The Synthesis of C-15 β-Substituted Estra-1,3,5(10)-trienes. I

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The synthesis of C-15 β-substituted estra-1,3,5(10)-trienes by the frontal addition of nucleophiles to the Δ^{15}-17-one moiety of 3-methoxyestra-1,3,5(10),15-tetraen-17-one is described. Arguments are presented to support the assignment of the C-15 β-configuration to these compounds and also to rationalize their mode of formation on a kinetic basis.

Johnson and Johns[1] have described the preparation of 3-methoxyestra-1,3,5(10),15-tetraen-17-one (**1**) in five steps from estrone methyl ether (**4a**). They observed that tetraene **1** is readily isomerized by *p*-toluenesulfonic acid in refluxing benzene to give a mixture consisting of 3-methoxy-14β-estra-1,3,5(10),15-tetraen-17-one (**2**) and 3-methoxy-estra-1,3,5(10),14-tetraen-17-one (**3**). However, attempted isomerization with potassium hydroxide in methanol provided a 15-methoxyestrone of undetermined configurations at C-14 and C-15. This facile conjugate addition of methanol suggested to us the possibility of utilizing the Δ^{15}-17-one (**1**) as an intermediate for the synthesis of C-15 substituted estrogens.

Accordingly, we have prepared the 15-methoxy compound described by Johnson and Johns,[1] and directed our attention initially toward elucidating its configurational aspects. Treatment of the Δ^{15}-17-one (**1**) with aqueous potassium hydroxide in methanol afforded the 15-methoxy adduct product (**4b**) in practically quantitative yield.[2] The product was then submitted to optical rotational analysis utilizing a number of known 15α- and β-substituted steroids and their corresponding C-15 unsubstituted compounds. From Table I it can be seen that a 15β-substituent produces a large levorotatory shift, while a dextrorotatory shift of comparable magnitude is observed with a 15α-substituent.[3] On the basis of this analysis the methoxyl group of compound **4b** has been assigned the 15β-configuration. The assumption is made, however, that isomerization at the C-14 ring juncture did not occur prior to addition. This possible structural alteration was considered unlikely in view of the following observations.

It has been found that treatment of the C/D *cis* isomer, 3-methoxy-14β-estra-1,3,5(10),15-tetraen-17-one (**2**)[1] under the same conditions previously described for compound **1** resulted in a mixture consisting of 56% of starting material **2**, 28% of the Δ^{14}-17-one (**3**), and 10–15% of a substance of probable structure 3,15β-dimethoxy-14β-estra-1,3,5(10)-trien-17-one (**5**) in about 90% purity. The purity of **5** was determined by thin layer chromatographic analysis. Many attempts to purify **5**, which was contaminated with starting material **2**, by partition chromatography failed. Regardless, the assigned structure was based on spectral analysis. Its infrared absorption spectrum possessed a saturated carbonyl group at 1725 cm.$^{-1}$, while its n.m.r. spectrum displayed two methyl groups at 6.16 (C-3) and 6.63 τ (C-15). In addition the splitting constant for the C-15 hydrogen (triplet centered at 5.87 τ) is 8 c.p.s. for **5** as compared with 5 c.p.s. for **4b** which suggests that the hydrogen atoms at C-14 and C-15 in **5** are *trans* diaxial to each other.[4] Also the spectrum of

TABLE I

MOLECULAR ROTATION ANALYSIS

Compound	$[\alpha]_D$	$[M]_D$	$\Delta[M]_D$
3-Keto-5β-etianic acid methyl ester	+ 70°[a]	+233°	
15β-Hydroxy-3-keto-5β-etianic acid methyl ester	+ 37°[a]	+129°	−104°
15α-Hydroxy-3-keto-5β-etianic acid methyl ester	+ 95°[a]	+331°	+ 98°
Androst-4-ene-3,17-dione	+190° (EtOH)[b]	+544°	
15β-Hydroxyandrost-4-ene-3,17-dione	+148°[c]	+477°	− 97°
15α-Hydroxyandrost-4-ene-3,17-dione	+206° (MeOH)[c]	+622°	+ 78°
3-Methoxyestra-1,3,5(10)-trien-17-one	+171°[d]	+486°	
3,15β-Dimethoxyestra-1,3,5(10)-trien-17-one	+ 94°	+295°	−191°
15β-Benzyloxy-3-methoxyestra-1,3,5(10)-trien-17-one	+ 38°	+148°	−338°
15β-Hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one	+103°	+309°	−177°
15β-Cyano-3-methoxyestra-1,3,5(10)-trien-17-one	+ 30°	+ 93°	−393°
3-Methoxyestra-1,3,5(10)-trien-17β-ol	+ 77°[e]	+220°	
15β-Cyano-3-methoxyestra-1,3,5(10)-trien-17β-ol	− 28°	− 87°	−307°
15α-Carboxamido-3-methoxyestra-1,3,5(10)-trien-17β-ol	+109° (MeOH)	+359°	+139°
15α-Carboxy-3-methoxyestra-1,3,5(10)-trien-17β-ol	+130° (MeOH)	+430°	+210°

[a] A. Lardon, H. P. Sigg, and T. Reichstein, *Helv. Chim. Acta*, **42**, 1457 (1959). [b] L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Co., New York, N. Y., 1959, p. 519. [c] S. Bernstein, M. Heller, L. I. Feldman, W. S. Allen, R. H. Blank, and C. E. Linden, *J. Am. Chem. Soc.*, **82**, 3685 (1960). [d] G. F. Marrian and G. A. D. Haslewood, *Biochem. J.*, **26**, 25 (1932). [e] A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.*, **75**, 5366 (1953).

