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The C-16 Halides of Estrone Methyl Ester

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Epimeric forms of four C-16 halides of estrone methyl ether are reported. Chemical reactions are presented which include proof of structure, isomerization, interconversion and reduction. Two C-17 halides of 16-estrone methyl ether are similarly discussed.

Noteworthy and often valuable alterations of clinical activity accompany the exchange of halogen for hydrogen at various points in the steroid nucleus. Progestational, cortical, and androgenic-anabolic steroids have received most attention in structure-activity studies.[1] Our interest in halogenated estrone derivatives was prompted by the possibility that we could retain the favorable lipid-shifting activity of this hormone while depressing its characteristic feminizing activity to the point that a useful clinical agent would evolve. Biological and clinical tests have been encouraging and have been published.[2] We wish to present the experimental work and additional compounds necessarily omitted from our earlier communication.

Direct halogenation of androstan-17-ones leads to substitution at C-16.[3] The necessary reaction conditions, however, may induce concomittant ring-A substitution of estrone derivatives.[4] We therefore chose to extend the use of 17-enol acetates to the synthesis of a variety of halides. This route has been used to prepare 16-bromoestratrienes[5,6] and androstanes[7,8,9] where in each example only the 16α-bromide was formed.

Our experience accords with the literature in that enol acetate bromination produced only 16α-bromo ketones. However, chlorination of IIa yielded, besides IIIf, 3.7% of IV, illustrative of 16β-substitution. The structure was assigned on the basis of analytical and spectral data, the assumption of *trans* halogen addition to a double bond and acid hydrolysis to the 16β-chloro ketone, Vc. The latter occurred under conditions which do not epimerize 16α-chloro ketones. The stability of IV is undoubtedly due to its structure in which the 17β-acetoxyl is shielded by adjacent β-methyl and β-chlorine substituents. This structure arises through β-attack of chloronium ion at C-16, leading to a *trans* adduct. Similar intermediates to the 16α-chloro ketone, initiated by the favored rearside of α route of attack, are presumably unstable and decomposed as formed or during extraction.

Also, from the reaction of IIa with *N*-iodosuccinimide, we isolated both 16α- and 16β-iodides, IIId and Va. Direct iodination, with or without mercuric acetate catalysis, gave the 16α-isomer. Inferential evidence for structure of the 16α-iodide was derived from analogy between its formation and that of the favored 16α-chlorides and 16α-bromides, *i.e.*, by "attack from the rear," and by its position in the molecular rotation sequence of the haloketones, (see the following paragraph). The 16β-iodide Va received its formulation from the latter criterion.

Two epimeric fluoroketones were prepared, the 16β-isomer Vd by silver fluoride displacement of the 16α-iodide IIId, and the 16α-fluoride[10] by electrophilic attack at C-16 with perchloryl fluoride. Presumptive evidence for the configurations assigned is based on the following considerations: fluoride displacement of 16α-iodide could reasonably occur with inversion while attack of the perchloryl fluoride reagent at an unsubstituted 16 carbon atom "from the rear" would be the favored assumption; either epimer, on treatment with alkali, yielded the same mixture of the two as characterized by infrared absorption; molecular rotatory dispersion curves (Table I) show Δa values in accord with the structures assigned and with the known "opposite" behavior of α-fluoro ketones (*cf.* reference, footnote 28); the molecular

(1) (a) G. Pincus, *Vitamins and Hormones*, New York, Academic Press, 1959, p. 307; (b) L. H. Sarett, *Annals of the New York Academy of Sciences*, **82**, 802 (1959).

(2) (a) G. P. Mueller, W. F. Johns, D. L. Cook, and R. A. Edgren, *J. Am. Chem. Soc.*, **80**, 1769 (1958); (b) A. U. Rivin, *Metabolism*, **8**, 704 (1959); (c) V. A. Drill, D. L. Cook, and R. A. Edgren, *Hormones and Atherosclerosis*, New York, Academic Press, Inc., 1959, p. 247; (d) H. Spencer, B. Kabakow, J. Samachson, and D. Laszlo, *J. Endocrinol. and Metabolism*, **19**, 1581 (1959); (e) G. Annoni, *Minerva med.*, **50**, 3084 (1959).

(3) J. Fajkos, *Coll. Czech. Chem. Comm.*, **20**, 312 (1955).

(4) R. B. Woodward, *J. Am. Chem. Soc.*, **62**, 1625 (1940).

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

(6) J. Fishman and W. R. Biggerstaff, *J. Org. Chem.*, **23**, 1190 (1958).

(7) R. Pappo, B. M. Bloom, and W. S. Johnson, *J. Am. Chem. Soc.*, **78**, 6347 (1956).

(8) J. Fajkos and F. Sorm, *Coll. Czech. Chem. Comm.*, **24**, 766 (1959).

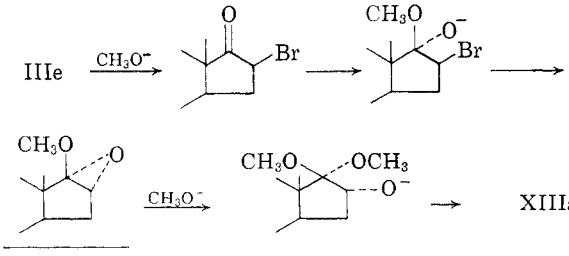
(9) C. W. Shoppee, R. H. Jenkins, and G. H. R. Summers, *J. Chem. Soc.*, 3048 (1958).

(10) Synthesis and equilibration of this compound was part of an independent study by our colleague, Dr. Arthur Goldkamp. He has graciously permitted us to describe the compound: it melted at 155.5–164.5°, $[\alpha]_D$ + 176.5°; $\nu_{max}^{CHCl_3}$ 1760 cm.$^{-1}$

rotation of each falls respectively in the straight-line relationships of the 16α- and 16β-halides, as explained below, where again the "opposite" effect of α-fluorine contributes to this interesting linear progression of molecular rotations.

Epimerization of 16α-bromide IIIe to 16β-bromide Vb in methanolic sulfuric acid led to a mixture containing about 62% of the latter, a result similar to those recently published.[11] Epimerization also resulted from treatment of the 16α-bromide at room temperature with lithium bromide in dimethylformamide. Inversion accompanied by exchange occurred when IIIe was treated instead with lithium chloride, and the 16β-chloride Vc was conveniently obtained. The latter could also be prepared by isomerizing the 16α-chloride with alkaline alumina in benzene.[12] The 16α-chloride, however, was not epimerized in the presence of lithium chloride.

Attempts to effect epimerization of IIIe with alkali led to loss of bromide. Following this approach, treatment of the 16α-bromo ketone with sodium methoxide in methanol generated the dimethylketal XIIIa. Its structure was suggested by analysis and by acid hydrolysis, which gave rise to the ketol XIVa, identical with an authentic sample.[13] Previous work with ring-D ketols[14] showed acid hydrolysis of a 16β-hydroxy-17-ketone to proceed with rearrangement to a 17β-hydroxy-16-ketone, whereas a system involving the 16α-hydroxy-17-ketone is stable. This provided strong presumptive evidence in favor of formulation XIIIa. However, in order to establish the presence of 16-hydroxyl in the latter and to preclude rearrangement of some other structure to the acid-stable XIVa, the tosylate XIIIb was prepared, hydrolyzed to XIVb and treated with lithium chloride, generating the 16β-chloro ketone Vc. With the structure XIIIa established in two ways, we were led to the following mechanism which, despite obvious objections, logically explains the experimental results:



As illustrated previously,[15] epoxide formation has supervened here where Faworskii rearrangement was precluded. Moreover opening of the epoxide intermediate was assumed to proceed at C-17 with inversion.[16] Finally, similar behavior of α-halocyclohexanones has been noted, although the configuration of the products was not completely defined.[17]

Reduction of the α-halo ketones IIIe and IIIf with lithium aluminum hydride produced a mixture of *cis*- and *trans*-halohydrins VII and VIII whose structures were confirmed by standard methods.[3,8,9,11,18] Thus, the bromo ketone yielded *cis*-bromohydrin VIIa which was oxidized again to the parent bromo ketone IIIe, converted with alkali to estrone methyl ether, Ia, and reduced with zinc to the olefin X; the *trans*-bromohydrin VIIIa also formed was reoxidized to IIIe and converted with alkali to the 16β,17β-epoxide IX. A similar sequence of reactions was applied to the bromohydrins VIIb and VIIIb, prepared but not isolated by Fishman and Biggerstaff,[6] as well as the chlorohydrins, VIIc and VIIIc.

Lithium aluminum hydride reduction of 16β-chloro ketone Vc gave VI, a *cis*-chlorohydrin that could be reoxidized to Vc or converted with alkali into estrone methyl ether Ia. No *trans*-chlorohydrin was found in the reduction products.

Both *cis*- and *trans*-bromohydrins have been shown to undergo elimination with zinc in acetic acid[19] and by such treatment the crude mixture of bromohydrins VIIa and VIIIa obtained by reduction was converted in good yield to the olefin X.[9,13] Conversion of the latter to the 16α,17α-epoxide[13] XI and treatment with hydrochloric acid afforded the *trans*-chlorohydrin XII, which was oxidized to Vc.

The singular conversion of 16α-bromoandrostan-17β-ol by alkali exclusively to androstan-17-one[9] has been challenged by Fajkos[11] on the basis of his own androstane work and is also contrary to our experience in the methoxyestratriene series. The *trans*-bromohydrin VIIIa is the more difficultly isolable product of reduction and must be purified; however, alkaline treatment of it produced 3-methoxy-16β,17β-epoxyestra-1,3,5(10)-triene, IX, in good yield.

Fajkos had obtained 3β-acetoxy-17α-bromoan-

(11) J. Fajkos, *J. Chem. Soc.*, 3966 (1959). For additional infrared data see M. Horak and J. Fajkos, *Coll. Czech. Chem. Comm.*, **24**, 1515 (1959).

(12) *Cf.* J. Fajkos, *Coll. Czech. Chem. Comm.*, **23**, 1559 (1958).

