37.2, 36.5, 34.9, 31.7, 24.7, 23.6, 19.9; mass spectrum, m/e calcd for $C_{21}H_{29}NO_3Se$ 423.1312, found 423.1328.

The high R_f isomer **42a** was isolated as white crystals: mp 203–206 °C dec; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.60–7.20 (m, Ar H), 5.20 (br, NH), 3.93 (m, OCH_2CH_2O), 3.41 (br, $W_H \sim 8$ Hz, CHSe), 2.50 (td, J = 14.4, 12.5, and 5.5 Hz) 2.10–1.20 (overlapping resonances), 1.96 (s, CH_3CO), 1.31 (s, CH_3CN); IR (Nujol) 3350, 1650, 1530, 1150, 1115, 1085, 915, 735, 685 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.4, 134.2, 130.9, 128.9, 127.0, 108.7, 64.3, 64.1, 56.6, 52.6, 42.3, 41.5, 39.6, 34.3, 33.3, 29.7, 24.6, 23.1, 19.6; mass spectrum, m/e calcd for $C_{21}H_{29}NO_3Se$ 423.1312, found 423.1290.

Amido Selenides 44 and 45. These isomers were synthesized from the *trans*-mercurial **43**[29] using the general procedure. The high R_f cis isomer **44** was isolated as a slightly yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.60–7.20 (m, Ar H), 5.78 (br, NH), 4.03 (m, CHN), 3.78 (m, $W_H \sim 9$ Hz, CHSe), 2.30–1.90 (overlapping resonances), 1.81 (s, CH_3CO), 1.80–1.35 (overlapping resonances); IR ($CHCl_3$) 3405, 2910, 2850, 1660, 1570, 1370, 1120, 970 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.0, 133.5, 129.0, 126.9, 52.3, 50.2, 33.0, 29.9, 25.0, 23.0, 22.0; mass spectrum, m/e calcd for $C_{14}H_{19}NOSe$ 297.0632, found 297.0641.

The low R_f *trans*-**45** was isolated as off-white crystals: mp 147–149 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.60–7.20 (m, Ar H), 5.55 (br, NH), 3.78 (br q, CHN), 2.99 (td, J = 11.0, 11.3, and 4.0 Hz, CHSe), 2.20–2.05 (br, overlapping resonances), 1.87 (s, CH_3CO), 1.70–1.10 (overlapping resonances); IR (Nujol) 3300, 3060, 1640, 1535, 1310, 1175, 980, 730, 690 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.1, 135.2, 128.9, 127.6, 53.2, 47.8, 33.9, 33.7, 26.5, 24.4, 23.3; mass spectrum, m/e calcd for $C_{14}H_{19}NOSe$ 297.0632, found 297.0639.

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Synthesis of Steroidal 16,17-Fused Unsaturated δ-Lactones[1]

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The synthesis of the [16,17-*e*] fused ring α-pyrones **2b** and **10** has been achieved in a one-step process from the corresponding hydroxymethylene compounds **3a** and **9** by using a titanium tetrachloride mediated Knoevenagel condensation with dimethyl malonate. The corresponding unsubstituted α-pyrone **2a** was prepared by a stepwise method utilizing a Wittig reaction of **3a** as the key step. Other approaches to these pyrones are also described.

In recent years many naturally occurring unsaturated lactones have been shown to possess cytotoxicity and/or antitumor activity.[2] By far the majority of these compounds are of the α-methylene γ-lactone type,[3] but certain endocyclic five- and six-membered α,β-unsaturated lactones such as the cardenolides,[4] bufadienolides,[5] withanolides,[6] and others[7] have also shown this kind of biological activity. Consequently a great deal of effort has been expended in the synthesis of naturally occurring unsaturated lactones and their analogues.[8,9]

Prompted by this situation and an early report of Pike[10] that certain steroidal [17,16-*d*] unsaturated γ-lactones exhibited an unusual order of cytotoxicity together with low whole animal toxicity, we embarked on a program of synthesis of 16,17-fused ring unsaturated steroidal δ-lactones. Up to that time the only synthesis of related systems had been reported by Kurath[11] and Valcavi[12] who prepared saturated [16,17-*e*]-lactones, by Igarashi[13] who transformed a kryptogenin derivative into a [16,17-d]-lactone, and by Gandolfi[14] who produced [16,17-*d*] enol lactones by means of a Reformatsky-type reaction on 16-

