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Factors Governing the Relative Stabilities of the C/D Cis and Trans Ring Junctures in Δ^8-11-Keto Steroids

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Pure 14α and 14β epimers of Δ^8-11-keto steroids with different 17β-alkyl groups were prepared and the position of their base-catalyzed equilibrium established by gas-liquid phase chromatography. In contrast to 15-keto steroids, where the nature of the 17β substituents crucially affects the cis/trans hydrindanone equilibrium, the 14β (C/D cis) isomer is greatly favored in the present series irrespective of the nature of the C-17 substituent. Using a previously described force-field method, the energies and conformations of the cis and trans isomers of the Δ^8-11-keto steroids were calculated and found to be in reasonable agreement with the experimentally established values.

One of the most interesting problems in steroid conformational analysis lies in the variation of the relative stabilities of the cis and trans (C/D) ring juncture, notably in steroidal hydrindanone systems.[1] Numerous variations observed in these systems led to a whole series of explanations.[1,2] A detailed experimental study using optical rotatory dispersion measurements of 17β-alkyl-5α,14ξ-androstan-15-ones[3] and a subsequent theoretical study using a force-field method[4] were in good agreement.[5] The data generated by this force-field method made it possible to understand the exact nature of the interactions which led to the observed energy differences.[5]

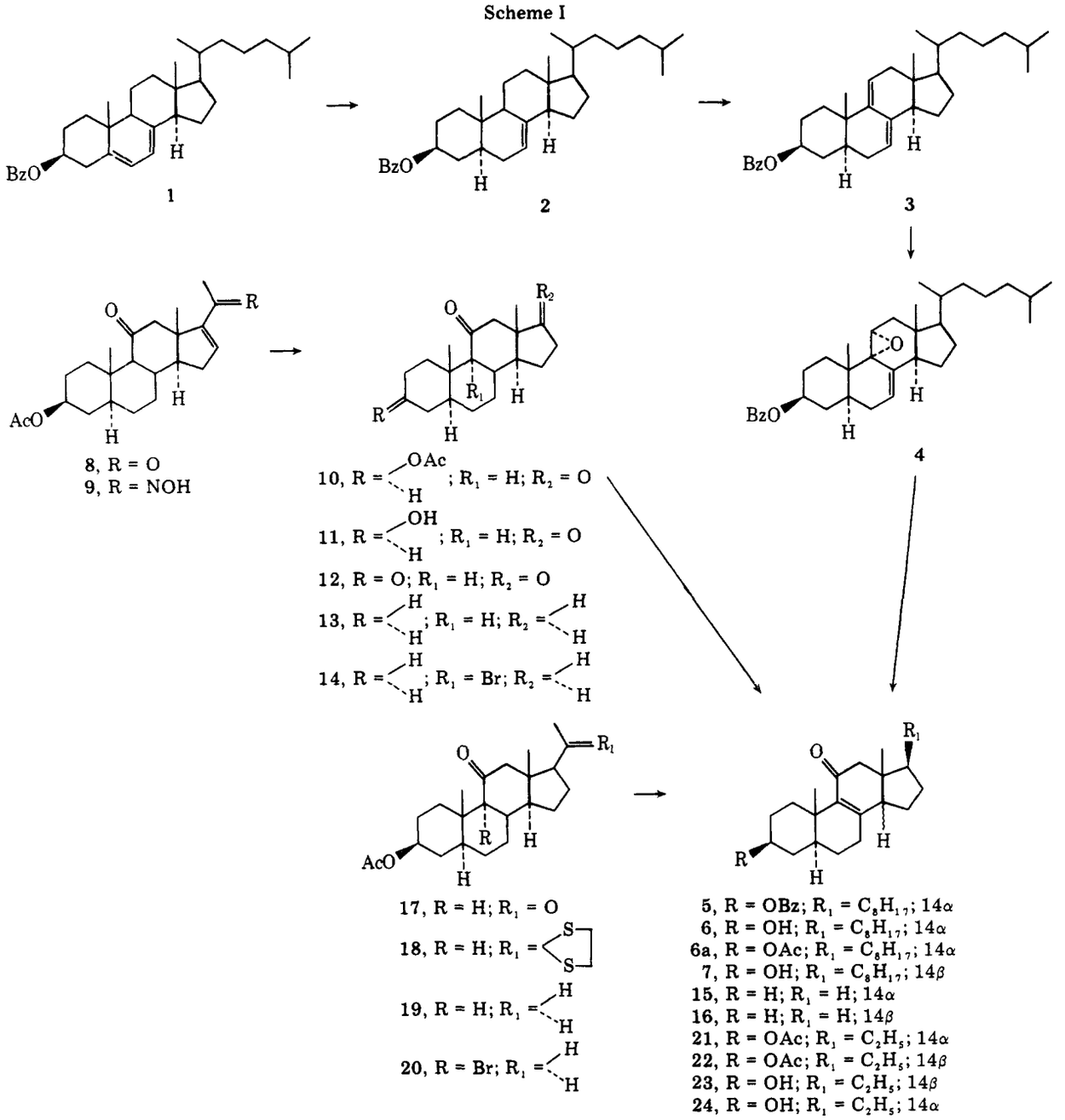
In the 8-methylhydrindane system the cis compound is the more stable one.[2a,5,6] The greater stability of the cis compound can be applied to steroid systems[2a] and Dreiding[7] summarized examples showing trans to cis isomerization of the C/D rings. Most of these compounds had either an isolated or aromatic double bond between C-8 and C-9. Djerassi and co-workers were able to isomerize a Δ^8-11-ketone in the sapogenin series from the 14α to the 14β epimer[8] and Eardley et al.[9] were able to effect a similar change with a Δ^8-11-ketone possessing a 17β-C_9H_{19} substituent.

The object of the present study was to investigate the base-catalyzed equilibration of 17β-alkyl-Δ^8-5α,14ξ-androsten-11-ones, in order to determine what role the size of the 17β-alkyl substituent plays in the relative stabilities of the cis and trans (C/D) ring juncture. In addition, theoretical calculations using the 1973 force-field method[10] were carried out in order to provide insight into the nature of the interactions involved. The results of the experimental study (Table I) are in accord with the theoretical predictions.