(13) We wish to acknowledge with thanks the cooperation of Dr. D. A. Tyner, G. D. Searle & Co., in providing us with physical data and samples of compounds from his own investigations.

(14) W. S. Johnson, B. Gastambide, and R. Pappo, *J. Am. Chem. Soc.*, **79**, 199 (1957).

(15) *Cf.* R. B. Loftfield, *J. Am. Chem. Soc.*, **73**, 4707 (1951).

(16) *Cf. Ionic Organic Reactions*, E. R. Alexander, John Wiley & Sons, Inc., New York, N. Y., 1950, p. 219; C. L. Stevens and T. H. Coffield, *J. Am. Chem. Soc.*, **80**, 1919 (1958); *J. Org. Chem.*, **23**, 336 (1958).

(17) C. L. Stevens, J. J. Beereboom, Jr., and K. G. Rutherford, *J. Am. Chem. Soc.*, **77**, 4590 (1955); C. L. Stevens and A. J. Weinheimer, *J. Am. Chem. Soc.*, **80**, 4072 (1958); D. A. Prins and C. W. Shoppee, *J. Chem. Soc.*, 494 (1946).

(18) B. Ellis, D. Patel, and V. Petrow, *J. Chem. Soc.*, 800 (1958).

(19) L. F. Fieser and R. Ettorre, *J. Am. Chem. Soc.*, **75**, 1700 (1953).

TABLE I

3-Methoxyestra-1,3,5(10)-triene	Rotation Differences				Rotatory Dispersions					
	$[\alpha]_D$	M_D	$\Delta(\beta-\alpha)$	Δ(Halogen-H)	ϕPeak	λ (mμ)	ϕTrough	λ (mμ)	Amplitude ($10^{-2}a$)	$10^{-2}\Delta a$[a]
17-one	+157	+446			+ 6900	315			+142	
16α-fluoro-17-one	+177	+534	− 59	+ 88	+13200	338	−10550	292	+238	+100
16β-fluoro-17-one	+157	+475		+ 29	+ 5860	338	− 3320	295	+ 92	− 50
16α-chloro-17-one	+161	+512	0	+ 66	+ 7650	330	− 4840[c]	290	+125	− 20
16β-chloro-17-one	+161	+512		+ 66	+ 9570	340	− 7170	295	+167	+ 30
16α-bromo-17-one	+127	+461	+134	+ 15	+ 5450	335	− 5400[c]	287	+109	− 30
16β-bromo-17-one	+164	+595		+149	+ 8450	340	− 5750	300	+142	0
16α-iodo-17-one	+ 89	+366	+350	− 80	+ 7540	348	− 5870	300	+134	− 10
16β-iodo-17-one	+175	+716		+270	+ 7650	348	− 5740	305	+134	− 10
16-one	−103	−293					−10800	312	−260	
17α-chloro-16-one	− 49	−156	−154	+137	+6320[c]	295	− 5170	340	−115	+150
17β-chloro-16-one	− 92	−310		− 17	+5470[c]	290	−10500	318	−160	+100
17α-bromo-16-one	− 5	− 18	−345	+275	+2060[c]	305	− 2200	342	− 43	+220
17β-bromo-16-one	−100	−363		− 70	+9750[c]	290	− 8900	322	−187	+ 70
17α-hydroxy[b]	+ 60	+172								
16α-chloro-17α-hydroxy	+ 68	+218	−64	+ 46						
16β-chloro-17α-hydroxy	+ 48	+154		− 18						
16α-bromo-17α-hydroxy	+ 75	+274		+102						
17β-hydroxy[d]	+ 77	+222								
16α-chloro-17β-hydroxy	+ 69	+222	0	0						
16β-chloro-17β-hydroxy	+ 69	+222		0						
16α-bromo-17β-hydroxy	+ 79	+288		+ 66						
16α-hydroxy	+ 80	+228								
16α-hydroxy-17α-bromo	+ 8	+ 29		−199						
16β-hydroxy[a]	+ 70	+199								
16β-hydroxy-17β-bromo	+ 70	+256		+ 57						

[a] Δa is the difference in amplitude from the unsubstituted 16- or 17-ketone (the androstanes were used for reference because aromatic absorption of the parent estratrienes obscured ketone absorption at second extremum); it may be regarded as the contribution of the halogen atom. Values are rounded off to the nearest 10 units. [b] See footnote 13. [c] The second extremum was not reached; the true amplitude may therefore be greater than that stated. The Δa value in each case would be subject to change, accordingly. [d] A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.*, **75**, 5366 (1953).

drostan-16β-ol from 3β-acetoxy-16β,17β-epoxyandrostane.[20] We extended these studies with epoxide IX. Ring opening with hydrobromic acid yielded the *trans*-bromohydrin XVa as an oil containing about 20% of VIIIa, as shown by oxidation of the mixture of bromohydrins followed by fractional crystallization or chromatography to separate 17α-bromo ketone XVIa from the contaminating 16α-bromo ketone IIIe. The 17α-chloro ketone XVIb prepared in a similar sequence from IX and hydrochloric acid.

Lithium aluminum hydride reduction of the new 17α-bromo ketone yielded the *cis*-bromohydrin XVIII which could be reoxidized to the original bromoketone. The *cis* configuration of the bromohydrin was evident from its conversion in alkali to the ketone XIX, and the α,α-orientation of the substituents was confirmed by hydrogenolysis to 3-methoxyestra-1,3,5(10)-trien-16α-ol.

Acid-catalyzed epimerization[21] of XVIa and XVIb afforded the 17β-isomers XXa and XXb. The structure of the 17β-bromide was confirmed by hydride reduction to a new bromohydrin XXI, of *cis* configuration by infrared criteria (see below) and conversion to the C-16 ketone, which was in turn converted into 3-methoxyestra-1,3,5(10),-16-tetraene, X, by reduction with zinc.

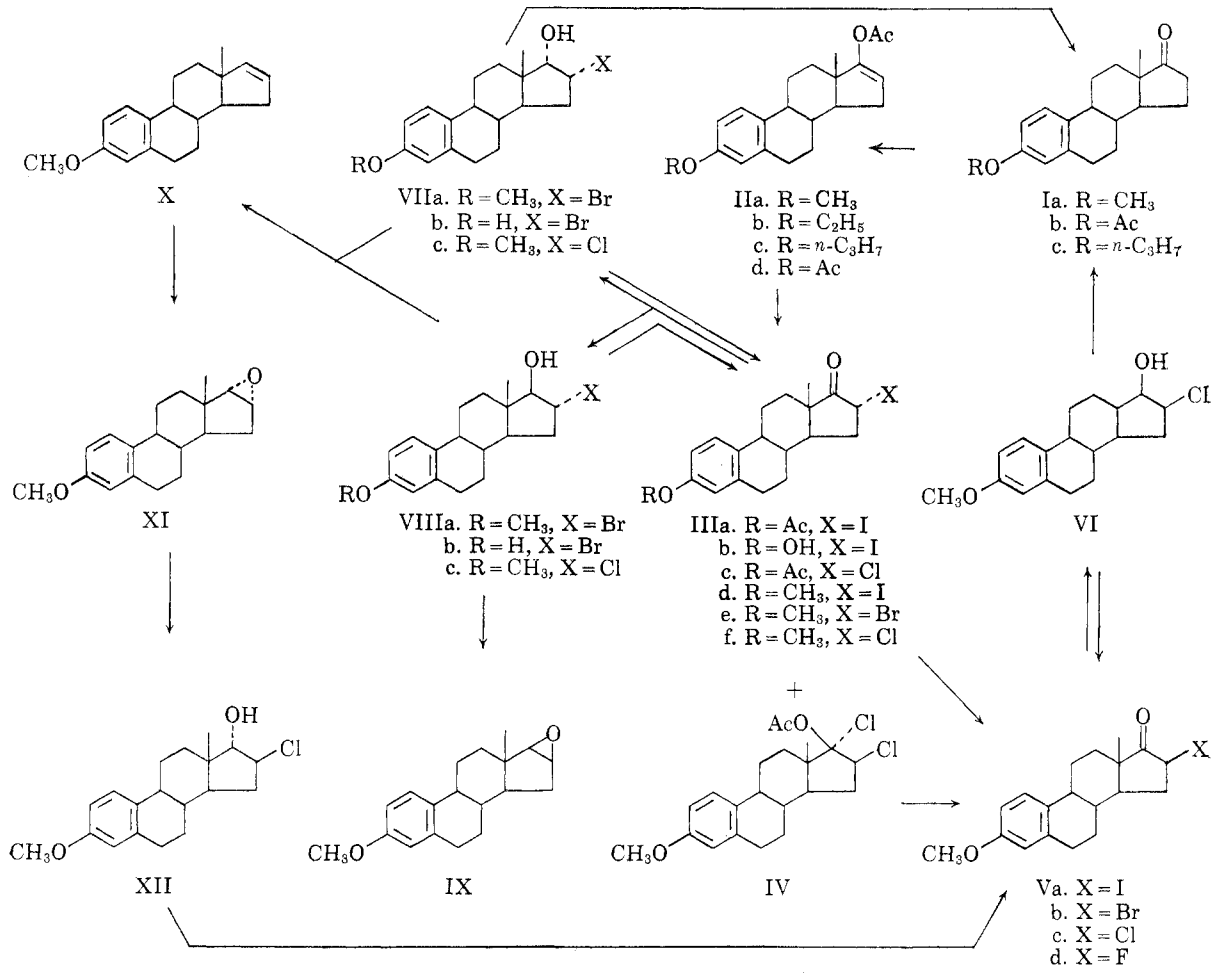
16,16-Dibromo ketones have been prepared through direct halogenation of saturated C-17 ketones.[3] We were unsuccessful, however, in obtaining dihalides through enol acetylation of the monohalo ketones. For example, enol-acetylating conditions applied for periods as long as sixty-four hours to 16α- and 16β-chloro ketones, IIIf and Vc, or the 16α-bromo ketone IIIe yielded only starting materials.[22]

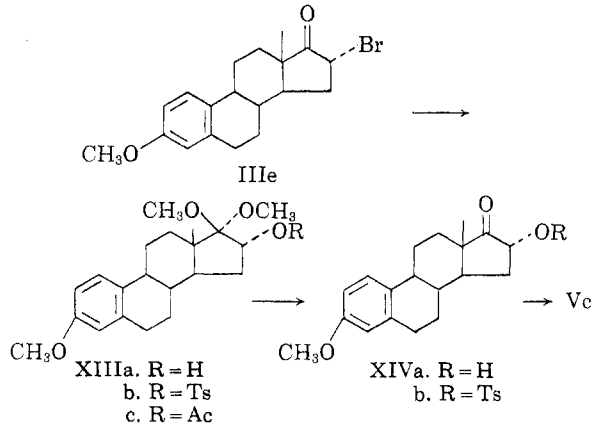
Infrared spectra were recorded routinely, using a sodium-chloride prism, with no attempt at high resolution analysis. Bands of principal interest are recorded here. Within our limits of accuracy and in agreement with Shoppee's observations,[9] there were no apparent shifts in carbonyl maxima as between 16α- and 16β-isomers, III and V, in any

(20) J. Fajkos, *Coll. Czech. Chem. Comm.*, **20**, 1478 (1955).

