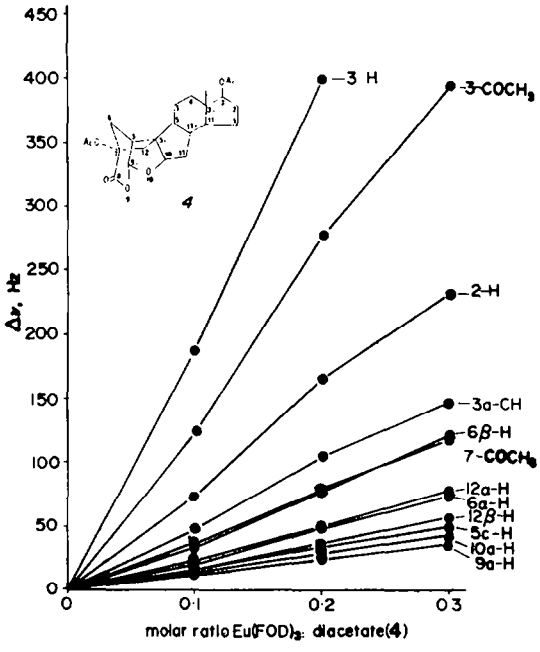


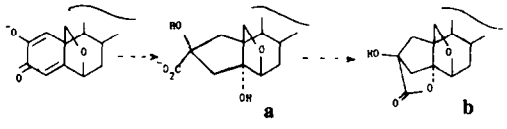
Fig. 3. Changes in chemical shifts of protons of the diacetate (**4**) as a function of the molar ratio of $Eu(FOD)_3$ to diacetate (**4**).

In the NMR spectrum of **6**, shown in Fig. 4, all of the signals which were due to the four protons of the C–1 and C–3 carbon atoms could be clearly identified and were consistent with the proposed structure. The C–1 methylene protons gave a simple AB pattern with a geminal coupling constant of 14 Hz. The C–3α methylene proton appeared as a doublet (J = 15 Hz) while the C–3β methylene proton appeared as a doublet of doublets (J = 15 and 2·1 Hz). The small splitting of the C–3β proton was shown by double resonance to be due to allylic coupling with the olefinic C–4 proton. This observation was consistent with the nearly perpendicular relationship of the plane of the double bond to the C–H bond of the C–3β proton.

Mechanism

In our first attempts to reconcile the spectral data with a structure, we assumed initial benzilic acid rearrangement followed by lactonization of the resultant carboxylic acid. This might occur by reaction with a 5α-hydroxy group formed by conjugate addition of hydroxide to the double bond as shown in Scheme 2 (**a** and **b**). However, molecule **b** did not satisfy the structural requirements demanded by our spectral data, since it would be expected to have a two proton NMR signal very similar to the AB pattern of the 19-methylene group of the starting material. The absence of this pattern in the NMR spectrum of **3** prompted consideration of the mechanism outlined in Scheme 3.

This mechanism involves migration of the 9,10-bond to the C–5 carbon atom (steroid numbering) and affords intermediate **a** (better represented by figure **a'**). Conjugated α-diketones have been shown to undergo benzilic



Scheme 2.

