Base-Catalyzed Equilibration of 2β- (XXII) and 2α- (XXIII)-t-Butylcholestan-3-one.—Either pure ketone (10 mg.) was dissolved in 2 cc. of 5% methanolic sodium methoxide solution and heated under reflux for 2 hr. The solution was poured into water and the product extracted with ether. After washing the latter with water and drying, the solvent was evaporated under reduced pressure and the residue (9 mg.) submitted directly to rotatory dispersion measurements in methanol solution (*c* 0.16). The equilibration mixture derived from the 2β-isomer XXII exhibited $[\Phi]_{315}^{peak}$ +1230°, $[\Phi]_{274}^{trough}$ −856°, while that from the 2α-isomer showed $[\Phi]_{315}^{peak}$ +1240°, $[\Phi]_{274}^{trough}$ −900°. Using the amplitude values of the pure ketones from Table I, the present results indicate an equilibrium composition of *ca.* 95% XXIII and 5% XXII.

For deuterium exchange, a 10-mg. sample of the 2α-*t*-butyl ketone XXIII was dissolved in 2 cc. of hot deuteriomethanol containing 5 mg. of sodium methoxide, a few drops of heavy water was added, and the mixture heated under reflux for 2 hr. Upon standing at room temperature overnight, crystals separated which were filtered, washed with heavy water, and dried. Mass spectrometric analysis showed that they consisted of 60% d_3- (*m/e* 445) and 40% d_2- (*m/e* 444) species.

Acknowledgment.—We are grateful to Dr. E. J. Eisenbraun for helpful advice during the earlier part of the investigation, and to Syntex, S.A., Mexico City, for a generous gift of pregnenolone acetate required in the preparation of the resolving agent.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY, STANFORD, CALIF.]

Optical Rotatory Dispersion Studies. XC.[1] The Octant Rule and the Isopropyl Group. Synthesis of Steroidal Isopropyl Ketones[2]

BY CARL DJERASSI, P. A. HART,[3] AND C. BEARD

RECEIVED AUGUST 5, 1963

In order to obtain standard values for the rotatory dispersion amplitude contribution of an equatorial or axial isopropyl group adjacent to a carbonyl group in a cyclohexanone, 2α- and 2β-isopropylcholestan-3-one, 2α- and 2β-isopropyl-19-nor-5α-androstan-3-one, and optically pure 2-isopropylcyclohexanone were synthesized. Consideration of these amplitude values and those derived from (−)-menthone and (+)-isomenthone confirm the earlier conclusion that the energy difference between an axial and an equatorial α-isopropylcyclohexanone is less than 1 kcal./mole. The utility of such amplitude values in conformational analysis is demonstrated further in a discussion of the conformational situation existing in 2-isopropylcyclohexanone and (+)-isomenthone.

The importance in conformational analysis of obtaining reliable values for the Cotton effect amplitude contribution of substituents adjacent to a carbonyl group in a cyclohexanone ring has already been pointed out in the preceding article.[1] Experiments and conclusions dealing with methyl[4] and *t*-butyl[1] substituents have been recorded and we should now like to describe similar studies with the isopropyl group. This substituent is of particular interest, since it is found frequently among naturally occurring terpenes and a proper evaluation of the rotatory contribution of this group is indispensable in applications of the octant rule[5] to such ketones.[6] Thus in a preliminary evaluation[7] of the optical rotatory dispersion curves of (−)-menthone (IV)[8] and (+)-isomenthone (V),[8] the then unexpected conclusion was reached that (+)-isomenthone (V) existed largely in the conformation Va in which the isopropyl group is axial rather than the *a priori* anticipated Vb. This conclusion was substantiated in recent studies by Allinger[9] and Rickborn.[10] In order to get more detailed information on the rotational and conformational role played by an isopropyl substituent, the simplest member—optically active 2-isopropylcyclohexanone (III)—as well as other pairs of epimeric α-isopropylcyclohexanones (analogous to IV and V) were required. Just as in the *t*-butyl series,[1] steroids seemed to represent admirable examples and we report herewith the synthetic studies, followed by an examination of the rotatory dispersion results.