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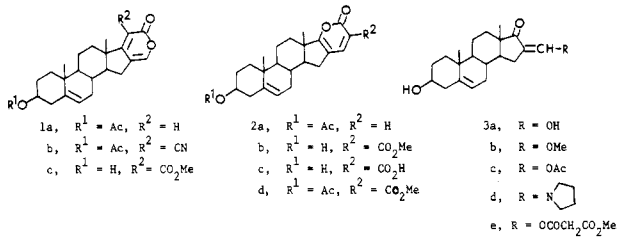
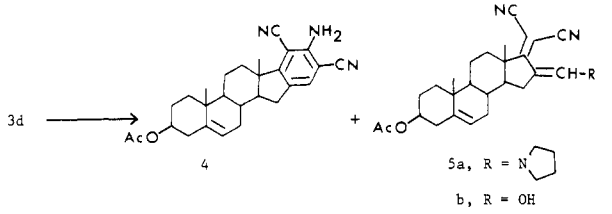
dehydropregnenolone acetate. Very recently Dieter[15] has described a versatile synthesis of α-pyrones which could well be applied to the synthesis of natural products of this type.

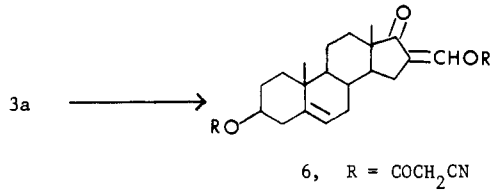
Our initial goals were [17,16-*d*]-α-pyrones, e.g., **1a** and [16,17-*e*]-α-pyrones **2a,b**. In the first approach to **1a**



abortive attempts were made to bring about condensation of malonic acid, diethyl malonate, and ethyl cyanoacetate with compounds such as the 16-oxygen substituted steroids **3a–c** under typical Knoevenagel conditions (NH_4OAc, HOAc, benzene, Dean–Stark). Condensation of the smaller malononitrile with 16-pyrrolidinylmethylene compound **3d** yielded the benzenosteroid **4** together with the desired product **5a**.[16] Unfortunately all attempts to hydrolyze **5a** to the hydroxymethylene analogue **5b** were unsuccessful.



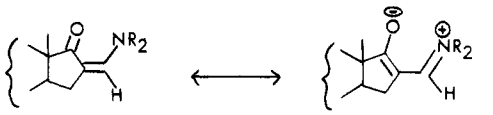
To circumvent these problems it was decided to employ an intramolecular condensation. Accordingly the hydroxymethylene compound **3a** was converted to the diester **6** by using cyanoacetyl chloride. Every attempt to bring



about an internal Knoevenagel condensation was unsuccessful leading to the conclusion, later verified, that the 16,16′ double bond had the *E* configuration and that isomerization to the required *Z* configuration did not occur under these conditions.

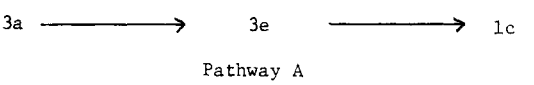
Application of a titanium tetrachloride catalyzed Knoevenagel reaction[17] to **3a** by using dimethyl malonate as the active methylene component yielded a product **2b** whose spectral properties indicated an ester-substituted α-pyrone. Evidence included a molecular ion at *m/e* 398 and IR carbonyl absorptions at 1755, 1730, and a strong peak at 1550 cm^{-1} characteristic of α-pyrones.[18] The ^1H NMR spectrum showed a 3p singlet at δ 3.8 (methyl ester) and a 1p singlet at δ 8.1 attributable to the hydrogen in the α-pyrone ring. A ^{13}C spectrum was in complete accord with this structure showing eight signals in lower field than 110 ppm. Peaks at 140.9 and 120.2 ppm could be assigned to C-5 and C-6 and a peak at 176.9 ppm to the methyl ester

Scheme I



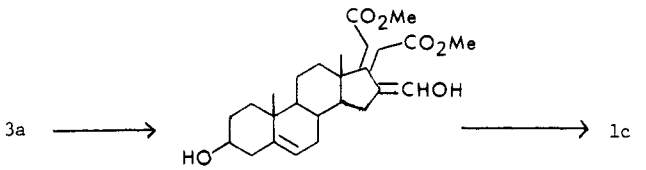
carbonyl group. The remaining peaks at 164.2, 158.6, 148.7, 114.6, and 111.5 ppm compared well with those reported for α-pyrones.[19] The 3-acetate **2d** was formed from **2b** in the usual way and showed all the expected physical properties.