(21) *Cf.* J. Fishman, Abstracts Organic Section, American Chemical Society, Cleveland, Ohio, April 5, 1960, p. 84-O.

(22) Enol acetates of α-halocyclohexanones have been prepared by treatment in the cold with sodium methoxide followed by acetyl chloride. *Cf.* K. G. Rutherford and C. L. Stevens, *J. Am. Chem. Soc.*, **77**, 3278 (1955).



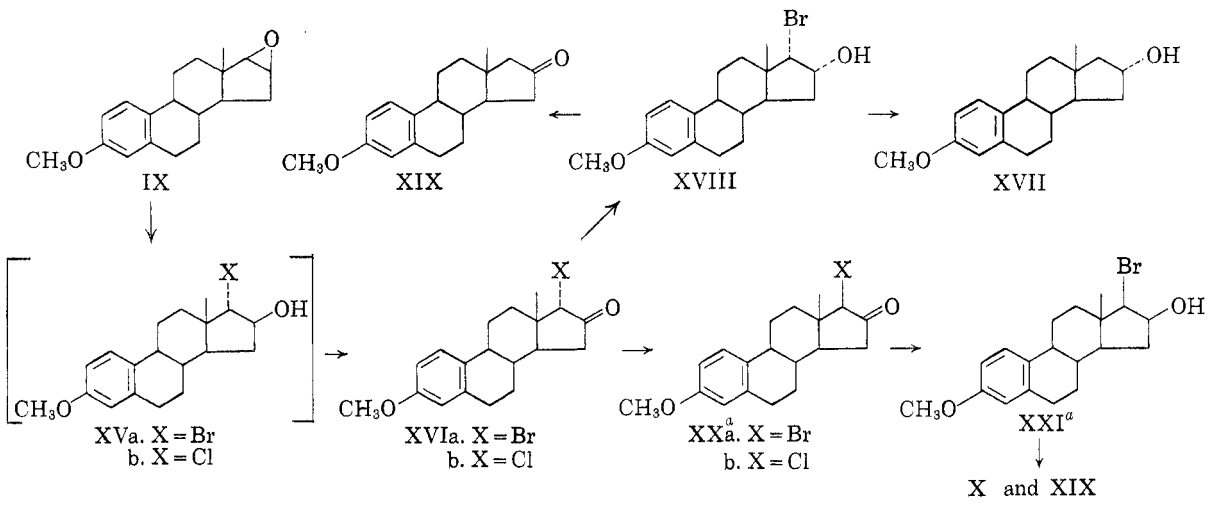


of the halides. However, relative to estrone methyl ether, absorbing at 1742 cm.$^{-1}$, maxima appeared at 1742, 1754, 1761, and 1766 cm.$^{-1}$, respectively, for the C-16 iodides, bromides, chlorides, and fluorides.[23,24]

Shoppee, Jenkins, and Summers[9] introduced Nickon's[25] relationship between conformation and infrared absorption in 1,2 chlorohydrins and bromohydrins without applying the concept to their own compounds. Fajkos[11] presented data affirming that the frequency of O—H stretching is indeed a sensitive indication of halohydrin configuration in the D ring. Our data, as expected from the foregoing, show no shift of the *trans* chlorohydrin XII absorption from that of the parent 17α-hydroxy steroid at 3642 cm.$^{-1}$ The *cis*-α-halohydrins exhibit shifts, where $\Delta\nu$ of VIIc and VIIa is -45 and -58 cm.$^{-1}$, respectively. Estradiol methyl ether absorbs at 3650 cm.$^{-1}$ and the *trans* halohydrins likewise. The *cis* isomer VI shows $\Delta\nu$ of -66 cm.$^{-1}$ Finally, the *cis* bromohydrin XXI has $\Delta\nu$ -70 cm.$^{-1}$ relative to 3-methoxyestra-1,3,5(10)-trien-16β-ol, 3680 cm.$^{-1}$[13]

Optical rotations and ancillary data are summarized in Table I. Some interesting correlations may be found here and comparison made with a similar summary of the data of Fajkos[11] and of Shoppee[9] in the androstane series. In particular we found that when molecular rotations were plotted linearly against molecular weight the four 16β-halo-17-ketones formed a straight line of positive slope intersecting almost perpendicularly a similar straight line containing the 16α-isomers. Intersection occurs at the value +512, common to

(23) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, London, Methuen and Co. Ltd., 1954, p. 121.
(24) F. V. Brutcher, Jr., T. Roberts, S. J. Barr, and N. Pearson, *J. Am. Chem. Soc.*, **78**, 1507 (1956).
(25) A. Nickon, *J. Am. Chem. Soc.*, **79**, 243 (1957).



[a] The compounds XX and XXI, including preparation, reactions and physical data, were appended to the manuscript on November 15, 1960.

both chlorides. This relationship proved useful, as mentioned earlier, in relating configurations of the 16-fluoro- and 16-iodo ketones to the corresponding chlorides and bromides.

Optical rotatory dispersion curves were obtained for all of the halogenated ketones.[26,27] The curves of the 16-halo 17-ketones showed the expected strong, positive Cotton effect[28] while those of 17-halo 16-ketones showed a negative Cotton effect. The amplitude and position of extrema appear to offer no definitive assignment of configuration in the ring-D halo ketones.

(26) We wish to thank Miss Jane Jackson, Postgraduate Medical School, London, for obtaining these curves, and Dr. W. Klyne for generously making the arrangements and interpreting the curves. His comments are as follows: The Δa values (Table I) may be interpreted according to the octant rule in its simplest form: (1) both 16-fluoro ketones have values of the expected sign; (2) the remaining 16α-halo ketones have negative values smaller than expected, indicating some ring distortion; (3) the remaining 16β-halo ketones are expected to have positive values and the fact that two have low or negative values probably indicates major distortion of ring D, presumably due to interaction of the β-halogen with the C-13 methyl group; (4) the 17α-halides have values of the expected sign and magnitude, indicating the halogens are occupying almost truly axial positions, although the 17β-halides show quasi-equatorial character with their small (but uncertain) $+\Delta a$ values. Perhaps most interesting here is the small $\Delta\lambda$ (6–10°, compared with the unsubstituted ketone) of the latter compared with a 20 to 30 mμ shift for the quasi-axial 17α- and bisectional 16α- and 16β-halides (see p. 290 and reference 27a).

(27) For discussions of this subject and the octant rule see, *Optical Rotatory Dispersion*, C. Djerassi, McGraw-Hill Book Co., Inc., New York, N. Y., 1960, and W. Klyne in "Advances in Organic Chemistry," vol. I, T. A. Raphael, E. C. Taylor, and H. Wynberg, editors, Interscience Publishers, Inc., New York, N. Y., 1960, p. 335.

(28) The similarity in dispersion curves of 16α- and 16β-bromo-17-ketosteroids has been described earlier by C. Djerassi, J. Osiecki, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **80**, 1216 (1958).

EXPERIMENTAL

All rotations were run at about 1% concentration in chloroform, and infrared spectra were recorded in chloroform. The term petroleum ether refers to the fraction boiling at 63–69°. Melting points are uncorrected.

Estrone n-propyl ether (Ic). Alkylation of 18.2 g. of estrone in 500 ml. of ethanol with 100 ml. of *n*-propyl iodide and 4 g. of potassium carbonate was carried out at reflux for 4 hr. Concentration to one-half volume, filtration from salts and further concentration gave 18.0 g. of product, m.p. 96–100°, which was recrystallized from methanol, yielding 14.2 g. of flat prisms, m.p. 98–99°, $[\alpha]_D$ + 143°.

Anal. Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.88; H, 9.24.

Enol acetates of estrone alkyl ethers (IIb), (IIc). The enol-acetylation procedure used has been described.[5] We found it convenient to dissolve the crude enol acetate in hot petroleum ether or cyclohexane and pour the warm solution quickly through a short column (*ca.* 1–2″ deep) of Florisil. This is quicker than conventional chromatography, tar absorption is complete, and there is less danger of decomposition of the enol acetate which sometimes occurs during chromatography.

3-Ethoxy-17-acetoxyestra-1,3,5(10),16-tetraene crystallized from pentane in flat, elongated plates, m.p. 107–108°.

Anal. Calcd. for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.46; H, 8.24.

3-*n*-Propoxy-17-acetoxyestra-1,3,5(10),16-tetraene crystallized from petroleum ether, m.p. 98–99°.

Anal. Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 78.02; H, 8.52.

3-Acetoxy-16α-iodoestra-1,3,5(10)-trien-17-one (IIIa). 3,17-Diacetoxyestra-1,3,5(10),16-tetraene,[29] 6.52 g., in 20 ml. of warm dioxane was covered with nitrogen, treated with 5 g. of *N*-iodosuccinimide, warmed in a stoppered flask at 65° for 3 hr., chilled and treated successively with concentrated solutions of 3.3 g. of potassium iodide and 5 g. of sodium thiosulfate. Dilution with water, extraction with chloroform and evaporation of the washed and dried chloroform extracts gave an oil which crystallized overnight from 30 ml. of ether; the yield was 3.50 g., m.p. 135–140°. Recrystallization from methanol, benzene-cyclohexane and finally pure ether yielded bundles of small, flat needles, m.p. 142.0–143.6°, $[\alpha]_D$ + 82°, ν_{max} 1742 cm.$^{-1}$

(29) N. S. Leeds, D. K. Fukushima, and T. F. Gallagher, *J. Am. Chem. Soc.*, **76**, 2943 (1954).

