acetate was hydrolyzed with 5% alcoholic sodium hydroxide in the usual manner. The crude material was converted to the hydrochloride for purification. After recrystallization from ethanol–water there was obtained 250 mg. of hydrochloride, m.p. > 300° (dec.).

Anal. Calcd. for $C_{25}H_{42}ClNO_6$: C, 61.50; H, 8.68. Found: C, 61.28; H, 8.72.

A 200 mg. sample of the hydrochloride was dissolved in warm ethanol–water and basified with 20% sodium hydroxide solution. The precipitate was removed by filtration and washed well with water and with ethanol yielding 120 mg. of base, m.p. 276–278°.

Anal. Calcd. for $C_{25}H_{41}NO_6$: C, 66.49; H, 9.15. Found: C, 66.36; H, 9.12.

17β-Amino-5α-androstan-3β-yl β-D-Glucoside Hydrochloride (XVIII).—A solution of 488 mg. of the above hydrochloride in 35 ml. of acetic acid was hydrogenated at atmospheric pressure using 250 mg. of platinum oxide catalyst. The theoretical amount of hydrogen, 24 ml., was taken up within 30 minutes. The catalyst was removed by filtration and the solvent evaporated *in vacuo*. The residue was dissolved in ethanol–water and a few drops of hydrochloric acid added. On standing the salt precipitated and was recrystallized from ethanol–water, 350 mg., m.p. > 300° (dec.).

Anal. Calcd. for $C_{25}H_{44}ClNO_4$: C, 61.27; H, 9.05; N, 2.80. Found: C, 60.49; H, 8.98; N, 2.90.

17β-Amino-5α-androstan-3β-yl L-Arabinoside Hydrochloride (XX).—3β-Hydroxy-5α-androstan-17-one (7.7 g.) was reacted with 18 g. of acetobromarabinose according to the procedure described previously for III and yielded 9.0 g. of crude product. Recrystallization from ethanol–water gave 3.5 g. of pure 17-keto-5α-androstan-3β-yl L-arabinoside triacetate, m.p. 186°.

Anal. Calcd. for $C_{30}H_{44}O_9$: C, 65.67; H, 8.08. Found: C, 65.42; H, 7.96.

Conversion of the above product to the 17-oxime and hydrogenation of this material in acetic acid solution produced 2.5 g. of 17β-amino-5α-androstan-3β-yl L-arabinoside triacetate (XIX), m.p. 105–110°.

Anal. Calcd. for $C_{30}H_{47}NO_8$: C, 65.55; H, 8.62; N, 2.55. Found: C, 65.33; H, 8.74; N, 2.27.

Hydrolysis of 2.0 g. of the triacetate with barium methoxide in methanol[18] and conversion of the resulting base to the hydrochloride yielded 1.0 g. of final product, m.p. 235° (dec.). In spite of repeated purification attempts a satisfactory analytical sample could not be obtained.

Anal. Calcd. for $C_{24}H_{42}ClNO_5$: C, 62.65; H, 9.20; N, 3.04; Cl, 7.71. Found: C, 60.85; H, 9.08; N, 2.79; Cl, 8.06.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A., MEXICO, D. F., MEX.]

Optical Rotatory Dispersion Studies. XXXVII.[1,2] Steroids. CXLVI.[3] On the Mechanism and Stereochemical Course of the Bromination of 3-Keto Steroids and their Enol Acetates

BY R. VILLOTTI, H. J. RINGOLD AND CARL DJERASSI

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Kinetically controlled bromination of 2α-methylandrostan-17β-ol-3-one acetate (VIII), androstan-17β-ol-3-one acetate (XIV), their 19-nor analogs (Xa, XIIa) and their respective enol acetates (IX, XI, XIII, XV) has led to the following conclusions: (a) in the presence of steric inhibition, the kinetic product is the equatorial and not the axial bromo ketone; (b) in the absence of such steric factors, appreciable amounts of equatorial bromo ketone may accompany the axial isomer. These results require some modification of Corey's (ref. 5) concept that the bromination product of kinetic control is always the axially oriented bromo ketone. Comparison experiments of ketones and their enol acetates indicate operation of a similar mechanism, which cannot involve diaxial opening of an intermediate bromonium ion since Br–Cl led to bromo- rather than chloro-ketones. Attention is called to the observation that the exclusive formation of Δ^2-enols of 3-keto steroids is altered upon removal of the angular methyl group, appreciable amounts of the Δ^3-enol being observed among 19-nor-3-keto steroids.

Introduction

In the two preceding papers[1,3] it was shown that kinetically controlled bromination of a 2α-methyl-3-keto-5α steroid I or its enol acetate leads to the 2α-bromo-2β-methyl-3-ketone II existing in the boat conformation, while the product of thermodynamic control is the 2β-bromo-2α-methyl-3-ketone III. This observation, which was first uncovered by optical rotatory dispersion measurements,[4] raises some interesting questions with respect to the stereochemical course and mechanism of the bromination of keto steroids and their enol acetates. The present investigation represents an experimental attempt to answer some of the outstanding problems in this field.

The most important and generally accepted views on the stereochemistry of the bromination of cyclohexanones in general and keto steroids in particular are due to Corey.[5] These generalizations state that the kinetically controlled bromination product is *always*[5b] that in which the bromine atom assumes an axial orientation, because orbital overlap in the transition state is most favorable in such a geometric arrangement. If there exist no serious steric interactions between the axial bromine atom and other substituents (*e.g.*, an axial methyl group two carbon atoms removed) then the kinetic product is also the thermodynamically favored one. In the presence of such steric interference, the axial bromo ketone is converted into the equatorial one under conditions of thermodynamic control. Application of these rules[5] to the bromination of 2α-methyl-3-keto steroids (I) leads to the conclusion[6] that the kinetic product should be the 2β-bromo-2α-methyl-3-ketone III which is contrary to the experimental observations.[1,3] A possible rationalization for this divergence would be the assumption that bromination of 2α-methyl-3-keto steroids pro-

(1) Paper XXXVI, C. Djerassi, N. Finch, R. C. Cookson and C. W. Bird, THIS JOURNAL, **82**, 5488 (1960).

(2) α-Haloketones (Part 8); for Part 7 see ref. 1

(3) Paper CXLV, R. Mauli, H. J. Ringold and C. Djerassi, THIS JOURNAL, **82**, 5494 (1960).

(4) C. Djerassi, "Optical Rotatory Dispersion. Applications to Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1960.

(5) (a) E. J. Corey, THIS JOURNAL, **75**, 2301 (1953); **76**, 175 (1954); (b) *Experientia*, **9**, 329 (1953).

(6) See Y. Mazur and F. Sondheimer, THIS JOURNAL, **80**, 5220 (1958).

ceeds by bottom-side attack on the "boat-like" form of the enol but, before discussing this further, two other possibilities must be considered.

Barton and Cookson[7] have suggested an alternate mechanism for the bromination of cyclohexanones by analogy to the well-documented[8] addition of bromine to cyclohexenes involving diaxial opening of an intermediate bromonium ion. In the case of a 3-keto steroid this could be visualized as proceeding through IV and V, in which case the final product would be a 2β-bromo-3-ketone VI in accord with Corey's prediction.[5] It should be noted, however, that if such a mechanism is operative, it would imply initial rearward approach of the reagent in the formation of the α-bromonium ion, rather than the originally envisaged[5] topside entry. As demonstrated in one of our preceding papers,[1] this cannot apply to the corresponding enol acetate, since kinetically controlled bromination led directly to the equatorial 2α-bromo-3-ketone VII. It remained to be seen whether the mechanism of bromination of ketones and their enol acetates is different as has in fact been suggested recently[9] in order to rationalize the predominant formation of an equatorial 6α-bromo-7-keto steroid in the kinetically controlled bromination of a 7-keto steroid enol acetate.