Synthesis of Δ^8-11-Keto Steroids. The synthesis of the various Δ^8-11-keto steroids is depicted in Scheme I. Hydrogenation (W-5 Raney nickel) of $\Delta^{5,7}$-cholestadien-3β-ol benzoate (**1**) gave in nearly quantitative yield the known[11] alkene **2**, which upon mercuric acetate oxidation in acetic acid afforded in 69% yield the known[12] $\Delta^{7,9(11)}$-5α-cholestadien-3β-ol benzoate (**3**). Oxidation at 0 °C with *m*-chloroperbenzoic acid gave the known[13] monoepoxide **4**, which was smoothly rearranged in the presence of boron trifluoride etherate to give a 74% yield of Δ^8-5α-cholesten-3β-ol-11-one benzoate (**5**). Owing to the facile alkaline isomerization at C-14, the benzoate **5** was saponified under mild conditions[8] to give the corresponding alcohol **6** which could be acetylated under normal conditions to give the known[14] Δ^8-5α-cholesten-3β-ol-11-one acetate (**6a**). Alternatively, saponification (5% methanolic KOH) of the benzoate **5** afforded in 83% yield the C-14 epimeric alcohol Δ^8-5α,14β-cholesten-3β-ol-11-one (**7**). Base-catalyzed equilibration of pure Δ^8-5α,14α (**6**) and Δ^8-5α,14β (**7**) gave an equilibrium mixture (see Table I) consisting of 96–97% of the 14β (**7**) and 3–4% of the 14α (**6**) epimers.

The versatile starting material Δ^{16}-5α-pregnene-11,20-dion-3β-ol acetate (**8**)[15,16] was chosen for the desired Δ^8-11-one compounds in the androstane and pregnane series. Beckmann rearrangement[17] of the oxime **9** gave 64% of 5α-androstane-11,17-dion-3β-ol acetate (**10**). Saponification to **11** followed

Scheme I



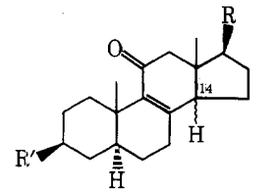
by oxidation to 5α-androstane-3,11,17-trione (**12**) and Wolff–Kishner reduction gave a 46% overall yield of 5α-androstan-11-one (**13**). Bromination[18] to the 9α-bromide **14** and subsequent dehydrobromination[9,18] for *30 s* afforded the desired Δ⁸-5α-androsten-11-one (**15**). Alternatively, dehydrobromination of **14** for *2 min* gave the C-14 epimeric Δ⁸-5α,14β-androsten-11-one (**16**). Base-catalyzed equilibration of Δ⁸-5α,14α (**15**) and Δ⁸-5α,14β (**16**) gave an equilibrium mixture (see Table I) consisting of 99 to <100% of the 14β (**16**) and ~1% of the 14α (**15**) epimers.

Hydrogenation (10% palladium on carbon) of Δ¹⁶-5α-pregnene-11,20-dion-3β-ol acetate (**8**)[15,16] gave a quantitative yield of **17** which was converted quantitatively with ethanedithiol and boron trifluoride etherate[19] to the 20-ethylene thioketal **18**. Raney nickel[20] (W-7) desulfurization proceeded in 85% yield to 5α-pregnan-3β-ol-11-one acetate (**19**). Bromination in acetic acid[18] led to the 9α-bromo derivative **20** which furnished in 97% yield Δ⁸-5α-pregnen-3β-ol-11-one acetate (**21**) upon dehydrobromination for *30 s* with calcium carbonate in refluxing dimethylacetamide. Alternatively, dehydrobromination of 9α-bromo-5α-pregnan-3β-ol-11-one acetate (**20**) for *20 min* furnished the C-14 epimeric acetate Δ⁸-5α,14β-pregnen-3β-ol-11-one acetate (**22**) which was then saponified to the desired alcohol Δ⁸-5α,14β-pregnen-3β-ol-11-one (**23**). Base-catalyzed equilibration of the 14β alcohol **23** gave an equilibrium mixture (see Table 1) consisting of 98% of the 14β (**23**) and 2% of the 14α (**24**) epimers. Mild saponification[8] of the 14α-acetate **21** furnished Δ⁸-5α-pregnen-3β-ol-11-one (**24**) which was also subjected to base-catalyzed equilibration (see Table I).

Results and Discussion

Table II summarizes the calculated[21] stabilities of tricyclic models[22] of 15-keto steroids and Δ⁸-11-keto steroids. In the saturated tricyclic ketone **25a**, the trans isomer is slightly more stable (by 0.3 kcal/mol). Adding a bridgehead methyl (**25b**) makes a major change, so that the cis isomer is now very strongly stabilized. On the other hand, placing a methyl substituent at the 17 position (steroid numbering) produces a trend in the opposite direction; nevertheless, in **25c** the cis isomer remains the preferred one. When an isopropyl group is attached at C-17 (**25d**), the order inverts again, and the trans

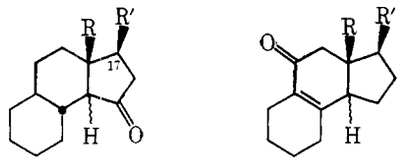
Table I. Position of Base-Catalyzed Equilibrium of 17β-R-Δ⁸-5α,14ξ-Androsten-3β-R′-11-one



R	R′	% 14β epimer	ΔG_{65}°, kcal/mol
H	H	99[a] to <100[b]	3.2
C_2H_5	OH	98[a,b]	2.6
C_8H_{17}	OH	96[a]–97[b]	2.2

[a] Base-catalyzed equilibration from the 14α epimer. [b] Base-catalyzed equilibration from the 14β epimer.