Synthetic Studies.—For the preparation of optically active 2-isopropylcyclohexanone, we resorted to the same route employed earlier[1] in the *t*-butyl series. *trans*-2-Isopropylcyclohexanol,[11] obtained by lithium–ammonia reduction of 2-isopropylcyclohexanone, was transformed into the 3β-acetoxy-Δ⁵-etienate (I), which yielded one pure diastereoisomer[12] upon repeated recrystallization. Cleavage of the ester with lithium aluminum hydride led to (+)-*trans*-2-isopropylcyclohexanol (II), which was then oxidized by the Jones procedure [13] to (+)-2-isopropylcyclohexanone (III). The absolute configuration could already be inferred at the alcohol stage II through the use of the Klyne–Stokes rule[14] and was confirmed by rotatory dispersion measurements of the ketone III as discussed below. Since the other diastereoisomer of the etienate could not be isolated in a pure state, the (−)-antipode of (+)-2-isopropylcyclohexanol (II) was not available and an alternate means had to be sought to establish the optical purity of the alcohol. This was accomplished by converting the alcohol (+)-II into its 3,5-dinitrobenzoate and comparing its physical constants (including rotation) with those of a sample derived from biological reduction[15] of 2-isopropylcyclohexanone.[16]

Optically pure (−)-menthone (IV) and (+)-isomenthone (V) had been prepared earlier[17] by Jones oxidation[13] of the corresponding menthols and there remained now the problem of synthesizing a steroidal

(1) Paper LXXXIX: C. Djerassi, P. A. Hart, and E. J. Warawa, *J. Am. Chem. Soc.*, **86**, 78 (1964).

(2) Supported by Grant No. 5T4-CA5061 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(3) Taken in part from the Ph.D. thesis of P. A. Hart, 1963.

(4) C. Beard, C. Djerassi, J. Sicher, F. Sipos, and M. Tichy, *Tetrahedron*, **19**, 919 (1963).

(5) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Am. Chem. Soc.*, **83**, 4013 (1961).

(6) For a recent application in the diterpene series, where information on the rotatory contribution of an isopropyl group is needed, see W. G. Dauben and R. M. Coates, *J. Org. Chem.*, **28**, 1698 (1963).

(7) C. Djerassi, "Optical Rotatory Dispersion: Applications to Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, pp. 105–106.

(8) For absolute configuration see A. J. Birch, *Ann. Rept. Progr. Chem.*, **47**, 192 (1951).

(9) N. L. Allinger and H. M. Blatter, *J. Am. Chem. Soc.*, **83**, 994 (1961).

(10) B. Rickborn, *ibid.*, **84**, 2414 (1962).

(11) W. Hückel and R. Neidlein, *Ber.*, **91**, 1391 (1958).

(12) Preliminary attempts by Dr. E. J. Warawa to effect a similar purification of *cis*-2-isopropylcyclohexyl Δ⁵-3β-acetoxyetienate failed.

(13) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946). For similar oxidations of substituted isopropylcyclohexanols see ref. 17.

(14) W. Klyne and W. M. Stokes, *J. Chem. Soc.*, 1979 (1954).

(15) For a similar approach in the 2-methylcyclohexanol series see C. Beard, C. Djerassi, T. Elliott, and R. C. C. Tao, *J. Am. Chem. Soc.*, **84**, 874 (1962).

(16) We are deeply indebted to Dr. Rosaline C. C. Tao of the Department of Pharmaceutics, University of Singapore, for providing us with a specimen of the dinitrobenzoate of (+)-II, which was derived from feeding 2-isopropylcyclohexanone to rabbits and isolating the glucosidouronate from the urine.

(17) G. Ohloff, J. Osiecki, and C. Djerassi, *Ber.*, **95**, 1400 (1962).

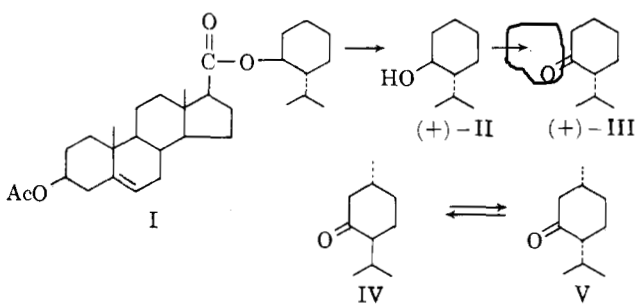
TABLE I

SUMMARY OF OPTICAL ROTATORY DISPERSION DATA

Compound	Extrema of O.R.D. Cotton effects (MeOH) [φ]	λ, mμ	[φ]	λ, mμ	Amplitude (a)
(+)-2-Isopropylcyclohexanone (III)	+2126°	312	−2126°	272	+43
(+)-3-Methylcyclohexanone (XXIII)[27]					+25
(−)-Menthone (IV)[17]					+8
(+)-Isomenthone (V)[17]					+90
Cholestan-3-one (VIa)[a]					+55
2α-(1-Methyl-1-hydroxy)-ethylcholestan-3-one (XVIII)	+1570	308	−3300	268	+49
2α-Isopropylcholestan-3-one (XVIa)	+2060	309	−1950	266	+40
2β-Isopropylcholestan-3-one (XXa)	+7500	310	−3850	272	+114
19-Nor-5α-androstan-3-one (VIb)	+3120	308	−2860	264	+60[b]
2α-Isopropyl-19-nor-5α-androstan-3-one (XVIb)	+2060	308	−1800	272	+39
2β-Isopropyl-19-nor-5α-androstan-3-one (XXb)	+8250	306	−7580	270	+158