Anal. Calcd. for $C_{20}H_{23}IO_3$: C, 54.80; H, 5.29; I, 28.96. Found: C, 54.57; H, 5.54; I, 28.64.

3-Acetoxy-16α-chloroestra-1,3,5(10)-trien-17-one (IIIc). The enol diacetate, 3.54 g., and 25 g. of anhydrous potassium carbonate in 125 ml. of carbon tetrachloride were treated at 12° with 15.2 ml. of 0.727*M* chlorine in carbon tetrachloride. The addition required 0.5 hr.; 20 g. of sodium thiosulfate in water was added, the layers separated, and the extraction completed with chloroform. The dried, evaporated organic solution yielded a clear glass, crystallizing as plates, m.p. 163–168°, 1.38 g. Recrystallization from methanol furnished long needles, m.p. 163–166°, $[\alpha]_D$ + 150°, ν_{max} 1761 cm.$^{-1}$

Anal. Calcd. for $C_{20}H_{23}ClO_3$: C, 69.25; H, 6.68; Cl, 10.22. Found: C, 69.62; H, 7.19; Cl, 10.27.

16α-Iodoestrone (IIIb). About 6 g. of crude acetate IIIa was dissolved in 125 ml. of methanol, treated with 5 ml. of concd. hydrochloric acid, warmed briefly to clear the solution, and set aside at room temperature overnight. A crop of 3.5 g. of crystals, m.p. (violet color at 185°, sweating at 200°) 210–211° (violent dec.), was collected. Two recrystallizations with decolorization from methanol yielded 1.21 g., m.p. 213.0–213.5° (violent dec., with violet color), $[\alpha]_D$ +137°.

Anal. Calcd. for $C_{18}H_{21}IO_2$: C, 54.55; H, 5.34; I, 32.03. Found: C, 54.83; H, 5.08; I, 32.21.

Reacetylation overnight of 0.1 g. in 5 ml. of pyridine with 5 ml. of acetic anhydride gave 0.12 g. of crude, oily product. This was recrystallized twice from ether-pentane, affording plates, m.p. 140–142°, $[\alpha]_D$ +87°. These showed infrared absorption identical with that of IIIa, suggesting the absence of inversion during the preceding hydrolysis. However, this conclusion may be open to question for want of a high yield in reacetylation.

16α-Chloroestrone. Hydrolysis of 1.1 g. of the acetate IIIc was accomplished by heating overnight at 100° with 20 ml. of 50% acetic acid. The product, 0.63 g., m.p. 233–239°, separated on cooling. It was recrystallized three times from acetone-pentane and melted at 238.5–240.5°, $[\alpha]_D$ +166°.

Anal. Calcd. for $C_{18}H_{21}ClO_3$: C, 70.92; H, 6.95; Cl, 11.63. Found: C, 70.93; H, 6.96; Cl, 11.70.

Assurance of configurational retention at C-16 was supplied by acetylating this phenol. The product, obtained in nearly quantitative yield and recrystallized from methanol, m.p. 164–169°, $[\alpha]_D$ +148°, was identical in all respects to IIIc.

The 3-methoxy-16-iodoestra-1,3,5(10)-trien-17-ones, (IIId) *and* (Va). A solution of 1.0 g. of 3-methoxy-17-acetoxyestra-1,3,5(10)-triene in 25 ml. of carbon tetrachloride, with 2 g. of anhydrous potassium carbonate, was treated with 0.8 g. of iodine in 25 ml. of carbon tetrachloride at 30° for 0.5 hr. The mixture was worked up with chloroform and aqueous sodium bisulfite and the residue remaining after evaporation of the solvent crystallized from methanol as rods, m.p. 161–167°, $[\alpha]_D$ +90.5°, of 3-methoxy-16α-iodoestra-1,3,5(10)-trien-17-one, IIId.

A more suitable preparation of this isomer resulted from treating 16.30 g. of the enol acetate, dissolved in 750 ml. of acetic acid, with 8.0 g. of mercuric acetate, stirring, cooling to 15°, and adding 13.0 g. of iodine dissolved in 750 ml. of acetic acid. The product was precipitated with water and washed several times by decantation. It was then extracted from the aqueous slurry with chloroform; this solution was washed successively with potassium iodide and sodium thiosulfate solutions and water, dried over magnesium sulfate and distilled *in vacuo*. Crystallization from 500 ml. of isopropyl alcohol, and from 400 ml. of methanol provided 7.8 g. of needles, m.p. 163–165.5°, with sweating at 148°. One further recrystallization from methanol gave 6.06 g. of IIId, m.p. 165–166° (sweating at 155°), $[\alpha]_D$ + 89.3°, ν_{max}1742 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{23}IO_2$: I, 30.93. Found: I, 30.27.

Both 16-iodo-epimers were obtained by heating 6.52 g. of the enol acetate at 70° with 5.0 g. of *N*-iodosuccinimide in 20 ml. of purified dioxane for 1.5 hr. This was done in a stoppered flask from which air had been displaced by nitrogen. The colored solution was treated successively with saturated aqueous solutions of 3.3 g. of potassium iodide, 5 g. of sodium thiosulfate, diluted with 200 ml. of water and extracted with three 50-ml. portions of chloroform, the extracts being washed, dried and evaporated. Direct recrystallization of the crude residue yielded 5.94 g. (71.5%) of the 16α-isomer. Slow evaporation of the mother liquors at room temperature yielded a mixture of elongated plates (16α-isomer) and rosettes of stout hexagonal staffs (16β-isomer). Manual separation and recrystallization of the latter from methanol-chloroform afforded 3-methoxy-16β-iodoestra-1,3,5(10)-trien-17-one(Va) m.p. 164–166° (with sweating at 157°), $[\alpha]_D$ + 175°, ν_{max} 1745 cm.$^{-1}$

Anal. Found: I, 30.42.

An alternate method of separating isomers depended on the greater solubility of the 16β-iodide in ether. Thus, the total iodination product was crystallized once from ether, and the mother-liquor material was crystallized carefully from ether, benzene or ethyl acetate to produce the β-isomer.

3-Ethoxy-16α-iodoestra-1,3,5(10)-trien-17-one. This was prepared from IIb and *N*-iodosuccinimide as described for the methyl ether above. The crude product was recrystallized from methanol, twice from ether, and again from methanol; m.p. 156–160°, $[\alpha]_D$ +91.5°.

Anal. Calcd. for $C_{20}H_{25}IO_2$: C, 56.61; H, 5.94; I, 29.91. Found: C, 56.78; H, 5.79; I, 29.90.

3-Methoxy-16α-bromoestra-1,3,5(10)-trien-17-one (IIIe). *A. By bromination of the enol acetate* IIa. This procedure was described by Johnson and Johns;[5] the product gave the constants: m.p. 179–182°, $[\alpha]_D$ +127°.

B. By oxidation of 3-methoxy-16α-bromoestra-1,3,5(10)-trien-17α-ol (VIIa). Oxidation of 0.11 g. of VIIa was accomplished by adding its pyridine solution to a slurry of 0.5 g. of chromic anhydride in 10 ml. of pyridine at 25°. After 18 hr. the mixture was diluted, worked up with water and ether and the dried ether solution concentrated. Crystallization from methanol afforded 65 mg. of bromoketone IIIe, m.p. 176–178°, $[\alpha]_D$ +124°, ν_{max} 1754 cm.$^{-1}$

C. By oxidation of 3-methoxy-16α-bromoestra-1,3,5(10)-trien-17β-ol (VIIIa). Similar treatment of the *trans*-bromohydrin, 0.30 g., in 10 ml. of pyridine with 0.50 g. of chromic anhydride overnight at 25°, yielded an ether-extractable product. This was recrystallized from methanol and proved to be the bromo ketone IIIe, 0.25 g., m.p. 178–181°, identical in infrared absorption to the above samples.

3-Methoxy-16α-chloroestra-1,3,5(10)-trien-17-one (IIIf). A. *By chlorination of the enol acetate* IIa. A solution of chlorine in carbon tetrachloride was prepared by scrubbing commercial chlorine with saturated copper sulfate followed by concentrated sulfuric acid, finally passing it through anhydrous potassium carbonate and into the solvent; in this experiment the chlorine concentration was 0.869*M*.

The 3-methoxy-17-acetoxyestra-1,3,5(10),16-tetraene(IIa), 32.68 g., was dissolved in 1200 ml. of carbon tetrachloride, treated with 35 g. of powdered anhydrous potassium carbonate suspended by powerful stirring, and cooled to 10°. Chlorine solution was added dropwise over a 15-min. period at 9–12°, an additional 35 g. of potassium carbonate being added near the half-way point. After another 30 min. stirring at 12–15°, 35 g. of sodium bisulfite in concentrated solution was added slowly. Gas evolution soon subsided; sufficient water was added to dissolve all salts and the layers were separated. The organic layer was washed twice with water and distilled (drying was unnecessary) to about 200-ml. volume, adding 500 ml. of methanol, concentrating, adding 500 ml. of methanol and concentrating finally to 200 ml. After standing 2 days at room temperature, the mixture was filtered to yield 26.67 g. of high-quality product appearing as elongated plates, m.p. 174–182° (with sweating, beginning at 150° and becoming heavy in the 160–165° region).

Recrystallization twice from methyl alcohol by dissolving, concentrating the solution to half volume and allowing it to stand at room temperature, gave heavy needles, m.p. 175–

179° (with slight sweating at 158°), $[\alpha]_D$ + 161°, ν_{max}1761 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{23}ClO_2$: C, 71.57; H, 7.27; Cl, 11.12. Found: C, 71.34; H, 7.52; Cl, 11.13.

