Stereochemical Studies. III.[1] Alkylation of Δ^4-3-Keto Steroids

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The stereochemistry of the alkylation of Δ^4-3-keto steroids lacking the angular methyl at C-10 was investigated. Configurations of the 4-alkyl substituents in the alkylation products were assigned by correlation with 4β-acetyl-4α-methylestr-5-en-17β-ol acetate (**1**), whose configuration was established using ultraviolet and circular dichroism data. The steric course of the alkylation was found to be dependent on the conformations of the 4,4-dialkylated products. The conformations were also established using the ultraviolet and CD data. It was found that the 1–3 *peri* interaction between the 4α-ethyl substituent and the vinylic hydrogen at C-6 changes the conformation of ring A in the 19-nor-Δ^5-3-keto steroids.

The current views on the steric course of alkylation of ketones assume an axial attack by the alkylating agents on the anions derived from these ketones.[3] When the ensuing alkylation product possesses an unfavorable stereochemistry, a subsequent change of its conformation can be anticipated resulting in an equatorial configuration of the alkyl substituent.[3a,d] On the other hand, when the axial approach of the alkylating agents is hindered by steric factors, the alkylation might proceed directly from the less hindered side of the reacting ketone, resulting also in equatorial substitution.[3] Suitable systems for investigation of the steric course of alkylation are Δ^4-3-ketones in the steroids and compounds possessing similar A/B ring systems with the same chromophore. The enolates derived from these unsaturated ketones have comparatively high stability, since the presence of the additional double bond stabilizes the negative charge of the enolate.[4] Hence, it is reasonable to assume that the conformation of the transition state in the alkylation of Δ^4-3-keto steroids and related compounds will closely resemble the conformation of the products, *e.g.*, 4,4-dialkyl Δ^5-3-ketones.[1,3a]

Most of the experimental data on the alkylation of the Δ^4-3-ketones have been obtained from systems possessing an angular methyl group in the position 10.[3]

In these compounds the alkylation proceeds firstly to give the 4-monoalkyl enolates. The second alkyl substituent enters predominantly from the α side of the molecule.[5] A direct α-side attack could be envisaged since the α side of the steroidal molecule is more accessible for such an attack. More likely, this alkylation could involve an axial attack, provided that the transition state assumes a boatlike conformation. Recently a quasi-boat conformation was postulated for the products of this reaction, *i.e.*, the 4,4-dialkyl-Δ^5-3-keto steroids.[1,6] It was therefore of interest to investigate the steric course of alkylations in compounds possessing similar chromophores whose alkylation products will have, however, a normal chair conformation of their ring A. The compounds chosen were 19-nor-Δ^4-3-keto steroids. It was shown recently that the conformation of the 4,4-dimethyl-19-nor Δ^5-3-ketones differs from that of the 19-methyl homolog by having the normal chair conformation.[1,6]

The key compound for establishing the configuration of the alkyl groups in Δ^5-3-keto steroids was the 4β-acetyl-4α-methylestr-5-en-17β-ol acetate (**1**) (Chart I). This compound was obtained from the dienol acetate **2**[7] derived from 19-nortestosterone, by a four-step sequence. Irradiation of the dienol acetate **2** with a low-pressure mercury lamp in cyclohexane solution, subsequent acid treatment, and reacetylation of the reaction products resulted in 4-acetyl-19-nortestosterone (**4**).

The primary irradiation product was presumably the enol **3** by analogy with the one isolated from irradiation of dienol acetate derived from testosterone.[8]

The total mixture of products obtained from irradiation of **2** reacted positively in the ferric chloride test, the reaction becoming negative after the acid treatment. Methylation of 4-acetyl-19-nortestosterone acetate (**4**) with methyl iodide and potassium in *t*-butyl alcohol and reacetylation resulted in 4β-acetyl-4α-methylestr-5-en-17β-ol-3-one acetate (**5**). In addition, a small amount of 4,4-dimethylestr-5-en-17β-ol-3-one acetate (**6**)[9] was isolated from the reaction mixture. The latter was derived probably from the methylation of 19-nortestosterone obtained by β cleavage of the diketone **4**. It is noteworthy that no epimer of **5** could be found in this reaction mixture even after careful rechromatography of the reaction products. The diketone **5** was further converted to its thioketal **7** with ethanedithiol and boron trifluoride etherate. Subsequent treatment of the thioketal with Raney nickel yielded the desired 4β-acetyl-4α-methylestr-5-en-17β-ol acetate (**1**) (mp 154–155°). The configuration of the acetyl group and its rotameric conformation in **1** were established by means of the ultraviolet and circular dichroism data. The ultraviolet spectrum of **1** (Figure 1)[10] shows the characteristics of a coupled unsaturated ketone. In this spectrum, both the enhanced transitions of the carbonyl

(1) Part II: M. Gorodetsky, A. Yogev, and Y. Mazur, *J. Org. Chem.*, **31**, 699 (1966).

(2) Holder of a Fellowship of the Italian Ministry of Education.

(3) (a) J. Valls and E. Toromanoff, *Bull. Soc. Chim. France*, 758 (1961), and references cited therein; (b) M. E. Kuehne, *J. Am. Chem. Soc.*, **83**, 1492 (1961); (c) G. Stork and J. W. Schulenberg, *ibid.*, **84**, 284 (1962); (d) G. Stork and S. D. Darling, *ibid.*, **86**, 1764 (1964); (e) E. Wenkert, A. Afonso, J. B. Bradenberg, G. Kaneko, and A. Tahara, *ibid.*, **86**, 2038 (1964).