(1) W. S. Johnson and W. F. Johns, *J. Am. Chem. Soc.*, **79**, 2005 (1957).

(2) The crude reaction product was analyzed by partition chromatography on Celite 545 and was found to be approximately 97% pure (see Experimental).

(3) See footnotes *a* and *c*, Table I, for previous rotational analyses of 15 substituted steroids.

(4) See, *e.g.*, H. Conroy, "Advances in Organic Chemistry," Vol. II, Interscience Publishers, Inc., New York, N. Y., 1960, p. 309.

5 has a doublet centered at 7.63 τ (C-16 methylene) in contrast to that (7.45 τ) observed for **4b**. This appears to be consistent with anticipated increased shielding at C-16 in a structure represented by **5**.

Further chemical support for the retention of configuration at C-14 in the formation of **4b** from **1** was obtained as follows. 15β-Benzyloxy-3-methoxyestra-1,3,5(10)-trien-17-one (**4c**), prepared by the base-catalyzed addition of benzyl alcohol to 3-methoxyestra-1,3,5(10),15-tetraen-17-one (**1**), was reduced with sodium borohydride and acetylated to give 17β-acetoxy-15β-benzyloxy-3-methoxyestra-1,3,5(10)-triene (**6b**). Hydrogenolysis of the latter with a 10% palladium–charcoal catalyst in acetic acid gave the corresponding 15β-hydroxy derivative **6c**, which was in turn oxidized with chromic acid–pyridine to 17β-acetoxy-3-methoxyestra-1,3,5(10)-trien-15-one (**7**). The optical rotatory dispersion curve[5] of the latter in methanol solution displayed a strong positive Cotton effect (Fig. 1) characteristic of a C/D *trans*-15-keto steroid.[6,7] Potassium hydroxide in methanol (0.012 *N*) was added to the aforementioned solution and equilibration was allowed to proceed for 17 hr. The resultant dispersion curve indicated that **7** had to a large extent isomerized to the more stable C/D *cis* structure.[8] C/D-*trans*-15-Keto steroids have been shown on lithium aluminum hydride reduction to give the corresponding C/D-*trans*-15β-hydroxy derivative.[7] The reduction of the 17β-acetoxy-15-one (**7**) with lithium aluminum hydride gave 3-methoxy estra-1,3,5(10)-triene-15β,17β-diol (**6a**) identical with the product obtained by a similar reduction of 15β-hydroxy-3-methoxyestra-1,3,5-(10)-trien-17-one (**4d**). The latter was prepared by hydrogenolysis of the benzyl group of **4c** with a 10% palladium–charcoal catalyst in acetic acid. Thus it is concluded that the nucleophilic addition of methoxide and benzyloxide ions to the Δ^{15}-17-keto system of **1** proceeds without isomerization at C-14 to provide the corresponding 15β-substituted products, **4b** and **4c**, respectively.[9]

The question arises as to whether the formation of these 15β-substituted steroids is kinetically or thermodynamically controlled. For this purpose isomerization studies at C-15 were undertaken,[10] and 15β-cyano-3-methoxyestra-1,3,5(10)-trien-17β-ol (**6e**), Δ-[M]D −393° was prepared from **1** in two stages (**1** → **4e** → **6e**). Treatment with potassium hydroxide in refluxing aqueous propanol gave the carboxamide **8a**. Its Δ[M]D +141 was indicative that the carboxamide group had epimerized to the thermodynamically more stable 15α-configuration. Similarly, hydrolysis of **6e** under more vigorous conditions (potassium hydroxide–aqueous ethylene glycol, 22-hr. reflux) afforded the carboxylic acid (**8b**) whose Δ[M]D +212° was also consistent with a 15α-configuration. Thus β-addition at C-15 represents kinetic control and appears to be irreversible.

