17β-acetoxy-6β-hydroxyandrost-4-en-3-one (**8**) (4 mg): mp 202–203.5°; uv max, 237 mμ (ε 19,600); ir (KBr), 3460 (–OH), 1730 (–$OCOCH_3$), 1668 (>C=O), and 1615 cm^{-1} (>C=C<); the nmr spectrum is recorded in Table I; the mass spectrum had a molecular ion peak at *m/e* 346.

The Oxidation of 17β-acetoxy-6β-hydroxyandrost-4-en-3-one (8).—A solution of 17β-acetoxy-6β-hydroxyandrost-4-en-3-one (**8**, 2 mg) in pyridine (0.5 ml) was added to a stirred suspension of chromium trioxide (67 mg) in pyridine (6 ml). The mixture was stirred for 17 hr and poured into sodium bicarbonate solution (25 ml) and extracted with ether (20 ml). The ether extract was washed with 3 *N* sulfuric acid (20 ml), saturated bicarbonate solution (20 ml), and salt solution until neutral. The ether solution was dried (Na_2SO_4) and filtered, and the solvent was evaporated to dryness. Glpc analysis of the product gave a single peak at retention time 29.6 min. The material failed to crystallize but demonstrated the spectral properties consistent with 17β-acetoxyandrost-4-ene-3,6-dione (**9**): uv max, 250 mμ (ε 17,000); ir (CCl_4), 1740 (–$OCOCH_3$), 1710 (>C=O), and 1690 cm^{-1} (>C=O). The product (1.5 mg) was partitioned between 5% sodium hydroxide (5 ml) and ether (5 ml). Glpc analysis indicated the retention of the product in the ether layer.

17β-Acetoxy-6β-acetylandrost-4-en-3-one (5).—A solution of 3,17β-diacetoxyandrosta-3,5-diene (**2**, 1.37 g) in acetic anhydride (20 ml) was treated with boron trifluoride etherate (4.1 ml) at 25° for 4 min, then poured into ice water (200 ml). The aqueous suspension was extracted with ether (100 ml), and the ether solution was washed with sodium bicarbonate solution (100 ml) and then with brine until neutral. The ether solution was dried ($MgSO_4$) and filtered, and the solvent was concentrated under reduced pressure. After cooling, the material was filtered and there was obtained 17β-acetoxy-6β-acetylandrost-4-en-3-one (**5**, 400 mg): mp 162–164°; uv max, 246 mμ (ε 12,000) [lit.[14] mp 165–166°; uv max, 246 mμ (ε 13,000)].

Saponification of Compounds 3 and 6. A.—To a solution of 3,17β-diacetoxy-6-acetylandrosta-3,5-diene (**3**, 20 mg) in methanol (5 ml) was added a saturated solution of sodium acetate (1 ml). The solution was refluxed for 3 hr, and the solvent was removed *in vacuo*. The residue was partitioned between ether (20 ml) and water (20 ml), the organic layer was dried (Na_2SO_4) and filtered, and the solvent was concentrated to dryness. Crystallization from acetone–hexane gave 17β-acetoxy-6β-acetylandrost-4-en-3-one (**5**, 6 mg): mp 151–155°, uv max, 246 mμ (ε 11,900); ir (KBr), 1735 (–$OCOCH_3$), 1712 (>C=O), 1678 (>C=C–C=O), and 1608 cm^{-1} (>C=C<). The ir spectrum was identical with that of an authentic sample. Admixture with authentic material gave a single tlc spot at R_f 0.86 and the mixture melting point was undepressed.

B.—Compound **6** (1 mg) was treated as above. The saponification product **7** had uv max 241 mμ; addition of 5% potassium hydroxide solution caused a bathochromic shift to 425 mμ. Insufficient material was available to characterize the compound further.

1,17β-Diacetoxy-4-methylestra-1,3,5(10)-triene.—To a solution of 17β-hydroxyandrosta-1,4-dien-3-one (1.0 g, mp 167–169°) in carbon tetrachloride (40 ml) and benzene (100 ml) was added a solution of acetic anhydride–70% perchloric acid (10 ml, 49:1). The mixture was stirred at room temperature for 2.5 hr after which the reaction mixture was diluted with ether (100 ml) and washed with two 150-ml portions of sodium bicarbonate solution. The ether layer was washed until neutral with brine and dried (Na_2SO_4). The solution was filtered and the solvent was removed under reduced pressure. Two crystallizations from acetone–hexane gave 1,17β-diacetoxy-4-methylestra-1,3,5(10)-triene (840 mg): mp 139–140° (lit.[31] mp 138.5–139°); uv max, 278 mμ (ε 257); ir (CCl_4), 1759 (>C=C–$OCOCH_3$) and 1740 cm^{-1} (–$OCOCH_3$).

An aliquot of the material was added to the reaction mixture consisting of **2** treated with acetic anhydride–perchloric acid reagent and a new peak was detected by glpc analysis at retention time 8.2 min.

Registry No.—Perchloric acid, 7601-90-3; acetic anhydride, 108-24-7; **1b**, 1045-69-8; **2**, 1778-93-4; **3**, 16853-04-6; **6**, 16803-41-1; **8**, 13096-48-5.

Acknowledgment.—We wish to thank Dr. G. Neville for the nmr spectra and Mr. A. Viau for technical assistance. We are also indebted to Professor P. Morand of the University of Ottawa for the mass spectral determinations.

(31) (a) A. L. Wilds and C. Djerassi, *J. Amer. Chem. Soc.*, **68**, 2125 (1946); (b) C. Djerassi, G. Rosenkranz, J. Romo, J. Pataki, and St. Kaufmann, *ibid.*, **72**, 4540 (1950).

Steroidal C-17 Allene Acetates and Their 17(20)-Unsaturated C-21 Aldehyde Derivatives

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A number of examples of steroid derivatives bearing an acetoxyallene side chain at C-17 have been synthesized. In the case of the 3-acetoxy-5-ene derivatives, both isomeric allenes **2a** and **3a** were isolated and the stereochemistry was established by their unique spectral properties. Hydrolysis of the allenic esters lead to conjugated C-21 aldehydes in high over-all yields.