(4) S. K. Malhotra and H. J. Ringold, *ibid.*, **86**, 1997 (1964).

(5) H. J. Ringold and S. K. Malhotra, *ibid.*, **84**, 3402 (1962).

(6) M. Gorodetsky and Y. Mazur, *Tetrahedron Letters*, 227 (1964); B. B. Dewhurst, J. S. E. Holker, A. Lablache-Combier, M. R. G. Leeming, J. Levisalles, and J. P. Pete, *Bull. Soc. Chim. France*, 3259 (1964).

(7) J. A. Hartman, A. J. Tomasewski, and A. S. Dreiding, *J. Am. Chem. Soc.*, **78**, 5662 (1956); R. Villotti, C. Djerassi, and H. J. Ringold, *ibid.*, **81**, 4566 (1959).

(8) M. Gorodetsky and Y. Mazur, *ibid.*, **86**, 5213 (1964).

(9) (a) A. Bowers and J. A. Ringold, *ibid.*, **81**, 424 (1959); (b) N. Atwater, *ibid.*, **82**, 2847 (1960).

(10) The ultraviolet spectra were taken on a Cary 14 spectrophotometer with cells of 0.1-cm width, in cyclohexane solution.

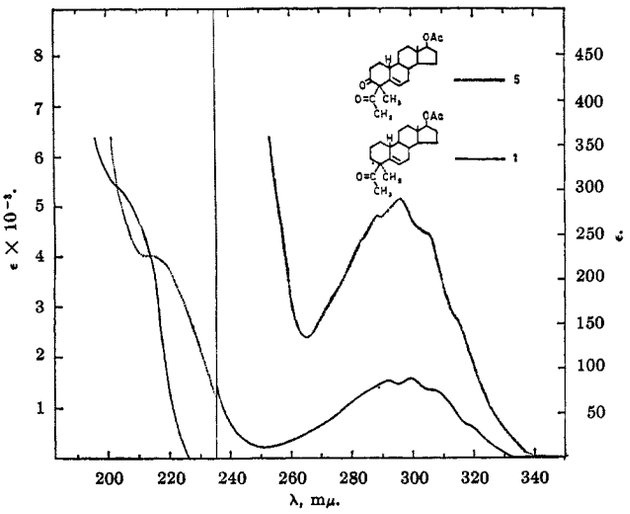


Figure 1.—Ultraviolet spectra of 4β-acetyl-4α-methylestr-5-en-17β-ol-3-one acetate (5) and of 4β-acetyl-4α-methylestr-5-en-17β-ol acetate (1) in cyclohexane.

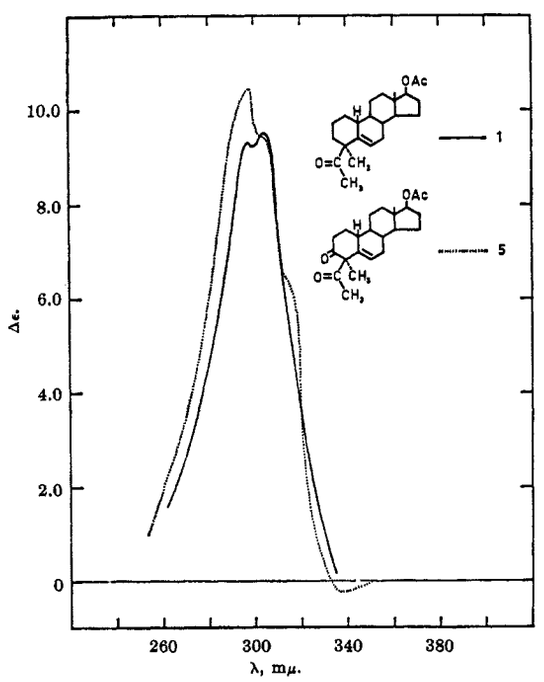


Figure 2.—Circular dichroism curves of 4β-acetyl-4α-methylestr-5-en-17β-ol-3-one acetate (5) and of 4β-acetyl-4α-methylestr-5-en-17β-ol acetate (1).

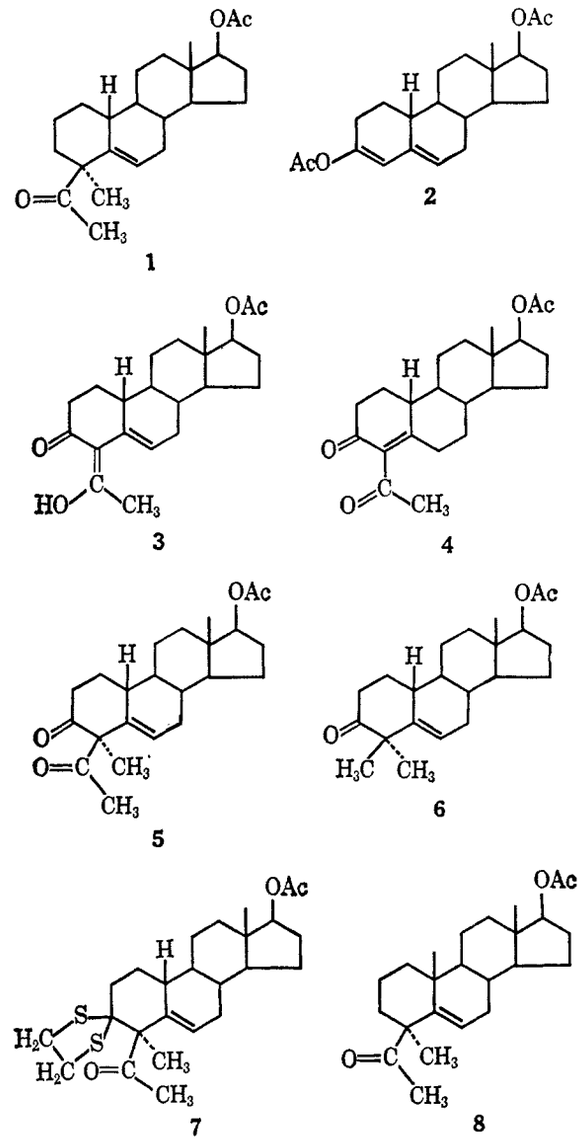
group (300-mμ region) and the charge-transfer $\pi \rightarrow \pi^*$ transition (220-mμ region) are seen.