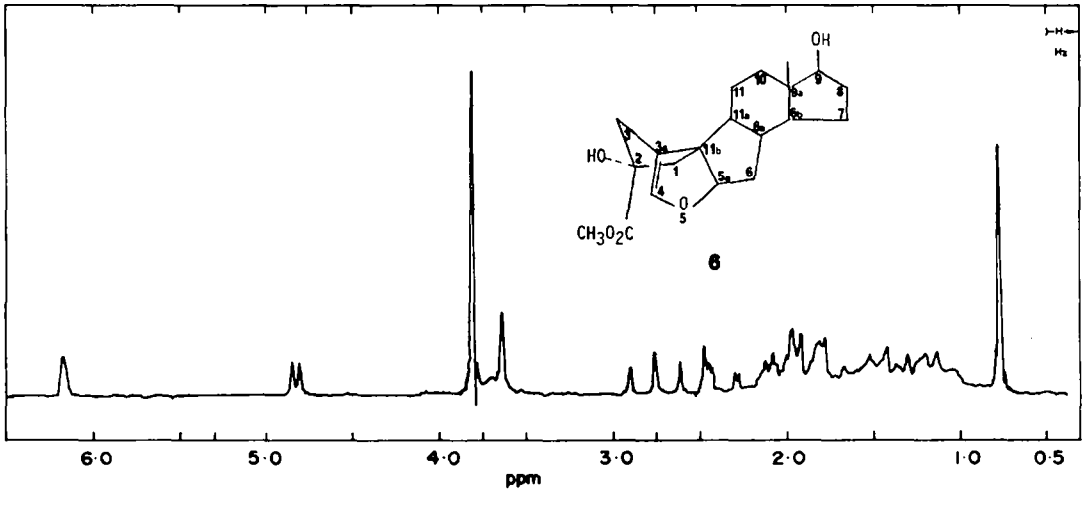
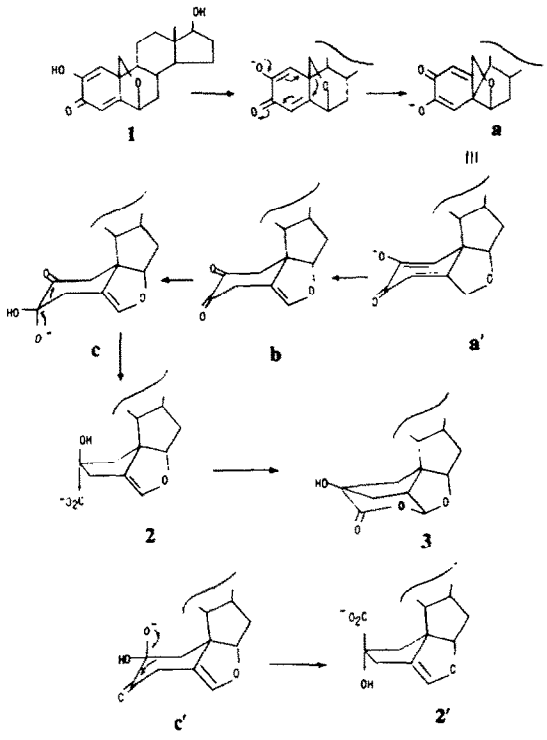


Fig. 4. 100 MHz NMR spectrum of the dihydroxyfurano ester (**6**) in $CDCl_3$.



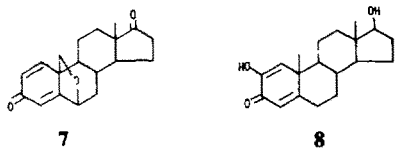
Scheme 3.

acid rearrangement in low yield.[3] The high yield of **3** suggests that double bond migration into the furan ring occurs prior to benzilic acid rearrangement (although reversal of this sequence cannot be precluded). Moreover, allyl ether isomerization[9] as well as deconjugation of conjugated carbonyls under basic conditions are well documented phenomena.[10] The isomerized intermediate, **b**, undergoes benzilic acid rearrangement *via* hydroxide adduct **c** to yield **2** as a single isomer at the carboxy-carbinol position. There is ample precedent for a single hydroxy acid resulting from this type of rearrangement.[11] It appears that the unidirectional course of this mechanism can be explained by the conformationally more stable hydroxide adduct **c** in which 1,3-diaxial interactions would be minimized.[12,13]

Attack of the hydroxide ion at the alternate carbonyl would result in intermediate **c'** which should give **2'** upon contraction. This carboxy-carbinol (**2'**) would be incapable of cyclizing and thus, in view of the high yield of **3**, must be much less favored.

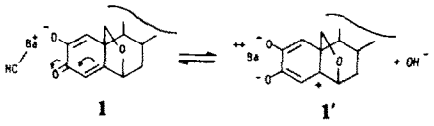
Intermediate **2** can be converted to the lactone **3** *via* hydration of the vinyl ether to a hemiacetal and subsequent lactonization with the carboxyl group under the acidic conditions of the work-up.[8] Alternatively, intramolecular proton transfer from the carboxyl group to the C-5c carbon atom and cyclization of the generated C-9a carbonium ion with the carboxy anion in a concerted manner is also possible.

Some experiments have been performed to determine the structural requirements necessary for this type of rearrangement. Compound **7**[14] gave no evidence of reaction when exposed to the conditions which caused rearrangement of **1**. Compound **8**[1] was also exposed to these conditions but for an extended reflux period of 48 hrs. After acidic work-up, both thin layer chromatography (TLC) and NMR spectroscopy indicated a predominance of recovered starting material (*ca.* 75%). The accompanying products were separated from the starting material by bicarbonate extraction. The NMR spectrum of this acidic fraction indicated at least two components but characterization was not pursued.