The allenic structure has proven to be a most intriguing system to the chemist from the standpoint of theoretical interest as well as synthetic challenge. The great span of time from van't Hoff's early prediction of the existence of asymmetry in the system to the successful demonstration of this fact stemmed from the lack of good synthetic methods of preparation and resolution. The past several years has seen the development of new routes of stereospecific syntheses of allenes. These are enumerated in the recent review of allene chemistry by Taylor.[1]

Noting the absence of examples of steroidal allenes, some years ago we embarked on a program directed toward the incorporation of this rather novel system into a representative group of steroids.[2] In this first paper we will describe the preparation of a series of steroidal allenic esters and some of the unsaturated aldehydes derived therefrom. The products under consideration are isomeric with, and in fact derived from, a class of compounds of considerable physiolog-

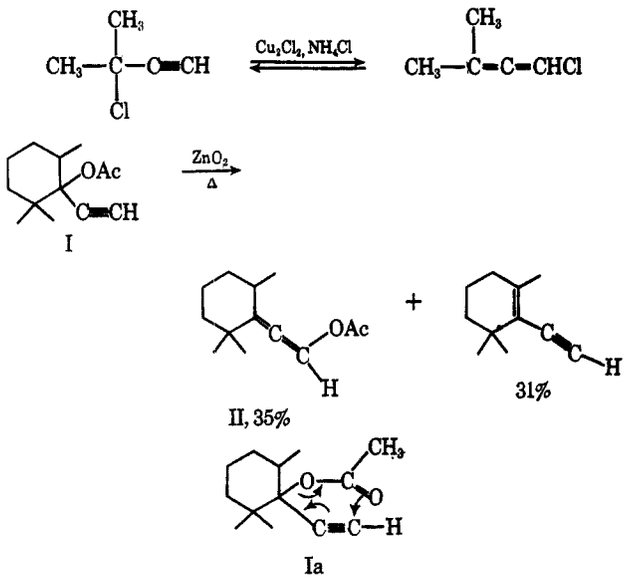
(1) (a) D. W. Taylor, *Chem. Rev.*, **67**, 317 (1967). (b) *Cf.* also the section on cumulenes in H. Fischer, "The Chemistry of Alkenes," S. Patai, Ed., Interscience Publishers, Inc., London, 1964, p 1025.

(2) Since this work has initiated, two papers have appeared describing examples of steroidal allenes: (a) R. Vitali and R. Gardi [*Gazz. Chim. Ital.*, **96**, 1125, 3203 (1966)] have employed the Claisen rearrangement of propargylic enol ethers to introduce the three carbon allenyl group adjacent to a carbonyl function; (b) *cf.* also N. K. Chaudhuri and M. Gut, *J. Amer. Chem. Soc.*, **87**, 3737 (1965).

ical importance, namely, steroidal C-17 ethynylcarbinols.[3] It appeared to us to be an attractive goal to synthesize the isomeric allenic esters in order to compare the biological activities with those of the parent compounds, as well as to study their use as intermediates for subsequent side-chain modifications.

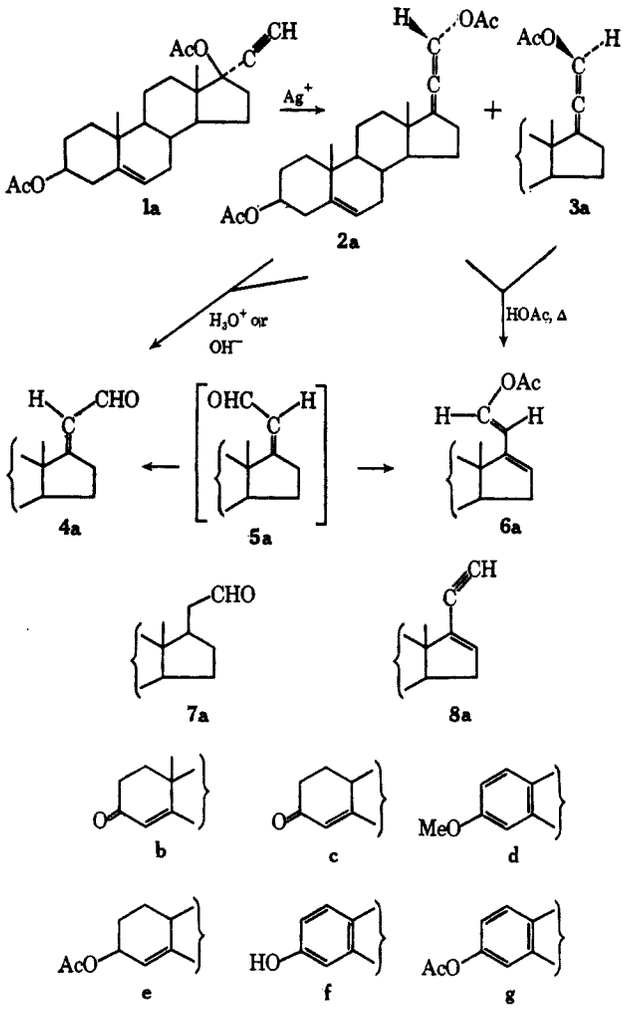
The most straightforward preparative method appeared to be the use of metal salts to catalyze the interconversion of acetylenic halides or esters to their isomeric allenes. Hennion[4] and coworkers in 1950 observed the catalytic influence of cuprous chloride on the equilibrium of a chloroacetylene with its isomeric allene (Scheme I). In 1956, Landor and Landor[5] demonstrated the influence of zinc salts on the acetylenic ester I to give a modest yield of the rearranged acetoxyallene II. Saucy[6] and coworkers at Hoffmann-La Roche found that silver salts were superior to copper and gold salts in catalyzing this latter type of transformation. The products were generally characterized by unique spectral properties and by hydrolysis to unsaturated aldehydes. The question of stereoisomerism of the acetoxyallenes was not considered in these papers. Landor[5] postulated that the migration occurred *via* an internal displacement involving a cyclic transition state such as Ia (Scheme I).