[a] See Table I in ref. 1. [b] N. L. Allinger and M. A. DaRooge, *J. Am. Chem. Soc.*, **84**, 4561 (1962), report +56 for the 17β-hydroxy analog.

ketone with equatorial and axial isopropyl groups adjacent to the carbonyl function. The chosen route was based on an earlier reported[18] sequence in the decalone series, which promised to provide pure axial and equatorial epimers.



Cholestan-3-one (VIa) was transformed *via* the glyoxalate VIIa into the earlier described[19] β-keto ester VIIIa. The carbonyl group was then protected as the ketal IXa, this step serving at the same time to fix the 2-carbomethoxy function in the more stable α-configuration.[20] Exposure to methylmagnesium bromide led to the tertiary carbinol XIIIa, which was dehydrated with phosphorus oxychloride in pyridine solution to the ketal XIVa of 2α-isopropenylcholestan-3-one. Catalytic hydrogenation to XVa and mild deketalization with *p*-toluenesulfonic acid in acetone[21] led to the desired 2α-isopropylcholestan-3-one (XVIa). The last two steps, however, introduced an element of stereochemical uncertainty. First, if the catalytic hydrogenation of the isopropenyl derivative XIVa proceeded through partial migration of the double bond to the isopropylidene position or into the ring, then contamination by the 2β-epimer could occur. The reality of such a double bond migration was confirmed by the course of the catalytic deuteration, since mass spectrometry indicated the presence of two through nine deuterium atoms and the isopropyl group itself could only accommodate seven of them. Second, in spite of the mild deketalization conditions,[21] the possibility of some inversion at C-2 was not excluded. Consequently, the product of this deketalization step was epimerized with base, reduced with lithium aluminum hydride, and the predominent and pure 2α-isopropylcholestan-3β-ol (XVII) isolated. Jones oxidation[13] of it then afforded the pure 2α-isopropylcholestan-3-one (XVIa), which was employed for the optical rotatory dispersion measurements (Table I).

For the preparation of the 2β-epimer XXa, the tertiary carbinol XIIIa from the original Grignard reaction was exposed at room temperature to methanolic hydrochloric acid, which led in 83% yield to the hydroxy ketone XVIII. More vigorous acid treatment of XVIII resulted in β-elimination with formation of 2-isopropylidenecholestan-3-one (XIXa), catalytic hydrogenation of which yielded the required 2β-isopropyl cholestan-3-one (XXa). Base-catalyzed equilibration of either pure ketone XVIa or XXa produced the same equilibration mixture, which was shown by rotatory dispersion measurements to contain over 95% of 2α-isopropylcholestan-3-one (XVIa).

This equilibrium composition is distinctly higher in favor of the equatorial isomer XVIa as compared to the 70% menthone (IV)–30% isomenthone (V) equilibrium.[22] The difference can obviously be ascribed to the presence of the axial angular methyl group in the steroid ketone XXa, thus giving rise to an additional (unfavorable) 1,3-diaxial interaction between the isopropyl and methyl substituents. It was important, therefore, to secure a second pair of epimeric steroidal α-isopropyl ketones, in which such steric interaction was absent, and consequently the synthesis of appropriate 19-nor-3-keto steroids was undertaken.

For this purpose, 17-deoxoestrone methyl ether (XXI)[23,24] was subjected to Birch reduction[25] to give 19-nor-Δ⁴-androsten-3-one (XXII), which was reduced with lithium–ammonia[26] to 19-nor-5α-androstan-3-one (VIb). Using modifications described in the Experimental section, this ketone was converted *via* the glyoxalate VIIb and β-keto ester VIIIb into a separable mixture of the 2α- (IXb) and 2β- (X) methoxycarbonyl-3-ketals and thence into the two isomeric tertiary carbinols XIIIa and XI. Dehydration (XIVb), hydrogenation (XVb), and deketalization in the 2α-series led to 2α-isopropyl-19-nor-5α-androstan-3-one (XVIb) containing *ca.* 8% of the 2β-isomer XXb, which could be separated by chromatography.