The increased $\Delta\epsilon$ values in the circular dichroism curve[11] of 1 (Figure 2) point to the same effect. These data established the β-axial configuration of the acetyl group in 1,[12] the rotameric conformation of the acetyl group being analogous to the one depicted previously for its 19-methyl homolog 8.[12] On the contrary, the conformation of the diketone 5 in the 19-nor series is different from that of its 19-methyl homolog. For the latter we have postulated a quasi-boat conformation of the ring A.[6] The ultraviolet spectrum (Figure 1) and the circular dichroism curve (Figure 2) of the

(11) The circular dichroism measurements were carried out by the courtesy of Dr. G. Snatzke, University of Bonn, to whom we are greatly indebted.

(12) M. Gorodetsky, D. Amar, and Y. Mazur, *J. Am. Chem. Soc.*, **86**, 5218 (1964).

CHART I



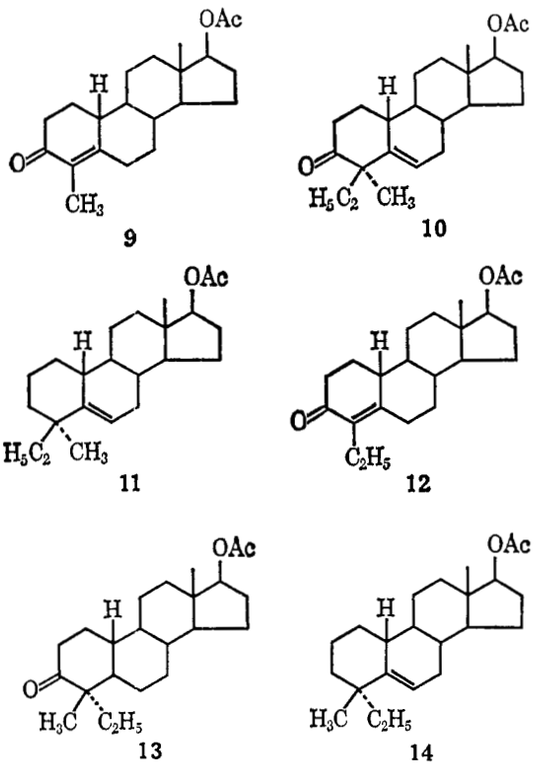
19-nor diketone 5 point clearly[12] to a normal chair conformation of the ring A.[13] This difference in the conformation of ring A in 5 and its 19-methyl homolog is analogous to the difference previously observed in 4,4-dimethylestr-5-en-17β-ol-3-one acetate (6) on one hand and 4,4-dimethylandrost-5-en-17β-ol-3-one acetate derivative on the other. The nonbonded interaction of the methyl group at C-10 with either the 4β-acetyl group or the 4β-methyl are responsible for the deformation of ring A. When this C-10 methyl group is absent, a normal chair conformation is permitted.

Having thus established the configuration at C-4 in 1 we can assign the configuration to the derived 4,4-dialkylated Δ^5-3-ketones in the 19-nor series.

Ethylation of 4-methyl-19-nortestosterone acetate (9)[9b] with ethyl iodide in the presence of potassium *t*-butoxide in *t*-butyl alcohol gave after reacetylation mainly the 4β-ethyl-4α-methylestr-5-en-17β-ol-3-one

(13) The considerably increased ε values found for the 19-nor diketone 5, whose magnitude is double than that found in the monoketone 1, could result from the superposition of the absorption bands due to both carbonyl groups. These bands are enhanced owing to coupling of the carbonyl and double bond orbitals. In addition, the two carbonyl groups could interact with each other, increasing further the ε value without enhancing their rotatory power. The latter effect was observed previously in the spectrum of the 19-methyl homolog of the diketone 5.[8]

CHART II



acetate (**10**) (mp 120–122°, $[\alpha]_D$ −35°) (see Chart II). Modified Wolff–Kishner reduction of the carbonyl group in **10** and subsequent reacetylation yielded the olefin **11** (mp 99–101°, $[\alpha]_D$ −23°). The latter was identical with the olefin obtained by Wolff–Kishner reduction of the 4β-acetyl-4α-methylestr-5-en-17β-ol acetate (**1**), thus establishing the configuration at C-4.