SCHEME I



We have found the silver ion catalyzed rearrangement to be a very facile method of preparing the desired steroidal allenes. Thus, when an acetone solution of 17α-ethynylandrost-5-ene-3β,17β-diol diacetate (**1a**) was maintained at reflux temperature together with about 5 mol % of silver perchlorate over a period of several days, thin layer chromatography (tlc) indicated the gradual disappearance of starting material and formation of two products in equal amounts. Precipitation of the catalyst as silver chloride followed by concentration of the acetone filtrate afforded by direct crystallization 42% of a pure product, **2a** (Scheme II). A second crystalline product, **3a**, having very similar spectral properties and tlc mobility, was isolated by chromatography of the filtrates. That these two products were the isomeric 21α- and 21β-acetoxy-17(20),20-allenes[7] resulting from the expected intramolecular rearrangement was shown by the characteristic 5.04-μ allenic stretching band in the infrared spectrum of each compound. The stereochemistry was established by inspection of the nmr spectra discussed below. Mild alkaline or acid hydrolysis afforded the known unsaturated *trans*-aldehyde **4a**.[8,9] These transformations may be considered as an example of a stepwise Meyer–Schuster rearrangement,[1b] in effect leading to hydration of the ethynyl group at the unsubstituted carbon. This route affords a convenient method for the synthesis of conjugated aldehydes of general structure **4**, generally in higher yields than had been observed by alternate synthetic procedures.[8]

SCHEME II



When the silver catalyzed rearrangement was carried out in boiling acetic acid, the initially formed allenes underwent a double-bond shift to give the 16,20-con-

(3) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp 476, 556, and 591.

(4) G. F. Hennion, J. T. Sheehan, and D. E. Maloney, *J. Amer. Chem. Soc.*, **72**, 3542 (1950).

(5) P. D. Landor and S. R. Landor, *J. Chem. Soc.*, 1015 (1956).

(6) (a) G. Saucy, R. Marbet, H. Lindlar, and O. Isler, *Helv. Chim. Acta*, **42**, 1945 (1959); (b) R. Marbet, *et al.*, U. S. Patent 3,211,780 (1965).

(7) Applying the sequence rule system of nomenclature to the isomeric allenes results in the *R* designation for the 21α-acetoxy compounds (**2**), and *S* for the 21β isomers (**3**). We feel that the conventional Fischer designation for the isomeric allenes is more descriptive to chemists working in this area. *Cf.* R. S. Cahn, *J. Chem. Educ.*, **41**, 116 (1964).

(8) H. Heusser, K. Eichenberger, and Pl. A. Plattner, *Helv. Chim. Acta*, **33**, 1088 (1950).

(9) When the mixture of epimeric allenes was subjected to very brief hydrolytic conditions there was evidence suggesting formation of some of the less stable *cis*-aldehyde **5a** (see Experimental Section).

jugated enol acetate **6**, together with some of the unsaturated aldehyde **4**. The interconversion of aldehyde **4b** and its enol acetate **6b** had been demonstrated by Miescher and coworkers.[10]

Variations in the ring-A portion of the molecule, while not affecting the nature of the acetylene–allene equilibrium, did influence the relative ease of isolation of the isomeric acetoxyallenes. Thus, in the estrane series with an aromatic A ring bearing either a 3-hydroxy (**1f**) or 3-acetoxy group (**1g**), only one of the isomeric allenes was isolated in crystalline form. In each case this proved to be the 21α isomer (**2f** and **2g**), the 21β epimer formed in equal amount remaining in the mother liquors. The 3-methoxy compound (**1d**) upon rearrangement afforded a noncrystalline 1:1 mixture of the isomeric allenes (**2d**:**3d**) which was hydrolyzed in good over-all yield to the *trans*-17(20)-aldehyde **4d**. Similarly the rearrangement of ethisterone acetate (**1b**) gave an equimolar mixture of 21 epimers that could not be separated nor crystallized. On the other hand, the corresponding 19-nor analog **1c** afforded a mixture of epimeric allenes from which the 21β isomer could be crystallized. In each case, however, hydrolysis led to a single crystalline aldehyde verifying the assignments made on the basis of spectral and elemental analyses. Compound **1e** underwent elimination of the 3-acetoxy function leading to an inseparable mixture of products. The 17(20) double bond of **4a** and **4d** could be selectively reduced over palladium on charcoal to give saturated 21-aldehydes **7a** and **7d**, respectively.

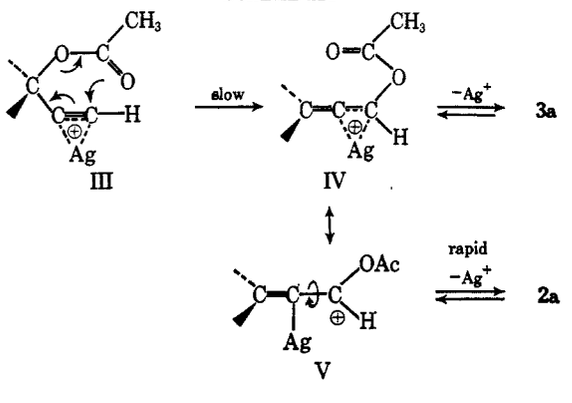
Stereochemistry.—The isolation of both crystalline isomers **2a** and **3a** permitted spectral comparison from which we may confidently make configurational assignments of the allene geometry. By examination of the positions of the C-18 angular methyl proton signals in the nmr spectra we have assigned the 21β-acetoxy configuration to that isomer having a C-18 methyl proton signal at lower field (**3a**, 57 Hz) relative to its isomer (**2a**, 53 Hz). The deshielding influence of a neighboring β-oriented acyloxy function on the C-18 protons is well documented.[11] In each series of compounds studied, the nmr spectrum of the total crude reaction product revealed the two C-18 methyl signals of about equal intensity separated by about 4 Hz, thus permitting the assignment of geometry to the crystalline form ultimately isolated.