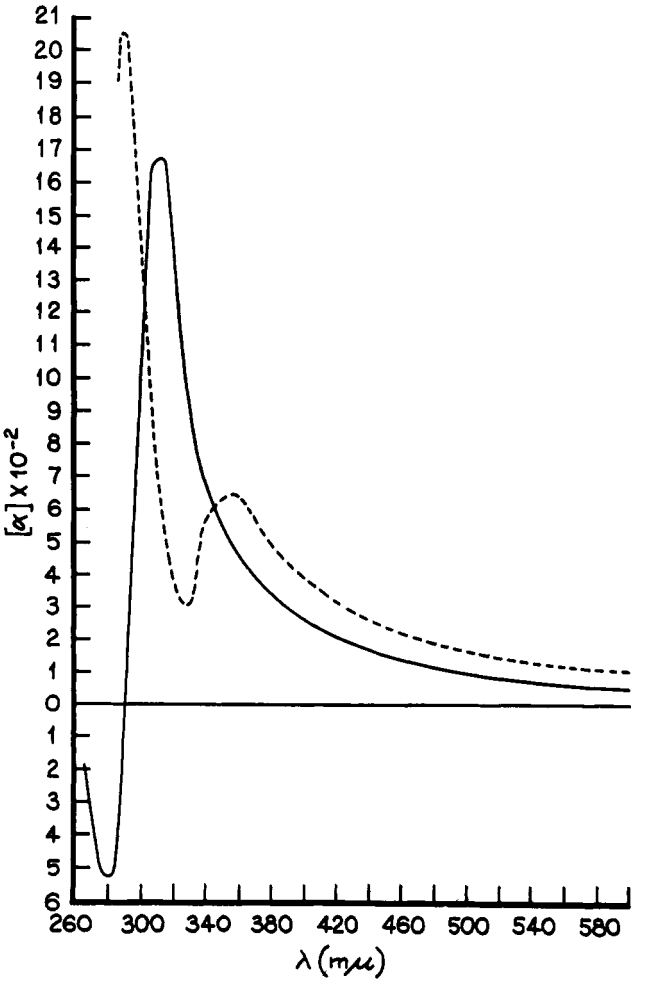


Fig. 1.—Optical rotatory dispersion curve of 17-β-acetoxy-3-methoxyestra-1,3,5(10)-trien-15-one. ———, *c* 0.034, 600–300; *c* 0.017, 320–290; *c* 0.0068, 300–265 mμ; - - - - -, *c* 0.0272, 600–290; *c* 0.01088, 310–284 mμ after addition of 1.00 ml. of 0.012 *N* KOH–CH_3OH.

If the addition of alkoxide to the *trans*-hydrindenone (**1**) were a readily reversible process, it would be anticipated that the corresponding 15α-alkoxy product or at least a mixture of it and the 15β-epimer would be formed. That the process is not reversible is demonstrated by the fact that **4b** is the exclusive product whether the reaction time is 15 min. or 24 hr.[11]

At this point the problem required an explanation or rationale for the formation of the C-15 β-substituted steroid by a frontal (β-face) approach of the nucleophile. One may have anticipated that the C-13 methyl

(5) We are indebted to Professor Kurt Mislow of New York University for the O.R.D. determinations.

(6) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p. 58.

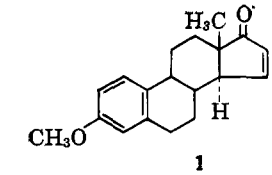
(7) Footnote *a*, Table 1.

(8) The relative stability of *cis*- and *trans*-hydrindanones has been studied by numerous investigators [*e.g.*, N. L. Allinger, R. B. Hermann, and C. Djerassi, *J. Org. Chem.*, **25**, 922 (1960), and references cited therein]. With 15-keto steroids the equilibrium between the C/D forms is apparently dependent on the size of the C-17-substituent. When the latter is small, or relatively so, the *cis* isomer is thermodynamically favored. Thus, Allinger, Hermann, and Djerassi have demonstrated that under equilibrium conditions the 14β *cis* isomer of 3β-acetoxy-15-ketoetianic acid methyl ester is preferably formed over the 14α *trans* isomer in the ratio of 87:13.

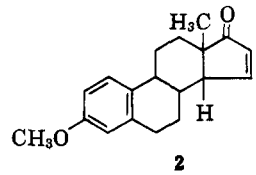
(9) J. Fajkos [*Chem. Listy*, **51**, 1894 (1957); *Collection Czech. Chem. Commun.*, **23**, 2154 (1958)] has reported a similar addition of methanol to 3β-acetoxyandrost-15-en-17-one without assigning a configuration to the methoxyl group. On the basis of rotational analysis (Δ[M]D −167°) and of its mode of preparation the compound most likely has a β-configuration at C-15.

(10) J. Fajkos and F. Sorm [*Chem. Listy*, **51**, 579 (1956); *Collection Czech. Chem. Commun.*, **22**, 1873 (1957)]; have shown that 16β-acetylandrost-4-en-3-one under equilibrating conditions isomerizes to the 16α-acetyl compound. Since 15β- and 16β-oriented groups are similarly related geometrically to the C-13 methyl group, it may then be expected that a 15β-substituent (quasi-axial) capable of isomerization would do so.

(11) In contrast to this, D. K. Fukushima and T. F. Gallagher [*J. Am. Chem. Soc.*, **73**, 196 (1951)] have shown that equilibration of 16α-methoxyprogesterone in methanolic potassium hydroxide at room temperature results in a mixture composed of 70% of starting material and 30% of 16-dehydroprogesterone.