Crystallization from concentrated solutions in methanol-chloroform, methanol-acetone, and acetone was also satisfactory.

B. By oxidation of 3-methoxy-16α-chloroestra-1,3,5(10)-trien-17α-ol (VIIc). A solution of 0.80 g. of VIIc in 15 ml. of pyridine was added to 1.0 g. of chromic anhydride in 10 ml. of pyridine. After 16 hr. stirring at room temperature, the mixture was diluted with water and extracted with ether. After the usual treatment with dilute hydrochloric acid, sodium bicarbonate, and solid sodium sulfate, the extract was evaporated. Recrystallization from acetone-methanol yielded the chloro ketone IIIf, m.p. 174–181°, identical in all other respects with the above.

C. By oxidation of 3-methoxy-16α-chloroestra-1,3,5(10)-trien-17β-ol (VIIIc). Compound VIIIc, 0.64 g., in 20 ml. of pyridine was oxidized for 20 hr. with 1 g. of oxidant in 10 ml. of pyridine as just described. Recrystallization of the crude product from acetone–petroleum ether, and from methanol, yielded 0.42 g. of IIIf, m.p. 177–180°, having infrared absorption identical with the foregoing preparation.

3-Methoxy-17β-acetoxy-16β,17α-dichloroestra-1,3,5(10)-triene (IV). In another preparation of IIIf by procedure A, special consideration was given the mother liquors remaining after removal of first and second crops of desired product. These liquors were evaporated *in vacuo* leaving a dark, oily semicrystalline mixture. Chromatography of 21.8 g. on 1800 g. of silica, with benzene elution and automatic collection of eluates, yielded an initial peak of 2.38 g., on which a molar yield of 3.74% was calculable from the weight of enol acetate chlorinated. Recrystallization of this fraction from acetone, acetone–petroleum ether, or methanol yielded IV as small rosettes of heavy needles, m.p. 135–136°, $[\alpha]_D$ +62.6°.

Anal. Calcd. for $C_{21}H_{26}Cl_2O_3$: C, 63.47; H, 6.60; Cl, 17.85. Found: C, 63.83; H, 6.14; Cl, 17.95.

3-Ethoxy-16α-chloroestra-1,3,5(10)-trien-17-one. Using the procedure outlined for the methyl ether, 3.40 g. of enol acetate, IIb, in 100 ml. of carbon tetrachloride, 20 g. of potassium carbonate, and 15.7 ml. of 0.727*M* chlorine solution yielded a colorless glass which crystallized from 175 ml. of methanol giving 1.92 g. of flat needles, m.p. 158–166°. Recrystallization from acetone-methanol gave analytical quality material, m.p. 164.5–166.8°, $[\alpha]_D$ +153.5°.

Anal. Calcd. for $C_{20}H_{25}ClO_2$: C, 72.16; H, 7.57; Cl, 10.65. Found: C, 71.95; H, 7.47; Cl, 10.46.

3-n-Propoxy-16α-chloroestra-1,3,5(10)-trien-17-one. The preparation from IIc was like that of the ethers described above. Recrystallization from acetone–petroleum ether gave pure material, m.p. 138–140°, $[\alpha]_D$ +149°.

Anal. Calcd. for $C_{21}H_{27}ClO_2$: C, 72.71; H, 7.85. Found: C, 72.71; H, 7.54.

3-Methoxy-16β-bromoestra-1,3,5(10)-trien-17-one (Vb). *A. By acid-catalyzed epimerization of 16α-bromide* IIIe. A solution of 1.0 g. of IIIe in 45 ml. of ethanol, 2 ml. of water, and 2 ml. of concd. sulfuric acid was refluxed for 18 hr., cooled, diluted with water, and filtered. The total solid showed the rotation, $[\alpha]_D$ +133°. Retreatment of this solid in the same way changed the rotation to $[\alpha]_D$ +142°. This value rose to +150° and remained constant after 72- and 144-hr. treatments. Careful crystallization from methanol of the product of a 144-hr. reflux period led to pure Vb, m.p. 145–148°, $[\alpha]_D$ +164°.

Anal. Calcd. for $C_{19}H_{23}BrO_2$: C, 62.81; H, 6.38. Found: C, 62.54; H, 6.12.

B. By epimerization of 16α-bromide IIIe *with lithium bromide.* A solution containing 5.0 g. of lithium bromide in 40 ml. of dimethylformamide was added to 2.0 g. of IIIe and the mixture stirred at room temperature for 24 hr., diluted with hot water, and filtered. The precipitate was extracted with benzene and this solution washed, dried, and evaporated *in vacuo*. Crystallization from methanol yielded 1.85 g. of impure 16β-bromide, m.p. 128–140°, $[\alpha]_D$ +147°. A similar product was obtained after 4.5-hr. reaction time. Rotational data suggest these products to be mixtures of isomers although infrared absorption in each case was nearly identical with the pure 16β-isomer Vb.

3-Methoxy-16β-chloroestra-1,3,5(10)-trien-17-one (Vc). *A. By displacement with the 16α-bromide* IIIe. Lithium chloride, 30 g., was dissolved in 200 ml. of warm dimethylformamide and 10.0 g. of 3-methoxy-16α-bromoestra-1,3,5(10)-trien-17-one was added at room temperature. The solution became homogeneous after stirring 2 hr., and after 6 hr. it was diluted with water and filtered. Recrystallization afforded 8.15 g. of crystals, m.p. 128–133°. Careful recrystallization from methylene chloride-methanol and from acetone–petroleum ether gave the pure 16β-chloro-ketone, m.p. 138–140°, $[\alpha]_D$ +161°, ν_{max} 1758 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{23}ClO_2$: C, 71.57; H, 7.27; Cl, 11.12. Found: C, 71.49; H, 7.58; Cl, 11.08.

By quenching aliquots at 0.5- and 3-hr. periods and determining the chloride and bromide content of the whole, precipitated samples, the reaction was estimated to be 31% and 98% complete at these times.

B. By isomerization of the 16α-chloro ketone IIIf. A solution of 0.5 g. of IIIf in 50 ml. of benzene was stirred 16 hr. with 10 g. of Woehlm alkaline alumina at room temperature. The solution was then filtered and chromatographed quickly on silica gel. Elution with 5% ethyl acetate yielded 0.37 g. of semicrystalline material separable by fractional crystallization from aqueous methanol and acetone–petroleum ether into IIIf, m.p. 163–172° and Vc, m.p. 133–138°. Infrared correlations of these preparations with those reported above were confirmatory.

C. By oxidation of the trans-chlorohydrin XII. A solution containing 0.90 g. of chlorohydrin in 30 ml. of pyridine was added to the complex from 2 g. of chromic anhydride in 50 ml. of pyridine. After stirring overnight at room temperature the reactants were diluted with water and processed with ether as described above. The ethereal residue crystallized from methanol, giving 0.40 g. of Vc, m.p. 132–134°, having an infrared pattern identical with an authentic sample.

D. By oxidation of the cis-chlorohydrin VI. Similar oxidation of 0.50 g. of *cis*-chlorohydrin in 10 ml. of pyridine with 1.0 g. of chromic anhydride in 10 ml. of pyridine and recrystallization of the product from methanol gave 0.33 g. of pure 3-methoxy-16β-chloroestra-1,3,5(10)-trien-17-one, m.p. 138–140°, whose identity was again confirmed by the infrared spectrum.

E. By hydrolysis of the adduct IV. A solution of the enol acetate dichloride IV, 0.10 g., in 50 ml. of methanol, containing 1.0 ml. of concd. hydrochloric acid, was stirred at room temperature for 18 hr., diluted with water, and filtered. Recrystallization of the precipitate from methanol yielded 55 mg. of pure 16β-chloride, m.p. 140–142°, again having an infrared curve identical with that of Vc.

F. By displacement of the 16α-p-toluenesulfonoxy group of XIVb. A solution of 2.0 g. of lithium chloride and 0.88 g. of the ketol tosylate XIVb in 100 ml. of dimethylformamide was stirred at room temperature for 28 hr. The mixture was diluted with water and filtered, yielding 0.75 g. of crystals, m.p. 126–132°. Recrystallization gave 0.50 g. of pure Vc, m.p. 137–139°, characterized by the correct infrared spectrum. The recrystallization liquors afforded a second crop, 0.15 g., m.p. 120–125°, which appeared to consist mainly of 16β-chloride contaminated with a small amount of 16α-chloride IIIf.

3-Methoxy-16β-fluoroestra-1,3,5(10)trien-17-one (Vd). Five grams of 3-methoxy-16α-iodoestra-1,3,5(10)-trien-17-one, IIId, was refluxed in 130 ml. of acetonitrile for 16 hr. under a Soxhlet extractor containing 25 g. of commercial silver fluoride. The solution was cooled, filtered, diluted with two volumes of chloroform, washed, dried over magnesium sulfate, and evaporated to a dark oil. This, in 20 ml. of benzene and 40 ml. of petroleum ether, was passed over 25 g. of 60-

mesh Florisil and eluted with 250, 200, and 200 ml. of 25%, 50%, and 100% benzene in petroleum ether, respectively. The heavy color remained adsorbed and the collected eluates were evaporated to leave 4.02 g. of oily plates. Chromatography on 100 g. of silica and elution with 75% benzene in petroleum ether brought down 2.35 g. of material which was crystallized from methanol, twice from benzene–petroleum ether, and from ethanol. The desired product formed irregular, heavy needles, m.p. 166–168°, $[\alpha]_D$ + 157°, ν_{max} 1766 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{23}FO_2$: C, 75.47; H, 7.67; F, 6.28. Found: C, 74.88; H, 7.58; F, 6.04.