The C-21 olefinic proton signal appeared as a triplet (J = 2.5 Hz) showing five-bond coupling with the C-16 protons. The C-21β proton of **2a** was centered at 439 Hz while the isomeric compound, **3a**, showed the C-21 proton signal at 446 Hz.[12] Lowe,[13] extrapolating from the principals of Brewster,[14] has studied the optical rotational properties of a series of allenes of known stereochemistry. He observed an apparent correlation in the sign of optical rotation and the handedness of the screw pattern of polarizability of substituents on the allene chain. In the present set of compounds the uncertainty as to the relative polarizability of the ring-D carbon substituents on the allene side chain reduces the reliability of any configurational assignments made on the basis of the relative signs of rotation of the isomers.

The ORD[15] spectra of the two isomers is noteworthy, generally bearing out the quasi-enantiomeric nature of the pair of compounds. Thus, the 21α-acetoxy compound **2a** has a negative curve with a plateau in the region 220–252 mμ, whereas the 21β-acetoxy compound **3a** shows a strong positive Cotton effect with a peak at 243 mμ.[16]

Any consideration of the mechanism of this silver ion catalyzed rearrangement must account for the apparent lack of stereospecificity. A significant point in this regard is the observation that pure acetoxyallene **2a** (or **3a**) together with 5 mol % of silver perchlorate in acetone, when held at reflux temperature for *24 hr*, equilibrated to an equimolar mixture of the two compounds. This was deduced on the basis of the equivalence of the heights of the C-18 methyl proton resonances relative to the single C-19 signal of the silver-free concentrate. This is in contrast with the several-day reaction period required for the initial rearrangement of the ethynyl ester. We believe the data to be consistent with the mechanism shown in Scheme III.

SCHEME III



Formation of a π complex between silver ion and allenic double bonds has received much less study than the corresponding acetylenic complex formation.[17] Nevertheless, such an intermediate as IV may explain the apparent loss of stereoselectivity of the rearrangement. Thus, a π complex or a bridged ion structure between silver and the acetylenic bond electrons (structure III) would result in increased electrophilicity of the terminal acetylenic carbon resulting in the initial stereospecific 1,3 migration of acetate. The intermediate IV, also bound to silver, may be expected to be in resonance with the symmetrical allyl cation form V. Reversible loss of argentous ion then gives either isomeric allene. Under the reaction conditions employed in this study the rate of equilibration of the products is

(10) K. Miescher, A. Wettstein, and C. Scholz, *Helv. Chim. Acta*, **22**, 892 (1939).

(11) *Cf.* W. R. Benn and R. M. Dodson, *J. Org. Chem.*, **29**, 1142 (1964), and references cited therein.

(12) Since this work was completed, two communications have appeared describing some acyclic, monocyclic, and bicyclic acetoxy allenes prepared by the general procedure described herein: (a) M. Apparu and R. Glenat, *C. R. Acad. Sci., Paris, Ser. C*, **265**, 400 (1967); (b) V. T. Ramakrishnan, K. V. Narayanan, and S. Swaminathan, *Chem. Ind.* (London), 2082 (1967). The nmr data cited by these groups, particularly that of the Indian authors, are entirely consistent with that observed in the present work.

(13) (a) G. Lowe, *Chem. Commun.*, 411 (1965); (b) *cf.* E. L. Eliel, *Tetrahedron Lett.*, No. 8, 16 (1960).

(14) J. H. Brewster, *J. Amer. Chem. Soc.*, **81**, 5475 (1959).

(15) We are indebted to Professor W. Klyne at the University of London, for making the ORD determinations of compounds **2a** and **3a** for us.

(16) *Cf.* S. F. Mason and G. W. Vane, *Tetrahedron Lett.*, 1593 (1965).

(17) Reference 1, p 342. For a recent discussion of the nature of the structure of the analogous mercurinium allene ion, see W. L. Waters and E. F. Kiefer, *J. Amer. Chem. Soc.*, **89**, 6261 (1967). These workers prefer the three-membered σ-bonded mercury bridge structure over the alternate simple polarized π complex.

greater than is the rate of the SNi′ rearrangement. This is analogous to the reaction of optically active ethynyl carbinols with thionyl chloride in which Landor and coworkers[18] observed retention of optical purity in the resulting chloroallene under anhydrous conditions and rapid racemization in the presence of traces of acid.

In light of the success of this reaction system, little attention was given to other catalysts or solvents. It is noteworthy that cuprous ion in either dimethyl sulfoxide or dimethylformamide resulted in loss of acetic acid to give the known enyne **8a**.[19] Landor and coworkers[20] observed an analogous result when chloroallenes were heated in the presence of cuprous cyanide in dimethylformamide suggesting an allene intermediate in the formation of **8a**.

Experimental Section[21]

Rearrangement of 17α-Ethynylandrost-5-ene-3β,17β-diol Diacetate. 5,17(20),20-Pregnatriene-3β,21α-diol Diacetate (2a).—A solution of 19.0 g of 17α-ethynylandrost-5-ene-3β,17β-diol diacetate and 619 mg (6 mol %) of silver perchlorate in 500 ml of dry acetone containing 10 drops of tetramethylguanidine (tmg) was refluxed under nitrogen for 96 hr. At the end of this time thin layer chromatography (tlc) indicated a spot corresponding to only a trace of starting material together with a single slightly less polar spot. The reaction mixture was cooled and 5 ml of saturated ammonium chloride solution was added. After stirring for 15 min the precipitated solids were removed by filtration and the filtrates concentrated to *ca.* two-thirds volume and allowed to cool slowly. From the acetone solution there was obtained by direct crystallization 7.03 g (42%) of the 21α-acetoxyallene (**2a**). Recrystallization from acetone containing a trace of pyridine (py) afforded analytically pure material: mp 199–202°; $[\alpha]_D$ −67.3°; ir (KBr) 3.25, 5.03, 5.76, and 8.05 μ; nmr signals appeared at 53 (18 H), 62.5 (19 H), 121 (3 Ac), 126.5 (21 Ac), 278 (3 H), 324 (6 H), and 439 Hz (t, J = 2.5 Hz, 21β-H).

Anal. Calcd for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 75.47; H, 8.86.

