Acid Treatment of Enolate Anions of Estra- and 19-Hydroxyandrosta-4,6-diene-3,17-dione and Related Reactions

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Base treatment of $\Delta^{4,6}$-3-keto steroids **1** and **2** in dimethyl sulfoxide followed by acidification of the basic mixtures with aqueous acetic acid affords precipitates which are considered to consist of the free enols **8** and **9**, respectively. When the acidification is effected with more concentrated solutions of acetic acid the unstable $\Delta^{5,7}$-3-ketones **10** and **11** are produced. The basic mixtures when treated with acetic anhydride in ether give 3-acetoxy-3,5,7-triene **13** or 3-acetoxy-19-hydroxy-3,5,7-triene **14**, respectively. Subsequent reactions lead to the formation of $\Delta^{5(10),7}$-, $\Delta^{4,7}$- and $\Delta^{5,7,9(10)}$-3-ketones **22**, **12**, and **23**, 3,3-dimethoxy-5,7-diene **20**, enol ethers **18**, **19**, and **17**, and enol acetates **15** and **16**.

It has recently been reported[1] that Δ^{4}-3-keto steroids can be deconjugated by base treatment with potassium *t*-butoxide in *t*-butyl alcohol and subsequent acidification of the basic mixture with weak acids. This method could not be extended to the deconjugation of $\Delta^{1,4}$- and $\Delta^{4,6}$-3-ketones. The deconjugation of $\Delta^{1,4}$-3-ketones to $\Delta^{1,5}$-3-ketones was subsequently accomplished when in the above method dimethyl sulfoxide instead of *t*-butyl alcohol was used as a solvent in the base treatment.[2] It thus appeared interesting to attempt the preparation of $\Delta^{5,7}$-3-ketones from $\Delta^{4,6}$-3-ketones under similar conditions.

Treatment of $\Delta^{4,6}$-3-ketone **1** with sodium methoxide in dimethyl sulfoxide followed by addition of the basic reaction mixture to excess 50% aqueous acetic acid afforded a precipitate which, even when dry, decomposed readily on standing in air (Scheme I). The material had $\lambda_{\max}^{\mathrm{MeOH}}$ 320 mμ and was, as also evidenced by its ir and nmr spectrum, considered to be the free enol **8**. A steroidal 17-en-20-ol has recently been isolated in the catalytic hydrogenation of a 16-methyl Δ^{16}-20-ketone.[3]

When 19-hydroxy $\Delta^{4,6}$-3-ketone **2** was treated as above, a precipitate could be collected after acidification which had $\lambda_{\max}^{\mathrm{MeOH}}$ 272 and 275 mμ and which was considered to consist largely of $\Delta^{5,7}$-3-ketone **11**, as further evidenced by its ir and nmr spectrum. When, however, the basic mixture was poured into excess 10% instead of 50% aqueous acetic acid, the resulting precipitate had $\lambda_{\max}^{\mathrm{MeOH}}$ 321 mμ and was considered to be 3,19-dihydroxy-3,5,7-triene **9**. On continued stirring the precipitate changed into $\Delta^{5,7}$-3-ketone **11**. Under similar reaction conditions free enol **8**, formed from $\Delta^{4,6}$-3-ketone **1**, isomerized at a much slower rate than enol **9**; when, however, a solution of free enol **8** in ethyl acetate was left to stand for several hours at room temperature under nitrogen, conversion into $\Delta^{5,7}$-3-ketone **10** could readily be accomplished. The latter compound was also obtained when the basic mixture, considered to contain enolate anion **6**, was poured into benzene–acetic acid (1:2) and when free enol **8** was heated briefly above its melting point (103°). On prolonged heating, even at a temperature as low as 80°, the enol **8** yielded the known[4] $\Delta^{4,7}$-3-ketone **12**. On treament with hydrochloric acid in tetrahydrofuran, $\Delta^{5,7}$-3-ketone **10** afforded $\Delta^{5(10),7}$-3-ketone **22** and a material which, on the basis of its uv spectrum and its thin layer chromatogram, was considered to consist mainly of a mixture of $\Delta^{4,7}$- and $\Delta^{4,6}$-3-ketones **12** and **1**.