A similar stereospecific approach to 2β-isopropyl-19-nor-5α-androstan-3-one (XXb) starting with the pure 2β-tertiary carbinol XI failed at the dehydration step,

(18) L. H. Zalkow, F. X. Markley, and C. Djerassi, *J. Am. Chem. Soc.*, **82**, 6354 (1960).

(19) N. A. Nelson and R. N. Schut, *ibid.*, **80**, 6630 (1958).

(20) In the absence of the angular methyl group, both epimers IXb and X can be isolated.

(21) See G. Rosenkranz, J. Pataki, and C. Djerassi, *J. Org. Chem.*, **17**, 290 (1952).

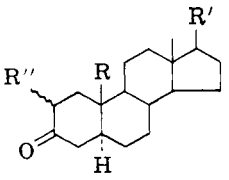
(22) Reference 10 as well as J. Osiecki, Ph.D. Thesis, Stanford University, 1960; see also A. Weissberger and D. S. Thomas, *J. Am. Chem. Soc.*, **65**, 402 (1943).

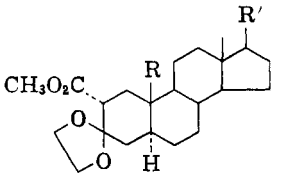
(23) A. Butenandt, I. Stormer, and U. Westphal, *Z. physiol. Chem.*, **208**, 170 (1932); J. W. Cook and A. Girard, *Nature*, **133**, 377 (1934).

(24) We are indebted to Syntex, S.A., Mexico City, for a generous gift of estrone methyl ether employed as starting material.

(25) For a recent review of experimental conditions in Birch reductions, see F. J. Kakis in C. Djerassi, Ed., "Steroid Reactions: An Outline for Organic Chemists," Holden–Day, Inc., San Francisco, Calif., 1963, Chapter 6.

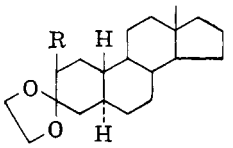
(26) For a review of metal–ammonia reductions of α,β-unsaturated ketones see J. E. Starr, ref. 25, Chapter 7.





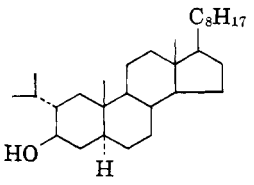
VIa, R = CH_3, R′ = C_8H_{17}, R″ = H
b, R = R′ = R″ = H
VIIa, R = CH_3, R′ = C_8H_{17}, R″ = $COCO_2CH_3$
b, R = R′ = H, R″ = $COCO_2CH_3$
VIIIa, R = CH_3, R′ = C_8H_{17}, R″ = CO_2CH_3
b, R = R′ = H, R″ = CO_2CH_3

X, R = CO_2CH_3
XI, R = $COH(CH_3)_2$
XII, R = $C(=CH_2)CH_3$

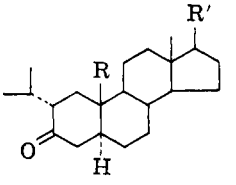


IXa, R = CH_3, R′ = C_8H_{17}
b, R = R′ = H

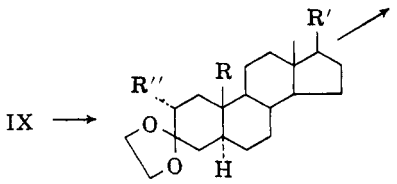
XIII



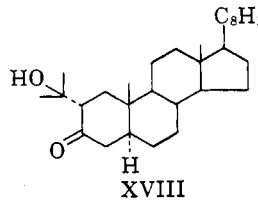
XVII



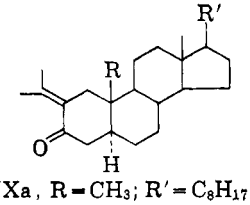
XVIa, R = CH_3, R′ = C_8H_{17}
b, R = R′ = H



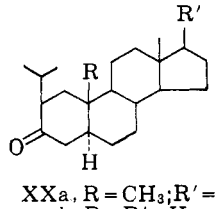
XIIIa, R = CH_3, R′ = C_8H_{17}, R″ = $COH(CH_3)_2$
b, R = R′ = H, R″ = $COH(CH_3)_2$
XIVa, R = CH_3, R′ = C_8H_{17}, R″ = $C(=CH_2)CH_3$
b, R = R′ = H, R″ = $C(=CH_2)CH_3$
XVa, R = CH_3, R′ = C_8H_{17}, R = $CH(CH_3)_2$
b, R = R′ = H, R″ = $CH(CH_3)_2$