The third possibility is that under certain circumstances direct equatorial bromination, *i.e.*, bottom-side approach to the enol of a 3-keto steroid, is possible and, as shown in the sequel, this is the alternative favored by us.

Discussion

We started out with two assumptions for which experimental evidence is provided below: (a) There exists no fundamental difference in the stereochemical course of the bromination of ketones and their enol acetates. (b) Corey's view[5] with respect to axial entrance (topside in a 3-keto steroid) of bromine under kinetic control is only operative when there is no steric hindrance to axial approach of the reagent and that direct equatorial entry (bottom-side approach to the enol of a 3-keto steroid) is the preferred course when such steric hindrance exists. Indeed Corey and Sneen[10] have shown that such (equatorial) approach by as small an atom as deuterium is possible in the ketonization of a steroidal Δ^6-en-7-ol, although axial entry predominates. The same authors have also noted that under apparent kinetic control, chlorination of this enol leads largely to the equatorial 6α-chloro-7-ketone.

In order to offer an experimental answer to as many of these problems as possible, we selected the following substrates: 2α-methylandrostan-17β-ol-3-one acetate (VIII)—a ketone of type I, whose kinetic bromination behavior first raised doubts as to the general applicability of the axial bromination concept.[5] 2α-Methyl-19-norandrostan-17β-ol-3-one acetate (Xa), a close analog of VIII but where removal of the angular methyl group now eliminates any steric hindrance to axial approach by an entering species. In order to examine the possible role which the methyl group at C-2 may be playing, 19-norandrostan-17β-ol-3-one acetate (XIIa) and androstan-17β-ol-3-one acetate (XIV) were also included. Furthermore, the enol acetates IX, XI, XIII and XV of these four ketones were also subjected, wherever possible, to identical bromination conditions so as to answer the question whether bromination of the enol acetate and ketone proceeded in a similar or different fashion.

Kinetic control in the bromination of the ketones is experimentally more difficult than of their enol acetates, because the former react only slowly and sometimes not at all in the absence of hydrogen bromide. Nevertheless, where possible, bromination was attempted in acetic acid solution in the presence of sodium acetate. Kinetically controlled bromination of the enol acetates was performed under conditions[1] (acetic acid–carbon tetrachloride–sodium acetate) where the unstable axial bromo ketone (*e.g.*, II, VI) remained largely unchanged and was not transformed into the thermodynamically favored isomer (*e.g.*, III, VII). Finally, in order to secure evidence for or against the possibility[7] of external nucleophilic attack on a bromonium ion (IV → V), all of the above-mentioned eight substrates were treated with Br–Cl. If such a mechanism were operative, then displacement of the bromonium ion by chloride should lead to chloro ketones, just as Br–Cl addition to Δ^5-steroidal olefins affords[11] the diaxial 5α-bromo-6β-chloro derivative.

We may anticipate the subsequent discussion by noting that in no case was a chloro ketone obtained and that kinetically controlled addition of Br–Cl afforded the same product as kinetically controlled bromination. External displacement[7] of an intermediate bromonium ion by nucleophilic halogen can therefore be excluded as a mechanism for the bromination of ketones or their enol acetates. We shall now turn to a detailed evaluation of the experimental evidence and its mechanistic and stereochemical implication. It should be noted that in practically each experiment, the total crude reaction product (prior to recrystallization or chromatography) was analyzed by procedures outlined below in order to preclude the possible enrichment of one isomer over another during subsequent purification steps.

Kinetically controlled bromination of 2α-methylandrostan-17β-ol-3-one acetate (VIII) or of its enol acetate IX has already been shown[3] to yield the 2α-bromo-2β-methyl-3-ketone XVI existing in the boat form II. As shown in the Experimental section, Br–Cl addition in the presence of sodium acetate leads to the same product with its characteristic[1,3] negative Cotton effect[4] of moderate amplitude.

Of crucial importance were the corresponding results with the hitherto undescribed 19-nor analog Xa. This substance was prepared by methylation (*via* the 2-glyoxalate[12]) of 19-norandrostan-17β-ol-3-one (XIIb)[13] or alternatively by lithium–am-

(7) D. H. R. Barton and R. C. Cookson, *Quart. Revs.*, **10**, 44 (1956).
(8) G. H. Alt and D. H. R. Barton, *J. Chem. Soc.*, 4284 (1954).
(9) E. R. H. Jones and D. J. Wluka, *ibid.*, 911 (1959).
(10) E. J. Corey and R. A. Sneen, THIS JOURNAL, **78**, 6269 (1956).
(11) See J. B. Ziegler and A. C. Shabica, *ibid.*, **74**, 4891 (1952).
(12) H. J. Ringold, E. Batres, O. Halpern and E. Necoechea, *ibid.*, **81**, 427 (1959).
(13) A. Bowers, H. J. Ringold and E. Denot, *ibid.*, **80**, 6115 (1958).

monia reduction of 2α-methyl-19-nortestosterone (XVII), which was synthesized from 19-nortestosterone through methylation of its sodium glyoxalate dervative, followed by acetylation at C-17. Treatment of 2α-methyl-19-norandrostan-17β-ol-3-one (Xb) with isopropenyl acetate in the presence of *p*-toluenesulfonic acid afforded the enol diacetate XI, which was also required for bromination studies.

In view of the fact that kinetically controlled bromination proceeds particularly easily and cleanly with enol acetates, 2-methyl-19-nor-Δ^2-androsten-3,17β-diol diacetate (XI) was treated first with bromine in the presence of sodium acetate. The resulting crystalline bromo ketone (after purification—the crude product containing actually 59% of XVIII and 41% of XIX) was shown to be the axial 2β-bromo-2α-methyl-19-norandrostan-17β-ol-3-one acetate (XVIII) by the following evidence:

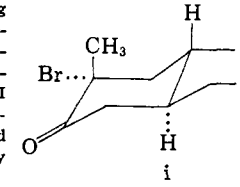
The location of the bromine atom at C-2 followed from the course of the dehydrobromination of this substance with lithium bromide and lithium carbonate[14] followed by saponification at C-17, which led smoothly to 2-methyl-19-nor-Δ^1-androsten-17β-ol-3-one (XX), uncontaminated by the Δ^4-isomer XVII. The axial orientation of the bromine atom was established by its ultraviolet absorption spectrum[15] and most importantly, by the strong positive Cotton effect[4] with a peak at $[\alpha]_{330-332.5}$ +3410°. In agreement with the axial haloketone rule[16] this is only consistent with a 2β-bromo-2α-methyl-3-keto formulation (XVIII) in which ring A has the usual chair conformation (III). That this isomer is also the thermodynamically preferred one is shown by the observation that it remains unchanged after equilibration with hydrogen bromide, conditions under which the corresponding analog with an angular methyl group (XVI = II) is isomerized (to III).

This experiment is of considerable significance when compared with the parallel one[3] of its homolog IX with an angular methyl group. It shows that this latter substituent plays the main role and that in its absence, axial entry of bromine can be accomplished readily. Furthermore, the above experiment shows that under proper circumstances, axial as well as equatorial bromination (*i.e.*, top and bottom-side approach) of enol acetates is feasible and that no special mechanism needs to be involved[9] for the bromination of enol acetates.

Kinetically controlled bromination of the corresponding ketone, 2α-methyl-19-norandrostan-17β-ol-3-one 17-acetate (Xa), with bromine and sodium acetate or Br–Cl and sodium acetate gave a similar result, the Cotton effect peak at 332.5 mμ of the crude products amounting to +2170° and +1865°, respectively (as compared to $[\alpha]_{330}$ +2450° for the crude product in the bromination of the enol acetate XI). This implied the presence of some of the equatorial isomer, 2α-bromo-2β-methylandrostan-17β-ol-3-one acetate (XIX),[17] as the *concurrent kinetic product*, since equilibration with hydrogen bromide raised the peak of the Cotton effect +3500° corresponding to the pure axial isomer XVIII.