1



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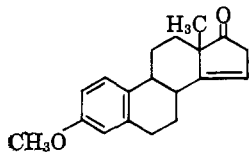

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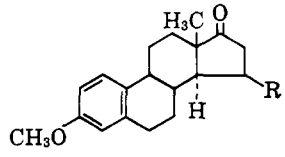
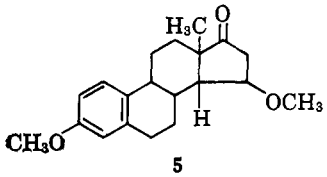


4a, R = H
4b, R = OCH_3
4c, R = $OCH_2C_6H_5$
4d, R = OH
4e, R = CN



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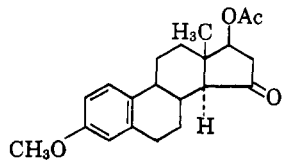

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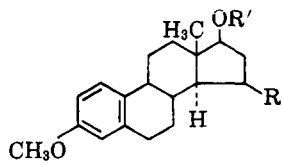
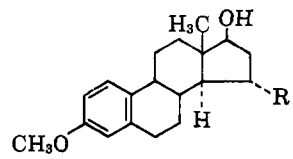
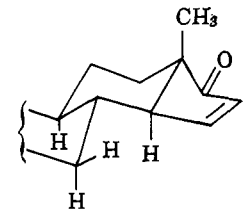


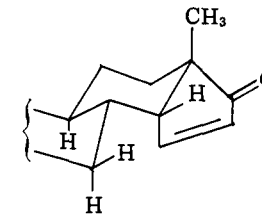
6a, R′ = H; R = OH
6b, R′ = Ac; R = $OCH_2C_6H_5$
6c, R′ = Ac; R = OH
6d, R′ = Ac; R = OCH_3
6e, R′ = H; R = CN



8a, R = $CONH_2$
8b, R = COOH



a



b

group would have a similar steric influence upon the course of addition to a Δ^{15}-17-ketone as it does with a Δ^{16}-20-ketone where the entering group assumes the 16α-configuration.[11,12] There is, however, precedence for β-addition to C-15 as exemplified by the catalytic reduction and epoxidation of a Δ^{14}-17-ketone to the corresponding 14β-17-ketone,[13] and 14β,15β-epoxide,[14] respectively.

Brutcher and Bauer[15] have concluded from a study of three possible ring D conformations (two "envelope" and one "half-chair" conformations) that for 17β-substituted steroids one of the "envelope" conformations is preferred, that is the one in which C-13 lies above the plane defined by carbons 14, 15, 16, and 17. With 17-keto steroids, this conformation results in less 1,3-interactions; however, this advantage is outweighed by the resultant torsional strain inherent in it. Thus, these investigators[15] suggested that ring D of androstan-17-one assumes one of the other two possible conformations.

An examination of Dreiding models of the partial structures **a** and **b** corresponding to the 14α-Δ^{15}-17-one (**1**) and 14β-Δ^{15}-17-one (**2**), respectively, reveals that ring D of **1** can assume only the depicted "envelope" conformation. In this conformation the plane defined by carbons 14, 15, 16, and 17 is slightly elevated from that of rings B and C, and the p-orbitals on the Δ^{15}-double bond have their upper lobe turned slightly toward the C-13 methyl group and the lower lobe at an oblique angle to rings B and C. If one draws an imaginary line through C-15 perpendicular to the carbons 14, 15, 16, and 17 plane and extending approximately 1.36 Å. (the C–O bond distance as measured from the models) one can *approximate* a depicting of a transition state. An examination of this working model reveals that geometrically frontal attack at C-15 would be favored over rear attack. We feel that the bar to rear attack may be ascribed principally to a marked eclipsed 1,2-interaction between a nucleophile entering on the α-face and the C-14 α-hydrogen in the transition state.

An examination of **b** in the same manner reveals that the α-face is shielded by the 7α- and 9α-hydrogens as to make addition in that manner less likely. Furthermore the low yield of the C-15 β-methoxy compound from **2** can be explained on the relative stability of the *cis*-hydrindenone over the *trans* isomer. The 14β-hydrogen of **2** should be removed more readily by base since the incipient anion would have its p-orbital β-oriented, thus retaining the C/D ring in the *cis* locking. This anion may then be re-protonated to give starting material or isomerized *via* the dienolate ion to give either starting material or nonconjugated ketone **3**. However in the case of the *trans*-hydrindenone (**1**), the strain inherent in that system can not be relieved by isomerization to **2** and/or **3** until the bond between C-14 and the 14α-hydrogen is ruptured. It is apparent, then, that the rate of nucleophilic addition to **1** is much greater than that for isomerization.

Experimental

Melting points are uncorrected. The optical rotations are for chloroform solution at 25° unless noted otherwise. The infrared absorption spectra were determined in potassium bromide disks, and the ultraviolet absorption spectra were determined in methanol. Petroleum ether refers to the fraction, b.p. 60–70°. The abbreviation HBV refers to holdback volume.

The authors are indebted to William Fulmor and associates for the infrared, ultraviolet, n.m.r., and optical rotation data. We wish also to thank Louis M. Brancone and associates for the analyses, and Charles Pidacks and associates for the partition chromatography.

3,15β-Dimethoxyestra-1,3,5(10)-trien-17-one (4b).—To a suspension of 3-methoxyestra-1,3,5(10),15-tetraen-17-one (**1**, 0.300 g., m.p. 175–177°, $[\alpha]_D$ −90°, lit.[1] m.p. 180–181°) in methanol (15 ml.) was added 5% aqueous sodium hydroxide (10 drops). The resulting solution was stirred at room temperature for 30 min. The product precipitated upon the addition of water and was collected, washed with water, and dried to give 0.314 g. of **4b**, m.p. 128–129°. Crystallization from ether gave 0.205 g., m.p. 130–131°, $[\alpha]_D$ +95°, lit.[1] m.p. 132–133°.