Table II. Calculated Enthalpies (kcal/mol) for Conformational Equilibria: 14β (Cis) ⇌ 14α (Trans)



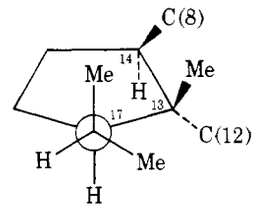
25 26

25	ΔH_{25}°	R	R′	26	ΔH_{26}°
a	−0.33	H	H	a	+0.70
b	+2.08	Me	H	b	+2.69
c	+1.01	Me	Me	c	+1.41
d	−1.14	Me	*i*-Pr	d	+1.14

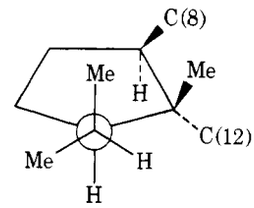
isomer is now preferred. Similar results have been encountered experimentally in a study of 17-alkyl-15-keto steroids.[3] This inversion of stability has been suggested to be mainly due to an unfavorable interaction between a C-20 methyl and the 14β hydrogen which are only 2.35 Å apart.[5]

If we now consider the Δ^8-11-keto steroids, in the simple tricyclic case (**26a**) the cis isomer is more stable by 0.7 kcal/mol. This inversion of stability from **25a** to **26a** can be attributed to the well-known effect of a cyclohexene system in stabilizing a five-membered ring fused cis at the observed position in the compounds under discussion.[7,23] This "cyclohexene effect" contributes about 1 kcal toward stabilizing the cis isomer when comparing **25a** and **26a.** Proceeding down the series from **26a** to **26d** the energy differences are consistently positive relative to those in the series **25a** to **25d.** The calculations (Table II) for the tricyclic unsaturated ketone indicate that the cis isomer is strongly favored irrespective of the side chain and this is what is found experimentally (Table I) for the Δ^8-11-keto steroids. The calculations also indicate that there are basically two different kinds of conformations for the C/D system when the juncture is cis. These two conformations **27** and **28** (Table III)[24] correspond to the two different half-chair conformations of the cyclohexene in ring C. In conformation **28,** models show that the 15α hydrogen interacts unfavorably (by about 1 kcal according to the calculation) with the 7α hydrogen. This unfavorable repulsion, and distortions imposed in an attempt to relieve it, seem to be the main source of the increase in relative stability of conformation **27.** In addition, for each of these conformations there are two separate conformations which differ mainly by twisting ring D in the pseudorotational itinerary.[25]

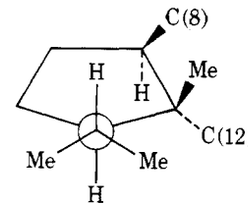
It is apparent from Table II that the same general trend is found in both the 15-ketone series (**25b** to **25d**) and the Δ^8-11-ketone series (**26b** to **26d**): the relative stability of the (C/D)-cis isomer decreases as the size (C-20) of the β-alkyl group attached to C-17 increases. The effect of the 17β-isopropyl group in the 15-ketone series was to actually invert the relative stability at the C/D ring juncture from the cis to the trans configuration.[3,5] The isopropyl group does not have the same effect in the Δ^8-11-ketone (**26d**) where the cis compound is still the overwhelming favorite (Table II). There are three orientations that the isopropyl group can assume, and their energies (relative to the best conformation of the cis isomer) are shown below along with values in parentheses for the corresponding saturated 15-ketones as recalculated with the 1973 force-field method.[10] The conformation with E = 1.14



E = 4.46 (3.77)



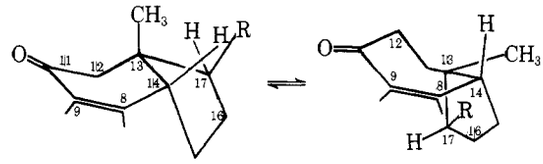
E = 3.12 (2.02)



E = 1.14 (0.00)

is the best conformation for the (C/D)-trans isomer of the Δ^8-11-ketone **26d** as well as for the (C/D)-trans isomer of the 15-ketone **25d.** The other conformations suffer from an extremely unfavorable interaction between the angular 18-methyl group and a methyl group of the isopropyl substituent. This interaction is similar to the syn-diaxial dimethyl interaction in a 1,3-dimethylcyclohexane.[26]

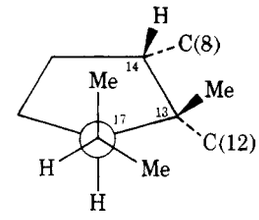
Table III. Calculated Energies for the Two Half-Chair Conformations of Ring C in the Δ^8-11-Keto Steroids



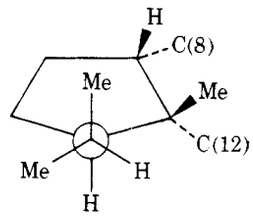
27 28

Conformer 27	Angle 8-14-13-17	Angle 12-13-14-15	ΔE, kcal/mol	R	Conformer 28	Angle 8-14-13-17	Angle 12-13-14-15	ΔE, kcal/mol
a	163.7	80.7	0.00	H	a	85.3	156.5	1.82
b	163.5	80.6	2.26	Me	b	78.6	165.4	3.21
c	150.9	98.6	6.54	*i*-Pr	c	78.4	167.6	7.57

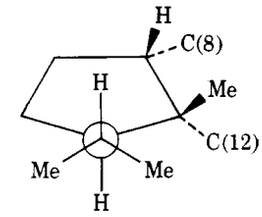
In the (C/D)-cis Δ^8-11-one (**26d**), surprisingly, the stable conformation (E = 0.00) has an extremely unfavorable interaction between the angular 18-methyl group and the isopropyl Me group. However, this conformation lacks the interaction between the C-20 methyl group and the 14β hydrogen which was apparently the major interaction responsible for the inversion of stability in going from a 17-methyl (**25c**) to a 17-isopropyl (**25d**) substituent in the 15-ketone series.[5] That the conformation of the isopropyl side chain in the most stable conformation of the cis isomer is different in the 15-ketones as compared to the Δ^8-11-ketones was not anticipated. From looking at plots of the structures and the accompanying tables of numbers obtained as computer output, the following observations were made.