In order to calculate the proportion of equatorial isomer XIX during the kinetically controlled bromination of the ketone Xa, we must decide on a value for the rotation of pure XIX at 330 mμ and the following approximations were used to arrive at a plausible figure. The obvious standard would be 2α-bromoandrostan-17β-ol-3-one acetate (XXI),[18] whose rotatory dispersion curve has already been reported.[19] Its peak (+650°) occurs at 307.5 mμ, a wave length shift in agreement with its equatorial orientation,[20] and for proper comparison the rotation (+400°) at 330 mμ corresponding to the peak of XVIII must be used. In terms of molecular rotation [φ],[21] this amounts to +1600°, but two corrections must be made. In general, 3-keto steroids of the 19-nor series shown an increased amplitude of their Cotton effect over their higher homologs with the angular methyl group and in terms of their peak rotations, this amounts roughly[22] to [φ] +1100°. Secondly, the axial[17] 2β-methyl group in XIX would be expected to make a dextrorotatory contribution of approximately [φ] +1200°,[23] so that the sum of these three factors, [φ] +3900°, is probably the most reasonable approximation for the molecular rotation of XIX at 330 mμ. By using $[\phi]_{330}$ +14300° ($[\alpha]_{330}$ +3500°) for the pure axial isomer XVIII, it is now possible to calculate the proportion of axial and equatorial bromo ketones in the two kinetically controlled brominations of 2α-methyl-19-norandrostan-17β-ol-3-one acetate (Xa) from their peak rotations of +2170° ([φ] +8900) and +1865° ([φ] +7900°). These amount to, respectively, 48 and 38% axial (XVIII) bromination and it is interesting to note that in the kinetically controlled brominations of the enol acetate XI, the crude bromo ketone exhibited (see Experimental) a peak rotation corresponding to 53% (Br–Cl addition) and 59% (direct bromine addition) of axial bromination product.

From these results, the conclusion must be reached that quantitatively, the proportion of axial and equatorial isomer may vary with the exact experimental conditions but that even in the absence of the angular methyl group, the equatorial bromoketone may be encountered under kinetic control. It is also clear from these observations



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(14) R. Joly and J. Warnant, *Bull. soc. chim. France*, 367 (1958).

(15) R. C. Cookson, *J. Chem. Soc.*, 282 (1954).

(16) C. Djerassi and W. Klyne, THIS JOURNAL, **79**, 1506 (1957); Chapter 9 in ref. 4.

(17) In contrast to its higher homolog XVI with the angular methyl group, we believe that this substance exists in the standard chair form (i) with an equatorial bromine atom as compared to the boat form II of XVI. This could not be proved directly, because XIX could not be isolated in pure form for spectroscopic or rotatory dispersion examination.

(18) J. Fajkos and F. Sorm, *Chem. Listy*, **52**, 2115 (1958).

(19) Figure 9-1 on p. 117 of ref. 4.

(20) See C. Djerassi, J. Osiecki, R. Riniker and B. Riniker, THIS JOURNAL, **80**, 1216 (1958).

(21) The symbol [φ] rather than [M] has been proposed by the late Prof. W. Moffitt and will be accepted by the appropriate IUPAC nomenclature commission.

(22) C. Djerassi, O. Halpern, V. Halpern and B. Riniker, THIS JOURNAL, **80**, 4001 (1956).

(23) Private communication from Dr. W. Klyne, Postgraduate Medical School, London.

that ketones and enol acetates behave in a very similar manner.

Turning now to 3-keto steroids without a 2α-methyl substituent, the kinetically controlled bromination (bromine and sodium acetate) of the enol acetate XXII of cholestan-3-one has already been reported[1] to yield essentially pure 2α-bromo-3-ketone (VII). We have also investigated the addition of Br–Cl in the presence of sodium acetate to androstan-17β-ol-3-one acetate (XIV) and to its enol acetate XV and in each instance, the total crude product consisted almost entirely of the equatorial 2α-bromo ketone XXI.[18] It follows, therefore, that kinetically controlled bromination of a 3-keto steroid with an angular methyl group *under the conditions employed by us* proceeds exactly as the corresponding reaction[1] with an enol acetate and leads directly to the equatorial bromo ketone—topside (axial) attack of the half-chair form of the enol by bromine being inhibited by the angular methyl group.

By analogy to the above-described experiments in the 2α-methyl-3-keto steroid series (VIII *vs.* Xa), one would also expect in the 3-keto steroid series (XIV *vs.* XIIa) a marked change upon removal of the steric factor—the angular methyl group. For this purpose, 19-norandrostan-17β-ol-3-one acetate (XIIa) was transformed into its crystalline enol acetate XIII and this apparently homogeneous substance was subjected to kinetically controlled bromination with bromine or Br–Cl in the presence of sodium acetate. The spectroscopic properties of the total crude reaction mixture indicated the anticipated formation of an axial bromo ketone and this was also supported by the positive Cotton effect with a peak at 332.5 mμ. This peak, however, was remarkably low (+738° and +962°) and its amplitude remained essentially unchanged upon equilibration with hydrogen bromide, indicating that the product formed under kinetic control was also the thermodynamically more favored one. When the crude product was subjected to dehydrobromination with lithium bromide and lithium carbonate,[14] there was isolated a chromatographically separable mixture of 19-nor-Δ^2-androsten-17β-ol-3-one acetate (XXVII) and the known[24] 19-nortestosterone acetate (XXVIII). Since these dehydrobromination conditions[14] do not cause rearrangement[1,3] (a further model reaction—dehydrobromination of XXI—yielded only Δ^1-androsten-17β-ol-3-one acetate), one must conclude that the product of bromination of the enol acetate XIII consists of a mixture of 2β-bromo-19-norandrostan-17β-ol-3-one acetate (XXIII) and its 4β-bromo isomer XXIV. Indeed, this conclusion is in excellent agreement with the rotatory dispersion data.

In order to arrive at standard values for the first extrema of the Cotton effects of the components of this mixture, XXIII and XXIV, one can take as reference compounds 2β-bromoandrostan-17β-ol-3-one acetate (XXV)[18] ($[\phi]_{332.5}$ +8200°)[19] and 4β-bromoandrostan-17β-ol-3-one acetate (XXVI)[18] ($[\phi]_{332.5}$ −7400°)[18] and add to these values $[\phi]$ +1100° as the increment (*vide supra*) of the 19-nor series. We thus obtain $[\phi]$ +9300° for the 2β-bromo-3-ketone XXIII and $[\phi]$ −8500° for the 4β-bromo isomer XXIV and from these values it can be calculated that in the bromination of the enol acetate XIII 31% (bromine and sodium acetate) and 37% (Br–Cl and sodium acetate) of the 4β-bromo isomer XXIV is formed, the rest being the 2β-bromo ketone XXIII. The calculations are substantiated by the dehydrobromination experiments, approximately twice as much Δ^1-19-nor-3-ketone XXVII (47%) having been isolated as compared to the Δ^4-isomer XXVIII (22%).

These results indicate that the enol acetate XIII represents actually a 2:1 mixture of the Δ^2- and Δ^3-enols, which is in marked difference to the homogeneity of the enol acetates containing an angular methyl group (XV, XXII) or a 2α-methyl substituent (XI). In the latter case, hyperconjugation probably plays the chief role, while in the former (XV, XXII) conformational factors have been cited[25] as being responsible for the exclusive enolization toward C-2. It is pertinent to note that removal of the angular methyl group (XIV *vs.* XIIa) considerably reduces the energy differences between the Δ^2- and the Δ^3-enols. That this is not just peculiar to the enol acetate XIII is demonstrated in the Br–Cl addition to the ketone 19-norandrostan-17β-ol-3-one acetate (XIIa) itself, the product composition derived from rotatory dispersion measurements amounting to 63% 2β-bromo- (XXIII) and 37% 4β-bromo- (XXIV) 3-ketone.