In another experiment with 0.300 g. of **1** conducted for the same period of time, the product(s) was precipitated with water

(12) (a) J. Romo, M. Romero, C. Djerassi, and G. Rosenkranz, *J. Am. Chem. Soc.*, **73**, 1528 (1951); (b) D. Gould, E. L. Shapiro, L. E. Finckenor, F. Gruen, and E. B. Hershberg, *ibid.*, **78**, 3158 (1956); (c) J. Romo, *Tetrahedron*, **3**, 37 (1958); (d) P. Bladon, *J. Chem. Soc.*, 3723 (1958); (e) R. H. Mazur and J. A. Cella, *Tetrahedron*, **7**, 130 (1959).

(13) A. F. St. Andre, H. B. MacPhillamy, J. A. Nelson, A. C. Shabica, and C. R. Scholz, *J. Am. Chem. Soc.*, **74**, 5506 (1952).

(14) F. Sondheimer, S. Burstein, and R. Mechoulam, *ibid.*, **82**, 3209 (1960).

(15) F. V. Brutcher, Jr., and W. Bauer, Jr., *ibid.*, **84**, 2233, 2236 (1962).

and subjected to partition chromatography on Celite 545[16] using an *n*-heptane–Methyl Cellosolve solvent system. A HBV of 0.4–1.0 gave 5 mg. of an oil, presumed to be 3-methoxyestra-1,3,5(10),14-tetraen-17-one (**3**) based on its polarity. A HBV of 1.5–2.1 gave 0.292 g. (97%) of 3,15β-dimethoxyestra-1,3,5(10)-trien-17-one (**4b**), which was identical by comparison of its infrared spectrum and its mobility on thin layer chromatography (silica G, benzene–acetone–water, 2:1:2) with the specimen described previously.

15β-Benzyloxy-3-methoxyestra-1,3,5(10)-trien-17-one (4c).—To a solution of 3-methoxyestra-1,3,5(10),15-tetraen-17-one (**1**, 2.0 g.) in benzyl alcohol (60 ml.) was added powdered potassium hydroxide (1.5 g.). The resulting mixture was stirred under a nitrogen atmosphere at room temperature for 3.5 hr., during which time the base completely dissolved. The addition of ethyl acetate resulted in the precipitation of a salt which was filtered and the filtrate was steam distilled. The residue was extracted with ethyl acetate and evaporated to give an oil. The latter was chromatographed on 100 g. of Florisil.[17] The fractions eluted with ether–benzene (1:10) gave 2.19 g. of an oil, which crystallized from ether–petroleum ether to give 0.490 g., m.p. 87–89°. The mother liquors from the crystallization were evaporated and subjected to partition chromatography on Celite 545[16] using the *n*-heptane–Methyl Cellosolve solvent system. The eluate from the second HBV was evaporated to give 1.3 g. of an oil which crystallized from methanol, thus providing an additional 0.660 g. of **4c**, m.p. 90–92°. A sample for analysis was recrystallized from ether–petroleum ether and had m.p. 96–98°; λ_{max} 222, 278, and 288 mμ (ε 8800, 2000, and 2000); $[\alpha]_D$ +38°; ν_{max} 1760, 1625, and 736 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{30}O_3$ (390.50): C, 79.96; H, 7.74. Found: C, 79.84; H, 7.92.

17β-Acetoxy-15β-benzyloxy-3-methoxyestra-1,3,5(10)-triene (6b).—A solution containing 15β-benzyloxy-3-methoxyestra-1,3,5(10)-trien-17-one (**4c**, 0.660 g.), sodium borohydride (0.600 g.), and 10% aqueous sodium hydroxide (5 drops) was stirred at room temperature for 3 hr. The product precipitated as a gelatinous precipitate upon the addition of water and was collected and dissolved in ethyl acetate. The latter solution was washed with saturated saline, dried, and evaporated to give an intractable oil whose infrared spectrum (neat) showed no carbonyl maximum. The crude reduction product was acetylated for 1 hr. at 95° with pyridine (4 ml.) and acetic anhydride (1 ml.). The mixture was evaporated *in vacuo* and the residue was crystallized from methanol to give 0.474 g. of **6b**, m.p. 118–120°. Further recrystallization from methanol did not alter the melting point. A sample for analysis had λ_{max} 222, 278, and 288 mμ (ε 8700, 2200, and 2000); $[\alpha]_D$ −13°; ν_{max} 1750, 1620, 1258, and 738 cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{34}O_4$ (434.55): C, 77.39; H, 7.89. Found: C, 77.58; H, 8.03.