E = 2.91 (2.81)



E = 1.53 (1.14)



E = 0.00 (3.48)

Since there are many interactions which differ in energy when the different series and conformations are compared, the interpretation is neither complete nor unambiguous, but rather is suggestive. The dihedral angle between the side chain and the 18-methyl group differs in the two systems. In the most stable conformation for the cis 11-ketone (E = 0.00) this dihedral angle is 21°. In the corresponding 15-ketone conformation (E = 3.48), the angle is only 15° and the interaction of the side chain and the 18-methyl is more serious. Thus in the 15-ketone the conformation where the methyl–side chain interaction is minimized (E = 1.14) will be preferred. The presence of the 15-ketone group introduces different torsional and angular interactions in the five-membered ring and apparently affects the crucial dihedral angle. In addition, the presence or absence of the unsaturation in the B ring may lead to further small distortions, and, probably more importantly, changes in the ease of distortions.

Experimental Section

General Information. Microanalyses were performed by E. H. Meier and J. Consul, Department of Chemistry, Stanford University. All melting points are uncorrected and were taken with a Thomas-Hoover capillary melting point apparatus. Infrared spectra were obtained for solutions in chloroform with a Perkin-Elmer 700 spectrometer. NMR spectra were recorded under the supervision of Dr. L. J. Durham on a Varian Associates T-60 of XL-100 spectrometer with deuteriochloroform as solvent and tetramethylsilane as internal reference. Ultraviolet spectra were recorded for solutions in absolute methanol with a Cary Model 14 spectrometer using 1-cm quartz cells. Routine optical rotations were recorded with a Perkin-Elmer Model 141 spectropolarimeter for solutions in chloroform. Circular dichroism curves were determined for solutions in absolute methanol by Mrs. R. Records with a JASCO J-40 circular dichrometer. Low-resolution mass spectra were determined by Mr. R. G. Ross with an AEI MS9 spectrometer operating at 70 eV by use of the direct inlet system. Exact masses were determined by Miss Annemarie Wegmann on a Varian-Mat 711 high-resolution mass spectrometer.

The progress of all reactions and column chromatographies was monitored by thin layer chromatography on silica gel (HF-254) microplates. The spots were detected by spraying with a 2% solution of cerium(IV) sulfate in 2 N sulfuric acid, followed by heating. Preparative thin layer chromatoplates had a thickness of 0.75 mm of silica gel (HF-254) and the bands were detected either visually or by viewing under ultraviolet light. Gas–liquid phase chromatography (GLC) was performed on a Hewlett-Packard Model 402 high-efficiency instrument using 6-ft glass columns packed with 1% OV-25 on Gas-Chrom Q (100–120 mesh) using helium as the carrier gas.

Δ^8-5α-Cholesten-3β-ol-11-one Benzoate (5). The epoxide[13] (**4**, 213 mg, 0.422 mmol) was dissolved in 30 mL of dry, thiophene-free benzene and 20 drops of freshly distilled boron trifluoride etherate[8] was added to the reaction mixture which was allowed to stand at room temperature for 70 h. The solution was then extracted with ether and washed with sodium bicarbonate and water. After drying over $MgSO_4$ and purification by thin layer chromatography on silica gel (10% ether–hexane) a white, crystalline material was obtained (**5**, 157.6 mg, 0.31 mmol, 74%). Crystallization from aqueous acetone afforded clear needles: mp 181–182 °C; $[\alpha]^{21.7}_D$ +117° (c 0.52); IR 5.82, 6.03 μ; NMR δ 4.97 (3α-H, $W_{1/2}$ ca. 24 Hz), 2.80 (d, 1 H, 12β-H, J = 14 Hz), 2.33 (d, 1 H, 12α-H, J = 14 Hz), 1.17 (s, 3 H, 19-CH_3, calcd[27] 1.11), 0.71 (s, 3 H, 18-CH_3, calcd[27] 0.68); UV 230 nm (ϵ 16 000), 257 (9200); CD $[\theta]_{215}$ −24 000, $[\theta]_{254}$ +42 000, $[\theta]_{332}$ −7400; mass spectrum m/e (rel intensity) 504.3602 [M^+ (92), calcd for $C_{34}H_{48}O_3$, 504.3603], 382 (61), 367 (36), 352 (100), 297 (100), 161 (29), 105 (86).

Anal. Calcd for $C_{34}H_{48}O_3$: C, 80.91; H, 9.58. Found: C, 80.65; H, 9.70.

Δ^8-5α,14α-Cholesten-3β-ol-11-one (6). The benzoate (**5**, 200 mg, 0.396 mmol), 320 mg of K_2CO_3, 4 mL of water, 40 mL of methanol, and 15 mL of chloroform were allowed to stand at room temperature for 49 h. After concentration under reduced pressure, dilution with water, and filtration, the product was chromatographed on silica gel (100% ether) and the early fractions provided 61 mg of the starting benzoate **5**. Further development provided 76.0 mg of the desired alcohol **6** which was crystallized from aqueous methanol to give fine needles: mp 132–133 °C; $[\alpha]^{20}_D$ +154° (c 0.26); IR 2.93 6.08, 6.29 μ; NMR δ 3.60 (3α-H, $W_{1/2}$ ca. 24 Hz), 2.78 (d, 1 H, 12β-H, J = 14 Hz), 2.30 (d, 12α-H, J = 14 Hz), 1.10 (s, 3 H, 19-CH_3, calcd[27] 1.09), 0.70 (s, 3 H, 18-CH_3, calcd[27] 0.68); UV 255 nm (ϵ 8500); CD $[\theta]_{216}$ −30 700, $[\theta]_{254}$ +46 800, $[\theta]_{332}$ −8200; mass spectrum m/e (rel intensity) 400.3321 [M^+ (100), calcd for $C_{27}H_{44}O_2$, 400.3341], 248 (61), 193 (60).

Acetylation under normal conditions of the alcohol **6** afforded the acetate **6a**: mp 105–106 °C (lit.[14] mp 104–106 °C); IR 5.82, 6.08, 6.28 μ.