On treatment with methanolic sulfuric acid the homoconjugated isomeric ketones **10** and **22** gave enol ether **18**. In the conversion of $\Delta^{5,7}$-3-ketone **10** into **18**, 3,3-dimethoxy-5,7-diene **20** could be isolated as an intermediate. Enol ether **19** could be directly obtained from 19-hydroxy $\Delta^{4,6}$-3-ketone **2** by base treatment as before and subsequent acidification with methanolic sulfuric acid. Presumably the acid treatment yields $\Delta^{5,7}$-3-ketone **11** from enolate anion **7** *via* free enol **9** and then proceeds further with incorporation of methanol to yield first 3,3-dimethoxy-5,7-diene **21**, the 19-hydroxymethyl analog of **20**, and then the enol ether **19** by elimination of one molecule of methanol.

Treatment of $\Delta^{5,7}$-3-ketones **10** and **11** with acetic anhydride at room temperature afforded readily enol acetates **13** and **15**, which previously have been obtained from $\Delta^{4,6}$-3-ketones **1** and **2**, respectively, on refluxing in a mixture of acetic anhydride and acetyl chloride in presence of a small amount of pyridine.[5] Treatment of the basic reaction mixture prepared from **1** with acetic anhydride in ether also yielded **13**, while under the same conditions $\Delta^{4,6}$-3-ketone **2** afforded 19-hydroxyenol acetate **14**.

The formation of free enols **8** and **9** or enol acetates **13** and **14** on treatment of the basic mixtures with aqueous acetic acid or acetic anhydride indicates that, in the basic medium, ketones **1** or **2** are converted into the corresponding long conjugated mesomeric enolate anions **6** or **7**, respectively. That O protonation or acetylation rather than C protonation or acetylation takes place in the above reactions follows from recently developed concepts predicting the influence of reactant polarizability on ionic reactions.[6] As the acidic hydrogen atom of acetic acid and the carbonyl carbon atoms of acetic anhydride are not very polarizable the two reagents behave like "hard" acids and thus prefer to match with the harder oxygen atom in position 3 instead of the "softer," more polarizable carbon

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(1) H. J. Ringold and S. K. Malhotra, *Tetrahedron Lett.*, No. 15, 669 (1962).

(2) E. L. Shapiro, T. Legatt, L. Weber, and E. P. Oliveto, *Steroids*, **3**, 183 (1964).

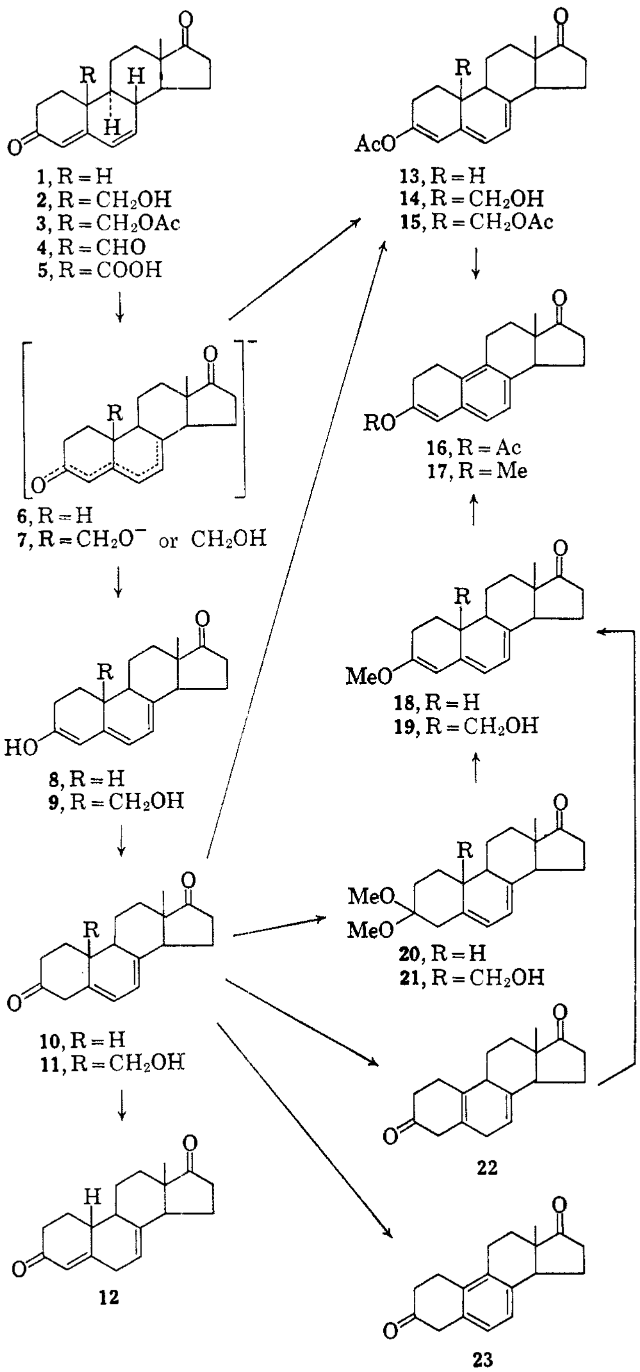
(3) J. Attenburrow, J. E. Connett, W. Graham, J. F. Oughton, A. C. Ritchie, and P. A. Wilkinson, *J. Chem. Soc.*, 4547 (1961).