17β-Acetoxy-3-methoxyestra-1,3,5(10)-trien-15β-ol (6c).—To a solution containing 15β-benzyloxy 17β-acetate **6b** (0.700 g.) in acetic acid (20 ml.) was added 10% palladium–charcoal catalyst (0.220 g.). The resulting mixture was stirred for 4.5 hr. in a hydrogen atmosphere at room temperature and atmospheric pressure. The catalyst was separated by filtration and washed with methanol. The combined filtrates were evaporated and the residue crystallized from acetone–petroleum ether to give 0.425 g., m.p. 126–128°. A sample for analysis was recrystallized from the same solvents and had m.p. 134–135°; λ_{max} 222, 278, and 288 mμ (ε 8800, 2030, and 1900); $[\alpha]_D$ +9°; ν_{max} 3500, 1720, 1612, and 1255 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{28}O_4$ (344.44): C, 73.22; H, 8.19. Found: C, 73.03; H, 8.40.

17β-Acetoxy-3-methoxyestra-1,3,5(10)-trien-15-one (7).—To a freshly prepared solution of chromium trioxide (0.345 g.) in pyridine (5 ml.) cooled to 0° was added **6c** (0.380 g.) in pyridine (10 ml.). The resulting mixture was stirred for 20 hr. at room temperature, diluted with chloroform, and filtered. The residue was washed twice with chloroform and the combined filtrates were evaporated to give an oil. The latter was triturated with water to give 0.200 g., m.p. 150–157°. Four crystallizations from acetone–petroleum ether gave the analytical sample, m.p. 156–158°; λ_{max} 222, 278, and 288 mμ (ε 10,300, 2500, and 2400); $[\alpha]_D$ +82°; ν_{max} 1740, 1612, and 1240 cm.$^{-1}$; O.R.D. in methanol (*c* 0.034, 600–300; *c* 0.017, 320–290; *c* 0.0068, 300–265 mμ), $[\alpha]_{600}$ +47°, $[\alpha]_{313}$ +1675°, $[\alpha]_{291}$ 0°, $[\alpha]_{281}$ −528°, $[\alpha]_{265}$ −176.5°.

Anal. Calcd. for $C_{21}H_{26}O_4$ (342.42): C, 73.66; H, 7.66. Found: C, 72.99, 73.10; H, 7.74, 7.75.

3-Methoxyestra-1,3,5(10)-triene-15β,17β-diol (6a). Method A. Reduction of 15β-Hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one (4d).—To a solution of **4d** (0.195 g.) in tetrahydrofuran (50 ml.) was added a filtered solution of lithium aluminum hydride (0.300 g.) in tetrahydrofuran (20 ml.), and the resulting mixture was stirred at room temperature for 3 hr. The excess reagent was decomposed with water and the mixture was filtered. The filtrate was evaporated and the residue was crystallized from methanol to give 0.156 g., m.p. 184–186°. Recrystallization did not alter the melting point. The product showed λ_{max} 220, 278, and 288 mμ (ε 8800, 2300, and 2100); $[\alpha]_D$ +31°; ν_{max} 3440 and 1612 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{26}O_3$ (302.40): C, 75.46; H, 8.67. Found: C, 75.75; H, 8.80.

Method B. Reduction of 17β-Acetoxy-3-methoxyestra-1,3,5(10)-trien-15-one (7).—A solution containing **7** (0.100 g.) and lithium aluminum hydride (0.150 g.) in tetrahydrofuran (50 ml.) was allowed to stand at room temperature for 18 hr. The reaction mixture was worked up as described previously to give 0.080 g., m.p. 182–184°. The product was recrystallized from methanol and had m.p. 183–185°, $[\alpha]_D$ +34°. Its infrared spectrum was identical to that of the product described in method A and showed no depression in an admixture melting point determination.

15β-Hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one (4d).—To a solution of 15β-benzyloxy-3-methoxy-estra-1,3,5(10)-trien-17-one (**4d**, 0.162 g.) in acetic acid (4 ml.) was added 10% palladium–charcoal catalyst (0.100 g.). The resulting mixture was hydrogenated at 28° and 729-mm. pressure for 4 hr. The catalyst was separated by filtration and was washed with methanol. The combined filtrates were evaporated, and the residue obtained was crystallized from acetone–ether to give 0.063 g. of **16**, m.p. 186–188°. A sample for analysis was recrystallized from acetone–petroleum ether and had m.p. 186–188°; λ_{max} 220, 278, and 288 mμ (ε 9000, 2180 and 2000); $[\alpha]_D$ +103°; ν_{max} 3500, 1730, and 1610 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{24}O_3$ (300.38): C, 75.97; H, 8.05. Found: C, 75.06, 75.22; H, 8.25, 7.98.

15β-Cyano-3-methoxyestra-1,3,5(10)-trien-17-one (4e).—To a solution containing **1** (0.200 g.) and water (5 drops) in tetrahydrofuran (7 ml.) was added sodium cyanide (0.500 g.). The mixture was refluxed for 2.5 hr., poured into ice–water, and the resulting precipitate was collected, washed with water, and dried to give 0.200 g. of **4e**, m.p. 131–135°. A sample for analysis was recrystallized three times from ether and had m.p. 154–155°; λ_{max} 222, 278, and 288 mμ (ε 8500, 2000 and 1850); $[\alpha]_D$ +30°; ν_{max} 2240, 1744, and 1615 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{23}O_2N$ (309.39): C, 77.64; H, 7.49; N, 4.53. Found: C, 77.62; H, 7.62; N, 4.62.