Of the two possible structures, **1c** and **2b**, for the 3β-hydroxy-α-pyrone the former could arise by transesterification at C-16 to yield **3e**, followed by intramolecular condensation (pathway A). Even though the pre-



Pathway A

ferred double-bond configuration of **3e** would be *E*, isomerization to the *Z* form could occur in the presence of the strong Lewis acid $TiCl_4$. An alternate but less likely route to **1c** would be by way of Knoevenagel condensation at C-17 to yield the unsaturated diester **7**, followed by cyclization (pathway B). Pyrone **2b** would be formed by



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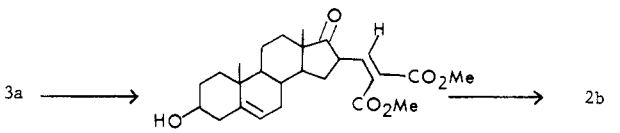
Pathway B

Knoevenagel condensation of the aldehyde tautomer of **3a** to yield intermediate **8**, which could then undergo enol lactonization (pathway C). There is ample precedent for



8
Pathway C

the attack of carbon nucleophiles at the masked aldehydic carbon atom of α-hydroxymethylene ketones and their derivatives. For example, we observed such reaction upon treatment of 16-(hydroxymethylene)-17-keto steroids with malononitrile,[16] and the reaction of Wittig reagents at this position has been reported.[20] In view of these facts the structure **2b** appears the most likely for the steroidal α-pyrone. This is borne out by the extreme sharpness (*W*/2 1.5 Hz) of the 4′-H signal in the NMR spectrum. In all 16-(alkoxymethylene) and 16-[(acyloxy)methylene] steroids studied, **3a,b,c,e**, the signal of the 16′-H appears as a close-packed triplet (*J* = 2.3 Hz) due to allylic coupling with the 15-CH_2 group. Similar coupling would be expected in lactone **1c** but not in **2b**. It is of considerable interest to point out that the 16′-H in N-substituted analogues, e.g., **3d**, appears consistently as a broadened singlet (*W*/2 3–4 Hz) in contrast to the oxygen systems described above. A tentative explanation is that the oxygen analogues prefer the *E* configuration due to dipole–dipole repulsion in the *Z* configuration whereas the ni-

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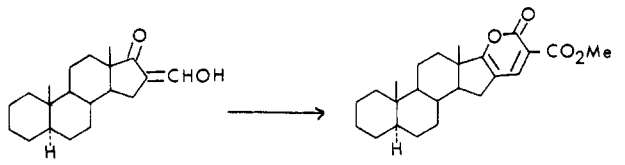
trogen compounds adopt the *Z* configuration by virtue of electrostatic attraction between the 17-oxygen and the 16′-nitrogen caused by electron delocalization (Scheme I).[21] This is also indicated by the low (1670 cm^{-1}) IR carbonyl absorption.

The A-ring unsubstituted hydroxymethylene compound **9** was converted in a similar fashion to the α-pyrone **10**,

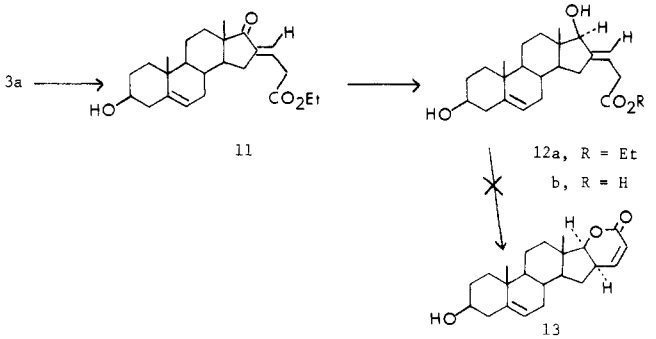


9 10

whose spectral properties were analogous to those of the counterparts **2b,d**.

It was thought that removal of the methyl ester group in **2b** might be achieved by conversion to the carboxylic acid **2c**, followed by decarboxylation under acidic conditions. Unfortunately all attempts to hydrolyze **2b** under very mild conditions led to intractable products in which the α-pyrone ring had been compromised as shown by IR data. Direct treatment of **2b** with acid led to similar results.

Attention now turned to methods of producing the unsubstituted [16,17-*e*] fused ring α-pyrone **2a**. Following a report that stabilized Wittig reagents attack the carbonyl group of the aldehyde tautomer of α-(hydroxymethylene) ketones[20] this reaction was attempted on the hydroxymethylene ketone **3a** by using (carbethoxymethylene)triphenylphosphorane. The single product formed in good yield was assigned structure **11** in which the double bond had moved into conjugation with the 17-keto group. In the IR spectrum a carbonyl peak at 1725 cm^{-1} was attributed to both the 17-ketone and the ethyl ester and a peak at 1650 cm^{-1} to the conjugated double bond. The ^1H NMR spectrum showed a triplet of triplets (J = 7.3, 2.2 Hz) at δ 6.62 for the 16^1-H and a doublet at δ 3.13 for the 16^2 hydrogens. The value of the allylic coupling constant was very similar to the value of 2.3 Hz in the hydroxymethylene derivatives **3b,c,e**, pointing to an *E* configuration. In order to synthesize the unsaturated lactone **13** the 17-keto group was reduced with sodium borohydride to the 17-alcohol **12a**. This compound was hydrolyzed to the