(4) J. A. Zderic, H. Carpio, A. Bowers, and C. Djerassi, *Steroids*, **1**, 233 (1963).

(5) J. F. Bagli, P. F. Morand, K. Wiesner, and R. Gaudry, *Tetrahedron Lett.*, No. 8, 387 (1964).

(6) R. E. Davis, *ibid.*, No. 41, 5021 (1966); R. G. Pearson, *J. Amer. Chem. Soc.*, **85**, 3533 (1963); R. G. Pearson, *Science*, **151**, 172 (1966); R. G. Pearson, *Chem. Brit.*, **3**, 103 (1967); K. M. Ibne-Rasa, *J. Chem. Educ.*, **44**, 89 (1967).

SCHEME I



atoms in position 4, 6, and 8 of the ambident[7] bases 6 or 7, respectively.

Successive base–acetic anhydride treatment of 19-aldehyde **4** instead of 19-nor ketone **1** also gave enol acetate **13**. Apparently, under the reaction conditions, deformylation[8] of the 19-aldehyde proceeds rapidly. When, in the above procedures of enol acetylation, 19-carboxylic acid **5** was used instead of aldehyde **4** or $\Delta^{4,6}$-3-ketone **1**, mainly starting material was recovered and it was found necessary to carry out the base treatment at 60° instead of at room temperature in order to obtain enol acetate **13**; apparently the carboxylate anion in position 10 prevents proton abstraction from position 8 and 3,5,7-trien-3-ol anion formation takes place only after decarboxylation[9,10] has occurred.

On oxidation with lead tetraacetate in carbon tetrachloride at 0° 19-alcohols **11**, **14**, and **19** aromatized to analogs **23**, **16**, and **17**, respectively. Previous work[11] has shown that 19-hydroxy Δ^5-steroids yield readily 6-acetoxy $\Delta^{5(10)}$-steroids when oxidized similarly so that possibly the aromatization of **11**, **14**, and **19** proceeds *via* the corresponding unstable 6-acetoxy-5(10),7-dienes, in which the acetoxy group in position 6 and the proton in position 9 are twofold allylicly activated for elimination.

The structure of the novel compounds prepared was verified by uv, ir, and nmr spectroscopy. The 5,7-dienes and 3,5,7-trienes prepared decomposed on standing in air at room temperature. The instability of 3,17-diacetoxyestra-3,5,7-triene has previously been noted.[4] Of the unstable free enols **8** and **9** and the unstable $\Delta^{5,7}$-3-ketones **10** and **11**, only **10** gave a fair elemental analysis.

Experimental Section[12]

Estra-5,7-diene-3,17-dione (10). A. Direct Route from $\Delta^{4,6}$-3-Ketone 1.—To a suspension of 1 g of finely divided estra-4,6-diene-3,17-dione[4] in 5 ml of dimethyl sulfoxide was added 1.0 g of sodium methoxide in one portion. The mixture was agitated under nitrogen for 5 min and then poured into 30 ml of acetic acid–benzene (1:2) at room temperature. The mixture, which had warmed to about 40° during the addition and which contained sodium acetate as a precipitate, was stirred for 15 min and was then extracted four times with 10 ml of water. The benzene solution was dried with sodium sulfate, 40 ml of hexane was added, and the brown precipitate was filtered off. Treatment of the filtrate with charcoal, followed by filtration through Celite and evaporation, yielded a slowly crystallizing residue containing, besides $\Delta^{5,7}$-3-ketone **10**, a small amount of the isomeric 4,7-diene **12**. The residue was dissolved in 20 ml of benzene and 100 ml of hexane was added. Treatment of the resulting emulsion with charcoal, followed by filtration through Celite and evaporation at room temperature and reduced pressure, gave a crystalline residue which was digested with a small amount of cold ether yielding 300 mg of crystals, mp 116–119°. Recrystallization from methanol, followed by drying under high vacuum and room temperature for 16 hr, gave the analytical sample: mp 121–124°; $\lambda_{\max}^{\mathrm{MeOH}}$ 272 mμ (ϵ 8420), 281 (8660), and 299.5 (4980); $\nu_{\max}^{\mathrm{CHCl_3}}$ 1715 (broad, 3,17-diketone), 1605 and 1655 cm^{-1} (>C=C<); the nmr showed maxima for two olefinic protons as a broadened singlet at 5.55 (6 and 7 position), two methylenic protons as a singlet at 3.11 (4 position), and three protons as a singlet at 0.83 ppm (18 position).