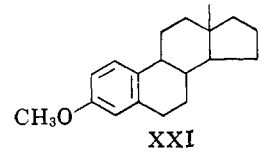
XVIII



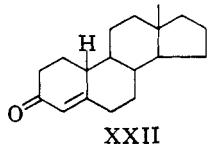
XIXa, R = CH_3; R′ = C_8H_{17}
b, R = R′ = H



XXa, R = CH_3; R′ = C_8H_{17}
b, R = R′ = H



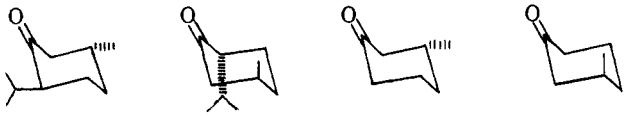
XXI



XXII

which yielded a mixture of the desired 2β-isopropenyl and 2-isopropylidene ketals. A mixture of the 2α- (XIIIb) and 2β- (XI) carbinols was, therefore, treated directly with sulfuric acid to give 2-isopropylidene-19-nor-5α-androstan-3-one (XIXb), which was then subjected to catalytic hydrogenation. A mixture of 2α- (XVIb) and 2β- (XXb) isopropyl-19-nor-5α-androstan-3-ones was secured, which was separated into its pure components by preparative thin-layer chromatography. Base-promoted equilibration and comparison of the rotatory dispersion curves of the equilibrium mixture with those (Table I) of the two pure isomers showed an 83% 2α (XVIb)–17% 2β (XXb) composition at equilibrium. The corresponding figures, derived from circular dichroism measurements, were 82% XVI–18% XXb.

Discussion of Optical Rotatory Dispersion Results.—As was done in earlier articles,[1,4,27] the rotatory dispersion results are summarized in Table I in terms of Cotton effect amplitudes (*a*), which offer a convenient, rough indication of rotational strength. In order to obtain a reasonable value for the rotatory contribution of an equatorial isopropyl substituent, one may use (−)-menthone (IV) as a suitable model, since it may be assumed to exist virtually completely in the diequatorial chair conformation IVa rather than the other diaxial chair conformer IVb or intermediate flexible forms. By subtracting the molecular amplitude (*a* = +25) of (+)-3-methylcyclohexanone (XXIIIa) from that (+8) of (−)-menthone (IVa), a value of 17 is derived for the amplitude contribution of the equatorial isopropyl group. Such a value is probably on the low side, since (+)-3-methylcyclohexanone (XXIII) does not just contain the dextrorotatory chair conformer XXIIIa, but also a small amount (<10%) of the chair form XXIIIb with the axial methyl group, or of a flexible form which should produce a negative Cotton effect.[28]



IVa IVb XXIIIa XXIIIb

A similar subtraction of the amplitude (see Table I) of cholestan-3-one (VIa) from that of 2α-isopropylcholestan-3-one (XVIa) leads to *a* = −15 for the contribution of the equatorial α-isopropyl group in the steroid. The identical operation with 2α-isopropyl-19-nor-5α-androstan-3-one (XVIb) and its parent ketone VIb gives *a* = −21, the (−)-menthone (IV) value (+17)[29] falling just between. The range of 15–21 may either be due to small and undetected contamination of an axial epimer in one of the examples or it may be due to a differing rotamer equilibrium, since not all three staggered rotamers of the isopropyl group (around C-2) will make exactly the same contribution.[28] In any event, the *a* = 15 to 21 range represents a useful parameter, suitable for semiquantitative applications of the octant rule to conformational problems,[27] and falls between the values established earlier for the equatorial methyl (<9)[4] and *t*-butyl (33 to 39)[1] substituents.

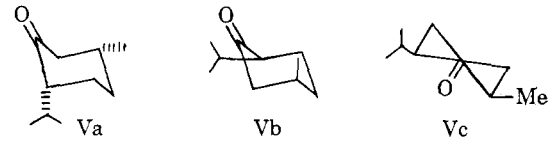
As noted previously,[7] the strongly positive Cotton effect (see Table I) of (+)-isomenthone (V) requires the partial or exclusive presence of a conformer different from that (Vb) with an equatorial isopropyl group, and the alternate chair form Va has been pro-

(27) C. Djerassi and W. Klyne, *J. Chem. Soc.*, 4929 (1962); 2390 (1963).

(28) This assumption has been validated experimentally by low temperature circular dichroism studies (K. M. Wellman, E. Bunnenberg, and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 1870 (1963)).

(29) The signs are reversed since the substituents are located in opposite octants.

posed.[7] The conformer Vb must exhibit an amplitude below +17 (as compared to the experimentally observed +90), since the +17 value of the equatorial isopropyl group (derived from IVa) would be reduced by the negative contribution of the axial methyl group (of type XXIIIb). If one assumes exclusive participation of the alternate chair form Va, then subtraction of +25 (contribution of equatorial β-methyl group—see XXIIIa and Table I) from +90 (experimental value of (+)-isomenthone (V)—see Table 1) offers a value of +65 for an axial isopropyl group adjacent to the keto function of a cyclohexanone.