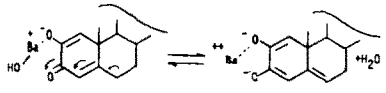
7 **8**

It was also observed that barium hydroxide appears unique in its ability to promote rearrangement of **1**.[15] When alternate bases such as potassium hydroxide, lithium hydroxide or calcium hydroxide were substituted, none of the rearrangement product was observed by TLC.[16] It can be postulated that this unique ability may be due to chelation of the divalent barium cation to the α-diketone moiety. This might then initiate positive

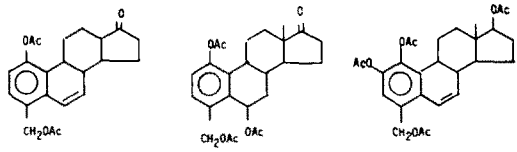


1 **1'**

charge formation at the C-5 carbon atom of **1** and trigger the migration of the 9,10-bond. Compound **8** does not undergo this type of migration since, in the absence of the 6,19-bridge, the charge is delocalized as shown below.



The migration of the 9,10-bond to the electron deficient C-5 carbon atom invoked in our mechanism is strikingly similar to the pathway of the diene-phenol rearrangement. Earlier work by Cross and coworkers[17] had examined the rearrangement of **7** under these conditions and found that cleavage of the 6,19-bridge occurs affording the aromatic compounds **9** and **10**. We have also observed a comparable reactivity of **1** which yielded **11** in the presence of aqueous perchloric acid and acetic anhydride.



9 **10** **11**

The observed novel rearrangement of **1**, however, is, to the best knowledge of the authors, the first reported example of a diene-phenol skeletal rearrangement under basic conditions. Moreover, it represents a unique case where the spiro ring fusion of the rearrangement intermediate is retained as a structural feature of the final product.

EXPERIMENTAL

M.ps were taken on a Thomas-Hoover capillary m.p. apparatus and are uncorrected. NMR spectra were taken on a Varian

A-60-A, Varian T-60, or Varian XL-100 spectrometer using TMS as an internal standard. IR spectra were recorded in chloroform on a Beckman IR-12 grating spectrophotometer. UV spectra were taken in MeOH on a Beckman DK-2A. Mass spectra were run on a CEC-491 at Dow Chemical Corporation of Midland, Michigan. TLC runs were on 7·6 cm microscope slides covered with 0·25 mm thickness Woelm F silica with a magnesium silicate binder. Solvents were EtOAc or EtOAc:PhH combinations. Visualization of spots was by 5% phosphomolybdic acid in EtOH (wt/vol) followed by heat. The spectroscopic determinations were performed under the supervision of Mr. Aristides J. Damascus and the microanalyses were performed under the direction of Mr. Emanuel J. Zielinski. The 100 MHz NMR spectra were determined by Elisabeth Hajdu and Charles N. Fahler. Spectroscopic data not given in this part are given in the table in the Spectroscopy Discussion Section.

Treatment of 6β,19 - *oxido* - 2,17 - *dihydroxyandrosta* - 1,4 - *dien* - 3 - *one* (1)[1] *with barium hydroxide.* To a soln of **1** (10·0 g) in 400 ml pyridine, barium hydroxide octahydrate (25 g) was added and the mixture was refluxed for 22 hr. Most of the solvent was then removed *in vacuo* and *ca* 50 ml of H_2O was added to the residue followed by sufficient 6N/HCl to make the resulting soln acidic. The small amount of brown ppt which formed was removed by filtration and the aqueous filtrate was extracted 4 times with $CHCl_3$. The combined extracts were washed once with 1N/HCl and once with sat NaCl aq and dried over Na_2SO_4. Solvent removal afforded 8·7 g of light yellow crystalline residue. Recrystallization from aqueous acetone gave pure [3S-(3β, 3aβ, 5aα, 5bR, 5cR, 7R, 9aR, 10aα, 11aβ, 11bα)] tetradecahydro - 3,7 - dihydroxy - 3a - methyl - 1H - 5b,7 - methano - 8H - *as* - indaceno [3', 2':4, 5]furo[2,3-b]pyran - 8 - one (**3**) as the hydrate, m.p. (115–125° loss of H_2O) 190–197°; IR 1745 cm^{-1} (C=O). (Found: C, 64·71; H, 8·12. Calc. for $C_{19}H_{26}O_5 \cdot H_2O$: C, 64·75; H, 8·01%).