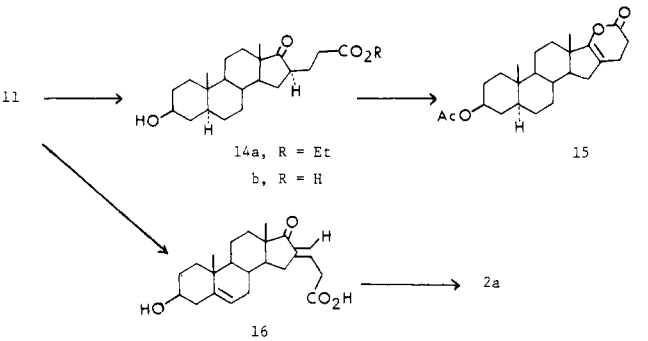


11 12a, R = Et
b, R = H
13

acid **12b** by potassium hydroxide in methanol, but attempts to lactonize this hydroxy acid under acidic conditions were unsuccessful. Two possible reasons for this failure could be (a) that the double bond did not move into conjugation with the carbonyl group or (b) that conjugation did occur but that the propenoic acid side chain assumed the less favorable α-configuration.

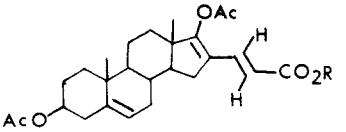
At this point it was decided to expedite matters by directing the C-16 side chain into the β-configuration by initial hydrogenation despite the consequent loss of one element of unsaturation. Accordingly the unsaturated keto ester **11** was converted to the completely saturated product **14a** by hydrogenation with palladium on charcoal in the presence of a trace of perchloric acid. The oily keto ester **14a** was converted directly to the enol lactone **15** by hydrolysis with aqueous potassium hydroxide to **14b**, followed by cyclization with acetic anhydride/perchloric acid. Compound **15** showed the expected IR peaks at 1775 and 1688 cm^{-1} together with NMR signals at δ 2.62 and 2.23 for the methylene groups of the lactone ring. Attempts to introduce a second double bond into the lactone ring by allylic bromination/dehydrobromination[9] were unsuccessful.

At this stage despite the fact that the unsaturated keto ester **11** existed in the *E* configuration it was decided to



14a, R = Et
b, R = H
15
16

hydrolyze it to the acid **16** in the expectation that under lactonization conditions a geometry suitable for cyclization could be attained. Hydrolysis was effected smoothly to give the sparingly soluble acid **16**, which was treated directly with acetic anhydride/sodium acetate. Extensive chromatography gave as the major product in moderate yield α-pyrone **2a** whose structure was established by the spectroscopic data. The mass spectral base peak at *m/e* 323 was explicable in terms of the combined loss of carbon dioxide and the 18-methyl group. The molecular ion (*m/e* 382) was of low intensity (32%). The IR spectrum displayed a broad carbonyl absorption at 1730 cm^{-1} for both the acetate and lactone groups, a double-bond peak at 1620 cm^{-1}, and the characteristic α-pyrone band at 1535 cm^{-1}.[18] An examination of the ^1H NMR spectrum revealed the olefinic protons of the pyrone ring as a pair of doublets (J = 9 Hz) at δ 7.20 and 6.00 in very good agreement with the values for the model compound 5,6,7,8-tetrahydrocoumarin. A minor product showed IR peaks at 1778, 1735, 1720, and 1638 cm^{-1} and NMR signals at δ 2.00 (s, 3 H), 2.20 (s, 3 H), 3.70 (s, 3 H), 5.71 (d, J = 16 Hz), and 7.27 (d, J = 16 Hz). This evidence clearly identified the product as the unsaturated enol acetate ester **17a** whose



17a, R = Me
b, R = H

formation undoubtedly occurred by esterification of the corresponding acid **17b** by methanol in the workup.

In summary, synthesis of steroidal fused ring [16,17-*e*]pyrones, with and without a methyl ester substituent at

(21) Cisoid allylic coupling in the α-methylene γ-lactone avenaciolide is smaller (2.17 ± 0.05 Hz) than the transoid coupling (2.56 ± 0.05 Hz): Brookes, D.; Sternhell, S.; Tidd, B. K.; Turner, W. B. *Austr. J. Chem.* **1965**, *18*, 373.

the 3′-position, has been achieved by reasonably direct procedures starting from the readily available 16-(hydroxymethylene)-17-keto steroids. Yields in the latter case were rather low.