Conclusion

(a) **Stereochemical Conclusions.**—Our results are in *qualitative* agreement with Corey's views[5] in that formation of axial bromo ketones is possible under kinetic control when there exists no steric hindrance to axial approach of the reagent. *Quantitatively*, there is a considerable discrepancy in that even in the absence of steric factors, substantial amounts of equatorial bromo ketone can be isolated.

The most important modification in Corey's scheme[5] which must be made is that the axial ketone is *not always* formed under kinetic control Indeed, as demonstrated for 3-keto steroids and enol acetates (XIV, XV, XXII), virtually exclusive formation of the equatorial isomer is possible and this would appear to be the preferred path in the presence of steric interference as is caused by the angular methyl group. We believe that precisely the same stereochemical course operates in the earlier discussed[1,3] bromination of 2α-methyl-3-keto steroids (I) and that the initial product is the equatorial 2α-bromo ketone XVI in the chair conformation, which subsequently "flips" into the boat conformation II, since such a change relieves both the unfavorable electrostatic interaction of the equatorial bromine atom as well as the diaxial interaction between the β-oriented methyl groups at C-2 and C-10. There seems to be no forceful argument (*vide infra* and ref. 27) to assume that in this instance axial bromination proceeds through the half-boat form of the enol, since

(24) J. A. Hartman, A. J. Tomasewski and A. S. Dreiding, THIS JOURNAL, **78**, 5662 (1956).

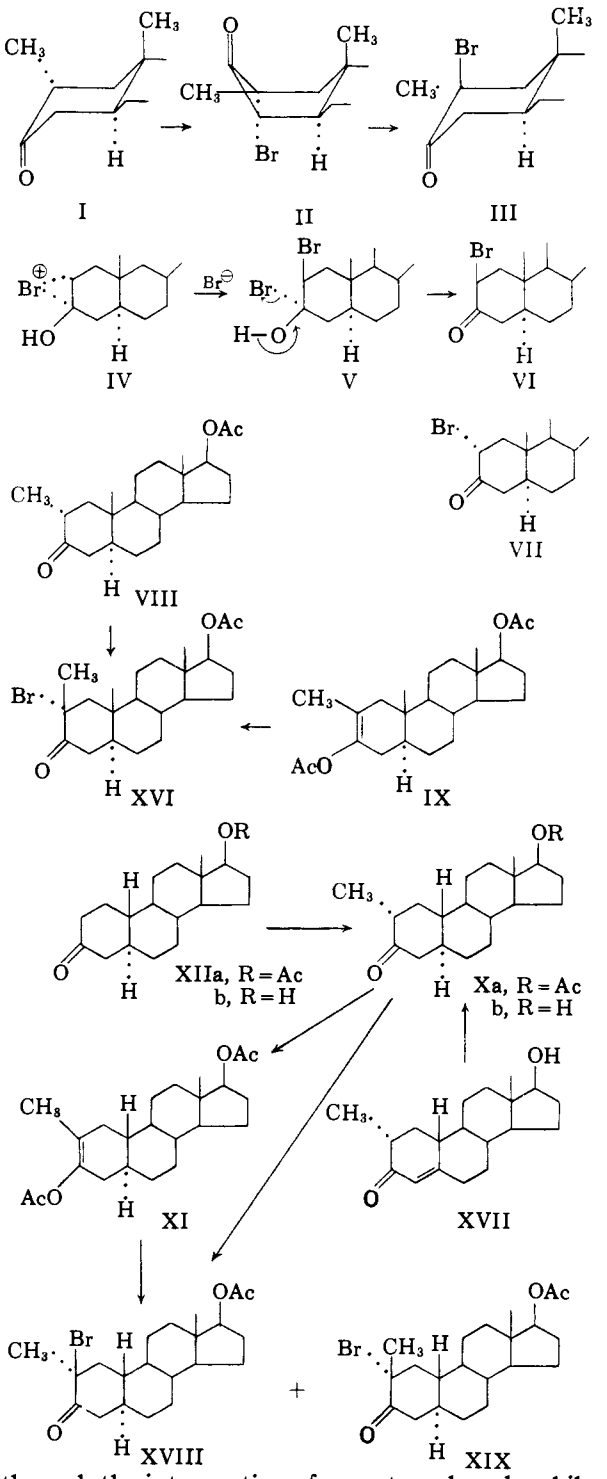
(25) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publ. Corp., New York, N. Y., 1959, pp. 276–279 and chapter 8.

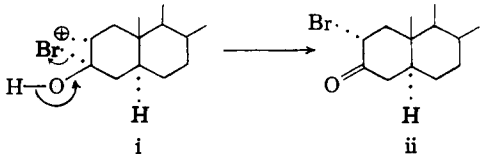
the half-chair form is energetically favored[25] and the additional methyl group at C-2 would tend to increase this energy difference.

Nevertheless, it should be noted that the general stereochemical picture of the halogenation of keto steroids is not completely consistent. Indeed, the only two examples cited by Corey[5] for axial bromination in the presence of steric interference by an angular methyl group are the 7-keto and 12-keto steroids. In both instances,[10,26] standard bromination at room temperature in acetic acid was not successful and either a change of solvent[26a] or elevated temperatures[26b] or five days reaction time[26b] had to be employed. Furthermore, the yield of 11β-bromo ketone was very poor and in any event it is not inconceivable that the product composition was changed during the purification. For instance, in the bromination of 7-ketocholestanyl acetate, chloroform had to be employed[26a] and evaporation of the solvent yielded a solid which was then recrystallized to afford predominantly the axial 6β-bromo-7-ketone. It is noteworthy that under different conditions and work-up, kinetically controlled bromination[9] of the enol acetate yielded predominantly the equatorial 6α-bromide.

We believe that a reinvestigation of the kinetically controlled bromination of 7- and 12-keto steroids and of the latter's enol acetate may be indicated. If the predominant presence of the axial bromo ketone can be demonstrated in the total crude reaction product, then only two possibilities remain, both of them rather intriguing ones. First, that there is something special about the stereochemical course of bromination of central rings in the steroid series. Or secondly, that our results, which apply to brominations in ring A with its increased conformational mobility, should be interpreted as follows: whenever there is steric hindrance to axial approach of the reagent to the half-chair of the enol, the ring reacts in a boat-like conformation to permit axial attack in the transition state[27] and that the product then "flips" immediately into the chair form in which the bromine atom is equatorial, provided there is no additional substituent at C-2 (*e.g.*, II). In other words, Corey's generalization[5] might be correct for the transition state, but not necessarily in terms of the products actually isolated. Irrespective of which of the two alternatives proves ultimately to be the right one, the rule[5] of axial bromination under kinetic control—with its directly stated application to isolated products—must be modified.

(b) **Mechanistic Conclusions.**—No special mechanism for the bromination of enol acetates seems necessary since our results indicate that enol acetates and ketones react very similarly. Diaxial opening of an intermediate bromonium ion[28] through the intervention of an external nucleophile is excluded by the observation that Br–Cl leads invariably to bromo- rather than chloroketones.