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.45; H, 8.06.

B. From $\Delta^{4,6}$-3-Ketone 1 *via* Enol 8.—A mixture of 5 g of **1**,[4] 5 g of sodium methoxide, and 25 ml of dimethyl sulfoxide was stirred under nitrogen for 5 min and then poured into partially frozen 50% aqueous acetic acid. After stirring for 10 min, 450 ml of ice-cold water was added and the precipitate was filtered off and dried for 16 hr under high vacuum at room temperature yielding 4.20 g of material, mp 93–100°, $\lambda_{\max}^{\mathrm{MeOH}}$ 320 mμ, considered to be crude **3-hydroxy-3,5,7-trien-17-one (8)**. Digestion with methanol gave the purified sample: mp 103–111 and 116–117° (double melting point, evacuated tube); $\lambda_{\max}^{\mathrm{MeOH}}$ 320 mμ (ϵ 15,370);

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[7] N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *J. Amer. Chem. Soc.*, **77**, 6269 (1955).

[8] H. Hagiwara, S. Noguchi, and M. Nishikawa, *Chem. Pharm. Bull. Jap.*, **8**, 84 (1960).

[9] A. Bowers, R. Villotti, J. A. Edwards, E. Denot, and O. Halpern, *J. Amer. Chem. Soc.*, **84**, 3204 (1962).

[10] H. Ueberwasser, K. Heusler, J. Kalvoda, Ch. Meystre, P. Wieland, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **46**, 344 (1963).

[11] D. Hauser, K. Heusler, J. Kalvoda, K. Schaffner, and O. Jeger, *ibid.*, **47**, 1961 (1964).

[12] Melting points are corrected. Nmr spectra were determined with a Varian A-60 spectrometer. Deuteriochloroform was used as a solvent unless otherwise stated. Chemical shifts are reported in parts per million downfield from tetramethylsilane.

$\nu_{\max}^{\text{Nujol}}$ 3320 (enolic HO–), 1730 (17-ketone), 1658 and 1568 cm^{-1} (>C═C<); the nmr spectrum in DMSO showed maxima for two olefinic protons as a quartet (J_{AB} = 6 H, $\delta_A - \delta_B$ = 0.22 ppm) centered at 5.27 (6 and 7 position), one olefinic proton as a singlet at 5.10 (4 position), one exchangeable proton as a singlet at 3.14 (enolic HO–), and three protons as a singlet at 0.62 ppm (18 position).

A solution of 100 mg of the free enol in 5.0 ml of ethyl acetate was left to stand at 5° for 16 hr in an atmosphere of nitrogen. The ethyl acetate was removed at reduced pressure yielding a resinous material, $\lambda_{\max}^{\text{MeOH}}$ 272 and 275 mμ, which was dissolved in a minimum of methanol. Extraction of the methanol solution with heptane followed by concentration of the heptane phase at reduced pressure at room temperature yielded 25 mg of a crystalline material having an ir spectrum identical with that of the pure sample of $\Delta^{5,7}$-3-ketone **10** prepared as above.

Alternatively, the latter compound could be obtained when 100 mg of free enol **8**, enclosed in an evacuated tube, was immersed briefly in an oil bath at 120° until the material was molten. Digestion of the melt with methanol gave 20 mg of $\Delta^{5,7}$-3-ketone **10** having an ir spectrum identical with that of the purified sample prepared as above.

Estra-4,7-diene-3,17-dione (**12**).—An evacuated tube containing 100 mg of **8** was heated at 80° for 16 hr. The crude product which had $\lambda_{\max}^{\text{MeOH}}$ 239 mμ was digested with ether and recrystallized from methanol yielding 18 mg of a material having mp 145–146° (lit.[4] mp 148–149°), $\lambda_{\max}^{\text{MeOH}}$ 238 mμ(ϵ 14,950); the ir spectrum was identical with that of an authentic[5] sample of **12**.