5,17(20),20-Pregnatriene-3β,21β-diol Diacetate (3a).—Concentration of the acetone filtrates above afforded upon cooling 1.5 g of a crystalline material melting at 122–130°. Concentration of the filtrate and chromatography over silica gel afforded more of this material from the fractions eluted by 1% ethyl acetate–benzene (total 23%). Crystallization from ether–petroleum ether (bp 64–68°) yielded pure **3a**: mp 128–131°; $[\alpha]_D$ −11°; ir (KBr) 3.29, 5.05, 5.68, 5.77, 8.05, and 8.20 μ; the nmr spectrum differed from that of the 21α isomer only in the position of the C-18 proton signal at 57 Hz and the 21α-H triplet at 446 Hz (J = 2.5 Hz).

Anal. Calcd for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 75.68; H, 8.60.

The lower melting isomer **3a** was isolated in lower yield than the higher melting material, **2a**. Nevertheless, in other experiments determination of the nmr spectrum on the total crude reaction product indicated equal amounts of the two compounds together with about 10% of the starting material (**1a**). A preliminary attempt to separate the isomers by vpc was unsuccessful.

Equilibration of 5,17(20),20-Pregnatriene-3β,21α-diol Diacetate.—**2a** (1 g) together with 68 mg of silver perchlorate was refluxed in 25 ml of acetone containing 1 drop of tmg for 24 hr. The reaction mixture was cooled, diluted with chloroform, washed with saturated ammonium chloride, dried, and concentrated to a noncrystalline residue. The nmr spectrum of the material was identical with that of a 1:1 mixture of the isomeric allenes **2a** and **3a**.

5,16,20-Pregnatriene-3β,21-diol Diacetate (6a).—A solution of 12.2 g of **1a** and 0.5 g of silver acetate in 250 ml of acetic acid and 100 ml of acetic anhydride was refluxed under nitrogen for 2 hr. The reaction mixture was concentrated under vacuum to one-half volume, poured into 800 ml of water, and then taken up in ether. The ether extract was washed with cold dilute sodium bicarbonate solution, dried over sodium sulfate, and concentrated to an amber gum weighing 11.1 g. This gum was chromatographed on silica and yielded, from the 2% ethyl acetate–benzene fractions, the conjugated enol acetate **6a**. Recrystallization from benzene–cyclohexane gave pure material: mp 145–150°; uv λ_{max} 247.5 mμ (18,650); ir (KBr) 3.21, 5.69, 5.78, 8,00, and 8.26 μ; the nmr spectrum displayed signals at 54.5 (18 H), 63.5 (19 H), 121.5 (3 Ac), 127.5 (21 Ac), 278, 322, 358.5 (d, J = 12.5 Hz, 20 H), and Hz 449 (d, J = 12.5 Hz, 21 H).

Anal. Calcd for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 74.97; H, 8.66.

The enol acetate was further characterized by hydrolysis to the unsaturated aldehyde **4a** (described below) by brief warming with 80% acetic acid. More polar eluates of the above chromatogram also afforded aldehyde **4a**.

***trans*-3β-Acetoxypregna-5,17(20)-dien-21-al (4a).**—A solution of 5 g of 5,17(20),20-pregnatriene-3β,21α-diol diacetate (**2a**) in 100 ml of 80% acetic acid was warmed on the steam bath under nitrogen for 1 hr and then diluted with 500 ml of water. The product was extracted with ether. The ether solution was washed with sodium carbonate solution and dried; the ether was then removed under reduced pressure affording 4.2 g of pale yellow prisms. Recrystallization from ethyl acetate–methylcyclohexane gave aldehyde **4a**: mp 180–185° (lit.[22] mp 184–185°); nmr 57 (18 H), 64 (19 H), 347 (20 H, doublet of triplets, J_{20-21} = 8, J_{20-16} = 2.5 Hz), and 594 Hz (d, J = 8 Hz, CHO).

Treatment of the isomeric allene **3a** or the enol acetate **6a** under these same conditions led to the identical aldehyde **4a**. Alternatively, the entire silver acetate–acetic acid–acetic anhydride reaction solution could be diluted with water such as to result in an 80% acetic acid solution. Warming for 1 hr followed by dilution with water afforded the unsaturated aldehyde **4a** directly in about 70% over-all yield. Hydrolysis of **2a**, **3a**, **6a**, or **4a** under alkaline conditions led to the corresponding 3-hydroxy-aldehyde, mp 181–190°[23] (lit.[22] mp 178–179°). The nmr spectrum showed the expected aldehyde proton doublet at 595 Hz (J = 7.5 Hz). In one experiment acetoxyallene **3a** was warmed in 80% acetic acid for 20 min. The nmr spectrum of the crude crystalline product obtained after work-up indicated the presence of what is believed to be the 17(20)-*cis*-aldehyde **5a**[24] as evidenced by an 18-methyl proton signal at 66 Hz. Attempts to separate the *cis* isomer from the more stable *trans* form were unsuccessful.

21α- and 21β-Acetoxypregna-4,17(20),20-trien-3-one (2b and 3b).—A solution of 8.0 g of 17β-acetoxy-17α-ethynylandrost-4-en-3-one in 150 ml of acetone containing 4 drops of tmg and 358 mg of silver perchlorate was refluxed under nitrogen for 2 days. The reaction mixture was cooled and 2 ml of saturated sodium chloride solution was added and stirred for 15 min. The precipitated solids were filtered off and the filtrates diluted with 300 ml of ether. This solution was then washed with saturated sodium chloride solution, dried over sodium sulfate, and concentrated to 8.0 g of a light yellow glass. This was taken up in benzene and chromatographed on silica gel. The product, eluted by the 2–5% ethyl acetate–benzene eluates, was obtained as a colorless glass consisting of a 1:1 mixture of 21α- and 21β-acetoxyallenes, **2b** and **3b** (36%). The absorption maximum in the ultraviolet spectrum occurred at 240 mμ (15,900); ir ($CHCl_3$) 5.05, 5.72, 6.01, 6.20, 8.10, and 8.18 μ. The nmr

(18) R. J. D. Evans, S. R. Landor, and R. T. Smith, *J. Chem. Soc.*, 1506 (1963); *Cf.* also ref 13b.