Δ^8-5α,14β-Cholesten-3β-ol-11-one (7). The benzoate (**5**, 924 mg, 1.82 mmol) was heated under reflux in an atmosphere of nitrogen for 130 min with 100 mL of 5% methanolic KOH. After concentration under reduced pressure, the reaction mixture was diluted with water and extracted into ether. The extracts were washed four times with water followed by drying over $MgSO_4$ and evaporation to give 742.5 mg (~100%) of slightly yellow, glassy solid. Column chromatography on silica gel (100% ether) afforded material which was again subjected to column chromatography on 12% $AgNO_3$ impregnated silica gel (30% acetone–hexane) to give 613 mg (83%) of the alcohol **7** which was crystallized from aqueous methanol to give white plates: mp 72–74 °C (presoftens); $[\alpha]^{20}_D$ +170°; IR 3.02, 6.03, 6.22 μ; NMR δ 3.61 (3α-H, $W_{1/2}$ ca. 24 Hz), 2.48 (d, 1 H, 12β-H, J = 14 Hz), 2.14 (d, 1 H, 12α-H, J = 14 Hz), 1.13 (s, 3 H, 19-CH_3), 1.01 (s, 3 H, 18-CH_3); UV 250 nm (ϵ 8700); CD $[\theta]_{209}$ −11 020, $[\theta]_{245.5}$ +19 320, $[\theta]_{333.5}$ −1162; GLC (265 °C) relative retention time (rrt) 0.69 (rrt of **6**, 1); mass spectrum m/e (rel intensity) 400.3354 [M^+ (100), calcd for $C_{27}H_{44}O_2$, 400.3341], 248 (18), 193 (14).

5α-Androstane-11,17-dion-3β-ol Acetate (10). Δ^{16}-5α-Pregnene-11,20-dion-3β-ol acetate (**8**) was reacted under conditions described in the literature[18] to give a 79% yield of the oxime **9** which was crystallized from absolute methanol to give small, white flakes: mp 219–224 °C (lit.[18] mp 217–222 °C); M^+ m/e 387; IR 2.95, 5.82, 5.88 μ (lit.[18] IR 5.82, 5.88 μ); NMR δ 8.43 (s, 1 H, =NOH, D_2O labile), 1.03 (s, 3 H, 19-CH_3), 0.85 (s, 3 H, 18-CH_3).

Beckmann rearrangement[17] of the oxime **9** afforded a 65% yield of the desired ketone **10** which was crystallized from acetone–hexane to give needles: mp 163–164.5 °C (lit.[18] mp 161–163 °C); M^+ m/e 346; IR 5.75, 5.79, 5.86, 8.0, 9.7 μ (lit.[18] IR 5.74, 5.78, 5.88, 8.06, 9.7 μ); NMR δ 1.05 (s, 3 H, 19-CH_3, calcd[27] 1.07), 0.82 (s, 3 H, 18-CH_3, calcd[27] 0.83).

5α-Androstane-11,17-dion-3β-ol (11). The acetate (**10**, 1.1 g, 3.17 mmol) and 50.72 g (63.4 mmol, 20-fold excess) of 5% methanolic KOH were allowed to stand at room temperature for 80 min followed by concentration under reduced pressure and dilution with water. Ether

extraction, washing (H_2O), drying ($MgSO_4$), and evaporation gave the desired alcohol (**11**, 965 mg, 100%) which was crystallized twice from ether–hexane to give needles: mp 169–170 °C; M^+ *m/e* 304; IR 2.82, 5.76, 5.86 μ; NMR δ 1.03 (s, 3 H, 19-CH_3, calcd[27] 1.06), 0.81 (s, 3 H, 18-CH_3, calcd[27] 0.83).

Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.92; H, 9.32.

5α-Androstane-3,11,17-trione (12). Jones oxidation of the alcohol (**11**, 829 mg, 2.72 mmol) gave the desired trione (**12**, 760 mg, 93%) which was crystallized from acetone–hexane to give white plates: mp 180–181 °C (lit.[13] mp 180.5–181.2 °C); M^+ *m/e* 302; NMR δ 1.23 (s, 3 H, 19-CH_3, calcd[27] 1.27), 0.85 (s, 3 H, 18-CH_3, calcd[27] 0.87).

5α-Androstan-11-one (13). The trione (**12**, 250 mg, 0.82 mmol) was dissolved in 22 mL of diethylene glycol and 1.8 mL of 85% hydrazine hydrate and the mixture heated under reflux for 1 h. Upon cooling to about 100 °C, 500 mg of KOH dissolved in 1 mL of water was added and heating was continued without a reflux condenser until the temperature reached 200 °C. After heating under reflux between 200 and 215 °C for an additional 195 min the reaction mixture was cooled and poured into water (110 mL). The aqueous phase was extracted five times with ether and the ether extracts washed with water, dried ($MgSO_4$), and evaporated to give 227 mg (100%) of a slightly yellow oil. Column chromatography on silica gel (50% benzene–hexane) provided the desired ketone (**13**, 114 mg, 50%) which was crystallized from aqueous methanol to give fine white needles: mp 51.5–53 °C (lit.[28] mp 49–50 °C); $[\alpha]^{20}_D$ +55° (lit.[28] $[\alpha]_D$ +65°); M^+ *m/e* 274; IR 5.89 μ (lit.[28] IR 5.89 μ).