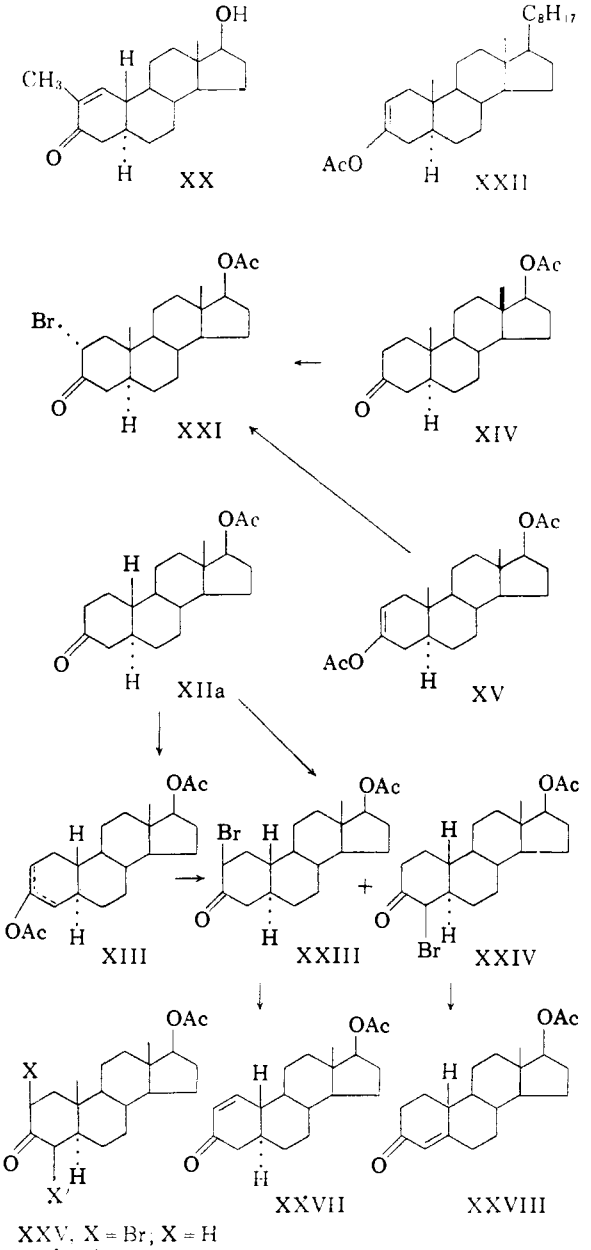




(26) (a) T. Barr, I. M. Heilbron, E. R. H. Jones and F. S. Spring, *J. Chem. Soc.*, 334 (1938); D. R. James and C. W. Shoppee, *ibid.*, 1064 (1956); (b) E. Seebeck and T. Reichstein, *Helv. Chim. Acta*, **26**, 536 (1943); T. F. Gallagher and W. P. Long, *J. Biol. Chem.*, **162**, 521 (1946).

(27) This implies, of course, that axial approach to the enol in the half-boat form must be much more rapid than equatorial attack on the predominant half-chair form, which is energetically favored.

(28) It is conceivable that in those cases where steric factors inhibit axial approach, the reaction proceeds by internal collapse of an intermediate bromonium ion i, the net result being the formation of the equatorial bromo ketone ii. Alternatively, the bromination may proceed by direct equatorial attack of positive halogens on the electron-rich center at C-2.



XXV, X = Br, X = H
XXVI, X = H; X = Br

It may also be pertinent to mention that while the conversion of a 2α-bromo-2β-methyl-3-ketone II to the 2β-bromo-2α-methyl-3-ketone III in the presence of hydrogen bromide must involve debromination—*cum* rebromination—this does not necessarily apply to bromo ketones bearing a hydrogen atom at the bromine-containing carbon atom. In the latter, inversion may proceed directly through the enol.

Experimental[29]

2α-Methyl-19-nortestosterone (XVII).—19-Nortestosterone[24,30] (10 g.) in 300 cc. of anhydrous, thiophene-free benzene was stirred at room temperature for 4 hr. in an atmosphere of nitrogen with 12 cc. of ethyl oxalate and 6.0 g. of sodium methoxide. Hexane (750 cc.) was added, the precipitated sodium salt was filtered, washed well with hexane and dried overnight in a desiccator. The dry solid was added in small portions with stirring to a cold solution of 40 cc. of concd. hydrochloric acid in 500 cc. of water, the precipitate was filtered after 45 min., washed with water and dried overnight *in vacuo*. The amorphous solid was then heated under reflux for 48 hr. with 300 cc. of acetone, 20 g. of potassium carbonate and 30 cc. of methyl iodide, an additional 15 cc. of methyl iodide having been added after the first 24 hr. The solution was filtered, the acetone was evaporated and the residue was taken up in methylene chloride, washed once with 2% sodium hydroxide, then water, dried and evaporated. The oil was dissolved in a solution of 4.0 g. of sodium in 500 cc. of absolute ethanol and allowed to stand at room temperature for 48 hr. Dilution with water, extraction with methylene chloride, washing with water, drying and evaporation afforded a gummy residue which was chromatographed on 350 g. of alumina (ethyl acetate-washed). Elution with benzene–ether (8:2) afforded a crystalline product, which was recrystallized twice from acetone–hexane; yield 6.5 g., m.p. 176–178°, $[\alpha]D$ +93° (chloroform); λ_{max}^{EtOH} 238–240 mμ, log ε 4.21, $\lambda_{max}^{CHCl_3}$ 6.02 and 6.17 μ; R.D. in dioxane (*c* 0.057): $[\alpha]_{700}$ +60°, $[\alpha]_{589}$ +91°, $[\alpha]_{321.5}$ −1065°, $[\alpha]_{300}$ −947°, $[\alpha]_{287.5}$ −967°, $[\alpha]_{250}$ +3770°.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12: H, 9.79; O, 11.10. Found: C, 78.71; H, 9.72; O, 11.57.

The **reddish 2,4-dinitrophenylhydrazone** was prepared by the acetic acid technique[31] and recrystallized from chloroform–ethanol; m.p. 206–207°, $\lambda_{max}^{CHCl_3}$ 384–386 mμ, log ε 4.45.

Anal. Calcd. for $C_{25}H_{32}N_4O_5$: C, 64.08: H, 6.88: N, 11.96; O, 17.07. Found: C, 64.44; H, 6.94; N, 11.62; O, 17.01.

For spectral comparison **2α-methyltestosterone**[12] **2,4-dinitrophenylhydrazone was also** prepared, m.p. 244–246°, $\lambda_{max}^{CHCl_3}$ 384–388 mμ, log ε 4.46.

Anal. Calcd. for $C_{26}H_{34}N_4O_5$: C, 64.71; H, 7.10; N, 11.61; O, 16.58. Found: C, 64.84; H, 7.18; N, 11.48; O, 16.42.

2α-Methyl-19-norandrostan-17β-ol-3-one (Xb). (a) **From 19-Norandrostan-17β-ol-3-one (XIIb).**—19-Nortestosterone (30 g.) was reduced with lithium in liquid ammonia as described earlier[12] and the entire crude product (29 g.) was stirred in 900 cc. of dry, thiophene-free benzene for 5 hr. with 30 cc. of ethyl oxalate and 18 g. of sodium methoxide. The glyoxalate was processed exactly as described above for 19-nortestosterone leading eventually to 15 g. of 2α-methyl-19-norandrostan-17β-ol-3-one (Xb), m.p. 135–137°, $[\alpha]D$ +70° (chloroform), λ_{max}^{EtOH} 274–280 mμ, log ε 1.99; R.D. in methanol (*c* 0.055): $[\alpha]_{589}$ +66°, $[\alpha]_{307.5}$ +1253°, $[\alpha]_{250}$ −1670°.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41; O, 11.02. Found: C, 78.64; H, 10.49; O, 11.24.

(b) **From 2α-Methyl-19-nortestosterone (XVII).**—To 300 cc. of anhydrous liquid ammonia containing 0.3 g. of lithium metal was added in a steady stream a solution of 3.0 g. of 2α-methyl-19-nortestosterone (XVII). After 2 min. of vigorous stirring, 15 g. of ammonium chloride was added in portions whereupon the blue color was discharged. The ammonia was allowed to evaporate over a period of 4–5 hr., water was added and the product was extracted with ether, washed with water, dried and evaporated. The residue was purified by chromatography on 95 g. of ethyl acetate-washed alumina and elution with mixtures of benzene and ether (8:2, 7.5:2.5). Recrystallization from acetone–hexane afforded 2.45 g. of 2α-methyl-19-norandrostan-17β-ol-3-one, m.p. 135–137°, $[\alpha]D$ +66° λ_{max}^{KBr} 5.86 μ, which proved to be identical with the material prepared according to procedure a.