(19) E. B. Hershberg, E. P. Oliveto, C. Gerold, and L. Johnson, *J. Amer. Chem. Soc.*, **73**, 5073 (1951).

(20) P. M. Greaves, S. R. Landor, and D. R. J. Laws, *J. Chem. Soc., Sect. C*, 1976 (1966).

(21) Melting points were taken on a Kofler microstage. Rotations were taken in chloroform at about 1% concentration at 26 ± 2° and the ultraviolet spectra were determined in methanol. All spectral and analytical results were carried out under the direction of Dr. R. T. Dillon of the Analytical Department of G. D. Searle & Co. Nmr spectra were determined in deuteriochloroform using a Varian Associates A-60 spectrometer operating at 60 MHz. Resonances are expressed in cycles per second (Hz) in the direction of decreasing field strength relative to an internal tetramethylsilane standard.

(22) H. Heuser, K. Eichenberger, and Pl. A. Plattner, *Helv. Chim. Acta*, **33**, 370 (1950); *cf.* ref 10.

(23) Melting points of the unsaturated aldehydes taken on the micro hot stage tended to be broad, no doubt as a result of the tendency of these compounds to undergo air oxidation at elevated temperatures; *cf.* ref 10.

(24) J. Romo and A. Romo DeVivar, *J. Amer. Chem. Soc.*, **79**, 1118 (1957).

spectrum exhibited 18-methyl proton signals at 55 and 59 Hz of equal amplitude and half the amplitude of the 19 proton signal at 72 Hz; the 20 H resonances appeared at 443 and 446 Hz (t, J = 2.5 Hz). The glass was dried for 3 hr at 80° (0.01 mm).

Anal. Calcd for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 77.73; H, 8.53.

21-Acetoxypregna-4,16,20-trien-3-one (6b) and *trans*-3-Keto-pregna-4,17(20)-dien-21-al (4b).—This reaction was carried out in an identical manner as that described above for the preparation of **6a**. The enol acetate **6b** crystallized directly from a benzene solution of the reaction product: mp 193–200° (lit.[10] mp 192–194°); uv_{max} 244 mμ (32,500).

The unsaturated aldehyde **4b** was obtained by hydrolysis of the enol acetate, either with 80% acetic acid as described above for the preparation of **4a**, or by brief treatment with methanolic sodium bicarbonate at reflux. The over-all yield from **1b** was 74%. The ketoaldehyde was crystallized from ether to give an analytically pure sample: mp 148–150°; uv λ_{max} 242.5 mμ (31,000) (lit.[10] mp 149–152°).

21β-Acetoxy-19-norpregna-4,17(20),20-trien-3-one (3c).—A solution of 10.6 g of 17β-acetoxy-17α-ethynyl-19-norandrost-4-en-3-one and 365 mg (5 mol %) of silver perchlorate in 150 ml of acetone containing 8 drops of tmg was maintained at reflux (nitrogen atmosphere) for 72 hr. The reaction was worked up as described above for the preparation of **2a**. The product was allowed to crystallize from ethyl acetate (2.56 g, 24%), and was then recrystallized from acetone–petroleum ether (py) to give the 21β-acetoxyallene **3c** as cubes: mp 187–190°; $[\alpha]_D$ 144°; uv λ_{max} 238.5 mμ (19,550); ir (KBr) 5.03, 5.69, 5.61, 6.15, 9.91, and 8.06 μ. The nmr resonances appeared at 60.5 (18 H), 128 (Ac), 350 (4 H), and 445 Hz (t, J = 2.5 Hz, 21 H).

Anal. Calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.87; H, 8.24.

Additional quantities of this isomer were obtained by chromatography of the crystallization filtrates on silica gel. The 21α-acetoxyallene **2c**, however, could not be isolated in crystalline form. Its presence in the crude reaction product and in the mother liquors following crystallization of isomer **3c** was established on the basis of the 18-methyl proton signal at 56.5 Hz as well as the characteristic allene absorption band in the infrared spectrum at 5.04 μ. On the basis of the greater deshielding of the 18-methyl protons the crystalline product was assigned the 21β configuration (**3c**) (see discussion).

21-Acetoxy-19-norpregna-4,16,20-trien-3-one (6c).—A solution of 4.9 g of 17β-acetoxy-17α-ethynyl-19-norandrost-4-en-3-one in 100 ml of acetic acid and 50 ml of acetic anhydride together with 200 mg of silver acetate was stirred under nitrogen at reflux temperature for 0.5 hr. The reaction mixture was cooled, decanted from deposited solids, and poured into 2 l. of water. After 1 hr, the suspension was extracted with ether. The organic phase was then washed successively with water, saturated sodium carbonate solution and saturated salt solution. The ether solution was dried, concentrated *in vacuo*, and chromatographed on silica gel. From the fractions eluted by 10–20% ether–benzene was obtained, following recrystallization from aqueous methanol, the conjugated enol acetate **6c** (52%) as rods: mp 122–129°; uv λ_{max} 243 mμ (33,200); ir (KBr) 5.69, 5.96, 6.15, and 8.18 μ.

Anal. Calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.62; H, 8.39.

***trans*-3-Keto-19-norpregna-4,17,(20)-dien-21-al (4c).**—Treatment of enol acetate **6c** or either acetoxyallene **2c** or **3c** with 80% acetic acid as described above resulted in hydrolysis to the unsaturated aldehyde **4c** in 80% yield. Recrystallization from aqueous acetone gave prisms having mp 142–145°; uv λ_{max} 242 mμ (35,500); ir (KBr) 3.59, 5.95, 6.11, and 6.15 μ; nmr 56.6 (18 H), 344 (m, 20 H), 347 (4 H), and 589 Hz (d, J = 8 Hz, CHO)

Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.07; H, 8.76.