Estra-5(10),7-diene-3,17-dione (**22**).—A solution of 1.89 g of **10** in 10 ml of tetrahydrofuran was stirred with 0.5 ml of concentrated hydrochloric acid for 3 min at room temperature in an atmosphere of nitrogen whereupon 20 ml of ether and 10 ml of water were added. The upper organic phase was washed well with water, dried with sodium sulfate, and evaporated at room temperature and reduced pressure. The residue was chromatographed on deactivated Davison silica gel. Elution with ethyl acetate–benzene (1:4) gave a crystalline material which, after two recrystallizations from methanol, gave 258 mg of the analytical sample: mp 124–126.5°; $\nu_{\max}^{\text{CHCl}_3}$ 1735 (17-ketone) and 1713 cm^{-1} (3-ketone); $\lambda_{\max}^{\text{MeOH}}$ 288 mμ (ϵ 102); the nmr spectrum showed maxima for one olefinic proton as a singlet at 5.42 (7 position) and three protons as a singlet at 0.79 ppm (18 position).

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.09; H, 8.30.

Further elution of the chromatographic column afforded a noncrystalline material which, on the basis of its thin layer chromatogram and its uv spectrum, was considered to consist of a mixture of $\Delta^{4,7}$- and $\Delta^{4,6}$-3-ketones **12** and **1**.

3-Methoxyestra-3,5,7-trien-17-one (**18**). **A. From $\Delta^{5,7}$-3-Ketone 10** *via* **Ketal 20**.—To a solution of 3.0 g of $\Delta^{5,7}$-3-ketone **10** in 150 ml of methanol, cooled to 0°, was added 150 ml of ice-cold methanol–sulfuric acid (1000:1). The mixture was agitated for 30 sec and half of the reaction mixture was then poured into 3000 ml of 0.1 *N* aqueous sodium hydroxide. Extraction with ether, evaporation at reduced pressure, and digestion of the residue with methanol gave 200 mg of 3,3-dimethoxyestra-5,7-dien-17-one (**20**): mp 137–145°; $\lambda_{\max}^{\text{MeOH}}$ 261.5 mμ (ϵ 7650), 271 (11,050), 281.5 (11,670) and 293.5 (6900); $\nu_{\max}^{\text{HCl}_3}$ 2835, 1732, 1668, 1620, 1108, and 1050 cm^{-1}.

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.9; H, 8.92. Found: C, 76.33; H, 8.85.

The other half of the methanol solution was left to stand at room temperature for 1 hr. The mixture was concentrated at reduced pressure at 30° and the crystalline precipitate was filtered off yielding 1.0 g of the crude product **18**, mp 160–170°. One recrystallization from methanol–methylene chloride in the presence of a small amount of pyridine gave the analytical sample with mp 178–185°; $\lambda_{\max}^{\text{EtOH}}$ 318 mμ (ϵ 14,400); $\nu_{\max}^{\text{CHCl}_3}$ 1730 (17-ketone), 1240 and 1160 (MeO–) 1570, 1620, and 1645 cm^{-1} (>C═C<); the nmr spectrum showed maxima for two olefinic protons as a triplet (unresolved quartet; J = 8 Hz) centered at 5.60 (6 and 7 position), one olefinic proton as a singlet at 5.34 (4 position), three protons as a singlet at 3.64 (enolic MeO–), and three protons as a singlet at 0.86 ppm (18 position).

Anal. Calcd for $C_{10}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 79.89; H, 8.31.

B. From $\Delta^{5(10),7}$-3-Ketone 22.—A solution of 30 mg of **22** in 0.30 ml of methanol–concentrated sulfuric acid (100:1) was left to stand at room temperature in an atmosphere of nitrogen for 16 hr. The crystalline precipitate obtained after filtration and digestion with methanol had an uv and an ir spectrum identical with those of **18** obtained from $\Delta^{5,7}$-3-ketone **10**.

3-Acetoxyestra-3,5,7-trien-17-one (**13**). **A. From $\Delta^{5,7}$-3-Ketone 10.**—A solution of 100 mg of **10** in 0.5 ml of acetic anhydride pyridine (1:2) was left to stand at room temperature for 6 hr. Working up by dilution with water, extraction with ether, and digestion of the crude product with methanol yielded 50 mg of a crystalline material having mp 173–176° (lit.[5] mp 175–178°) and an ir spectrum identical with that of an authentic[5] sample of **13**.