3-Acetoxy-16β-fluoroestra-1,3,5(10)-trien-17-one. A saturated solution was prepared by heating 25 g. of purified acetonitrile with 10 g. of commercial silver fluoride and filtering the hot mixture. To the filtrate 3.5 g. of 3-acetoxy-16α-iodoestra-1,3,5(10)-trien-17-one, IIIa, was added and the mixture heated on the steam bath for 1.5 hr., treated with an additional 10 g. of silver fluoride, heated for a like period and set aside for 3 days. It was again heated to boiling, filtered, and the cooled filtrate diluted with ether, washed, dried, and evaporated. The resulting brown gum was reacetylated for 30 min. in 20 ml. of refluxing acetic anhydride, the excess being removed *in vacuo*. This residue in 50 ml. of benzene and 30 ml. of petroleum ether was passed over 100 g. of silica and eluted with mixtures of benzene–petroleum ether through pure benzene. The crude product, 1.05 g., was removed with 5% ethyl acetate in benzene. It was recrystallized twice from ether and three times from benzene-pentane. The pure product melted at 182–184°, $[\alpha]_D$ +145°.

Anal. Calcd. for $C_{20}H_{23}FO_3$: C, 72.70; H, 7.02; F, 5.75. Found: C, 72.80; H, 6.72; F, 6.2.

3-Methoxy-16β-chloroestra-1,3,5(10)-trien-17β-ol (VI). The ketone Vc was reduced by adding 5.15 g., dissolved in 40 ml. of tetrahydrofuran, to a stirred solution of 0.80 g. of lithium aluminum hydride in 100 ml. of ether at 0° during 10 min. After careful dilution with water, acidification with dilute hydrochloric acid, extraction with benzene and washing the benzene solution with aqueous sodium bicarbonate, drying, and concentrating to dryness *in vacuo*, the chlorohydrin was obtained. This crystallized nicely from acetone–petroleum ether as fine, felted rods, 3.05 g., m.p. 116–118°. Further crystallization from aqueous methanol raised the melting point to 118–120°, $[\alpha]_D$ +69°, ν_{max} 3584 cm.$^{-1}$ The sample appeared to be homogeneous by column and paper chromatography.

Anal. Calcd. for $C_{19}H_{25}ClO_2$: C, 71.12; H, 7.85. Found: C, 71.16; H, 7.85.

The acetate was prepared by heating 0.33 g. of chlorohydrin with 4 ml. of acetic anhydride in 8 ml. of pyridine at 100° for 20 min., diluting with water and extracting with benzene. The usual washing, drying, and concentration gave 0.15 g. of 3-methoxy-16β-chlorestra-1,3,5(10)-trien-17β-ol acetate, m.p. 116–120°, crystallizing from methanol. Further recrystallization gave the sample for analysis, m.p. 126–127°, $[\alpha]_D$ +101°.

Anal. Calcd. for $C_{21}H_{27}ClO_3$: C, 69.50; H, 7.50. Found: C, 69.64; H, 7.59.

The structure of chlorohydrin VI was confirmed by refluxing 0.64 g. of the substance under nitrogen with 1.0 g. of potassium hydroxide in 50 ml. of methanol for 48 hr., cooling, diluting, and filtering the mixture. The precipitate was recrystallized from aqueous acetone, affording 0.52 g. of estrone methyl ether, m.p. 168–171°, identical to an authentic sample.

3,17-17-Trimethoxyestra-1,3,5(10)-trien-16α-ol (XIIIa). Sixty-three grams of 16α-bromo ketone IIIe was dissolved in 700 ml. of anhydrous methanol, containing 20 g. of dissolved sodium metal, and stirred at room temperature in a stoppered flask for 65 hr. Dilution with 2 l. of water followed by filtration and washing yielded 57.3 g. of XIIIa, m.p. 132–134°. Recrystallization of a portion of this from petroleum ether gave analytical material, m.p. 136–138°, $[\alpha]_D$ +11.5°, ν_{max} 3542 cm.$^{-1}$

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73; OCH_3, 26.87. Found: C, 73.09; H, 8.83; OCH_3, 25.80.

The acetate XIIIc was prepared by treating 0.10 g. of hydroxyketal with 2 ml. of pyridine and 1 ml. of acetic anhydride for 18 hr. at room temperature, diluting with water, collecting, and recrystallizing the crude product from petroleum ether. The purified 3,17,17-trimethoxyestra-1,3,5(10)-trien-16α-ol acetate melted at 124–125°.

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.17; H, 8.28.

3,17,17-Trimethoxyestra-1,3,5(10)-trien-16α-ol p-toluenesulfonate (XIIIb). A solution containing 2.0 g. of XIIIa and 2.0 g. of *p*-toluenesulfonyl chloride in 30 ml. of pyridine was set aside overnight, stirred for 10 min. with aqueous potassium bicarbonate and finally precipitated completely with an excess of water. The crude product, washed and dried, weighed 2.50 g., m.p. 158–165°. Recrystallization of a portion from methylene chloride-methanol afforded pure material, m.p. 166–167°, $[\alpha]_D$ +12°.

Anal. Calcd. for $C_{28}H_{36}O_6S$: C, 67.17; H, 7.25. Found: C, 67.00; H, 7.35.

3-Methoxy-16α-hydroxyestra-1,3,5(10)-trien-17-one (XIVa). Hydrolysis of 0.20 g. of the dimethylketal XIIIa was achieved by treating with 150 ml. of *t*-butyl alcohol, 30 ml. of water, and 0.40 g. of *p*-toluenesulfonic acid, distilling slowly for 45 min., cooling, diluting with water, and filtering. The precipitate, dried and recrystallized from acetone–petroleum ether, amounted to 85 mg. of pure product, m.p. 156–157°, $[\alpha]_D$ +176°.

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.81; H, 8.22.

The identity of this product was shown by comparing with an authentic sample.[13]

3-Methoxy-16α-hydroxyestra-1,3,5(10)-trien-17-one p-toluenesulfonate (XIVb). The dimethylketal XIIIb, 2.50 g., was boiled for 4 min. with 200 ml. of ethanol containing 5 ml. of concd. hydrochloric acid. The precipitate, which had appeared shortly upon heating, was collected from the chilled mixture and washed generously with water. The dried product, 2.05 g., m.p. 203–204°, was recrystallized from acetone–petroleum ether, giving a pure sample, m.p. 204–205°, $[\alpha]_D$ +114°.

Anal. Calcd. for $C_{26}H_{30}O_5S$: C, 68.70; H, 6.65. Found: C, 68.39; H, 6.71.

3-Methoxy-16α-bromoestra-1,3,5(10)-trien-17α-ol (VIIa) *and 3-methoxy-16α-bromoestra-1,3,5(10)-trien-17β-ol* (VIIIa).[30] Twenty grams of 16α-bromo ketone IIIe in 120 ml. of tetrahydrofuran was added in 10 min. to a stirred suspension of 2.0 g. of lithium aluminum hydride in 200 ml. of anhydrous ether at an internal temperature of 5–10°, maintained by an ice-salt bath. Cautious addition of water followed by 50 ml. of 5% hydrochloric acid, the usual extraction with benzene, water, sodium bicarbonate, and drying, followed by distillation *in vacuo*, gave a colorless glass. This was dissolved in 10% benzene–petroleum ether and chromatographed on Florex; elution of the two main fractions was accomplished with 25% benzene and 75% benzene in petroleum ether, respectively.

The first peak, 7.46 g. of crude, crystalline product, was recrystallized from acetone, the pure product appearing as heavy staffs, m.p. 149–150°, $[\alpha]_D$ +75°, ν_{max} 3584 cm.$^{-1}$ This was the *cis*-bromohydrin VIIa.

Anal. Calcd. for $C_{19}H_{25}BrO_2$: C, 62.46; H, 6.90. Found: C, 62.61; H, 6.72.

Proof of the *cis* configuration of VIIa was obtained by refluxing 0.20 g. of the compound in 20 ml. of methanol for 5 hr. with 1.0 g. of potassium hydroxide under nitrogen. The product, 0.15 g., was obtained by dilution, filtration, and washing; it melted at 172–175° and displayed the infrared pattern of estrone methyl ether.

(30) We wish to acknowledge with thanks the assistance of Mr. P. Yonan of the Division of Chemical Research in carrying out large scale preparations.

Fractions constituting the second peak, 13.8 g., crystallized slowly. Recrystallization of 3 g. from ether–petroleum ether yielded 1.7 g. of *trans*-bromohydrin VIIIa, m.p. 104–105°, $[\alpha]_D$ +79°, ν_{max} 3650 cm.$^{-1}$

Anal. Found: C, 62.65; H, 6.77.

3,17α-Dihydroxy-16α-bromoestra-1,3,5(10)-triene (VIIb) *and 3,17β-dihydroxy-16α-bromoestra-1,3,5(10)-triene* (VIIIb). Reduction of bromo-ketone IIIb, 3.2 g., in 30 ml. of tetrahydrofuran, with 1.0 g. of lithium aluminum hydride in 100 ml. of ether was carried out during 10 min. at 0°. After an additional 10 min. of stirring, addition of water and then dilute hydrochloric acid and extraction with benzene, 2.70 g. of crystalline product (no infrared carbonyl absorption) was obtained. This was chromatographed on 150 g. of Florisil. The *cis*-bromo-hydrin VIIb was eluted first with benzene; after recrystallization from acetone this amounted to 0.25 g. of pure product, m.p. 253–255°, $[\alpha]_D$ +71.5°.

Anal. Calcd. for $C_{18}H_{23}BrO_2$: C, 61.54; H, 6.60. Found: C, 61.78; H, 6.79.

Continued elution with benzene brought down a mixture of the two bromohydrins followed by the pure *trans* isomer VIIIb. This was recrystallized from acetone–petroleum ether, giving 1.40 g. of good product, m.p. 217–219°, $[\alpha]_D$ +81.5°.

Anal. Found: C, 61.65; H, 6.30.

The *cis* configuration of VIIb was confirmed by refluxing 53 mg. of the latter with alcoholic potassium hydroxide under nitrogen for 6 hr. Dilution and acidification yielded 32 mg. of crystals, m.p. 250–262°, identical by infrared absorption with estrone.

3-Methoxy-16α-chloroestra-1,3,5(10)-trien-17α-ol (VIIc) *and 3-methoxy-16α-chlorestra-1,3,5(10)-trien-17β-ol* (VIIIc). Reduction of 15.0 g. of chloro ketone IIIf in 100 ml. of tetrahydrofuran with 2.0 g. of lithium aluminum hydride and 100 ml. of ether was performed exactly as described for IIIe above. Direct recrystallization of the benzene-extracted material from methanol yielded 3.67 g. of the *cis*-chlorohydrin VIIc as rods, m.p. 163–164°, $[\alpha]_D$ +68°, ν_{max} 3597 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{25}ClO_2$: C, 71.12; H, 7.85. Found: C, 71.39; H, 7.80.