21α- and 21β-Acetoxy-19-norpregna-1,3,5(10),17(20),20-pentaen-3-ol 3-Methyl Ether (2d and 3d).—17β-Acetoxy-17α-ethynylestratr-1,3,5(10)-trien-3-ol 3-methyl ether (mestranol acetate, **1d**) was treated with silver perchlorate in acetone as described above. Integration of the nmr signals produced by the 18-methyl and acetate protons indicated the crude product to consist of **2d**, **3d**, and **1d** in the ratio 40:40:20. Passage through a column of silica separated the allene fraction as a pure 1:1 mixture of **2d** and **3d** in the form of colorless glass: $[\alpha]_D$ +25°; ir ($CHCl_3$) 5.05, 5.72, and 8.02 μ. Pertinent features of the nmr spectra consisted of signals of equal intensity at 54.5 and 58.5 Hz attributed to the 18-methyl protons of **2d** and **3d**, respectively. The C-21 proton signals were somewhat obscured by the ring-A aromatic proton signals at 438 to 448 Hz. The glass was dried for analysis for 3 hr at 75° (0.01 mm).

Anal. Calcd for $C_{23}H_{28}O_3$: C, 78.37; H, 8.01. Found: C, 78.44; H, 8.10.

***trans*-3-Methoxy-19-norpregna-1,3,5(10),17(20)-tetraen-21-al (4d). Alkaline Hydrolysis.**—A solution of 16.7 g of an equimolar isomeric mixture of **2d** and **3d** in 300 ml of methanol containing 15 ml of saturated sodium bicarbonate solution was refluxed under nitrogen for 45 min. Tlc at this time indicated no starting material. The product began to crystallize spontaneously from the reaction mixture. Cooling afforded 10.8 g of material having mp 170–172°, and a second crop of 0.55 g, mp 169–172° (77% from **1d**). The analytical sample was recrystallized from acetone–hexane and had mp 175–177°; $[\alpha]_D$ +63.5°; uv λ_{max} 234–242 mμ (20,900), λ_{inf} 276 and 285 mμ; ir (KBr) 3.63, 5.98, and 6.10 μ; nmr 54.5 (18 H), 227 (OCH_3), 348.5 (d of t, J = 8 and 2.5 Hz, 20 H), 399, 418 (q, aromatic), and 595 Hz (d, J = 8 Hz, CHO).

Anal. Calcd for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 81.19; H, 8.39.

The *trans*-unsaturated aldehyde **4d** could also be obtained by acid hydrolysis using 80% acetic acid as described above.

19-Norpregna-1,3,5(10),17(20),20-pentaene-3,21α-diol Acetate (2f).—Treatment of 15.6 g of the 17-monoacetate of 17α-ethynylestradiol (**1f**) under the conditions described above for the corresponding 3-methyl ether (**1d**) resulted in the isolation from ether of 7.1 g of crystalline material. Recrystallization from acetone and from ethyl acetate gave pure 21α-acetoxyallene **2f** as needles: mp 206–208° dec (sample inserted at 200°); $[\alpha]_D$ −6°; ir (KBr) 2.92, 3.24, 5.01, and 5.81 μ; nmr 54 (18 H), 127 and 438 Hz (t, J = 2.5 Hz, 21 H).

Anal. Calcd for $C_{22}H_{26}O_3$: C, 78.07; H, 7.74. Found: C, 78.26; H, 7.76.

Examination of the nmr spectrum of the residues from the isolation of the 21α-acetoxyallene (above) showed a signal at 57.5 Hz attributed to the 18-methyl proton resonance of the isomeric 21β acetate **3f**. Attempts to isolate this compound in pure form were unsuccessful.

***trans*-3-Hydroxy-19-norpregna-1,3,5(10),17(20)-tetraen-21-al (4f).**—Alkaline hydrolysis of either the pure 21α-acetoxyallene **2f** or a mixture of the two isomers **2f** and **3f** by sodium bicarbonate methanol treatment as described in the preparation of aldehyde **4d** led to the corresponding 3-hydroxy compound, **4f**. Purification by recrystallization from acetone–methylcyclohexane gave prisms: mp 243–248° dec (inserted at 240°); ir (KBr), 3.05, 6.05, 6.31 μ; nmr (pyridine) 46, 352 (d of t, J = 8, 2.5 Hz, 20 H) and 599 Hz (d, J = 8, CHO).

Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.25; H, 8.11.

19-Norpregna-1,3,5(10),17(20)-pentaene-3,21α-diol Diacetate (2g).—Subjecting 16.5 g of 17α-ethynylestradiol diacetate (**1g**) to the silver perchlorate rearrangement conditions as described above gave, upon work-up, 12.26 g of a crystalline mixture of acetoxyallenes. Crystallization from acetone–hexane afforded one pure isomer, the 21α-acetoxy compound **2g** in 27% yield. A sample crystallized from ethyl acetate (py) as platelets: mp 145–148°; $[\alpha]_D$ −12.5°; ir (KBr) 3.23, 5.03, 5.68, and 8.09 μ; nmr 54 (18 H), 127.5 (21 Ac), 136 (3 Ac), and 440.5 Hz (m, 21 H, partly obscured by aromatic proton signals).

Anal. Calcd for $C_{24}H_{28}O_4$: C, 75.76; H, 7.42. Found: C, 75.90; H, 7.52.

Attempts to isolate the 21β isomer were unsuccessful. Impure samples of this material displayed 18-methyl proton resonance in the nmr at 58 Hz in a manner consistent with the other examples studied. Hydrolysis of the mixture of allene diacetates **2g** and **3g** under the alkaline conditions described above led to the same 3-hydroxy aldehyde **4f** in 70% over-all yield.

3β-Acetoxypregn-5-en-21-al (7a).[25]—A solution of 9.4 g of **4a** in 1 l. of ethanol was shaken in an atmosphere of hydrogen together with 3 g of 5% palladium on calcium carbonate at room temperature for 3.5 hr. Removal of the catalyst and recrystallization from acetone–petroleum ether afforded the product **7a** in 80% yield: mp 141–144°; ir (KBr) 3.66, 5.78, and 8.06 μ.

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.85; H, 9.64.

(25) We are indebted to Dr. Robert Garland of these laboratories for the preparation of this compound.