Experimental Section

Melting points (Thomas-Hoover) are uncorrected. IR spectra were obtained on a Perkin-Elmer 457 instrument. UV spectra were run on a Perkin-Elmer/Coleman 124 spectrophotometer. ^{1}H NMR spectra ($CDCl_3$) were recorded on a Varian A-60 or Perkin-Elmer R-20B equipped with a Nicolet TT-7 FT unit, ^{13}C NMR on Jeol FX-90Q instrument; chemical shifts are expressed in parts per million downfield from internal Me_4Si. Mass spectra were taken on a Du Pont 491 instrument equipped with a direct inlet. Silica gel HF254 (E. Merck) was used for TLC analysis. Microanalyses were performed by W. Galbraith Laboratories, Knoxville, TN, and by A. Bernhardt Laboratories, Elbach über Engelskirchen, W. Germany. Ether extracts were dried with Na_2SO_4 or $MgSO_4$.

3β-(Cyanoacetoxy)-16-[(cyanoacetoxy)methylene]-androst-5-en-17-one (6). Compound **3a**[22] (10.4 g, 32.9 mmol) and freshly prepared cyanoacetyl chloride[23] (7.0 g, 67 mmol) were dissolved in anhydrous ether (250 mL) and stirred at room temperature for 24 h. The solid product was collected by filtration and leached with chloroform and the chloroform solution evaporated to yield the crude product which was recrystallized from hexane–chloroform as needles (8.59 g, 58%): mp 179–181 °C; IR ($CHCl_3$), 1790 (enol ester), 1750 (ester, ketone), 1670 (conjugated double bond) cm^{-1}; ^{1}H NMR 0.93, 1.09 (18,19-methyls), 3.48, 3.72 (side-chain methylenes), 8.1 (t, J = 2.5 Hz, 16′-H) ppm. Anal. Calcd for $C_{26}H_{30}N_2O_5$: C, 69.31; H, 6.71; N, 6.22; O, 17.76. Found: C, 69.71; H, 6.60; N, 6.23; O, 17.86.

3β-Hydroxyandrost-5-eno[16,17-*e*]-3′-carbomethoxy-2′-pyrone (2b). To a stirred suspension of 3β-hydroxy-16-(hydroxymethylene)androst-5-en-17-one (**3a**, 10 g, 31.6 mmol) in tetrahydrofuran (500 mL) at 0 °C under nitrogen was added titanium tetrachloride (17.4 mL, 158 mmol) in carbon tetrachloride. The resulting deep red solution was then treated with dimethyl malonate (4.0 mL, 34.8 mmol), followed by pyridine (12.7 mL, 158 mmol) in tetrahydrofuran (25 mL) during 90 min. After 6 days at room temperature, ether (100 mL) and water (100 mL) were added. The aqueous layer was separated and extracted with ether, after which the combined etheral extracts were washed successively with water, 5% $NaHCO_3$ solution, water, 5% HCl, and water. Drying and evaporation furnished a yellow, waxy solid, which was treated with chloroform (200 mL), followed by filtration (0.2 g of starting material recovered) and evaporation to give a yellow solid. Recrystallization from methanol gave fine needles of pyrone **2b** (7.28 g, 58%) melting behavior: 215–220 °C turns yellow and shrinks, 250 °C deep yellow needles, 320 °C dark red oil. The analytical specimen was obtained by two further recrystallizations from methanol: IR ($CHCl_3$) 3620, 3500 (hydroxyl), 1755 (lactone), 1730 (ester), 1700, 1610, 1545 (conjugated diene), 1268, 1120, 1040 (ester, lactone) cm^{-1}; ^{1}H NMR 1.05 (s, 6 H, 18,19-methyls), 3.83 (s, 3 H, CO_2Me), 8.1 (s, 1 H, 4′H) ppm; ^{13}C NMR 179.6 (CO_2Me), 164.2 (2′-C), 114.6 (3′- or 5′-C), 148.7 (4′-C), 111.6 (5′- or 3′-C), 158.6 (6′-C) ppm; MS m/e 398 (93, M$^+$), 380 (39). Anal. Calcd for $C_{24}H_{30}O_5$: C, 72.33; H, 7.59. Found: C, 72.13; H, 7.75.

Acetate 2d. The pyrone **2b** (0.25 g) was acetylated by using pyridine (25 mL) and acetic anhydride (5 mL) at room temperature overnight. The crude product was recrystallized from ether as very fine needles: mp 186–88 °C dec; IR (KBr) 1770 (lactone), 1740 (esters), 1705, 1555 (conjugated diene) 1245, 1030 (esters, lactone) cm^{-1}; ^{1}H NMR δ 1.05 (s, 6 H, 18,19-methyls), 1.98 (s, 3 H, acetate), 3.81 (s, 3 H, methyl ester), 4.5 (br, 1 H, 3α-H), 8.1 (s, 1 H, 4′-H); MS, m/e 380 (91), 365 (15). Anal. Calcd for $C_{26}H_{32}O_6$: C, 70.91; H, 7.27; O, 21.82. Found: C, 70.76; H, 7.34; O, 21.94.