Acetylation at room temperature for 24 hr. with acetic anhydride–pyridine and recrystallization from hexane provided **2α-methyl-19-norandrostan-17β-ol-3-one acetate (Xa)**, m.p. 135–137°, $[\alpha]D$ +54° (chloroform), λ_{max}^{EtOH} 280–286 mμ, log ε 1.76; $\lambda_{max}^{CS_2}$ 5.76, 5.84 and 8.06 μ; R.D. in methanol (*c* 0.059): $[\alpha]_{589}$ +61°, $[\alpha]_{307.5}$ + 1520°, $[\alpha]_{250}$ −1617.

(29) All melting points are uncorrected and were obtained on the Fisher–Johns block. We are indebted to Dr. J. Matthews and staff for all physical measurements as well as for many halogen analyses. The remaining microanalyses were performed by Mr. J. F. Alicino, Metuchen, N. J.

(30) A. J. Birch, *J. Chem. Soc.*, 367 (1950); A. L. Wilds and N. A. Nelson, THIS JOURNAL, **75**, 5366 (1953).

(31) C. Djerassi, *ibid.*, **71**, 1003 (1949).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70: O, 14.44. Found: C, 75.56; H, 9.92; O, 14.64.

2-Methyl-Δ^2-19-norandrostene-3,17β-diol Diacetate (XI).—A mixture of 1.5 g. of 2α-methyl-19-norandrostan-17β-ol-3-one (Xb), 100 cc. of isopropenyl acetate and 300 mg. of p-toluenesulfonic acid monohydrate was distilled slowly for 2 hr., approximately 10 cc. of solvent being removed during this time and the solution was then heated under reflux for 24 hr. Evaporation of the solvent *in vacuo* left a brownish oil, which was taken up in ethyl acetate, washed with water, dried and evaporated. The semi-crystalline residue was decolorized with Norit in methanol solution and after two recrystallizations from methanol, the enol acetate XI (1.20 g.) exhibited m.p. 155–157°, $[\alpha]_D$ +79° (chloroform); $\lambda_{max}^{CCl_4}$ 5.69, 5.74, 8.09 and 8.23 μ. The identical product (405 mg.) was obtained when 600 mg. of Xb was heated under reflux for 4 hr. with 20 cc. of acetic anhydride and 3 cc. of acetyl chloride.

Anal. Calcd. for $C_{26}H_{34}O_4$: C, 73.76; H, 9.15; O, 17.09. Found: C, 73.97; H, 9.09; O, 16.99.

Δ^2-Androstene-3,17β-diol Diacetate (XV).—Androstan-17-β-ol-3-one (dihydrotestosterone) (1.0 g.) was treated with isopropenyl acetate as described in the preparation of XI to yield, after recrystallization from methanol, 0.85 g. of the enol acetate XV, m.p. 168–170°, $[\alpha]_D$ +48° (chloroform).

Anal. Calcd. for $C_{25}H_{34}O_4$: C, 73.76: H, 9.15; O, 17.09. Found: C, 73.96; H, 9.09; O, 16.82.

$\Delta^{2(\text{and } 3)}$-19-Norandrostene-3,17$\beta$-diol Diacetate (XIII).—Similar treatment of 1.05 g. of 19-norandrostan-17β-ol-3-one (XIIb)[18] with isopropenyl acetate and recrystallization from methanol provided 0.90 g. of the enol acetate XIII, m.p. 110–111°, $[\alpha]_D$ +48.5° (chloroform); λ_{max}^{KBr} 5.71, 5.78, 8.10 and 8.18 μ.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 73.30; H, 8.95; O, 17.75. Found: C, 73.15; H, 8.65; O, 18.32.

19-Norandrostan-17β-ol-3-one Acetate (XIIa).—19-Norandrostan-17β-ol-3-one (XIIb)[18] was acetylated with acetic anhydride–pyridine by heating for 2 hr. on the steam-bath, dilution with water, filtration and recrystallization from methanol; m.p. 97–98°, $[\alpha]_D$ +38° (chloroform); λ_{max}^{KBr} 5.78, 5.84 and 8.13 μ.

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50; O, 15.07. Found: C, 75.38; H, 9.41; O, 15.23.

General Procedure for the Kinetically Controlled Br–Cl Addition.—A Br–Cl solution was prepared by combining exactly equivalent quantities (as determined by titration) of carbon tetrachloride solutions of bromine and of chlorine. To one volume of this Br–Cl solution were added four volumes of acetic acid as well as an amount of anhydrous sodium acetate corresponding exactly to the quantity of Br–Cl present.

The steroid (1.5 millimoles) was dissolved in 40 cc. of acetic acid–carbon tetrachloride (4:1); when an enol acetate was employed, there was also added 0.5 g. of anhydrous sodium acetate. In the case of ketones, this was eliminated since no halogenation occurred in the presence of such an excess of sodium acetate.

The above described Br–Cl–sodium acetate solution[32] (1.52 millimoles) was added dropwise to the steroid at room temperature over a period of 30 min., decolorization proceeding immediately with enol acetates. With ketones, it was necessary to start the reaction by the addition of 1–2 drops of a 30% hydrogen bromide in acetic acid solution.

At the end of the addition, the reaction mixture was poured into water, extracted with methylene chloride, washed with water, dilute sodium bicarbonate, again water, dried and evaporated to dryness *in vacuo* without applying any heat. The resulting crude bromination product was submitted directly to elementary, spectroscopic and rotatory dispersion examination before attempting further purification.

(a) **2α-Methylandrostan-17β-ol-3-one acetate (VIII)**[3]: yield of crude bromo ketone, 84%; λ_{max}^{EtOH} 306–308 mμ, log ϵ 2.06; $\lambda_{max}^{CCl_4}$ 5.78, 5.85, 8.06 μ; negative Cotton effect (c 0.078 in methanol) with trough at $[\alpha]_{327.5}$ −432°.

Anal. Calcd. for $C_{22}H_{33}BrO_3$: C, 62.12; H, 7.82; Br, 18.78. Found: C, 61.97; H, 8.27; Br, 16.40; Cl, 0.0.

Recrystallization from methanol afforded 40% of 2α-bromo-2β-methylandrostan-17β-ol-3-one acetate (XVI),[3] m.p. 109–111°, $[\alpha]_D$ −5°.

(b) **2-Methyl-Δ^2-androstene-3,17-diol diacetate (IX)**: yield of crude bromo ketone, 97%; λ_{max}^{EtOH} 306 mμ, log ϵ 2.01; $\lambda_{max}^{CCl_4}$ 5.78, 5.86, 8.10 μ; negative Cotton effect (c 0.06 in methanol) with trough at $[\alpha]_{340}$ −304°.

Anal. Calcd. for $C_{23}H_{33}BrO_3$: C, 62.12; H, 7.82; Br, 18.78; O, 11.28. Found: C, 64.41; H, 7.62; Br, 17.59; Cl, 0.46; O, 12.01.

Crystallization from methanol gave 80% of 2α-bromo-2β-methylandrostan-17β-ol-3-one acetate (XVI),[3] m.p. 110–113°, $[\alpha]_D$ −3.5° (chloroform).

(c) **2α-Methyl-19-norandrostan-17β-ol-3-one acetate (Xa)**: yield of crude bromo ketone, 80%; λ_{max}^{EtOH} 302–304 mμ, log ϵ 1.95; $\lambda_{max}^{CCl_4}$ 5.80, 5.84, 8.09 μ; positive Cotton effect (c 0.056 in methanol) with peak at $[\alpha]_{332.5}$ +1865°, which corresponds (see Discussion) to a mixture of 38% of XVIII and 62% of XIX.[17]

Anal. Calcd. for $C_{21}H_{31}BrO_3$: C, 61.32; H, 7.59; Br, 19.43. Found: C, 61.97; H, 8.27; Br, 16.40; Cl, 0.0.