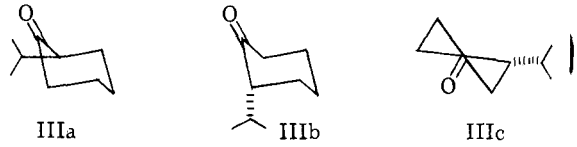
Va Vb Vc

The availability of the two steroidal 2β-isopropyl ketones XXa and XXb offer a means of examining the validity of these assumptions. If their observed amplitudes (+114 and +158—see Table I) are corrected for the contribution (+55 and +60) of the parent ketones (VIa and VIb), values of +59 (XXa) and +98 (XXb) are obtained for an axial isopropyl group. Of these, +59 is certainly an unrealistic figure, since 2β-isopropylcholestan-3-one (XXa) probably does not exist to any large extent in the undisturbed chair form because of the diaxial interaction with the angular methyl group. The +98 value from the 19-nor series (XXb − VIb), on the other hand, appears as the most plausible one, since an undisturbed chair form for this substance (XXb) can be visualized readily.

If one accepts a = 98 for an axial isopropyl group, combination of this value with +25 derived from XXIIIa for the equatorial β-methyl group leads to an approximate calculated amplitude of +123 for the chair form Va of (+)-isomenthone as contrasted to the observed +90. The discrepancy between these two values should then be attributable to contributions of conformers other than Va. Using Rickborn's value[10] of −0.56 kcal./mole for an axial isopropyl substituent adjacent to a carbonyl group and −1.4[30] to −1.8[10] kcal./mole for the axial methyl group in the β-position, a difference of 0.84 to 1.24 kcal./mole in favor of conformer Va over Vb is deduced, which corresponds approximately to an 80–88% Va 12–20% Vb equilibrium mixture, depending upon which axial methyl energy value[10,30] is used. The 12–20% *non*-Va conformer, therefore, can be attributed a −33 amplitude contribution (123 − 90), which leads to calculated amplitude values of −165 to −275 if 100% of that other conformer were present.

Such a hypothetical figure for conformer Vb of (+)-isomenthone is certainly too high, since the equatorial isopropyl group in Vb would contribute +17, thus leading to −182 to −292 as the calculated value for an axial β-methyl substituent in a negative octant, *i.e.*, the calculated amplitude of the unknown chair form XXIIIb of 3-methylcyclohexanone. It should be noted that the twist form Vc would be predicted[31] to exhibit a strongly positive Cotton effect and if it participates in addition to, or in place of, the chair conformer Va, then the above calculation with respect to the hypothetical rotatory contribution of an axial methyl group β to a cyclohexanone ketone function (XXIIIb) would be altered greatly. In any event, the present values of a = 15 to 21 for an equatorial and a = 98 for an axial isopropyl group adjacent to a carbonyl group confirm definitely the original assumption[7] that conformer Vb cannot be the exclusive or even the predominant conformational representation of (+)-isomenthone (V).

We are now in a position to examine the conformational situation in 2α-isopropylcyclohexanone (III), for which the chair forms IIIa and IIIb and the twist IIIc need to be considered.



IIIa IIIb IIIc

With the information deduced from the rotatory dispersion amplitudes collected in Table I, one would predict a = +15 to +21 for IIIa, +98 for IIIb, and a strongly positive Cotton effect (of undetermined magnitude[31]) for IIIc. The observed amplitude (Table I) of +43 thus automatically establishes the absolute configuration of the (+)-antipode in terms of stereoformula III. Since the energy difference between IIIa and IIIb is only about 0.56 kcal./mole,[10] while that between the twist form IIIc and either chair forms IIIa or IIIb must be of the order of 2 kcal./mole,[32] we feel justified in neglecting IIIc for the purposes of the following rough calculation. Using the "standard" values of +15 to +21 for pure IIIa and +98 for pure IIIb, the observed a = +43 leads to an equilibrium composition of 66–71% IIIa and 29–34% IIIb or an energy difference of 0.4–0.52 kcal./mole in favor of an equatorial over an axial isopropyl group adjacent to a ketone function. Considering the assumptions which were made to arrive at the "standard" amplitude values, the agreement between these energy values and Rickborn's 0.56 kcal./mole[10] is quite satisfactory.