Methylation of 4-ethyl-19-nortestosterone acetate (**12**) with methyl iodide under identical conditions yielded a mixture of two dialkyl Δ^5-3-ketones. One was identical with the ketone **10** (mp 120–122°) and the second proved to be its epimer, *i.e.*, 4α-ethyl-4β-methylestr-5-en-17β-ol-3-one acetate (**13**) (mp 114–115°, $[\alpha]_D$ −14°). Wolff–Kishner reduction of the 4α-ethyl-4β-methyl derivative **13** afforded the 4α-ethyl-4β-methyl olefin **14** (mp 107–108°, $[\alpha]_D$ −23°).

The exact amounts of the two epimers in the methylation of 4-ethyl-19-nortestosterone acetate (**12**) could be deduced from the nmr spectra.[14] The signal of the C-4α methyl protons in the 4β-ethyl-4α-methyl ketone **10** appeared at 70 cps and the corresponding signal of the C-4β methyl in the 4α-ethyl-4β-methyl ketone **13** at 67.5 cps. In the total dialkylation product both peaks were observed but in unequal intensity. Comparison of the peak area assigned to the methyls at C-4 established the ratio of the two keto olefins **10** and **13** as 2:1. The nmr spectrum of the total dialkyl fraction from the ethylation of 4-methyltestosterone **9** revealed that the 4α-ethyl-4β-methyl ketone **13** was also produced in this reaction, albeit in much smaller quantity. The integration of the corresponding peaks established the ratio of **10** and **13** as *ca.* 8:1.

(14) The nmr spectra were taken in deuteriochloroform on a Varian A-60 (60 Mc/sec) instrument. The peak positions are given in cycles per second downfield from tetramethylsilane serving as internal reference.

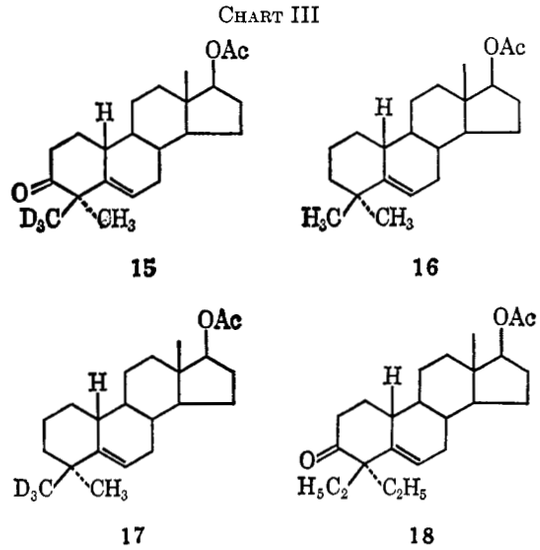
Because of the unexpected differences in the steric course of alkylation of 4-methyl-19-nortestosterone acetate (**9**) and 4-ethyl-19-nortestosterone acetate (**12**), we were interested to find if these were caused by the nature of alkylating agent (methyl iodide *vs.* ethyl iodide) or by the nature of reacting ketone.

Thus, alkylation of 4-methyl-19-nortestosterone acetate (**9**) was repeated with methyl-d_3 iodide replacing ethyl iodide. The nmr spectrum of the total alkylated product was compared with the spectrum of 4,4-dimethylestr-5-en-17β-ol-3-one acetate (**6**). The latter spectrum reveals two separate peaks at 75 and 73 cps, assigned to the 4α-methyl and 4β-methyl protons, respectively. The nmr spectrum of the total d_3-alkylated material shows both peaks assigned to the methyl protons at C-4, but with unequal intensity; the integrated area of the signal at 73 cps possesses only *ca.* 10% of the area of the signal at 75 cps.

The alkylated product was further submitted to Wolff–Kishner reduction, and the nmr spectrum of the resulted olefin mixture was compared with that of the dimethyl olefin **16**. The latter was prepared by analogous reduction of the 4,4-dimethylestr-5-en-17β-ol-3-one acetate (**6**). The dimethyl olefin **16** showed two signals at 63 and 61 cps (C-4 methyl protons). The ratio of the intensity of these two signals in the d_3-alkylated olefin was similar to the one found in the d_3-keto olefin mixture.

We assigned to the epimer obtained in major proportion in the d_3-methylation experiment the structure of 4β-methyl-d_3-4α-methylestr-5-en-17β-ol-3-one acetate (**15**) and to the related olefin the structure **17** (Chart III).[15]

CHART III



It seems that the differences in the steric course of the alkylation reactions are due to the nature of the reacting ketone only. It was expected that these can be correlated to the differences in the conformations of the transitions states of the anions derived from the unsaturated ketones **9** and **12**. From these reasons it was of interest to compare the conformation of the dialkylated products **10** and **13** whose conformation is

(15) This assignment is based on the assumption that there is an analogy with the ethylation of **9** where the β isomer was obtained in preponderance.