Acetylation of 0.25 g. in 10 ml. of pyridine and 5 ml. of acetic anhydride at 100° for 30 min. and recrystallization of the crude product from aqueous acetone gave 0.25 g. of 3-methoxy-16α-chloroestra-1,3,5(10)-trien-17α-ol acetate, m.p. 141–143°, $[\alpha]_D$ +1.9°.

Anal. Calcd. for $C_{21}H_{27}ClO_2$: C, 69.50; H, 7.50. Found: C, 69.47; H, 7.79.

The structure of VIIc was confirmed by refluxing 1.28 g. in 50 ml. of ethanol and 1.0 g. of potassium hydroxide under nitrogen for 80 hr. Extraction with benzene as usual, and chromatography on silica gel, yielded 0.36 g. of estrone methyl ether.

Mother liquors from crystallization of VIIc yielded a residue which, chromatographed on 200 g. of Florex and eluted with 30% benzene–petroleum ether, produced initially more of the *cis* isomer. Continued elution with this solvent brought down the *trans* isomer which, recrystallized from acetone–petroleum ether, amounted to 5.9 g. of VIIIc, m.p. 113–115°, $[\alpha]_D$ +69.0°, ν_{max} 3650 cm.$^{-1}$

Anal. Found: C, 71.40; H, 7.71.

Acetylation as above resulted in 0.25 g. of 3-methoxy-16α-chloroestra-1,3,5(10)-trien-17β-ol acetate, m.p. 168–169°, $[\alpha]_D$ +50.6°.

Anal. Found: C, 69.39; H, 7.90.

3-Methoxyestra-1,3,5(10),16-tetraene (X). Treatment of 1.0 g. of *cis*-bromohydrin VIIa for 3 hr. at reflux with 2 g. of zinc dust stirred in 40 ml. of acetic acid, followed by cooling, filtration, and dilution with water, precipitated 0.68 g. of product. This was collected, washed, and dried. It melted at 65–67° and was recrystallized from isopropyl alcohol, giving 0.42 g. of long rods, m.p. 71–72°, $[\alpha]_D$ +113°, having the correct analysis and infrared spectrum for the structure X.[13]

Pure *cis*-bromohydrin was not required for this preparation and a simpler method utilized the crude mixture of VIIa and VIIIa obtained directly from lithium aluminum hydride reduction: 42.5 g. of the mixture was stirred at reflux with 20 g. of zinc in 300 ml. of acetic acid. At 10-min. intervals during 1 hr., 10-g. increments of zinc dust were added. Processing as above yielded initially 28.0 g. of crystals, m.p. 55–63°. Chromatography on 200 g. of silica gel and elution with 10% benzene–petroleum ether gave 23.6 g. of crystals, purified from isopropyl alcohol to 19.8 g. of X, m.p. 67–69°.

3-Methoxy-16α,17α-epoxyestra-1,3,5(10)-triene (XI).[13] Epoxidation of 19.75 g. of X in 100 ml. of benzene with 540 ml. of 0.12*M* perbenzoic acid, initially at 10°, at room temperature for 16 hr. followed by three extractions with 2% potassium hydroxide and three extractions with water, drying (anhydrous magnesium sulfate), and concentration *in vacuo* gave a residue which was recrystallized from aqueous methanol to yield 13.5 g. of XI, m.p. 117–119°.

3-Methoxy-16β-chloroestra-1,3,5(10)-trien-17α-ol (XII). Concentrated hydrochloric acid, 40 ml., was cooled to 0°, stirred with 4.3 g. of XI in 100 ml. of chloroform at 0° for 5 min. and the mixture transferred to a separatory funnel, shaken for 5 min., and the layers separated. The chloroform layer was washed three times with water, dried over magnesium sulfate, and evaporated *in vacuo*. Crystallization of the residue from petroleum ether gave 3.85 g. of fluffy crystals, m.p. 62–64°; recrystallization provided an analytical sample XII, m.p. 64–66°, $[\alpha]_D$ +48°, ν_{max} 3643 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{25}ClO_2$: C, 71.12;H, 7.85 Found: C, 71.12; H, 7.69.

3-Methoxy-16β,17β-epoxyestra-1,3,5(10)-triene (IX). *A. From the transbromohydrin* VIIIa.[30] The crude *trans*-bromohydrin as eluted from the chromatographic column, 27.8 g., was refluxed with stirring for 18 hr. with 1000 ml. of methanol and 5.0 g. of potassium hydroxide. An atmosphere of nitrogen was employed. The solution was cooled, diluted with 2.5 l. of cold water, and the product collected. It was washed with water and dried below 60°; it weighed 22 g. In order to free the oxide from traces of estrone methyl ether this was dissolved in 150 ml. of benzene, adsorbed onto 800 g. of Florex packed under petroleum ether, and eluted with 50% benzene–petroleum ether. The yield of crystalline oxide here was 12 g.; 45 g. of such material was crystallized by adding pentane to a concentrated ether solution and chilling to give 39 g. of epoxide IX, m.p. 110–113°. Analytical material showed m.p. 116–117°, $[\alpha]_D$+115°.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.04; H, 8.75.

B. From the trans-chlorohydrin VIIIc. A solution of 1.28 g. VIIIc and 1.0g. of potassium hydroxide in 50 ml. of methanol was treated for 3 days under the above conditions. Dilution with water and extraction with benzene yielded 1.22 g. of an oil which was crystallized from aqueous methanol and recrystallized from ether to give 0.13 g. of the pure oxide, m.p. 116.0–116.5°, $[\alpha]_D$ +115°, having the correct analysis and infrared spectrum.

Proof of structure was obtained by treating 0.56 g. of IX in 30 ml. of ether with 0.3 g. of lithium aluminum hydride in 30 ml. of ether with stirring at room temperature for 3 days. The usual work-up yielded a residue which was chromatographed on 30 g. of silica gel. Elution with 2% ethyl acetate in benzene resulted in 0.33 g. of an oil, crystallizing from aqueous ethanol to give 3-methoxy-16β-hydroxyestra-1,3,5-(10)-triene, m.p. 102–105°.[13,31]

3-Methoxy-17α-bromoestra-1,3,5(10)-trien-16-one (XVIa) *A. From the β-oxide* IX. A solution of 5.2 g. of β-oxide IX in 125 ml. of chloroform was chilled in ice and shaken 5 min. with 50 ml. of chilled 48% hydrobromic acid. A rose color developed quickly. Ice water was added, the layers separated, and the chloroform solution washed thoroughly, dried, and

(31) M. N. Huffman and M. H. Lott, *J. Biol. Chem.*, **213**, 343 (1955).

concentrated to dryness *in vacuo* below 50°. The residual glass, a mixture of bromohydrins VIIIa and XVa, would not crystallize. It was dissolved in 60 ml. of pyridine and added at 23° to a suspension of 12.0 g. of chromic anhydride in 120 ml. of pyridine (prepared at 10°). The mixture was stirred 3 hr. and the resulting suspension of black tar then diluted with 500 ml. of cold water and extracted with 900 ml. of ether in four passes. The collected extracts were washed thoroughly with water, 3% hydrochloric acid, water, and brine. Upon drying and concentrating to a small volume this solution deposited crystals which were collected and washed with cold ether, 4.92 g., m.p. 128–160°. This material was dissolved in 100 ml. of ether and the solution decanted from crystals deposited after one hour at room temperature. The decantate, concentrated to 35 ml. and crystallized at room temperature, deposited rosettes of long, hexagonal needles, m.p. 135–137° which were recrystallized twice from ether, once at room temperature and once with chilling, to give pure XVIa, m.p. 135.2–136.9°, $[\alpha]_D$ −5°, ν_{max} 1756 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{23}BrO_2$: 62.81; H, 6.38; Br, 22.00. Found: C, 62.74; H, 6.40; Br, 21.84.

In another experiment, the rotation of the total crude product, $[\alpha]_D$ +19°, suggested the presence of about 80% of XVIa contaminated with IIIe. Proof of this point was obtained when the collected mother liquors on standing, deposited a "tree" of heavy needles, m.p. 134.6–136.1, $[\alpha]_D$ −4.5°, in the presence of short hexagonal rods, m.p. 176–181°, $[\alpha]_D$ +109°, having all the properties of IIIe.

B. By oxidation of the cis-bromohydrin XVIII. A solution of 0.75 g. of *cis*-bromohydrin, m.p. 125.0–126.5°, in 10 ml. of pyridine was oxidized, as above with 1.8 g. of chromic anhydride. The ethereal extracts yielded 0.64 g. of crystals, purified to 0.45 g. of XVIa, m.p. 135–136°, $[\alpha]_D$ −4.4°, having the correct infrared spectrum.

3-Methoxy-17α-chloroestra-1,3,5(10)-trien-16-one (XVIb). One gram of oxide IX in 25 ml. of chloroform was chilled in ice, shaken for 15 min. with 20 ml. of chilled concd. hydrochloric acid, and worked up with addition of water. Evaporation of the dried chloroform solution left 1.25 g. of a clear oil, the chlorohydrin XVb, which could not be crystallized. The latter in 15 ml. of pyridine was added to a stirred suspension of 2.4 g. of chromic anhydride in 24 ml. of pyridine at room temperature. After 1.5 hr. and mixture was treated as usual with ether and water. The ethereal residue was a clear glass weighing 1.14 g. Chromatography on 30 g. of 100-mesh silicic acid with chloroform yielded 0.91 g. of crystalline material which was further purified through slow crystallization from an evaporating ether solution to give clusters of heavy needles, 0.3 g. Recrystallization once more from ether resulted in pure chloro ketone XVIb, m.p. 111.1–112.5°, $[\alpha]_D$ −49.0°, ν_{max} 1761 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{23}ClO_2$: C, 71.57; H, 7.27; Cl, 11.12. Found: C, 71.36; H, 7.30; Cl, 11.42.