It is interesting to note that some additional factor must operate either among monocyclic cyclohexanones (IIIa ⇄ IIIb) or in the more highly fused steroids. The former show an approximate 70% equatorial–30% axial isopropyl composition (*ca.* 0.5 kcal./mole), while the base-catalyzed isomerization (*vide supra*) in the 2-isopropyl-19-nor-3-keto series (XVIb ⇄ XXb) corresponds to an 82% equatorial−18% axial isopropyl mixture (*ca.* 0.9 kcal./mole). Whatever this additional factor may be (contribution of a third flexible conformer?), the above results show quite conclusively that the original assumption[7] about the relatively low unfavorable energy requirement of an axial isopropyl group adjacent to the carbonyl function of a cyclohexanone is quite justified.[9,10]

The availability, during the synthetic studies, of the equatorial 2α-(1-methyl-1-hydroxy)-ethylcholestan-3-one (XVIII) made it possible to determine whether its rotatory contribution would be equal to that (a = 33–39)[1] of a *t*-butyl or of an isopropyl (a = 15–21) substituent. Inspection of Table I (VIa–XVIII) shows that the observed value (−6) is closer to that of the isopropyl group. Since this figure changed considerably (−6 *vs.* +5) in going from methanol to isooctane, fixation of one rotamer through hydrogen bonding of the hydroxyl group with the carbonyl oxygen may play an important role.

Experimental[33]

Resolution of *trans*-2-Isopropylcyclohexanol.—Lithium metal (4.0 g.) was added to 1.5 l. of liquid ammonia, followed by the addition of a solution of 2-isopropylcyclohexanone (10.0 g.) in 40 cc. of ether. The mixture was stirred and cooled in Dry Ice for 20 hr., whereupon water was added and the ammonia allowed to evaporate. Extraction with ether, washing, drying, and evaporation left a solid residue (9.9 g.), still containing some unreacted

(30) N. L. Allinger and L. A. Freiberg, *J. Am. Chem. Soc.*, **84**, 2201 (1962).

(31) C. Djerassi and W. Klyne, *Proc. Natl. Acad. Sci. U. S.*, **48**, 1093 (1962).

(32) N. L. Allinger, *J. Am. Chem. Soc.*, **81**, 5727 (1959).

(33) For details see footnote 39 in ref. 1.

ketone. Recrystallization from hexane at 0° yielded 5.3 g. of pure *trans*-2-isopropylcyclohexanol,[11] m.p. 63.5–64.5°, 4.27 g. of which was dissolved in 20 cc. of pyridine and added to a solution of 3β-acetoxy-Δ⁵-etienyl chloride (prepared[1] from 10.8 g. of the acid and 25 g. of oxalyl chloride) in 60 cc. of pyridine. After processing in the usual way,[1] that portion of the residue which was soluble in benzene was passed through a column of 40 g. of activity II alumina and the eluted material recrystallized from acetone; yield 3.5 g., m.p. 125–137°. After five recrystallizations from acetone or hexane, constant-melting (m.p. 144.5–145.5°) **etienate I** (1.6 g.) was obtained, $[\alpha]_D$ 0°.

Anal. Calcd. for $C_{31}H_{48}O_4$: C, 76.81; H, 9.98. Found: C, 76.95; H, 9.91.

The above etienate (0.76 g.) was cleaved in ether solution by heating under reflux for 0.5 hr. with 0.7 g. of lithium aluminum hydride. The reaction mixture was worked up by the sodium sulfate technique and the residue was freed of steroid diol by extraction with hexane, which provided 0.25 g. of crude (+)-*trans*-2-isopropylcyclohexanol (II). Two recrystallizations from hexane at −15° gave 0.1 g. of the pure alcohol, m.p. 74–74.5°, $[\alpha]_D$ +46° (*c* 0.53).

Anal. Calcd. for $C_9H_{18}O$: C, 76.00; H, 12.76. Found: C, 75.74; H, 12.43.

The 3,5-dinitrobenzoate, prepared in pyridine solution, exhibited m.p. 155–156°, $[\alpha]_D$ +72° (*c* 0.56) and proved to be identical (mixture melting point determination, infrared comparison, and $[\alpha]_D$ +72°) with a specimen of biological provenance.[15,16]

Anal. Calcd. for $C_{16}H_{20}N_2O_6$: C, 57.13; H, 6.00; N, 8.33. Found: C, 57.25; H, 6.03; N, 8.56.