Recrystallization from acetone–hexane afforded 41% of 2β-bromo-2α-methyl-19-norandrostan-17β-ol-3-one acetate (XVIII), m.p. 138–140°, $[\alpha]_D$ +172° (chloroform), whose infrared spectrum was identical with that of the analytical specimen described below.

(d) **2-Methyl-Δ^2-19-norandrostene-3,17β-diol diacetate (XI)**: yield of crude bromo ketone 89%; λ_{max}^{EtOH} 306–308 mμ, log ϵ 1.99; $\lambda_{max}^{CCl_4}$ 5.78, 5.83, 8.12 μ; positive Cotton effect (c 0.062 in methanol) with peak at $[\alpha]_{332.5}$ +2295°, corresponding (see Discussion) to a composition of 53% of XVIII and 47% of XIX.[17]

Anal. Calcd. for $C_{21}H_{31}BrO_3$: C, 61.32; H, 7.59; Br, 19.43; O, 11.67. Found: C, 62.53; H, 7.65; Br, 17.27; O, 12.59; Cl, 0.33.

Recrystallization from acetone–hexane led to 70% of 2β-bromo-2α-methyl-19-norandrostan-17β-ol-3-one acetate (XVIII), m.p. 140–142°, $[\alpha]_D$ +161° (chloroform).

(e) **19-Norandrostan-17β-ol-3-one acetate (XIIa)**: yield of crude bromo ketone, 80%; λ_{max}^{EtOH} 302–304 mμ, log ϵ 1.89, $\lambda_{max}^{CCl_4}$ 5.76, 5.84, 8.10 μ; positive Cotton effect (c 0.065 in methanol) with peak at $[\alpha]_{327.5}$ +687°, which corresponds (see Discussion) to a mixture of 63% of 2β-bromo (XXIII) and 37% of 4β-bromo (XXIV) 3-ketone.[33]

Anal. Calcd. for $C_{20}H_{29}BrO_3$: C, 60.45; H, 7.35; Br, 20.11; O, 12.08. Found: C, 62.11; H, 7.65; Br, 18.10; O, 13.00; Cl, 0.00.

Attempts to crystallize this material from various solvents or by chromatography failed.

(f) **$\Delta^{2(\text{and } 3)}$-19-Norandrostene-3,17$\beta$-diol diacetate (XIII)**: yield of crude bromo ketone, 96%; λ_{max}^{EtOH} 306–308 mμ, log ϵ 1.94; $\lambda_{max}^{CCl_4}$ 5.78, 5.81, 8.06 μ; positive Cotton effect (c 0.077 in methanol) with peak at $[\alpha]_{332.5}$ +738°, corresponding (see Discussion) to 64% of XXIII and 36% of XXIV.

Anal. Calcd. for $C_{20}H_{29}BrO_3$: C, 60.45; H, 7.35; Br, 20.11; O, 12.08. Found: C, 61.14; H, 7.48; Br, 18.19; Cl, 0.48; O, 12.83.

The product could not be crystallized and when 100 mg. was allowed to stand at room temperature for 22 hr. in acetic acid containing 3 drops of 30% hydrogen bromide in acetic acid, the resulting material (86 mg.) showed no important change in its Cotton effect (peak at $[\alpha]_{332.5}$ +677°).

The presence of the 2- and 4-bromo ketones in the original bromination product was confirmed by dehydrobromination of 620 mg. of this material in 10 cc. of dimethylformamide

(32) In order to demonstrate the suitability of this Br–Cl solution for the formation of bromo-chloro derivatives from olefins, 1.5 g. of Δ^5-androstene-3β,17β-diol was treated under the above described conditions and the crude, crystalline product (m.p. 137–141°) was recrystallized twice from methanol to provide 0.80 g. of colorless prisms, m.p. 142–144°, $[\alpha]_D$ −66° (dioxane). *Anal.* Calcd. for $C_{18}H_{28}BrClO_3$: C, 56.21; H, 7.44; O, 7.88; Br, 19.69; Cl, 8.74. Found: C, 56.58; H, 7.30; O, 7.79: Br, 19.27: Cl, 8.46.

(33) The slight hypsochomic displacement of the ultraviolet absorption maximum and of the rotatory dispersion peak indicates that this calculation may not be completely correct and that some equatorial bromo ketone is present. Indeed equilibration of 100 mg. of this mixture in acetic acid with hydrogen bromide for 22 hr. afforded 80 mg. of oil, whose rotatory dispersion peak was now $[\alpha]_{332.5}$ +1020° (corresponding to 71% of XXIII and 29% of XXIV).

with 900 mg. of lithium bromide and 1.2 g. of lithium carbonate. After heating under reflux for 4 hr. and standing overnight, the inorganic salts were filtered, washed well with hot ethyl acetate and the combined filtrate and solvents removed *in vacuo*. Since infrared examination of the semi-crystalline residue indicated loss of the 17-acetate function, the material was reacetylated with pyridine–acetic anhydride (12 hr., room temperature) and the resulting product (410 mg., λ_{max}^{EtOH} 232–236 mμ) was chromatographed carefully on activated alumina (Brockmann No. II). Elution with hexane–benzene (2:8) and recrystallization from hexane provided 230 mg. (47%) of **Δ¹-19-norandrosten-17β-ol-3-one acetate (XXVII)**, m.p. 133–134°, $[\alpha]_D$ +119° (chloroform), λ_{max}^{EtOH} 230 mμ, log ε 4.01; λ_{max}^{KBr} 5.78, 5.98 and 8.06 μ; R.D. in dioxane (*c* 0.052): $[\alpha]_{589}$ + 123°, $[\alpha]_{380}$ −45°, $[\alpha]_{370}$ +111°, $[\alpha]_{365}$ + 69°, $[\alpha]_{280}$ + 2210°.

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92; O, 15.17. Found: C, 75.79; H, 8.87; O, 15.38

After an intermediate fraction (40 mg., λ_{max}^{EtOH} 234–238 mμ) corresponding to a mixture of XXVII and XXVIII, elution with benzene–ether (9:1) and recrystallization from methylene chloride (containing a few drops of pentane) gave 110 mg. (22%) of **19-nortestosterone acetate (XXVIII)**, m.p. 91–93°, $[\alpha]_D$ +49° (chloroform), λ_{max}^{EtOH} 240 mμ, log ε 4.20. Identity with an authentic specimen[24] was established by mixture melting point determination and infrared comparison.

(g) **Androstan-17β-ol-3-one acetate (XIV)**: yield of crude bromo ketone, 78%; $\lambda_{max}^{CHCl_3}$ 284–286 mμ, log ε 1.49 (as compared to $\lambda_{max}^{CHCl_3}$ 286–288 mμ for XIV); $\lambda_{max}^{CCl_4}$ 5.78, 8.06 μ; positive Cotton effect (*c* 0.075 in methanol) with peak at $[\alpha]_{307.5}$ +634°.

Anal. Calcd. for $C_{21}H_{31}BrO_3$: C, 61.32; H, 7.59; Br, 19.43. Found: C, 62.40; H, 7.90; Br, 16.32; Cl, 0.00.

Crystallization from methanol yielded 42% of 2α-bromoandrostan-17β-ol-3-one acetate (XXI),[18] m.p. 179–180°, $[\alpha]_D$ +43° (chloroform).

(h) **Δ²-Androstene-3,17β-diol diacetate (XV)**: yield of crude bromo ketone, 98% $\lambda_{max}^{CHCl_3}$ 286–288 mμ, log ε 1.60, $\lambda_{max}^{CCl_4}$ 5.78, 8.06 μ; positive Cotton effect with peak at $[\alpha]_{307.5}$ +695°.

Anal. Calcd. for $C_{21}H_{31}BrO_3$: C, 61.32; H, 7.59; Br, 19.43. Found: C, 60.91; H, 8.14; Br, 17.94; Cl, 1.22.