B. From Estra-4,6-diene-3,17-dione (**1**).—A mixture of 1 g of $\Delta^{4,6}$-3-ketone **1**, 1.5 g of sodium methoxide, and 10 ml of dimethyl sulfoxide was stirred at room temperature under nitrogen for 5 min, whereupon 55 ml of acetic anhydride–ether (1:10), cooled to −15°, was added in one portion. The mixture was stirred for 10 min under nitrogen and 50 ml of 2 *N* aqueous acetic acid was added in one lot with stirring. Stirring was continued for 5 min and the ethereal phase was washed well with water and then dried with sodium sulfate. Evaporation at reduced pressure and digestion with methanol yielded 0.51 g of a crystalline material, mp 174–177°, which had an ir spectrum identical with that of an authentic[5] sample of **13**.

C. From 19-Aldehyde 4.—The preparation of **13** from **4** was carried out by a procedure identical with the one starting with **1** outlined above. Product **13**, mp 171–176°, was obtained in 43% yield and had an ir spectrum identical with that of an authentic[5] sample of **13**.

D. From 19-Carboxylic Acid 5.—The preparation of **13** from **5** was carried out by a procedure identical with the one starting with **1**, outlined above, except that the base treatment was carried out at 60° and that the ether–acetic anhydride solution was cooled to −60°. Product **13**, mp 171–176°, was obtained in 25% yield and had an ir spectrum identical with that of an authentic[5] sample of **13**.

3-Methoxy-19-hydroxyandrosta-3,5,7-trien-17-one (**19**).—A mixture of 5 g of 19-hydroxyandrost-4,6-diene-3,17-dione (**2**),[13] 3.75 g of sodium methoxide, and 25 ml of dimethyl sulfoxide was stirred for 5 min in an atmosphere of nitrogen, whereupon 250 ml of hexane, cooled below −60°, and a solution of 9 ml of concentrated sulfuric acid in 100 ml of methanol, also cooled below −60°, were added in quick succession. The mixture was stirred for 17 min in an ice bath, whereupon the lower methanolic phase was added in a thin stream to 300 ml of 1 *N* aqueous sodium hydroxide cooled to 0°. The precipitate formed, which had $\lambda_{\max}^{\text{MeOH}}$ 255 (sh), 308 (sh), 321 (major peak), and 337 mμ (sh), was filtered and dissolved in 150 ml of methanol–pyridine (3:1) at the boiling point. The solution was treated with charcoal, filtered through Celite, diluted with 600 ml of water, and cooled to 0°. The precipitate was filtered off and dried at 30° under high vacuum yielding 1.24 g of a white crystalline material: $\lambda_{\max}^{\text{MeOH}}$ 310 (sh), 321, and 337 mμ. One recrystallization from methanol–pyridine (50:1) gave the analytical sample with mp 188–191°; $\lambda_{\max}^{\text{MeOH}}$ 320 mμ (ϵ 18,450); $\nu_{\max}^{\text{CHCl}_3}$ 1734 (17-ketone), 1625 and 1649 cm^{-1} (>C═C<); the nmr spectrum showed maxima for two olefinic protons as a sextet (ABX system) centered at 5.66 (J_{AB} = 6, J_{AX} = 2 Hz; 6 and 7 position), one olefinic proton as a singlet at 5.30 (4 position), two methylenic protons as a singlet at 3.72 (19 position), three protons as a singlet at 3.60 (enolic methyl ether), and three protons as a singlet at 0.88 ppm (18 position).

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.68; H, 8.47.

Preparation of 3,19-Diacetoxyandrosta-3,5,7-triene (15) *via* **3,19-Dihydroxy-3,5,7-triene (9) and 19-Hydroxy $\Delta^{5,7}$-3-Ketone 11.**—A mixture of 2.0 g of 19-hydroxy $\Delta^{4,6}$-3-ketone **2**,[13] 2.0 g of sodium methoxide, and 10 ml of dimethyl sulfoxide was stirred for 5 min at room temperature in an atmosphere of nitrogen, whereupon it was poured into 200 ml of partially frozen 10% aqueous acetic acid. The aqueous suspension was stirred for 10 min under nitrogen and a small sample was withdrawn and filtered. The precipitate was washed well with water and dried at room temperature under high vacuum for 1 hr. The dried precipitate, considered to be **3,19-dihydroxyandrosta-3,5,7-trien-17-one** (**9**), had $\lambda_{\max}^{\text{MeOH}}$ 320 mμ, mp 90–95 and 199–206° (double melting point; evacuated tube); the melt had $\lambda_{\max}^{\text{MeOH}}$ 239 and 283 mμ and was considered, in conjunction with its thin layer chromatogram, to consist largely of a mixture of **2** and 19-