9α-Bromo-5α-androstan-11-one (14). Bromination[18] of the ketone (**13**) gave after preparative TLC and crystallization in absolute methanol a 21% yield of **14** as small, white, soft needles: mp 74–75.5 °C (lit.[18] mp 71–72 °C); M^+ *m/e* 352/354; IR 5.90 μ. The chromatography also afforded 4.0 mg of pure starting ketone **13.**

Δ^8-5α,14α-Androsten-11-one (15). 9α-Bromo-5α-androstan-11-one (**14**, 60 mg, 0.17 mmol) was dehydrobrominated for 30 s with calcium carbonate (51 mg, 0.51 mmol) in refluxing dimethylacetamide (1.5 mL, which had been stirred with KOH and distilled from CaO). The mixture was then poured into water and ether. The ether extracts were washed, dried ($MgSO_4$), and evaporated to give semicrystalline material which was purified by thin layer chromatography on silica gel (50% benzene–hexane) to give after crystallization in aqueous methanol (20.0 mg, 43%) fine white needles: mp 112–113.5 °C (lit.[18] mp 113–114 °C); $[\alpha]^{20}_D$ +168° (*c* 0.16) [lit.[18] $[\alpha]_D$ +180° (*c* 1.3)]; IR 6.07, 6.28 μ (lit.[15] IR 6.07, 6.24 μ); NMR δ 2.54 (d, 1 H, 12β-H, *J* = 14 Hz), 2.26 (d, 1 H, 12α-H, *J* = 14 Hz), 1.10 (s, 3 H, 19-CH_3, calcd[27] 1.075), 0.73 (s, 3 H, 18-CH_3, calcd[27] 0.725); UV 255 nm (ε 8900) [lit.[18] UV 253 nm (ε 8300)]; CD $[\theta]_{220}$ −13 940, $[\theta]_{255}$ +29 570, $[\theta]_{335}$ −6337; mass spectrum *m/e* (rel intensity) 272.2138 [M^+ (100), calcd for $C_{19}H_{28}O$, 272.2140], 257 (84), 243 (56), 177 (47), 161 (41).

Δ^8-5α,14β-Androsten-11-one (16). Crude 9α-bromo-5α-androstan-11-one (**14**, 458 mg, 1.29 mmol) was dehydrobrominated for 2.0 min with calcium carbonate (387 mg, 3.87 mmol) in refluxing dimethylacetamide (10.0 mL, which had been stirred with KOH and distilled from CaO). The reaction mixture was then poured into water and extracted with ether. The ether extracts were washed, dried ($MgSO_4$), and evaporated to give 354.6 mg of semicrystalline material which was purified by thin layer chromatography on silica gel (50% benzene–hexane) to give after crystallization in aqueous methanol (142.4 mg) fine white needles: mp 64–65.5 °C; $[\alpha]^{20}_D$ +192° (*c* 0.13); IR 6.04, 6.22 μ; NMR δ 2.53 (d, 1 H, 12β-H, *J* = 14 Hz), 1.92 (d, 1 H, 12α-H, *J* = 14 Hz), 1.12 (s, 3 H, 19-CH_3, calcd[27] 1.05), 1.05 (s, 3 H, 18-CH_3, calcd[27] 1.025); UV 251 nm (ε 8700); CD $[\theta]_{210}$ −11 210, $[\theta]_{247.5}$ +17 390, $[\theta]_{325}$ −2445; GLC (205 °C) rrt 0.74 (rrt of **15**, 1); mass spectrum *m/e* (rel intensity) 272.2128 (M^+ (100), calcd for $C_{19}H_{28}O$, 272.2140], 257 (76), 243 (43), 177 (11), 161 (18).

Anal. Calcd for $C_{19}H_{28}O$: C, 83.76; H, 10.36. Found: C, 83.70; H, 10.33.

5α-Pregnane-11,20-dion-3β-ol Acetate (17). Δ^{16}-5α-Pregnene-11,20-dion-3β-ol acetate (**8**, 5 g, 13.4 mmol) was hydrogenated over 10% palladium on carbon in ethyl acetate to give white, crystalline **17**: mp 134–135 °C (lit.[16] mp 143–145 °C); $[\alpha]^{20}_D$ +78° (lit.[16] $[\alpha]^{20}_D$ +86.5°); M^+ *m/e* 374; IR 5.75, 5.85 μ (lit.[29] IR 5.75, 5.85 μ); NMR δ 1.02 (s, 3 H, 19-CH_3, calcd[27] 1.05), 0.56 (s, 3 H, 18-CH_3, calcd[27] 0.58).

5α-Pregnan-3β-ol-11-one Acetate (19). Boron trifluoride etherate (3.0 mL) was added to a solution of the acetate (**17**, 1.68 g, 4.49 mmol) in 3.0 mL of ethanedithiol. The stirred mixture became hot and deposited a thick paste within 2 min. After being kept at room temperature for a further 7 min, methanol (20 mL) was added with stirring and the solid material filtered, washed with methanol, and dried under reduced pressure to give 1.95 g (97%) of the thioketal **18** which was crystallized from 95% ethanol–methylene chloride to give white plates: mp 234.5–235.5 °C; $[\alpha]^{20}_D$ +22°; M^+ *m/e* 450; IR 5.80, 5.85 μ; NMR δ 4.69 (3α-H, $W_{1/2}$ ca. 22 Hz), 3.28 (m, 4 H, SCH_2CH_2S), 2.02 (s, 3 H, OAc), 1.83 (s, 3 H, 21-CH_3) 1.03 (s, 3 H, 19-CH_3), 0.77 (s, 3 H, 18-CH_3).

Anal. Calcd for $C_{25}H_{38}S_2O_3$: C, 66.62; H, 8.50; S, 14.23. Found: C, 66.48; H, 8.51; S, 14.42.

The thioketal (**18**, 1.1 g, 2.44 mmol) which was dissolved in 95% ethanol (100 mL) was heated under reflux with fresh W-7 Raney nickel[20] (prepared from 30 g of alloy) for 5.5 h. The catalyst was removed by filtration and washed well with ethanol. To the ethanol solution was added 100 mL of benzene and the solvents evaporated to give 987 mg of crude material which was dissolved in ether, hexane added, and the product allowed to crystallize in the freezer to give the desired ketone (**19**, 664 mg, 85%) as white plates: mp 163–165 °C; M^+ *m/e* 360; IR 5.82, 5.87 μ; NMR δ 4.68 (3α-H, $W_{1/2}$ ca. 24 Hz), 2.53 (dt, 1 H, 1β-H, *J* = 13.5, 3.5, 3.5 Hz), 2.31 (d, 1 H, 12β-H, *J* = 12 Hz), 2.12 (d, 1 H, 12α-H, *J* = 12 Hz), 2.01 (s, 3 H, OAc), 1.04 (s, 3 H, 19-CH_3, calcd[27] 1.05), 0.52 (s, 3 H, 18-CH_3, calcd[27] 0.52).

Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.06. Found: C, 76.26; H, 10.23.

A second crop was obtained, 101 mg, mp 145–160 °C cloudy, 162 °C clear.

9α-Bromo-5α-pregnan-3β-ol-11-one Acetate (20). A solution of 32% hydrogen bromide in acetic acid (8 drops) was added to a solution of the ketone (**19**, 140.5 mg, 0.38 mmol) in acetic acid (2.0 mL) followed by the dropwise addition of 0.022 mL (0.43 mmol, 0.069 g, 1.1 mol %) of bromine in acetic acid (0.6 mL). After keeping the solution for 225 min at room temperature in the dark under a current of nitrogen, the crude product (171 mg), isolated by dilution with water and ether extraction followed by drying ($MgSO_4$) and evaporation, was purified by thin layer chromatography on silica gel (40% ether–hexane). The product (**20**, 91.8 mg, 55%) was crystallized from absolute methanol to give 60.3 mg of large leaflets: mp 178.5–180 °C; $[\alpha]^{20}_D$ +158° (*c* 0.85); IR 5.83, 5.88 μ; NMR δ 4.68 (3α-H, $W_{1/2}$ ca. 24 Hz), 3.25 (broadened d, 1 H, 12α-H, *J* = 13.5 Hz), 2.52 (broad d, 1 H, 1β-H, *J* = 13 Hz), 2.25 (d, 1 H, 12β-H, *J* = 13.5 Hz), 2.01 (s, 3 H, OAc), 1.20 (s, 3 H, 19-CH_3, calcd[27] 1.18), 0.54 (s, 3 H, 18-CH_3, calcd[27] 0.55); CD $[\theta]_{235}$ −5707, $[\theta]_{325}$ +16 000; mass spectrum *m/e* (rel intensity) 438/440 (M^+, 5), 299 (100), 246 (28), 205 (24), 152 (92), 147 (35).

Anal. Calcd for $C_{23}H_{35}BrO_3$: C, 62.86; H, 8.03; Br, 18.18. Found: C, 62.76; H, 8.20; Br, 18.20.

A second crop of 10.0 mg, mp 177–177.5 °C, as well as 35.5 mg of the unreacted starting material **19**, was also obtained.

Δ^8-5α,14α-Pregnen-3β-ol-11-one Acetate (21). 9α-Bromo-5α-pregnan-3β-ol-11-one acetate (**20**, 250 mg, 0.56 mmol) was dehydrobrominated for 30 s with calcium carbonate (168 mg, 1.68 mmol) in refluxing dimethylacetamide (8.0 mL). The same workup as before afforded 214 mg of white, semicrystalline material which was purified by thin layer chromatography on silica gel (50% ether–hexane) to give the desired acetate (**21**, 195 mg, 97%) as a white, crystalline material. Crystallization twice from ether–hexane furnished rosettes of small needles which was greater than 97% the 14α isomer by GLC: mp 144–146 °C (presoftens); IR 5.82, 6.07, 6.29 μ; NMR δ 4.72 (3α-H, $W_{1/2}$ ca. 24 Hz), 2.91 (dt, 1 H, 1β-H, *J* = 14, 3.5, 3.5 Hz), 2.56 (d, 1 H, 12β-H, *J* = 14 Hz), 2.19 (d, 1 H, 12α-H, *J* = 14 Hz), 2.03 (s, 3 H, OAc), 1.12 (s, 3 H, 19-CH_3, calcd[27] 1.12), 0.62 (s, 3 H, 18-CH_3, calcd[27] 0.591); mass spectrum *m/e* (rel intensity) 358.2501 [M^+ (71), calcd for $C_{23}H_{34}O_3$, 358.2508], 298 (73), 290 (100), 283 (64), 269 (21), 235 (97), 230 (22), 175 (42), 161 (54), 121 (35), 109 (37).

Δ^8-5α,14β-Pregnen-3β-ol-11-one Acetate (22). 9α-Bromo-5α-pregnan-3β-ol-11-one acetate (**20**, 250 mg, 0.56 mmol) was dehydrobrominated for 20 min with $CaCO_3$ (125 mg, 1.25 mmol) in refluxing dimethylacetamide (8 mL). The usual workup afforded 200 mg of a clear, thick oil. purification twice by column chromatography on silica gel (40% ether-hexane) afforded 100 mg (50%) of semicrystalline **22**: M^+ *m/e* 358; IR 5.82, 6.03, 6.22 μ; NMR δ 4.68 (3α-H, $W_{1/2}$ ca. 22 Hz), 2.45 (d, 1 H, 12β-H, *J* = 14 Hz), 1.98 (d, 1 H, 12α-H, *J* = 14 Hz), 1.98 (s, 3 H, OAc), 1.10 (s, 3 H, 19-CH_3), 0.90 (s, 3 H, 18-CH_3); GLC (265 °C) rrt 0.78 (rrt of **21**, 1).

Δ^8-5α,14β-Pregnen-3β-ol-11-one (23). To the acetate (**22**, 50 mg, 0.13 mmol) was added 8.0 g (10 mmol) of 5% methanolic KOH. The reaction mixture was left at room temperature for 80 min followed by dilution with water, ether extraction, washing, drying ($MgSO_4$), and evaporation. This material was purified by column chromatography on silica gel (100% ether) to give after two recrystallizations from aqueous methanol the desired alcohol (**23**, 14 mg, 34%) as white plates: mp 169–170 °C; $[\alpha]^{20}_D$ +183°; IR 2.75, 6.03, 6.20 μ; NMR δ 3.62 (3α-H, $W_{1/2}$ ca. 24 Hz), 2.71 (dt, 1 H, 1β-H, *J* = 14, 3.5, 3.5 Hz), 2.47 (d, 1 H, 12β-H, *J* = 14 Hz), 2.04 (d, 1 H, 12α-H, *J* = 14 Hz), 1.12 (s, 3 H, 19-CH_3, calcd[27] 1.075), 0.92 (s, 3 H, 18-CH_3, calcd[27] 0.891); UV 250

nm (ε 9700); CD $[\theta]_{207}$ −15 200, $[\theta]_{246}$ +21 580, $[\theta]_{334}$ −2225; GLC (262 °C) rrt 0.77 (rrt of **24**, 1); mass spectrum *m/e* (rel intensity) 316.2408 [M^+ (100), calcd for $C_{21}H_{32}O_2$, 316.2402], 301 (12), 298 (13), 288 (15), 283 (37), 269 (12), 257 (8), 248 (11), 193 (9), 161 (18), 109 (20), 91 (21).