Acetylation of **3**. To **3** (1·15 g) in 10 ml pyridine Ac_2O (5 ml) was added and the heterogeneous mixture was stirred at room temp. overnight. After cooling to 0°, about 40 ml water was added to the now homogeneous mixture causing precipitation of 1·1 g of crude product. Recrystallization from ethyl acetate-Skelly B gave the pure **4**, m.p. 229–230°; IR: 1765, 1755, 1735 cm^{-1} (C=O's). (Found: C, 65·80; H, 7·12. Calc. for $C_{20}H_{30}O_7$: C, 66·01; H, 7·23%).

Oxidation of **3**. To **3** (4·0 g) in acetone (175 ml) cooled to −10° was added 10 ml of Jones reagent at a rate so as to maintain a temp. below −5° during addition. The mixture was then kept at 0° for 0·5 hr before destruction of the excess oxidizing agent with isopropanol. After removal of the precipitated inorganic salts by filtration, the volume of the filtrate was reduced to 25 ml *in vacuo* before addition of 100 ml water whereupon 1·6 g of white solid which formed was isolated by filtration. Material recovered from the extracted ($CHCl_3$) aqueous mother liquors contained additional product (determined by TLC) along with more polar contaminants. No attempts were made to separate or characterize these components. The precipitated product was recrystallized from aqueous acetone to afford pure 3aR - (3aβ, 5aα, 6aβ, 6bα, 9aβ, 11aα, 11bR) - decahydro - 9a - methyl - 1H,7H - cyclopent[*c*] - as - indaceno[2,3 - *b*]furan - 2,4,9(8H) - trione (**5**), m.p. 286–289° (dec); IR: 1755, 1775 cm^{-1} (C=O's); $\delta_{ppm}^{CDCl_3}$ 0·93 (3H, s, 9a–CH_3), 3·12 (1H, brd t, J = 7·5 Hz, 3a–H), 4·81 (1H, d, J = 6 Hz, 5a–H). (Found: C, 71·46; H, 7·56. Calc. for $C_{18}H_{22}O_4$: C, 71·50; H, 7·33%).

3S - (3β, 3aβ, 5aα, 5bR, 5cR, 7R, 9aR, 10aα, 11aβ, 11bα) - 3,7 - *diacetoxytetradecahydro* - 3a - *methyl* - 1H - 5b,7 - *methano* - 8H - *as* - *indaceno* - 3',2':4,5 - *furo* - 2,3 - b *pyran* - 8 - *one* (**6**). To **1** (5·0 g) in 125 ml pyridine was added 10 g of barium hydroxide octahydrate and the mixture was refluxed for 17 hr. Complete solvent removal *in vacuo* afforded a light brown solid. The residue was dissolved into 125 ml DMF and anhyd. K_2CO_3 (4 g) was added to the soln. The heterogeneous mixture was cooled in an ice bath before the dropwise addition of 9 ml of dimethyl sulfate. The mixture was stirred for 4·5 hr at room temp. before addition of 7 ml H_2O and solvent removal *in vacuo* to afford 30 to 40 ml of oily residue. Slow addition of 200 ml of H_2O with virorous stirring caused formation of a solid which was isolated by filtration. Taking up the filtered solid into 75 ml acetone resulted in a heterogeneous soln which was filtered free of inorganic salts by passing through a cake of diatomaceous earth. Solvent removal gave an oil which was dissolved into EtOAc, dried over Na_2SO_4 and filtered. Skelly B was added until the soln became turbid; after addition of activated charcoal and filtration, the volume of the soln was reduced and upon cooling 2·5 g of **6** resulted. Further recrystallization from EtOAc-Skelly B gave the pure product, m.p. 150–152·5°; IR: 1765, 1740 cm^{-1} (C=O's); $\delta_{ppm}^{CDCl_3}$ 0·77 (3H, s, 9a–CH_3), 1·83, 2·53 (2H, dd, J_{AB} = 14 Hz, 1–CH_2), 2·35, 2·82 (2H, dd, d, J_{AB} = 15 Hz, J_{AX} = 2·1 Hz, 3–CH_2), 3·67 (1H, m, 9–H), 3·80 (3H, s, –OCH_3), 4·82 (1H, d, J = 4·4 Hz, 5a–H), 6·18 (1H, brd s, 4–H). (Found: C, 68·67; H, 8·08. Calc. for $C_{20}H_{28}O_5$: C, 68·94; H, 8·10%).