3-Methoxy-19-norpregna-1,3,5(10)-trien-21-al (7d).—Unsaturated aldehyde **4d** (2 g) was shaken with 0.2 g of 5% palladium on charcoal in 600 ml of ethanol in an atmosphere of hydrogen at room temperature for 1 hr. Concentration of the filtrates following removal of catalyst and recrystallization from benzene–methylcyclohexane afforded pure **7d** in 75% yield: mp 110–112.5°; $[\alpha]D$ +69°; ir (KBr) 3.65, 5.79 μ; nmr 38 (18 H), and 590 Hz (t, J = 2.5 Hz, CHO).

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.49; H, 9.18.

Catalytic Effect of Cuprous Ion.—When **1a** was refluxed with 10 mol % of cuprous cyanide in dimethylformamide for 2 hr and the reaction mixture concentrated and chromatographed over silica, the only crystalline product isolated was 17-ethynylandrosta-5,16-dien-3β-ol acetate, **8a**: mp 174–176°; $[\alpha]D$ −68° {lit.[19] mp 174°, $[\alpha]D$ −64.2° (di)}.

Registry No.—**2a**, 16934-40-0; **2b**, 16934-41-1; **2d**, 16934-42-2; **2f**, 16934-43-3; **2g**, 16960-05-7; **3a**, 16934-44-4; **3b**, 16934-45-5; **3c**, 16934-46-6; **3d**, 16934-47-7; **4a**, 16934-48-8; **4c**, 16934-49-9; **4d**, 16934-50-2; **4f**, 16934-51-3; **6a**, 16934-52-4; **6c**, 16934-53-5; **7a**, 16934-54-6; **7d**, 16934-55-7.

Carbon 1–Carbon 11 Interactions in Some Oxygenated 5β-Pregnanes and Androstanes[1]

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5β-Androstane-1,3,11,17-tetrone (**3**), 5β-androstane-1,3,17-trione (**6**), 5α-androstane-1,3,17-trione, and 25α_F-5α-spirostane-1,3-dione have been compared with regard to degree of enolization in methanol and dioxane solution and in KBr dispersion. In contrast to the normal behavior of the 11-deoxy-β diketones, the 11-keto-β diketone **3** is but half-enolized even in methanol solution, and is largely or wholly ketonized in less polar solvents. From an examination of the ratio of the enol methyl ethers prepared from each β diketone, it was shown that the tetrone **3** enolizes chiefly to the 1-hydroxy form **7**. Additional examples of 1,11 interaction include the observations that the two 1,11 diketones **26** and **28** are resistant to metal hydride or catalytic reduction, and that the chromic anhydride–pyridine oxidation of 5β-androstane- or 5β-pregnane-1β,3α-diols in the 11-deoxy series furnishes only the 1-keto-3α-ols, whereas similar oxidation of the corresponding 11-keto-1β,3α-diols also affords appreciable amounts of the 3-keto-1β-ols. These results are variously attributed to conformational distortion, hydrogen bonding, or polarization of keto groups.

In an earlier publication[2] we described the isolation from urine of 1β,3α,17α,20β,21-pentahydroxy-5β-pregnan-11-one (**1**, Scheme I) following the administration of 3α,17α,20β,21-tetrahydroxy-5β-pregnan-11-one (β-cortolone, a known metabolite of cortisol in man) to the senior author. The position of the metabolically introduced hydroxyl group in **1** was established by degrading it to the known 5β-androst-1-ene-3,11,17-trione; its configuration was determined primarily from the nuclear magnetic resonance (nmr) spectrum of a second degradation product, namely 1β-hydroxy-3α-acetoxy-5β-androstane-11,17-dione. In this paper the preparation of additional derivatives and degradation products of this metabolite, the partial synthesis of some related steroids, and evidence for the occurrence of various types of 1,11 interaction among certain of these compounds are described.

Oxidative cleavage of the side chain of **1** with sodium periodate[2] followed by further oxidation of the 17-keto steroid **2** thus obtained by Jones' method[3] gave the β diketone, 5β-androstane-1,3,11,17-tetrone (**3**). This product crystallized readily, analyzed correctly, and was chromatographically homogeneous, but its extinction coefficient in methanol (ϵ 6400 at 256 mμ) was only about half the value for the corresponding 11-deoxy-β diketone, namely 5β-androstane-1,3,17-trione [**6**, Scheme I, λ_{max} 258 mμ (ϵ 12,650)].[4] The latter was prepared from **1** *via* **4** and **5** by the sequence outlined in Scheme I.[2]

In view of this observation, we examined in detail the ultraviolet (uv) and infrared (ir) spectra of the tetrone **3** and the trione **6** as well as two β diketones in the 5α series.[5] Table I gives the λ_{max} values and extinction coefficients (ϵ) of these β diketones in neutral and alkaline methanol and in dioxane solution, and their principal bands in the infrared region. The tetrone **3**, which is highly enolized in alkaline methanol, is, like 5α-cholestane-1,3-dione and 25α_F-5α-spirostane-1,3-dione, largely ketonized in dioxane solution and wholly so in KBr dispersion. In contrast, the trione **6** and its 5 epimer are as fully enolized in dioxane solution and in KBr dispersion as they are in methanol.

Tamm and Albrecht[6] attributed the unusual stability of the keto form of 5α-cholestane-1,3-dione in KBr dis-

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(2) J. J. Schneider and N. S. Bhacca, *J. Biol. Chem.*, **241**, 5313 (1966).

(3) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(4) Professor Ch. Tamm and his associates have prepared a number of 11-deoxy-1,3-diketo-5β steroids derived from sapogenins and cardenolides as well as members of the androstane and pregnane series. Their extinction coefficients at 256–257 mμ in ethanol ranged from 15,500 to 15,900 with a mean value of 15,700. We wish to thank Professor Tamm for supplying us with these data prior to publication as well as for samples of 5α-cholestane-1,3-dione and the enol methyl ethers derived from it.

(5) 5α-Androstane-1,3,17-trione was prepared from 5α-androstan-3β-ol-17-one (isoandrosterone) and 25α_F-5α-spirostane-1,3-dione from ruscogenin (see Experimental Section).

(6) Ch. Tamm and R. Albrecht, *Helv. Chim. Acta*, **43**, 768 (1960).