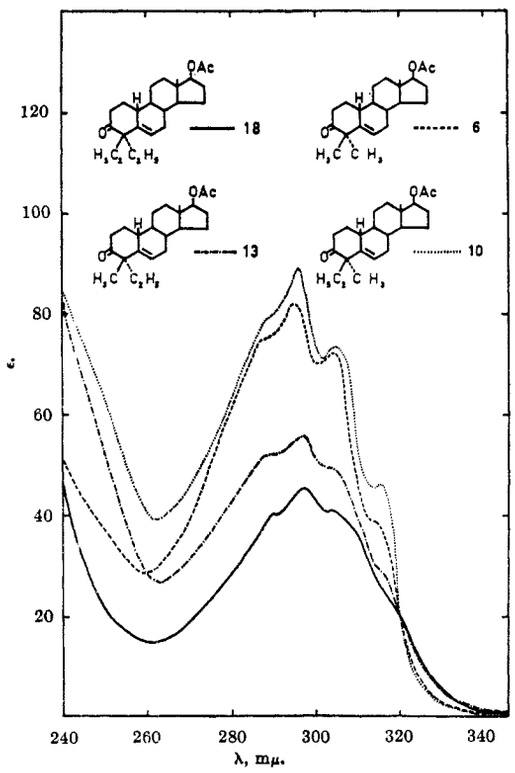


Figure 3.—Ultraviolet spectra of 4,4-dialkylestr-5-en-17β-ol-3-one acetates in cyclohexane.

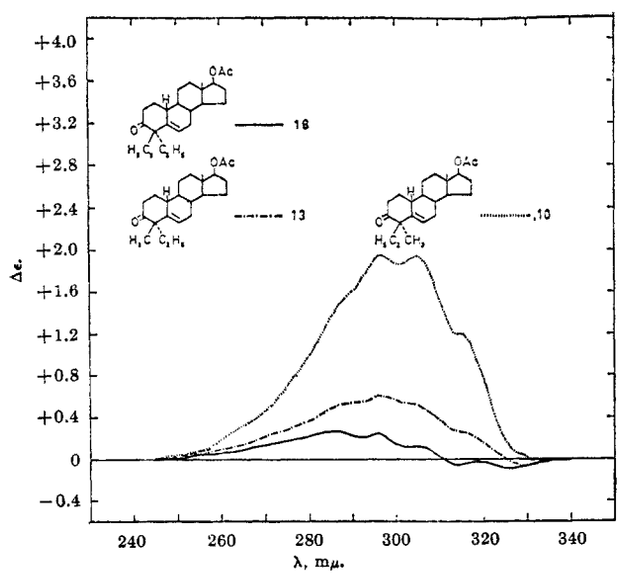


Figure 4.—Circular dichroism curves of 4,4-dialkylestr-5-en-17β-ol-3-one acetates.

assumed to be similar to their anions in the transition state.

In Figure 3 the ultraviolet spectra of the four methyl and ethyl dialkylated 19-nor-Δ^5-3-keto steroids **10**, **13**, **6**, and **18** are depicted. It is evident that similarity exists between extinction values and pattern of these spectra in 4β-ethyl-4α-methyl ketone **10** and the 4,4-dimethyl ketone **6** on one hand, and 4α-ethyl-4β-methyl ketone **13** and 4,4-diethyl ketone **18** on the other hand. The circular dichroism curve of the ketone **10** (Figure 4) resembles that of the 4,4-dimethyl ketone **6**,[1,16] and that of the epimer **13** possesses values resembling the one of the 4,4-diethyl ketone **18**.

These results show that the similarity in the 4,4-dialkylated 19-nor Δ^5-ketones is determined by similarity in α substitution, and the effect of β substitution is comparatively small. The higher extinction and ellipticity values of the n → π* absorption of the 4β-ethyl-4α-methyl epimer **10** points to a normal ring-A chair conformation in this compound previously indicated for the 4,4-dimethyl ketone **6**. The 4α-ethyl-4β-methyl epimer **13** and the 4,4-diethyl ketone **18** both have much smaller extinction and circular dichroism values, indicating a nonchair conformation for the ring A. This latter could be explained by assuming that a *peri* nonbonded interaction between the equatorial ethyl substituent at C-4 and the hydrogen at C-6 plays an important role in the steric relations of these molecules and distorts the A ring considerably out of its normal chair conformation. Similar distortion of ring A could also exist in the transition state of the alkylation of the 4-ethyl-19-nortestosterone acetate (**12**). Therefore, the attack of the alkylating agent would be less discriminating, leading to a higher proportion of the dialkyl ketone with the entering alkyl group in the α position.

The exact conformation of rings A in the dialkyl ketones **13** and **18** cannot be deduced from our data. It is possible that these are intermediate between a chair and a boat, but being rather closer to the chair form than the conformation postulated previously for the 4,4-dialkyl Δ^5-3-ketones possessing the angular methyl at C-10.[1,6]

It seems reasonable to postulate that the alkylation of 4-methyl Δ^5-3-ketones occurs mainly axially and the steric course of these alkylations is dependent on the conformation of the transition state which resembles the conformation of the ensuing product.

This generalization does not apply apparently to Δ^4-3-ketones substituted in the position 4 by an acetyl group. The methylation of 4-acetylnortestosterone acetate (**4**) described above led only to the 4α-methyl derivative **5** in analogy to the methylation of 4-acetyltestosterone acetate (**8**). An enolate of the acetyl derivative **4** which undergoes methylation has probably the structure **3**. Alkylation of this enolate, possessing an exocyclic double bond could well proceed from the less hindered α side of the steroid.[17]

Experimental Section

All melting points were taken in capillaries and were uncorrected. Infrared spectra were determined on a Perkin-Elmer Infracord. The rotations were done in chloroform. The irradiation was performed with an immersion Hanau low-pressure NT 6/20 ultraviolet lamp, in an externally cooled tube of 40-mm diameter and *ca.* 150-cc volume. The chromatographic separations were done on Merck acid-washed alumina, unless otherwise specified.