17β-Acetoxy-3,15β-dimethoxyestra-1,3,5(10)-triene (6d).—To a solution of 3,15β-dimethoxy-estra-1,3,5(10)-trien-17-one (**4b**, 0.500 g.) in tetrahydrofuran (75 ml.) was added lithium aluminum hydride (0.5 g.) and the mixture was refluxed for 2 hr. The mixture was cooled and the excess reagent was decomposed by the dropwise addition of aqueous tetrahydrofuran. The salts were separated, washed with tetrahydrofuran, and the combined filtrates were evaporated to an oil which failed to crystallize. An infrared spectrum (neat) of the latter was devoid of any carbonyl absorption. Acetylation of the crude reduction product with acetic anhydride (1 ml.) and pyridine (1 ml.) for 1 hr. at 90° gave 0.43 g. of an oil which was shown to be homogeneous by thin layer chromatography. The oil was crystallized from ether–petroleum ether (b.p. 30–60°) and had m.p. 102–104°, $[\alpha]_D$ +10°.

Anal. Calcd. for $C_{22}H_{30}O_4$ (358.46): C, 73.71; H, 8.44. Found: C, 73.20, 73.21; H, 8.64, 8.38.

15β-Cyano-3-methoxyestra-1,3,5(10)-trien-17β-ol (6e).—A solution of 15β-cyano-3-methoxyestra-1,3,5(10)-trien-17-one (**4e**, 2.0 g.) and sodium borohydride (1.8 g.) in tetrahydrofuran–methanol (1:5, 180 ml.) was stirred for 3 hr. at room temperature. The solvents were evaporated, the residue was dissolved in benzene, and the extract washed with saturated saline, dried, and evaporated. One crystallization of the residue from benzene afforded 1.8 g. of **6e**, m.p. 193–195°, $[\alpha]_D$ −28°.

(16) Celite 545 is a trade-mark of the Johns-Manville Corp. for a grade of diatomaceous earth. That used for partition chromatography was washed with 6 *N* hydrochloric acid, water, and methanol, and was dried to constant weight.

(17) Florisil, a trade-mark of the Floridin Company for a synthetic magnesium silicate.

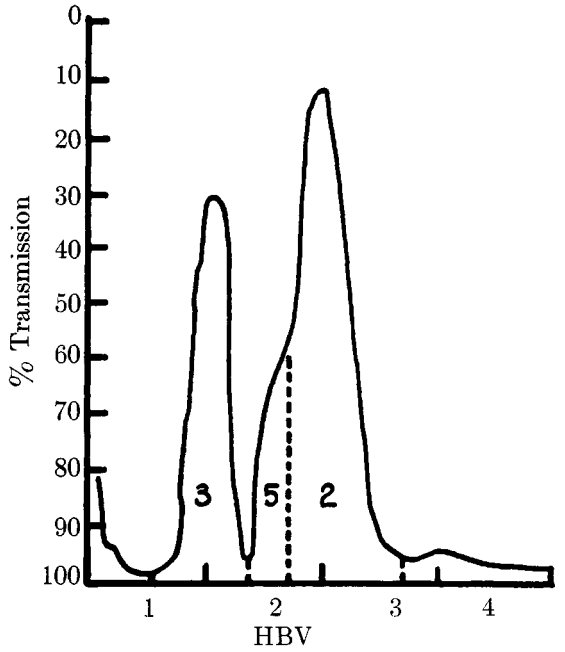


Figure 2

Anal. Calcd. for $C_{20}H_{25}O_2N$ (311.41): C, 77.13; H, 8.09; N, 4.50. Found: C, 76.78; H, 8.10; N, 4.44.

3-Methoxy-15α-carboxamido-estra-1,3,5(10)-trien-17β-ol (8a).—To a solution of benzene-solvated 15β-cyano-3-methoxyestra-1,3,5(10)-trien-17β-ol(**6e**, 0.800 g.) in ethanol (35 ml.) was added potassium hydroxide (2.5 g.) in water (7 ml.) and the solution was heated to reflux for 6 hr. A thin layer chromatographic analysis of the reaction mixture revealed that no hydrolysis had taken place. The ethanol was displaced with 1-propanol and the resulting solution was heated to reflux overnight. The reaction mixture was diluted with ethyl acetate, washed with dilute hydrochloric acid solution and with water, dried, and evaporated to 0.800 g. of a semicrystalline solid which was crystallized once from acetone–water and twice from acetone–petroleum ether to give 0.240 g., m.p. 208–210°, $[\alpha]_D$ +109° (methanol).

Anal. Calcd. for $C_{20}H_{27}O_3N$(329.42): C, 72.92; H, 8.26; N, 4.25. Found: C, 72.43, 72.40; H, 8.41, 8.18; N, 4.40.

A second crop, 0.170 g., m.p. 206–208°, was obtained from the mother liquors.