Crystallization from methanol furnished 73% of 2α-bromoandrostan-17β-ol-3-one acetate (XXI),[18] m.p. 180–181°, $[\alpha]_D$ +36° (chloroform).

Kinetically-controlled Bromination of 2α-Methyl-19-norandrostan-17β-ol-3-one Acetate (Xa).—To a solution of 400 mg. of 2α-methyl-19-norandrostan-17β-ol-3-one acetate (Xa) in 15 cc. of acetic acid was added dropwise with stirring over a period of 30 min., 10.2 cc. of a bromine solution (consisting of 1.0 g. of bromine, 0.50 g. of anhydrous sodium acetate and 50 cc. of acetic acid). Decolorization started within 5 min. and at the end of the reaction, ice-water was added, the precipitate was collected, dried *in vacuo* (positive Cotton effect in methanol (*c* 0.056) with peak at $[\alpha]_{330}$ +2170°) and recrystallized from acetone–hexane containing one drop of pyridine. There was thus obtained 315 mg. of bromo ketone, m.p. 141–143°, $[\alpha]_D$ +142° (chloroform), λ_{max}^{EtOH} 304–306 mμ, log ε 1.84; $\lambda_{max}^{CS_2}$ 5.77, 5.81, 8.06 μ; positive Cotton effect (*c* 0.07 in dioxane) with peak at $[\alpha]_{332.5}$ +2400°, which corresponds (see Discussion) to a mixture consisting of 57% of the axial bromo ketone XVIII and 43% of the equatorial isomer XIX.[17]

Anal. Calcd. for $C_{21}H_{31}BrO_3$: C, 61.32; H, 7.59; Br, 19.43; O, 11.67. Found: C, 61.03; H, 7.65; Br, 19.20; O, 12.22.

The presence of the equatorial isomer XIX was confirmed when 100 mg. of the product was allowed to stand overnight in acetic acid solution with 2 drops of 30% hydrogen bromide–acetic acid. Precipitation with water, filtration and drying *in vacuo* left 85 mg. of solid, m.p. 137–139° (*Anal.* Found: C, 60.66; H, 7.22; Br, 18.31) whose infrared spectrum was essentially identical with that of the starting material but whose positive Cotton effect (*c* 0.069 in dioxane) now exhibited a peak at $[\alpha]_{332.5}$ +3535°.

A 200-mg. sample of the bromo ketone mixture (prior to hydrogen bromide equilibration) was dehydrobrominated with lithium bromide and lithium carbonate exactly as described above and the crude product was saponified by heating under reflux for 45 min. with 5% methanolic potassium hydroxide solution.[34] Chromatography on alumina, elution with benzene and one crystallization from acetone furnished 145 mg. of **2-methyl-Δ¹-19-norandrosten-17β-ol-3-one (XX)**, the absence of the 6.17 μ infrared band associated with the Δ⁴-isomer XVII (*vide supra*) demonstrating that no contamination with that isomer had occurred. The analytical specimen exhibited m.p. 166–167°, $[\alpha]_D$ +108° (chloroform), λ_{max}^{EtOH} 240–242 mμ, log ε 4.02, $\lambda_{max}^{CHCl_3}$ 6.01 μ; R.D. in dioxane (*c* 0.065): $[\alpha]_{700}$ +88°, $[\alpha]_{589}$ +94°, $[\alpha]_{475}$ +209°, $[\alpha]_{367.5}$ +46°, $[\alpha]_{362.5}$ + 127°, $[\alpha]_{360}$ +26°, $[\alpha]_{280}$ +2718°.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79; O, 11.10. Found: C, 79.34; H, 9.75; O, 11.37.

The red **2,4-dinitrophenylhydrazone** was recrystallized from chloroform–ethanol, m.p. 244–246°, $\lambda_{max}^{CHCl_3}$ 384–388 mμ, log ε 4.40.

Anal. Calcd. for $C_{25}H_{32}N_4O_5$: C, 64.08; H, 6.88; N, 11.96; O, 17.07. Found: C, 64.13: H, 7.05; N, 11.75; O, 16.95.

Kinetically-controlled Bromination of 2-Methyl-Δ²-19-norandrostene-3,17β-diol Diacetate (XI).—The enol acetate XI (500 mg.) was dissolved in 40 cc. of a solution[1] of the following composition: 150 cc. of acetic acid, 40 cc. of carbon tetrachloride and 2.0 g. of anhydrous sodium acetate. To this solution was added dropwise over a 30-min. period 4.7 cc. of a bromine solution (0.75 cc. of bromine in 50 cc. of the above-described solvent mixture). Decolorization occurred very rapidly and at the end of the addition, the mixture was poured into ice-water, rapidly extracted with ether, washed, dried and evaporated. The resulting semi-crystalline product (λ_{max}^{EtOH} 304–308 mμ, log ε 1.90; positive Cotton effect in methanol (*c* 0.058) with peak at $[\alpha]_{330}$ +2450° corresponding to 59% of XVIII and 41% of XIX[17]) was dissolved in 45 cc. of hexane and 5 cc. of benzene and passed rapidly over a column of 6 g. of alumina deactivated with 0.4 cc. of water. The eluate was evaporated to dryness *in vacuo* without heating and the crystalline residue was recrystallized twice from acetone to afford 245 mg. of **2β-bromo-2α-methyl-19-norandrostan-17-β-ol-3-one acetate (XVIII)**, m.p. 142–144°, $[\alpha]_D$ +170° (chloroform), λ_{max}^{EtOH} 304–308 mμ, log ε 2.00; $\lambda_{max}^{CS_2}$ 5.76, 5.84, 8.06 μ; R.D. in methanol (*c* 0.06): $[\alpha]_{700}$ +107°, $[\alpha]_{589}$ +162°, $[\alpha]_{330}$ +3410°, $[\alpha]_{300}$ −1810°.

Anal. Calcd. for $C_{21}H_{31}BrO_3$: C, 61.32; H, 7.59; Br, 19.43; O, 11.67. Found: C, 61.49; H, 7.50; Br, 19.34; O, 12.23.

The purity of this axial bromo ketone was demonstrated by the fact that equilibration of a sample with hydrogen bromide afforded a crude product (m.p. 136–138°, λ_{max}^{EtOH} 306 mμ; R.D. peak at $[\alpha]_{332.5}$ +3200°) which after one recrystallization showed m.p. 142–144°, R.D. peak at $[\alpha]_{330}$ +3440°.

Dehydrobromination of 60 mg. of the bromo ketone (prior to hydrogen bromide treatment) by the above-described procedure followed by saponification led to 40 mg. of 2-methyl-Δ¹-19-norandrosten-17β-ol-3-one (XX), m.p. 165–167°, $[\alpha]_D$ +102° (chloroform), λ_{max}^{KBr} 6.02 μ.

Kinetically-controlled Bromination of Δ²(and ³)-19-Norandrostene-3,17β-diol Diacetate (XIII).—This enol acetate (130 mg.) was treated with a buffered bromine solution exactly as described in the preceding experiment with the enol acetate XI. The crude oily product (148 mg.) exhibited a positive Cotton effect (*c* 0.053 in methanol) with a peak at $[\alpha]_{332.5}$ +962° (corresponding to 69% of XXIII and 31% of XXIV), in good agreement with the above-described reaction of XIII and Br–Cl.

Dehydrobromination with lithium bromide and lithium carbonate afforded, after careful chromatographic separation, 37% of pure Δ¹-19-norandrosten-17β-ol-3-one acetate (XXVII) and 19% of 19-nortestosterone acetate (XXVIII).

In an identical bromination of 100 mg. of 19-norandrostan-17β-ol-3-one acetate (XIIa) in which the intermediate bromo ketone mixture was dehydrobrominated without further measurements, there was isolated 30 mg. of the Δ¹-(XXVII) and 18 mg. of the Δ⁴-(XXVIII) 3-ketones.

(34) An earlier pilot experiment had shown that the 17β-ol crystallized better than the corresponding acetate.