Irradiation of Estra-3,5-diene-3,17β-diol Diacetate (**2**).—A solution of dienol acetate **2**[7] (1 g) in 100 ml of cyclohexane was irradiated for 3 hr. Aliquots were taken out every hour and their absorbance at 230 mμ was established. After 3 hr, the ε reached a constant value of 5600 and the irradiation was stopped. The solvent was then evaporated under reduced pressure. The

(16) P. Witz, H. Herrman, J. M. Lehn, and G. Ourisson, *Bull. Soc. Chim. France*, 1101 (1963).

(17) In addition, in this respect the steric course of methylation is analogous to the stereochemical behavior of protonation and bromination. For the latter, in acetylcyclohexane derivatives, see H. E. Zimmerman and T. W. Cutshall, *J. Am. Chem. Soc.*, **81**, 4305 (1959); P. T. Herzig and M. Ehrenstein, *J. Org. Chem.*, **16**, 1050 (1951); and ref 8.

oily residue, which showed violet coloration with ferric chloride solution, was dissolved in 50 ml of methanol and was treated with 0.5 ml of 20% sulfuric acid. The material isolated from ether was acetylated with 5 ml of acetic anhydride and 5 ml of pyridine overnight at room temperature. The products isolated from ether (790 mg) were chromatographed on silica gel (50 g).

The crystalline fraction eluted with pentane–ether (9:1) gave 150 mg of 4-acetylestr-4-en-17β-ol-3-one acetate (**4**): mp 106–107.5°; $[\alpha]_D$ +36°; λ_{max}^{KBr} 5.78, 6.05, and 6.29 μ; $\lambda_{max}^{cyclohexane}$ 233 mμ (ϵ 13,600).

Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.86; H, 8.61.

Methylation of 4-Acetyl-19-nortestosterone Acetate (4).—A solution obtained from the reaction of potassium (600 mg) in *t*-butyl alcohol (30 ml) was treated with a solution of 500 mg of **4** in *t*-butyl alcohol (20 ml) and then with methyl iodide (5 ml). The reaction mixture was stirred overnight at room temperature and filtered, and the filtrate was evaporated to dryness. The residue was acetylated with acetic anhydride and pyridine (5 ml each). The acetylated material was chromatographed on alumina (60 g).

The fraction eluted with pentane–ether (9:1) gave 70 mg of 4,4-dimethylestr-5-en-17β-ol-3-one acetate (**6**),[9] mp 132–133°, identified by comparison with an authentic sample.

The second fraction, eluted with pentane–ether (3:1), yielded 200 mg of 4β-acetyl-4α-methylestr-5-en-17β-ol-3-one acetate (**5**): mp 127–129° (after recrystallization from ether–pentane); $[\alpha]_D$ +110°; λ_{max}^{KBr} 5.76, 5.82, and 5.86 μ.

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.28; H, 8.74.

4β-Acetyl-4α-methylestr-5-en-17β-ol Acetate (1).—A solution of 140 mg of **5** in ethanedithiol (2 ml) was treated with boron trifluoride etherate (1 ml) for 3 hr. The product was isolated with ether, washed with cold sodium hydroxide solution, and recrystallized from ether–pentane. The thioketal **7** thus obtained (140 mg) had mp 216–218°; $[\alpha]_D$ +119°; λ_{max}^{KBr} 5.78 and 5.86 μ.

Anal. Calcd for $C_{25}H_{36}O_3S_2$: C, 66.94; H, 8.09. Found: C, 67.06; H, 8.18.

A solution of 130 mg of the thioketal **7** in 40 ml of ethanol was treated with Raney nickel suspension in ethanol (2 teaspoonfuls) and then boiled under reflux overnight. Evaporation of the filtered solution gave a residue (110 mg) which was chromatographed on alumina (20 g.). The fraction eluted with pentane–ether (16:1) gave 45 mg of **1**: mp 154–155° (after recrystallization from ether–pentane); $[\alpha]_D$ +120°; λ_{max}^{KBr} 5.78 and 5.87 μ.

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.33; H, 9.71.

Ethylation of 4-Methyl-19-nortestosterone Acetate (9).—A solution of 700 mg of **9**[9b] in 20 ml of *t*-butyl alcohol was treated with a solution obtained from the reaction of potassium (500 mg) in *t*-butyl alcohol (20 ml) and then dropwise with ethyl iodide (2 ml) in 50 ml of *t*-butyl alcohol. The reaction mixture was then heated under reflux until it became neutral (12 hr). It was then filtered and the filtrate was evaporated to dryness. The residue was reacetylated with acetic anhydride and pyridine (7 ml of each) and the acetylated material (640 mg) was chromatographed on alumina (130 g). Elution with pentane–ether (4:1) gave 280 mg of 4β-ethyl-4α-methylestr-5-en-17β-ol-3-one acetate (**10**): mp 120–122° (after recrystallization from ether–pentane); $[\alpha]_D$ −35°; λ_{max}^{KBr} 5.75 and 5.78 μ.

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.35; H, 9.25.