17β-Hydroxy-3-methoxyestra-1,3,5(10)-trien-15α-carboxylic acid (8b).—To a solution of 15β-cyano-3-methoxyestra-1,3,5(10)-trien-17β-ol(**6e**, 0.900 g.) in 40 ml. of ethylene glycol was added a solution of 3.0 g. of potassium hydroxide in 7 ml. of water. The resulting solution was refluxed for 22 hr., cooled, and acidified with dilute hydrochloric acid solution. The product was collected by filtration, washed with water, and dried to give 0.460 g., m.p. 181–184°. A sample for analysis was crystallized twice from methanol–water and twice from acetone and had m.p. 238–240°, $[\alpha]_D$ +130° (methanol).

Anal. Calcd. for $C_{20}H_{26}O_4$ (330.41): C, 72.70; H, 7.93. Found: C, 72.62; H, 8.15.

Attempted Addition of Methanol to 3-Methoxy-14β-estra-1,3,5(10),15-tetraen-17-one (2).[18]—To a solution of **2** (0.300 g.) in methanol (14 ml.) was added a 5% sodium hydroxide solution (0.7 ml.). The resulting solution was stirred 30 min. at room temperature, diluted with water, and the products were extracted with ethyl acetate. The extract was dried and evaporated to give 0.270 g. of an oil.

A pilot partition column on Celite 545[16] using an *n*-heptane–Methyl Cellosolve solvent system indicated the reaction mixture to contain 28.5% of **3**, 56.5% of **2**, and 15% of an unknown **5** occurring as a shoulder at HBV 1.5–1.8 on the peak corresponding to **2** (Fig. 2) A similar column run on a mixture obtained from a second run which was stirred for 24 hr. indicated the exact composition previously described. The remaining crude products of the two runs were combined (0.570 g.) and partitioned as described previously to give 0.100 g. of **3** and 0.235 g. of **2** (these compounds were identical by comparison of their thin layer chromatograms and their infrared spectra with the specimens described in ref. 18). In a larger run (0.900 g.) that peak corresponding to **5** was repartitioned twice using the same solvent system to give 0.060 g. of impure **5**. The latter was crystallized from methanol to give 0.028 g., m.p. 82–85°; the thin layer chromatogram indicated it to contain *ca.* 10% of **2**. The infrared spectrum of the crystallized sample showed only a 5-membered ring carbonyl maximum at 1725 cm.$^{-1}$ and its n.m.r. spectrum showed two O-methyl maxima at 6.16 (C-3) and 6.63 τ (C-15).

(18) 3-Methoxyestra-1,3,5(10),15-tetraen-17-one (**1**) was isomerized with *p*-toluenesulfonic acid for 15 min. in refluxing benzene according to the procedure of Johnson and Johns.[1] The resulting mixture was partitioned on Celite 545[16] using an *n*-heptane–Methyl Cellosolve solvent system. Holdback volumes 0.5–1.5 gave 3-methoxyestra-1,3,5(10),14-tetraen-17-one (**3**), m.p. 93–94°, $[\alpha]_D$ +293°. A HBV of 1.5–2.2 gave 3-methoxy-14β-estra-1,3,5(10),15-tetraen-17-one (**2**), m.p. 102–103°, $[\alpha]_D$ +477°.

Photodimerization of $\Delta^{4,6}$-Diene-3-keto Steroids

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Photoirradiation of heteroannular dienones such as $\Delta^{4,6}$-androstadien-3-on-17β-ol propionate and related steroids in homogeneous solution leads to formation of a single one of twenty possible dimeric products. This has been assigned the structure IIA or IID on the basis of physical properties and catalytic hydrogenation followed by thermal cleavage and identification of cleavage products. The dimerization can be reversed photochemically; the photostationary state has the composition 31% monomer and 69% dimer.

Although the photochemical reactions of conjugated and cross-conjugated dienones have been of considerable interest in recent years,[1] attention has been concentrated on homoannular systems where molecular rearrangement, valence-bond tautomerization, and ring cleavage are the predominant reaction paths. This paper describes the results obtained on reaction of a heteroannular dienone system where the more familiar photodimerization reaction of conjugated carbonyl compounds[2] is observed, albeit in an unexpected manner.[3]

Solutions of $\Delta^{4,6}$-androstadien-3-on-17β-ol propionate[4] (IA) in benzene–petroleum ether or benzene–

(1) For leading references see J. J. Hurst and G. H. Whitham, *J. Chem. Soc.*, 710 (1963); C. Ganter, E. C. Utzinger, K. Schaffner, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **45**, 2403 (1962); D. H. R. Barton, *ibid.*, **42**, 2604 (1959); P. de Mayo, "Advances in Organic Chemistry," Vol. II, Interscience Publishers, Inc., New York, N. Y., 1960, pp. 367–425.

(2) A. Mustafa, *Chem. Rev.*, **51**, 1 (1952).

(3) After this work was completed, a report appeared [H. C. Throndsen, G. Cainelli, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **45**, 2342 (1962)] describing the determination of structure of the photodimer of $\Delta^{4,6}$-cholestadien-3-one. Our results confirm, by different methods, and extend the conclusions reached in this report.

(4) L. Ruzicka and W. Bosshard, *ibid.*, **20**, 328 (1937). The more convenient chloranil dehydrogenation procedure of E. J. Agnello and G. O. Laubach [*J. Am. Chem. Soc.*, **82**, 4293 (1960)] was used in this work.