16-(Hydroxymethylene)-5α-androstan-17-one (9). A solution of 5α-androstan-17-one[24] (55 g, 0.2 mol) in benzene (1000 mL) distilled from CaH_2 was treated with ethyl formate (80 mL, 1 mol) and sodium hydride (21 g, 0.5 mol, 57% mineral oil dispersion) and the mixture stirred under nitrogen for 7 days. Dilution with dilute sulfuric acid was followed by ether extraction. The ether layer was separated and washed successively with 5% aqueous sodium bicarbonate and water, followed by drying and evaporation to yield crude product, which was crystallized from hexane as a solid (13.35g, 22%). Chromatography of the mother liquor on silica gel failed to provide further product. An analytical sample was obtained by two crystallizations from ether as clusters of plates: mp 170–73 °C; IR (Nujol) 3000–3500, 2300–2850 (hydrogen-bonded hydroxyl), 1702 (ketone), 1628 (double bond), 1310, 1270, 1240 (hydroxymethylene) cm^{-1}; ^{1}H NMR 0.77, 0.93 (2s, 6 H, 18,19-CH_3), 7.05 (s, 16^1-H), 8.25 (br, exchangeable D_2O, OH), 9.74 (s, 16-CHO) (mixture of tautomers) ppm; MS, m/e 302 (33), 287 (13), 274 (39), 271 (37), 217 (100).

5α-Androstano[16,17-*e*]-3′-carbomethoxy-2′-pyrone (10). 16-(Hydroxymethylene)-5α-androstan-17-one (**9**) (4 g, 12.05 mmol) in tetrahydrofuran (200 mL) was treated with titanium tetrachloride (7 mL) in carbon tetrachloride (12 mL) followed by dimethyl malonate (2 g, 15.17 mmol) and pyridine (5 mL). The reaction was allowed to proceed for 5 days at room temperature and then worked up as described for **2b** with the addition of a sodium hydroxide (10%) wash. The neutral fraction furnished a yellow oil which slowly deposited crystals (2.19 g, 47%). Two recrystallizations from methanol were followed by two recrystallizations from methanol/methylene chloride to yield prisms: mp 170–174 °C; IR (Nujol) 1750 (lactone), 1705 (ester), 1545 (conjugated diene), 1270, 1254, 1180, 1110 (ester, lactone) cm^{-1}; ^{1}H NMR 0.81, 1.00 (2s, 6 H, 18,19-CH_3), 3.87 (s, 3 H, CO_2Me), 8.2 (s, 1 H, 4′-H) ppm. Anal. Calcd for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39. Found: C, 74.79; H, 8.30.

Wittig Reaction of 3α-Hydroxy-16-(hydroxymethylene)-androst-5-en-17-one (3a) with (Carbethoxymethylene)triphenylphosphorane. To a stirred slurry of **3a** (21.24 g, 67 mmol) in tetrahydrofuran (400 mL) was added a solution of (carbethoxymethylene)triphenylphosphorane (23.38 g, 67 mmol) in tetrahydrofuran (400 mL). After it refluxed under nitrogen for 18 h the mixture was cooled, a small amount of solid filtered off, and the solvent evaporated to yield a viscous yellow gum, which was chromatographed on silica gel (400 g). A colorless gum was obtained from mixtures of 4/1–3/1 hexane/ethyl acetate. Recrystallization from ethanol–water yielded ester **11** as flakes: mp 118–9 °C (16.5 g, 64%); IR (KBr) 3325 (hydroxyl) 1725 (ester, ketone), 1650 (double bond) 1250, 1155, 1090, 1050 (hydroxyl, ester) cm^{-1}; ^{1}H NMR 0.88 (s, 3 H, 19-CH_3), 1.03 (s, 3 H, 18-CH_3), 1.25 (t, 3 H, J = 7.0 Hz, ester CH_3), 3.13 (d, br, 2 H, J = 7.3 Hz, 16^2-H), 4.13 (q, 2 H, J = 7.0 Hz, ester CH_2), 5.33 (br, 1 H, 6-H), 6.62 (tt, 1 H, J = 7.3, 2.2 Hz, 16^1-H) ppm; MS, m/e 386 (100, M$^+$), 368 (25), 353 (19), 340 (30), 307 (29). Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87; O, 16.56. Found: C, 74.61; H, 8.90; O, 16.63.