4β-Ethyl-4α-methylestr-5-en-17β-ol Acetate (11). A.—4β-ethyl-4α-methylestr-5-en-17β-ol-3-one acetate (**10**, 50 mg) was added to a solution of sodium (150 mg) and hydrazine (0.7 ml) in diethylene glycol (5 ml). The solution was heated under reflux for 3 hr and the temperature was slowly increased until it reached 215°. Additional reflux for 2 hr at this temperature, extraction with ether, and reacetylation with acetic anhyride and pyridine (1.5 ml of each) gave a residue (31 mg) which was chromatographed on alumina (10 g). The fraction eluted with pentane–ether (19:1) gave 18 mg of **11**: mp 99–101° (after recrystallization from methanol); $[\alpha]_D$ −23°; λ_{max}^{KBr} 5.76 μ.

Anal. Calcd for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 80.37; H, 10.26.

B.—4β-Acetyl-4α-methylestr-5-en-17β-ol acetate (**1**, 21 mg) was added to a solution of sodium (200 mg) and hydrazine (1 ml) in diethylene glycol (5 ml). Treatment as in A gave a residue which was chromatographed on alumina (4.5 g). Elution with pentane–ether (16:1) gave 6 mg of **11**, mp 99–100°, identical with the sample obtained in A.

Ethylation of 19-Nortestosterone.—A solution of 5 g of 19-nortestosterone in *t*-butyl alcohol (70 ml) was treated with a solution obtained from the reaction of potassium (1 g) in 70 ml of *t*-butyl alcohol and then heated under reflux. It was then treated dropwise with 2.2 ml of ethyl iodide in 200 ml of *t*-butyl alcohol over 2.5 hr. After a further 0.5-hr reflux, the solution was filtered. The filtrate was evaporated to dryness under reduced pressure and the residue was acetylated with acetic anhydride and pyridine (25 ml of each). The acetylated material (5.6 g) was chromatographed on alumina (600 g).

The fraction eluted with pentane–ether (9:1) gave 900 mg of 4,4-diethyl-19-nortestosterone acetate (**18**): mp 85–86° (after recrystallization from pentane); $[\alpha]_D$ −42°; λ_{max}^{KBr} 5.80 and 5.87 μ.

Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.37; H, 9.74. Found: C, 77.71; H, 9.54.

The second fraction eluted with pentane–ether (3:1) yielded 2.9 g of 4-ethyl-19-nortestosterone acetate (**12**): mp 89–90°; $[\alpha]_D$ +42°; λ_{max}^{KBr} 5.76, 5.99, and 6.20 μ.

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.47; H, 9.43.

Methylation of 4-Ethyl-19-nortestosterone Acetate (12).—A solution of 700 mg of **12** in *t*-butyl alcohol (20 ml) was treated with a solution obtained from the reaction of potassium (500 mg) in *t*-butyl alcohol (20 ml). It was then heated under reflux and treated dropwise with a solution of methyl iodide (2 ml) in *t*-butyl alcohol. The heating was continued for 5 hr until the reaction mixture became neutral. The filtered solution was evaporated to dryness and was reacetylated with acetic anhydride and pyridine (7 ml of each). The acetylated material was chromatographed on alumina (130 g).

The first fraction eluted with pentane–ether (4.5:1) gave 170 mg of 4α-ethyl-4β-methylestr-5-en-17β-ol-3-one acetate (**13**): mp 114–115° (after recrystallization from ether–pentane); $[\alpha]_D$ −14°; λ_{max}^{KBr} 5.76 and 5.89 μ.

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.16; H, 9.54.

The second crystalline fraction eluted with pentane–ether (4:1) gave 80 mg of 4β-ethyl-4α-methylestr-5-en-17β-ol-3-one acetate (**10**), mp 120–122°, identical with the product obtained previously by ethylation of 4-methyl-19-nortestosterone acetate (**9**).

4α-Ethyl-4β-methylestr-5-en-17β-ol Acetate (14).—4α-Ethyl-4β-methylestr-5-en-17β-ol-3-one acetate (**13**, 50 mg) was added to a solution of sodium (200 mg) and hydrazine (0.7 ml) in diethylene glycol (5 ml). Similar treatment as described above gave a crystalline residue (50 mg), which was purified by chromatography. The fraction eluted with pentane–ether (17:1) gave 16 mg of **14**: mp 107–108° (after recrystallization from methanol); $[\alpha]_D$ −23°; λ_{max}^{KBr} 5.75 μ.

Anal. Calcd for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 80.31; H, 10.64.

d_3-Methylation of 4-Methyl-19-nortestosterone Acetate (9).—A solution of 100 mg of **9** in 5 ml of *t*-butyl alcohol was treated with a solution obtained from the reaction of potassium (150 mg) in 10 ml of *t*-butyl alcohol and then with methyl-d_3 iodide (2 ml). After being stirred overnight at room temperature the reaction mixture was filtered and the filtrate was evaporated to dryness. Reacetylation with acetic anhydride and pyridine (1 ml of each) and chromatography of the residue (100 mg) on alumina (10 g) gave a crystalline fraction (32 mg) which was eluted with pentane–ether (6:1). This material had mp 125–130°; λ_{max}^{KBr} 4.50, 4.86, 5.75, and 5.87 μ.

This material consisted mainly of 4β-methyl-d_3-4α-methylestr-5-en-17β-ol-3-one acetate (**15**) (see discussion). Analogous results were obtained when the d_3-methylation was carried out under identical conditions described before for ethylation of **9**.