Treatment of 6β,19 - *oxido* - 2,17 - *dihydroxy* - *androsta* - 1,4 - *dien* - 3 - *one* (1) *with* (*a*) *lithium hydroxide monohydrate*, (*b*) *calcium hydroxide, or* (*c*) *potassium hydroxide.* (a) To 100 mg of **1** in 5 ml of pyridine was added 100 mg of lithium hydroxide monohydrate and the mixture was refluxed overnight. Solvent removal *in vacuo* gave a residue which was treated as in the case where barium hydroxide was used. TLC of the chloroform extracts indicated considerable starting material accompanied by polar contaminants but with no indication of **3**. The polar components were not characterized.

(b) To 100 mg of **1** in 5 ml of pyridine was added 200 mg of calcium hydroxide and after overnight reflux and acidic work-up, TLC of the chloroform extracts showed only minor spots in addition to starting material. No evidence of **3** was indicated.

(c) To 200 mg of **1** in 10 ml of pyridine was added 100 mg of potassium hydroxide and after overnight reflux and acidic work-up, TLC indicated absence of **3**.

Treatment of 6β,19 - *oxido* - *androsta* - 1,4 - *dien* - 3,17 - *dione* (**7**) *with barium hydroxide octahydrate.* A heterogeneous mixture of **7** (0·25 g) in pyridine (10 ml) and $Ba(OH)_2 8H_2O$ (0·65 g) was refluxed overnight. After solvent removal *in vacuo* enough 1N/HCl was added to make the aqueous soln acidic. The resultant ppt was isolated by filtration affording 0·23 g of recovered starting material as indicated by TLC and the NMR and UV spectra of the material.

Treatment of 2,17 - *dihydroxyandrosta* - 1,4 - *dien* - 3 - *one* (**8**) *with barium hydroxide.* To a solution of **8** (0·4 g) in pyridine (20 ml) $Ba(OH)_2 8H_2O$ (1·2 g) was added and the mixture was refluxed for 48 hr. The cooled soln was acidified with dil HCl and then extracted three times with chloroform. The extracts were washed with sat NaCl aq, dried and upon solvent removal 0·3 g of residue remained. The NMR spectrum of this material, as well as TLC, indicated *ca* 75% recovered starting material. The more polar components proved to be extractable into 5% $NaHCO_3$aq but their separation and characterization was not attempted.

Treatment of 2,17 - *dihydroxy* - 6,19 - *oxido* - *androsta* - 1,4 - *dien* - 3 - *one* (1) *with perchloric acid in acetic anhydride.* To **1** (1·0 g) suspended in Ac_2O (15 ml) was added 1 ml of a soln made from 5 ml of Ac_2O and 0·1 ml of 70% perchloric acid. After being stirred for 20 min at room temp, the now homogeneous mixture was poured into 5% $NaHCO_3$ aq and the aqueous mixture was extracted several times with ether. The combined extracts were then washed with additional bicarbonate soln and sat NaCl aq and dried over Na_2SO_4. Solvent removal gave an oil which was taken up into hot MeOH and upon being cooled, **11** (0·6 g; 40%) resulted,

m.p. 127–128·5°; IR: 1770, 1735 cm^{-1} (–O$\overset{O}{\overset{\|}{C}}CH_3$'s); UV 268 nm (11,600), 228 nm (~18,000), 222 nm (24,200); NMR $\delta_{ppm}^{CDCl_3}$ 0·82 (3–H, s, 18–CH_3), 2·05 (3H, s, –OAc), 2·08 (3H, s, –OAc), 2·28 (3H, s, –OAc), 5·14 (2H, s, benzilic methylene), 6·08 (1H, brd d, $^3J_{6,7}$ *ca.* 9·5 Hz, olefinic proton), 6·67 (1H, brd d, $^3J_{6,7}$ *ca.* 9·5 Hz, olefinic proton), 7·13 (1H, s, aromatic proton). (Found: C, 66·76; H, 6·68. Calc. for $C_{27}H_{32}O_8$: C, 66·92; H, 6·66).

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