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(13) K. Heusler, J. Kalvoda, Ch. Meystre, H. Ueberwasser, P. Wieland, G. Anner and A. Wettstein, *Experientia*, **18**, 464 (1962).

hydroxyandrosta-4,7-diene-3,17-dione.[5] After drying for 20 hr at room temperature under high vacuum, the uv spectrum of the precipitate showed additional maxima at 240, 270, and 272 mμ indicating decomposition to **11** and 19-hydroxyandrosta-4,7-diene-3,17-dione.

The major portion of the aqueous suspension was stirred under nitrogen for 3.5 hr, filtered, and digested several times with water and once with 40% aqueous AR methanol. Drying at room temperature under high vacuum for 16 hr yielded 1.2 g of solid material considered to be **19-hydroxyandrosta-5,7-diene-3,17-dione (11)**: mp 87–90°; λ_{max}^{MeOH} 271 mμ (ϵ 8120) and 281 (8600); $\nu_{max}^{CHCl_3}$ 3480 (–OH), 1725 cm^{-1} (broad, 3- and 17-ketone); the nmr spectrum showed maxima for two olefinic protons as multiplets between 5.8 and 6.0 (6 position) and 5.4 and 5.7 (7 position), two methylenic protons as a quartet (J = 11 Hz, $\delta_A - \delta_B = 0.18$ ppm) centered at 3.74 (19 position), two methylenic protons as a multiplet (distorted quartet) between 3.0 and 3.5 (4 position), and three protons as a singlet at 0.89 ppm (18 position).

A solution of 200 mg of $\Delta^{5,7}$-3-ketone **11** in 10 ml of acetic anhydride–pyridine (1:3) was left to stand for 16 hr at room temperature in an atmosphere of nitrogen. Dilution with water and extraction with ether yielded a residue on evaporation which was triturated with methanol and then recrystallized from the same solvent yielding 100 mg of a crystalline material, mp 116–120° (lit.[5] mp 116–120°), having an ir spectrum identical with that of an authentic sample of 3,19-diacetate **15**.

When 1.0 g of $\Delta^{4,6}$-3-ketone **2** was subjected to the procedure of preparing 19-hydroxy-3,5,7-triene **9** as outlined above, except that the basic mixture was poured into 10 ml of 50% instead of 10% aqueous acetic acid, 520 mg of a precipitate was obtained after drying which had an ir spectrum identical with that of $\Delta^{5,7}$-3-ketone **11** prepared from enol **9** as described above.

3-Acetoxy-19-hydroxyandrosta-3,5,7-trien-17-one (14).—Enol acetylation of 5.0 g of $\Delta^{4,6}$-3-ketone **2**[13] by the procedure used for the conversion of **1** into **13**, outlined above, gave 4.1 g of **14** upon evaporation of the ethereal extracts and digestion of the residue with methanol: mp 153–156°; λ_{max}^{MeOH} 315 mμ (ϵ 20,000); $\nu_{max}^{CHCl_3}$ 1735 (17-ketone), 1582 and 1660 cm^{-1} (>C=C<); the nmr spectrum showed maxima for three olefinic protons as a multiplet between 5.4 and 6.0 (4, 6, and 7 position), two methylenic protons as a singlet at 3.75 (19 position), three protons as a singlet at 2.12 (enol acetate), and three protons as a singlet at 0.89 ppm (18 position).

Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66. Found: C, 73.43; H, 7.57.

Tlc of the mother liquor obtained after digestion of the crude product revealed substantial amounts of acetate **14** and only a minor amount of diacetate **15**.

When 50 mg of free enol **9** was left to stand with 0.1 ml of acetic anhydride and 0.2 ml of pyridine in an atmosphere of nitrogen, working up of half the mixture after 5 min gave a resin consisting of, besides polar by-products, some acetate **14** and a trace of 3,19-diacetate **15**, while working up after 16 hr gave a resin containing some diacetate **15** and no acetate **14** as indicated by thin layer chromatography.