3-Methoxy-17α-bromoestra-1,3,5(10)-trien-16α-ol (XVIII). A solution of 6.45 g. of XVIa in 60 ml. of tetrahydrofuran was added in 10 ml. to a stirred suspension of 1.0 g. of lithium aluminum hydride in 100 ml. of dry ether at 1–6°. After another 3 min. water was cautiously added, followed by processing as described previously, leaving 6.50 g. of solvent-free residue, a thick, colorless oil. During chromatography on 200 g. of Florex, elution with 40% benzene–petroleum ether provided 4.51 g. of crystalline material. Two recrystallizations from acetone-pentane afforded XVIII, 2.68 g., as transparent plates, m.p. 125.0–126.5°, $[\alpha]_D$ +7.9°, ν_{max} 3558 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{25}BrO_2$: C, 62.46; H, 6.90; Br, 21.88. Found: C, 62.46; H, 6.64; Br, 21.66.

We were unable to demonstrate the presence of another isomer in any of the chromatographic fractions.

Reoxidation of this bromohydrin to the original ketone, described above, showed retention of halide configuration. Confirmation of the *cis* configuration was obtained by refluxing 0.50 g. of XVIII with 1 g. of potassium hydroxide in 25 ml. of methanol for 20 hr. under nitrogen. Extraction with ether and crystallization of the product twice from ether-pentane yielded 0.15 g. of square plates of 3-methoxyestra-1,3,5(10)-trien-16-one, XIX, m.p. 128.9–130.0°[13,32] depressing the melting point of IX but not that of an authentic specimen of the 16-ketone, with which the infrared spectrum was also identical.

The α-configuration of hydroxyl, and hence of bromide, was demonstrated by hydrogenolysis. A solution of 0.20 g. of XVIII in 60 ml. of ethyl alcohol was stirred 30 hr. with 0.5 g. of 5% palladium on calcium carbonate in a hydrogen atmosphere. After addition of an equal amount of catalyst stirring was continued for 40 hr. Concentration of the filtered solution gave a semicrystalline residue which was triturated with 50 ml. of ether and again filtered. Addition of petroleum ether to the filtrate followed by concentration to a small volume gave 0.12 g. of long rods, m.p. 113–116°. Recrystallization from ether–petroleum ether yielded pure 3-methoxyestra-1,3,5(10)-trien-16α-ol, m.p. 115–116°,[33] $[\alpha]_D$ +79.5°, ν_{max} 3660 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.72; H, 9.24.

Since the properties of the latter had apparently not been previously reported, it was prepared otherwise by hydrolysis of 0.54 g. of the acetate[34] in 20 ml. of methanol and 5 ml. of 10% aqueous potassium hydroxide for 2 hr. The solution, cooled, diluted, and filtered, yielded 0.49 g. of compound, m.p. 115–116°, identical in its infrared absorption with the above.

3-Methoxy-17β-bromoestra-1,3,5(10)-trien-16-one (XXa). A solution of 0.20 g. of 17α-bromo ketone XVIa and 0.50 g. of *p*-toluenesulfonic acid in 10 ml. of acetic acid was refluxed for 68 hr. The crude product, 0.17 g., obtained by evaporation *in vacuo* of a washed and dried benzene extract of the diluted reaction mixture, was chromatographed in benzene on 4 g. of silica. The semicrystalline material, 0.16 g., eluted with 1% ethyl acetate was recrystallized from methylene chloride–methanol and finally methanol, giving the pure XXa, m.p. 226–229° (softening at 223°), $[\alpha]_D$ −100°, ν_{max} 1761 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{23}BrO_2$: C, 62.81; H, 6.38. Found: C, 62.87; H, 6.69.

3-Methoxy-17β-chloroestra-1,3,5(10)-trien-16-one (XXb). The 17α-chloro ketone XVIb was epimerized exactly as described above during 75 hr. Chromatography of 0.15 g. of crude benzene-extracted product on 4 g. of silica yielded first 35 mg. of starting material. Further elution with benzene followed by 1% ethyl acetate, afforded 65 mg. of semicrystalline material. This was recrystallized from aqueous methanol to give 20 mg. of XXb crystallizing as a monohydrate, m.p. 211–213°, $[\alpha]_D$ −92°, ν_{max} 1762 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{23}ClO_2 \cdot H_2O$: C, 67.74; H, 7.48. Found: C, 67.65; H, 7.28.

3-Methoxy-17β-bromoestra-1,3,5(10)-trien-16β-ol (XXI). The bromo ketone XXa, 0.15 g. in 4 ml. of tetrahydrofuran, was reduced at −5° with 70 mg. of lithium aluminum hydride in 10 ml. of ether during 2 min. After the addition of 0.5 ml. of water and 0.1 ml. of 10% potassium hydroxide, the mixture was filtered through a Supercel-magnesium sulfate bed and the solvent removed. Recrystallization of the product, 145 mg., from acetone–petroleum ether yielded 100 mg. of the *cis*-bromohydrin XXI, m.p. 150–151° (softening at 136°). The analytical sample was obtained after two further recrystallizations from petroleum ether, m.p. 150–151°, $[\alpha]_D$ +70°, ν_{max} 3610 cm.$^{-1}$

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(32) M. N. Huffman and M. H. Lott, *J. Am. Chem. Soc.*, **75**, 4327 (1953).

(33) This compound has been mentioned but not characterized by M. N. Huffman, U. S. Pat. **2,779,773.**

(34) This was prepared from the 16β-hydroxy compound according to the directions given by M. N. Huffman and M. H. Lott, *J. Biol. Chem.*, **215**, 627 (1955).

Anal. Calcd. for $C_{19}H_{25}BrO_2$: C, 62.46; H, 6.90. Found: C, 62.47; H, 6.94.

The bromohydrin, 0.22 g. in 20 ml. of acetic acid, was refluxed with stirring and treated with three 2-g. portions of zinc dust at 30-min. intervals. The mixture was cooled, filtered, and concentrated; it was extracted with 1:1 ether–petroleum ether, the extracts being washed, neutralized, dried, and evaporated. Chromatography of the residue on 4 g. of silica and elution with 1:1 benzene–petroleum ether gave 130 mg. of semicrystalline material, recrystallized to 80 mg. of X, m.p. 67–69°, identical with earlier preparations.

Finally, treatment of XXI with alcoholic alkali by the procedure described earlier yielded 3-methoxyestra-1,3,5(10)-trien-16-one, XIX, identical with other samples.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY, SHIONOGI & CO., LTD.]

Angular-Substituted Polycyclic Compounds. I. Cyanation of Δ^4-Cholesten-3-one

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Optimum conditions for the cyanation of Δ^4-cholesten-3-one were found to be in dimethylformamide in the presence of ammonium chloride. By this method we have been able to synthesize pure samples of 5α- (IV) and 5β-cyanocholestanone (V). The rate of hydrolysis of these compounds has been examined and the respective configurations determined. Some interesting properties of the corresponding acid amides (II and III) of the 5α- and 5β-cyano compounds are discussed.

The introduction of a C-substituent to the angular position of a condensed alicyclic-ring system has been already achieved by many authors.[1] As far as it is known the C_5-substituted cholestane derivatives are Westphalen's diol,[2] Claisen rearrangement products of 3β-vinyloxy-Δ^4-cholestene,[1c] and the product from the fission of 5(6) β-epoxycholestan-3β-ol by a Grignard reagent.[3]

The action of a Grignard reagent on Δ^4-cholesten-3-one[4] or 7-ketocholesterol[5,6] produced only 1,2-addition products and not the anticipated 1,4-addition products. This clearly shows that in the case of a sterically hindered C_5 position the introduction of a bulky substituent, such as the solvated-Grignard reagent, is difficult. Therefore, we attempted the 1,4-addition of the small yet sufficiently nucleophilic CN^- ion on Δ^4-cholesten-3-one. It is well known that the 1,4-addition reaction of potassium cyanide to α,β-unsaturated ketones is a very useful preparative method in organic chemistry.[7]

When Δ^4-cholesten-3-one (I) was treated with potassium cyanide in boiling methanol, four reaction products together with some starting material were obtained and separated by chromatography on alumina. Following the order of the elution, cholestenone, 5α-cyanocholestanone (IV), the dimer (IX), 3α-amino-3β-hydroxy-5α-carboxycholestane lactam (II), and finally 3β-amino-3α-hydroxy-5β-carboxycholestane lactam (III) were obtained in 17.8%, 21.2%, 3.6%, 2.3%, and 26.2% yield, respectively. 5α-Cyanocholestanone (IV) could also be separated by direct crystallization from the reaction mixture before chromatography. It melts at 181–183° and the analytical values are in good agreement with the formula $C_{28}H_{45}ON$. The infrared spectrum in chloroform solution showed absorption bands at 2237 cm.$^{-1}$ (nitrile) and 1723 cm.$^{-1}$ (six-membered ring ketone) but no band corresponding to the α,β-unsaturated ketone. It did not exhibit selective absorption in the ultraviolet spectrum.

The (5 → 3) α-lactam (II) melted at 249–251° and in chloroform solution in the infrared it exhibited bands at 3697 cm.$^{-1}$ (free-OH), 3477 cm.$^{-1}$ (free —NH), 3327 cm.$^{-1}$ (bonded —N—H), 1705 cm.$^{-1}$ (lactam carbonyl), and 1682 cm.$^{-1}$ (associated lactam carbonyl). The (5 → 3)β-lactam (III) (m.p. 200–202°) displayed similar bands in the infrared, *i.e.* 3605 cm.$^{-1}$ (free —OH), 3445 cm.$^{-1}$ (free —N—H), 3300 cm.$^{-1}$ (bonded —NH), 1702 cm.$^{-1}$ (lactam carbonyl), and 1690 cm.$^{-1}$ (associated lactam carbonyl). Neither lactam showed the band of the noncyclic amide in the 1510–1620 cm.$^{-1}$ region.[8] These findings suggest that II and III are C_5 acid amides epimeric at C_5 and furthermore that they exist in the hemiketal

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