Hydrogenation of Unsaturated Ester 11. To a solution of unsaturated ester **11** (4.04 g, 10.5 mmol) in ethyl acetate (175 mL) was added palladium–charcoal (400 mg, 10%) and perchloric acid (0.25 mL, 70%), and the mixture was shaken in an atmosphere of hydrogen until no more was absorbed. The catalyst was removed by filtration and washed several times with small amounts of ethyl acetate. The combined organic solution was washed successively with water (3 × 100 mL), $NaHCO_3$ solution (2 × 50 mL, 5%), and brine (100 mL). After drying, the solvent was evaporated to yield 16β-(2-carbethoxyethyl)-3β-hydroxy-5α-androstan-17-one (**14a**) as a colorless gum (3.43 g, 84%), which resisted all attempts at crystallization. It gave only one spot on TLC. IR (KBr) 3450 (hydroxyl), 1730 (ester) 1150, 1030 (ester, hydroxyl) cm^{-1}; ^{1}H NMR 0.83 (s, 6 H, 18,19-CH_3), 1.20 (t, 3 H, J = 7.5 Hz, CH_3 of ethyl ester), 4.05 (q, 2 H, J = 7.5 Hz, CH_2 of ethyl ester) ppm.

Formation of Enol Lactone 15. The keto ester **14a** (3.25 g, 8.3 mmol) was dissolved in methanol (75 mL) and treated with KOH (5 g) in water (25 mL). The mixture was refluxed for 4 h, cooled, and diluted with water (15 mL), followed by extraction with ether. The aqueous layer was acidified with dilute hydrochloric acid and then extracted with ether (4 × 50 mL). Washing

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of this ether extract with brine was followed by drying and evaporation to give the keto acid **14b** (2.96 g, 98%): IR (KBr) 3540, 2600 (hydroxyl, carboxyl), 1730 (ketone), 1705 (carboxyl), 1040 (hydroxyl) cm^{-1}; ^1H NMR (acetone-d_6) 0.80, 0.83, (2s, 6 H, 18,19-methyls), 3.8 (br, 1 H, 3α-H) ppm. This compound (2.96 g, 8.17 mmol) was dissolved in methylene chloride (150 mL) and the solution treated with acetic anhydride (30 mL) and perchloric acid (2 drops, 70%). After stirring for 5 h at room temperature the solution was washed successively with water (100 mL), $NaHCO_3$ solution (100 mL, 5%), and brine (100 mL), followed by drying and evaporation. The gummy product was treated with methanol (50 mL) and the solution evaporated to yield a brown solid, which was chromatographed on silica gel using 8% ethyl acetate in hexane. The enol lactone **15** was eluted as the second component following an unidentified forerunner. Recrystallization of **15** from ethanol-water gave microcrystalline needles (1.33 g, 42%): mp 172-74 °C; IR (KBr) 1770 (lactone), 1732 (acetate), 1040, 1025 (lactone, acetate) cm^{-1}; ^1H NMR 0.85 (s, 3 H, 19-CH_3), 0.91 (s, 3 H, 18-CH_3), 2.00 (s, 3 H, 3-acetate), 2.32, 2.62 (br, 4 H, 3',4'-H), 4.51 (br, 1 H, 3α-H) ppm; MS, *m/e* 386 (71), 371 (100), 358 (M*), 312 (64), 269 (6), 262 (*m**), 218 (22). Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87; O, 16.65. Found: C, 74.71; H, 8.91; O, 16.50.