4,4-Dimethylestr-5-en-17β-ol Acetate (16).—4,4-Dimethylestr-5-en-17β-ol-3-one acetate (**6**, 50 mg) was reduced with a solution of sodium (300 mg) and hydrazine (1 ml) in diethylene glycol (5 ml) as described above. The reacetylated product was chromatographed on alumina (8 g). Elution with pentane–ether (12:1) afforded 31 mg of **16**, mp 145–147°, λ_{max}^{KBr} 5.75 μ.

Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.57; H, 10.45.

Wolff–Kishner Reduction of the d_3-4,4-Dimethylestr-5-en-17β-ol-3-one Acetates.—The crude crystalline alkylated material (24 mg), mp 125–130°, obtained by d_3-methylation of 4-methyl-19-nortestosterone acetate (9) was reduced with a solution of sodium (200 mg) and hydrazine (0.6 ml) in diethylene glycol (3 ml). Analogous treatment as described above gave an oily material (27 mg) which was chromatographed on alumina (8 g.) Elution with pentane–ether (13:1) gave 8 mg of material, mp 144–146°, which consisted mainly of 4β-methyl-d_3-4α-methylestr-5-en-17β-ol acetate (17) (see discussion).

Mass Spectrometry in Structural and Stereochemical Problems. XCI.[1] The Electron Impact Induced Elimination of Water from 3-Hydroxy Steroids

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One of the ubiquitous fragmentation modes of 3-hydroxy steroids is the loss of 33 mass units (methyl radical plus water). By deuterium labeling in the cholestane series it could be shown that in the case of the axial 3α-alcohol the M − 15 ion loses water exclusively by 1,3 elimination of the hydroxyl function and the 1α- and the 5α-hydrogen atoms, respectively. The 3β-alcohol shows more random loss of water after elimination of the C-19 methyl group. An explanation for this apparently inconsistent behavior is given.

Studies of cyclic alcohols (cyclopentanol[2] and cyclohexanol[3,4]) have shown that electron impact induced loss of water occurs as a 1,3 or 1,4 elimination. However, it could not be determined with these model compounds whether this reaction occurs in a stereospecific manner. In the steroid series studies of this type seemed feasible and our results are reported herewith.

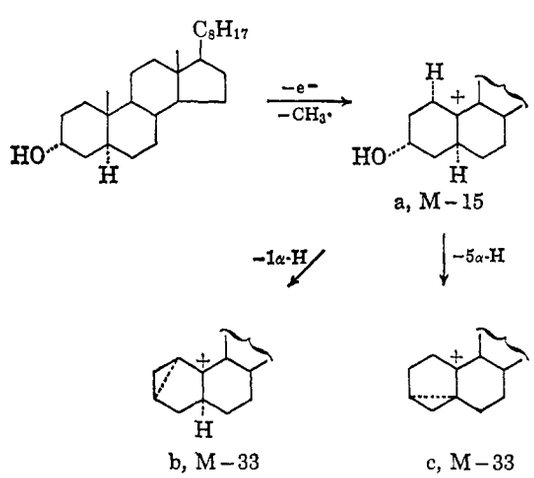
The spectrum of 5α-androstan-3β-ol shows a prominent M − 18 peak and would, therefore, have been suitable for our studies. We wanted, however, to rule out any possible falsification of the results by thermal loss of water prior to electron impact and chose, therefore, a different substance. The M − 18 fragment in the case of cholestan-3α- and -3β-ol is negligible when direct insertion of the sample in the ion source is used.[5,6] However, loss of water can be observed (see Figure 1) starting from the M − 15 fragment (supported by appropriate metastable ion at *m/e* 338.0, calcd 337.8), and we chose this process for our further studies.

The data obtained with various deuterium-labeled analogs of cholestan-3α-ol are given in Table I (the estimated error is ±2%). These results show that no 1,2 elimination occurs in this fragmentation process. Most of the deuterium lost stems from the 5α-position, while comparison of the 1,1,3β-d_3 and the 1α-d_1 analogs shows that some deuterium comes from the 1α-position. Assuming that the total (about 80%) accounts for all the loss of water from the M − 15 species, an isotope effect of 0.8 has to be invoked which lies well within the observed range.[7,8] The driving force of this sequence is apparently the stabilization of the C-19 carbonium ion by conjugation with a cyclopropane ring. Preferential loss of the 5α-hydrogen (from a tertiary position) compared with the secondary 1α locus has its parallel in other fragmentations.[9]

TABLE I

ORIGIN (%) OF HYDROGEN IN M − 34 FRAGMENT OF LABELED CHOLESTAN-3α-OLS

Compound	M − 34 (CH_3 + HDO)
Cholestan-3α-ol	0
Cholestan-3α-ol-2,2,4,4-d_4 (V)	0
Cholestan-3α-ol-1,1,3β-d_3 (XIX)	7 ± 2
Cholestan-3α-ol-1α-d_1 (IX)	4.5 ± 2
Cholestan-3α-ol-5α-d_1 (XIII)	73 ± 2



The analogous data for the isomeric cholestan-3β-ol are compiled in Table II and show that this compound follows different fragmentation paths. No loss of deuterium is observed from the 1α-, 2-, 3α-, or 4-positions, while elimination from the 1β- and 5α-(!) position totals only about 40%. On the assumption that the same isotope effect operates as in the 3α-hydroxy isomer, only about one-half of the loss of water from the M − 15 ion is accounted for and the remaining hydrogen must be abstracted from carbon atoms other than in ring A.

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