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.69; H, 10.10.

Δ^8-5α,14α-Pregnen-3β-ol-11-one (24). A mixture of the acetate (**21**, 20.4 mg, 0.056 mmol), 41 mg (0.3 mmol) of K_2CO_3, 0.15 mL of water, 7.5 mL of methanol, and 1 mL of ether was allowed to stand at room temperature for 20 h. After concentration under reduced pressure, dilution with water, ether extraction, washing, drying ($MgSO_4$), and evaporation, the product was purified by thin layer chromatography on silica gel (100% ether) and crystallized (**24**, 16.4 mg, 93%) from aqueous acetone to give white plates; mp 159–163 °C (presoftens); IR 6.07, 6.28 μ; NMR δ 3.59 (3α-H, $W_{1/2}$ ca. 24 Hz), 2.86 (dt, 1 H, 1β-H, J = 14, 3.5, 3.5 Hz), 2.54 (d, 1 H, 12β-H, J = 14 Hz), 2.16 (d, 1 H, 12α-H, J = 14 Hz), 1.10 (s, 3 H, 19-CH_3, calcd[27] 1.10), 0.60 (s, 3 H, 18-CH_3, calcd[27] 0.591); UV 255 nm (ε 8800); CD $[\theta]_{215}$ −21 710, $[\theta]_{255}$ +31 330, $[\theta]_{331}$ −6187; mass spectrum *m/e* (rel intensity) 316.2406 [M^+ (100), calcd for $C_{21}H_{32}O_2$, 316.2402], 301 (16), 298 (13), 288 (7), 283 (34), 269 (15), 257 (6), 248 (96), 193 (92), 161 (32), 109 (28), 91 (35).

Equilibration of the Δ^8-11-Ones 6, 7, 15, 16, 23, and 24. The Δ^8-11-ketones were dissolved in excess 5% methanolic KOH and the resulting mixtures heated under reflux. The equilibrations were followed by GLC analysis of aliquots and when the equilibration appeared to be complete the solution was poured into water followed by ether extraction, washing (H_2O), drying ($MgSO_4$), and concentration under reduced pressure.

Analysis of Equilibrium Mixtures. The analysis of the reaction mixtures was carried out by GLC. The recorder was run at the highest chart speed (2 in./min) in order to maximize the peak areas. The relative product ratios were obtained by cutting out and weighing the appropriate peaks. Each equilibration value given in Table I is the average of three to five separate injections and the average reproducibility in the ratios of peak weights for successive injections of the same mixture was ±1.2%.

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Registry No.—**4**, 62250-87-7; **5**, 62250-88-8; **6**, 62250-89-9; **6a**, 40225-72-7; **7**, 62279-64-5; **8**, 2724-68-7; **9**, 2800-40-0; **10**, 4731-15-1; **11**, 7090-90-6; **12**, 1482-70-8; **13**, 1755-32-4; **14**, 5976-21-6; **15**, 54498-82-7; **16**, 62318-96-1; **17**, 3684-81-9; **18**, 62250-90-2; **19**, 62250-91-3; **20**, 62250-92-4; **21**, 62250-93-5; **22**, 62279-65-6; **23**, 62250-94-6; **24**, 62279-66-7; 14α-**25a**, 62250-95-7; 14β-**25a**, 62250-96-8; 14α-**25b**, 62250-97-9; 14β-**25b**, 62250-98-0; 14α-**25c**, 62250-99-1; 14β-**25c**, 62251-00-7; 14α-**25d**, 62251-01-8; 14β-**25d**, 62251-02-9; 14α-**26a**, 62251-03-0; 14β-**26a**, 35841-06-6; 14α-**26b**, 62251-04-1; 14β-**26b**, 62251-05-2; 14α-**26c**, 62251-06-3; 14β-**26c**, 62251-07-4; 14α-**26d**, 62251-08-5; 14β-**26d**, 62251-09-6.

References and Notes

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(21) The numbers in Table II are not exactly the same as those published earlier (see ref 5). The reason for this is mainly that the computer program now has more stringent requirements for determining an energy minimum. Small changes in the force field were also made in the interim (see ref 10). These results are now more reliable (although not necessarily better insofar as agreement with experiment).

(22) In the case of compound **26b** only, ring A was added and the calculation was repeated for the actual steroid. It was noted that there was an interference between the C-11 oxygen and the equatorial C-1 hydrogen which was substantially worse in the trans isomer than in the cis (0.22 kcal/mol in the fully relaxed structure). Thus the energy difference of 2.69 kcal/mol in the tricyclic analogue was increased to 3.19 kcal/mol in the tetracyclic steroid. Similar increases would be expected for the other compounds **26a–d**, in Table II.

(23) For a discussion of this "cyclohexene effect" see N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *J. Am. Chem. Soc.*, **90**, 5773 (1968), and references cited therein.

(24) The conformation with C-13 above the plane of the double bond (**27**) appears to be the most stable for each compound. It is possible to get a stable conformation with the cyclohexene geometry such that C-12 is above the plane and C-13 is below the plane. The potential well in which the molecule finds itself in this case is apparently not very deep, as it changes rather easily to the conformation **27**.

(25) It is not certain whether these two pseudorotational conformations correspond to discrete energy minima or whether they are just different places at opposite ends of a wide, flat potential well. If an actual energy maximum does separate them it is probably small. In most cases these two conformations have essentially the same energy, but with the isopropyl group the energies are quite different. The latter occurs because the pseudorotational motion involved causes the isopropyl group to interact with other parts of the molecule.

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