Formation of [16,17-*e*] Fused Lactone 2a. The unsaturated keto ester 11 (2.79 g, 7.2 mmol) was dissolved in methanol (25 mL) to which a solution of KOH (1.5 g) in water (7.5 mL) had been added. This solution was refluxed for 30 min, diluted with water, and washed with ether. The aqueous layer was acidified with dilute hydrochloric acid to give a yellow solution, which was extracted with ether (4 × 100 mL). The organic extract was washed with brine (100 mL), dried, and evaporated to form a yellow gum, which was dissolved in acetone and evaporated again to yield a yellow powder (2.52 g, 97%) of the unsaturated keto acid **16**: IR (KBr) 3420, 2500 (hydroxyl, carboxyl), 1720 (carboxyl, ketone), 1645 (double bond), 1042, 1035 (hydroxyl) cm^{-1}; ^1H NMR (acetone-d_6) 0.83 (s, 3 H, 19-CH_3), 1.03 (s, 3 H, 18-CH_3), 3.15 (d, 2 H, 16^2-H), 4.3-4.9 (br, 2 H, 3α-H, 16^1-H), 5.20 (br, 1 H, 6-H) ppm. This crude product (4.5 g, 2.5 mmol) was dissolved in acetic anhydride (125 mL) and refluxed for 4.5 h with sodium acetate (950 mg) followed by cooling, dilution with ether, and successive washing with water (3 × 100 mL), 5% aqueous Na_2HPO_4 (3 × 100 mL), and brine (3 × 100 mL). The product was treated with methanol (50 mL) and pyridine (0.5 mL) with subsequent drying overnight and solvent removal to furnish a viscous brown liquid, which was chromatographed on Florisil starting with hexane and progressing to 15% ethyl acetate in hexane. The major component was the fused pyrone **2a**, which was recrystallized from ethanol-water as needles (340 mg, 7%): mp 191-92 °C; IR (KBr), 1730 (lactone, acetate), 1620, 1535 (conjugated diene), 1235, 1030 (lactone, acetate) cm^{-1}; ^1H NMR 1.01 (s, 3 H, 19-CH_3), 1.05 (s, 3 H, 18-CH_3), 2.00 (s, 3 H, 3-acetate), 4.50 (br m, 1 H, 3-H), 5.32 (m, 1 H, 6-H), 6.00 (d, 1 H, J = 9 Hz, 3'-H), 7.20 (d, 1 H, J = 9 Hz, 4'-H) ppm; MS, *m/e* 382 (32), 323 (100), 322 (39), 307 (18), 295 (25), 281 (7). Anal. Calcd for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91; O, 16.73. Found: C, 75.23; H, 7.83; O, 16.84.

A minor component (80 mg) which eluted from the column before **2a** was the unsaturated enol ester **17a**: mp 175-76 °C; IR (KBr) 1778 (enol ester), 1735 (methyl ester), 1720 (acetate), 1638 (double bonds), 1438, 1245, 1180 (esters) cm^{-1}; ^1H NMR 0.95 (s, 3 H, 19-CH_3), 1.05 (s, 3 H, 18-CH_3), 2.00 (s, 3 H, 3-acetate), 2.20 (s, 3 H, 17-acetate), 3.70 (s, 3 H, OCH_3), 4.55 (br, 1 H, 3α-H), 5.40 (m, 1 H, 6-H), 5.40 (d, 1 H, J = 16 Hz, 16^2-H), 7.27 (d, 1 H, J = 16 Hz, 16^1-H) ppm. Anal. Calcd for $C_{27}H_{36}O_6$: C, 71.02; H, 7.95. Found: C, 71.05; H, 8.09.

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Registry No. **2a**, 94459-33-3; **2b**, 94459-34-4; **2d**, 94459-35-5; **3a**, 94535-34-9; **6**, 94459-36-6; **9**, 3127-21-7; **10**, 94459-37-7; **11**, 94459-38-8; **14a**, 94459-39-9; **14b**, 94459-40-2; **15**, 94459-41-3; **16**, 94459-42-4; **17a**, 94459-43-5; cyanoacetyl chloride, 16130-58-8; titanium tetrachloride, 7550-45-0; dimethyl malonate, 108-59-8; 5α-androstan-17-one, 963-74-6; (carbethoxymethylene)triphenylphosphorane, 1099-45-2; ethyl formate, 109-94-4.

Conformational Analysis. 25.[1] ^{13}C NMR Chemical Shifts—Sensitive Detectors in Structure Determination. 3.[2] The Proposal for Non-Chair Conformations in Methyl-Substituted 2-Oxo-1,3,2-dioxathianes Challenged

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The ^{13}C chemical shifts of 2-oxo-1,3,2-dioxathiane and 39 methyl derivatives as analyzed from the derived substituent effects show that the 2-oxo-1,3,2-dioxathiane ring attains exclusively chair conformations, preferably with an axial (19 cases) but often also with an equatorial S=O group (8 cases). Of the remaining 13 derivatives 11 fit excellently into the shift increment parameterization as mixtures of two interconverting chair forms. Only two of the most heavily substituted derivatives appear in a chair-chair equilibrium which cannot be precisely defined. These results are in close agreement with conclusions based on ^1H NMR spectra, dipole moments, IR, and mass spectrometry but challenge some recent reports on the (frequent) participation of twist forms in this system.

Introduction

In 1976 we first pointed out that the ^1H NMR spectra of a number of methyl-substituted 2-oxo-1,3,2-dioxathianes[3] (**14**, **21-26**, **31**, and **33**) are, in contrast to earlier reports on the significant contribution of twist forms, indicative of a single chair form or a chair-chair equilibrium. In 1982 we briefly reviewed the publications on the structure and conformations of alkyl-substituted 2-oxo-1,3,2-dioxathianes[4,5] and carried out a thorough analysis of the ^1H NMR spectra of all methyl-substituted and several other alkyl-substituted 2-oxo-1,3,2-dioxathianes.[4]

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