Estra-5,7,9(10)-triene-3,17-dione (23).—A suspension of 8.0 g of **11** in 800 ml of carbon tetrachloride was cooled to 0° and 24 g of commercial lead tetraacetate containing about 4% of acetic acid was added in one portion. The mixture was stirred under nitrogen for 30 min and filtered. The filtrate was concentrated to 130 ml at 35° and reduced pressure, diluted with 65 ml of ethyl acetate, and chromatographed on 420 g of silica gel which had been deactivated with wet ether. Elution with carbon tetrachloride–ethyl acetate (2:1) gave 200 mg of **23**, mp 90–92°, which, on digestion with ether, gave the pure material: mp 94.5–96.5°; λ_{max}^{EtOH} 269 mμ (ϵ 509); $\nu_{max}^{CHCl_3}$ 1722 cm^{-1} (3,17-diketone); the nmr spectrum showed maxima for two aromatic protons as a singlet at 7.01 (6 and 7 position), two methylenic protons as a singlet at 3.58 (4 position), and three protons as a singlet at 0.76 ppm (18 position).

Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.69; H, 7.40.

When a solution of **23** in methanol was treated with solid sodium methoxide a blue color developed (tetralone blue).[14]

The precipitate which had been obtained on filtration of the reaction mixture was extracted with carbon tetrachloride. Evaporation yielded a residue which, on the basis of its uv spectrum and thin layer chromatogram, consisted mainly of starting material.

3-Methoxyestra-3,5,7,9(10)-tetraen-17-one (17).—A suspension of 1.0 g of **19** in 200 ml of carbon tetrachloride was cooled to 0° and 3.0 g of lead tetraacetate was added in one portion. The mixture was stirred in an atmosphere of nitrogen for 5 min and then filtered. The filtrate was concentrated at 30° under reduced pressure to 70 ml, diluted with 15 ml of ethyl acetate, and chromatographed on 60 g of deactivated silica gel. Elution with ethyl acetate–carbon tetrachloride (1:4) gave 300 mg of a product having mp 180.5–185.5° and 200 mg of a less pure fraction. Chromatography of the latter fraction on 30.0 g of neutral alumina gave, on elution with benzene–ethyl acetate (6:1), 50 mg of the analytical sample: mp 180.5–183.5°; $\lambda_{max}^{CHCl_3}$ 277 mμ (ϵ 14,150); $\nu_{max}^{CHCl_3}$ 2840 (methyl ether), 1735 (17-ketone), 1650 (>C=C<), and 1165 cm^{-1} (ether); the nmr spectrum showed maxima for two aromatic protons as a singlet at 6.85 (6 and 7 position), one olefinic proton as a singlet at 5.50 (4 position), three protons as a singlet at 3.69 (enolic methyl ether), and three protons as a singlet at 0.75 ppm (18 position).

Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.83; H, 7.71.

3-Acetoxyestra-3,5,7,9(10)-tetraen-17-one (16).—A suspension of 3.5 g of **14** in 350 ml of carbon tetrachloride was cooled to 0° and 5.25 g of lead tetraacetate was added in one portion. The mixture was stirred in an atmosphere of nitrogen for 10 min and a second portion of 5.25 g of lead tetraacetate was added. After 20 min of further stirring the mixture was filtered. The filtrate was diluted with 40 ml of ethyl acetate and chromatographed on 210 g of deactivated silica gel. Elution with ethyl acetate–carbon tetrachloride (1:4) gave 2.0 g of crystalline material, mp 125–129°, which, on digestion with ether, gave the pure sample: mp 127–130.5°; λ_{max}^{EtOH} 217.5, 230.5, and 271 mμ; $\nu_{max}^{CHCl_3}$ 1735–1760 (17-ketone and 3-enol acetate) and 1675 cm^{-1} (>C=C<); the nmr spectrum showed maxima for two aromatic protons as a singlet at 6.90 (6 and 7 position), one olefinic proton as a singlet at 6.18 (4 position), three protons as a singlet at 2.18 (3-enol acetate), and three protons as a singlet at 0.74 ppm (18 position).

Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.50; H, 7.15.

Registry No.—**8**, 16055-08-6; **9**, 16054-97-0; **10**, 16054-98-1; **11**, 13593-52-7; **14**, 16055-01-9; **16**, 16055-02-0; **17**, 16055-03-1; **18**, 16055-04-2; **19**, 16055-05-3; **20**, 16055-06-4; **22**, 13809-66-0; **23**, 16055-07-5.

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(14) H. H. Rodd, "Chemistry of Carbon Compounds," Vol. III^B, Elsevier Publishing Co., Amsterdam, The Netherlands, p 1344.