(+)-*trans*-2-Isopropylcyclohexanone (III).—A slight excess of 8 *N* chromic acid solution[18] was added dropwise at 0° to a stirred solution of 24 mg. of the (+)-alcohol II in 1.5 cc. of acetone containing a small amount of magnesium sulfate. After stirring at that temperature for an additional 4 min., neutralization was achieved by addition of sodium bicarbonate, ether added, and the filtered solution evaporated at 25° (150 mm.). The residual oil (15 mg.) was distilled using a vacuum line technique to provide 7 mg. of the pure, optically active ketone III, the rotatory dispersion characteristics of which are listed in Table I. The purity of this material was established by infrared and gas-phase chromatographic comparison with racemic 2-isopropylcyclohexanone.

2α-Methoxycarbonylcholestan-3-one Ethylene Ketal (IXa).—A mixture of 11.9 g. of 2-methoxycarbonylcholestan-3-one (VIIIa),[19] 800 cc. of benzene, 40 cc. of ethylene glycol, and 0.5 g. of *p*-toluenesulfonic acid was heated under reflux with vigorous stirring under a Soxhlet extractor filled with Linde 5A Molecular Sieves, the course of the reaction being followed by comparing the relative intensities of the 5.8 μ band (strong in IXa) and 6–6.5 μ absorption (absent in ketal, but strong in keto ester VIIIa). The ratio of starting material to product reached a minimum value after 40 hr., whereupon the solution was cooled, washed with dilute bicarbonate solution, and evaporated under reduced pressure. The resulting amber sirup (12 g.) still showed a positive ferric chloride reaction and thin-layer chromatography pointed toward the presence of several products. Chromatography on 200 g. of activity I alumina with benzene elution and t.l.c. monitoring of the various fractions provided (after recrystallization from acetone) 4.2 g. of ketal (m.p. 140–142°), which was recrystallized once more to give the analytical sample, m.p. 144–145° (with sintering at 135–139°), $\lambda_{max}^{CHCl_3}$ 5.79 μ, $[\alpha]_D$ +14° (*c* 0.55).

Anal. Calcd. for $C_{31}H_{52}O_4$: C, 76.19; H, 10.72. Found: C, 76.51; H, 10.70.

2α-(1-Methyl-1-hydroxy)-ethylcholestan-3-one Ethylene Ketal (XIIIa).—The above-described ketal IXa (0.4 g.), dissolved in 4 cc. of dry ether, was added to a solution of 0.68 cc. of 3 *M* ethereal methylmagnesium bromide (Arapahoe Chemicals) in 20 cc. of ether. After heating under reflux for 4.5 hr., there was obtained a colorless oil, which exhibited infrared carbonyl and hydroxyl absorption. The Grignard treatment was, therefore, repeated and the product recrystallized from acetone to give 0.26 g. of colorless needles, m.p. 149–150.5°, $\lambda_{max}^{CHCl_3}$ 2.9 μ, $[\alpha]_D$ +8° (*c* 0.66).

Anal. Calcd. for $C_{32}H_{56}O_3$: C, 78.64; H, 11.55. Found: C, 79.00; H, 11.73.

2α-Isopropenylcholestan-3-one Ethylene Ketal (XIVa).—A mixture of 1.0 g. of the ketal XIIIa, 10 cc. of dry pyridine, and 5 cc. of freshly distilled phosphorus oxychloride was kept at room temperaturre for 3 hr. and then poured into ice water. The product was isolated with ether and crystallized from acetone to give 0.75 g. of the isopropenyl ketal XIVa, m.p. 140–144°. The analytical specimen crystallized as colorless needles from the same solvent; m.p. 142–145°, $\lambda_{max}^{CHCl_3}$ 6.13 μ, $[\alpha]_D$ +19°, n.m.r. signals at 4.8 (olefinic protons) and 1.77 p.p.m. (methyl on double bond).

Anal. Calcd. for $C_{32}H_{54}O_2$: C, 81.65; H, 11.57. Found: C, 81.58; H, 11.78.

2α-Isopropylcholestan-3-one Ethylene Ketal (XVa).—Catalytic hydrogenation of the unsaturated ketal XIVa (0.2 g.) was effected at room temperature and atmospheric pressure with 22 mg. of 10% palladium-on-charcoal in 8 cc. of ethyl acetate solution. Filtration of the catalyst, evaporation of the filtrate to dryness, and recrystallization from acetone–methanol yielded 0.17 g. of fine needles, m.p. 82–83°, $[\alpha]_D$ +5° (*c* 0.64).

Anal. Calcd. for $C_{32}H_{56}O_2$: C, 81.30; H, 11.94. Found: C, 81.30; H, 12.09.

When deuterium was substituted for hydrogen, mass spectrometry indicated the presence of 19% d_2, 10% d_3, 10% d_4, 10% d_5, 13% d_6, 15% d_7, 17% d_8, and 6% d_9 species.

2α-Isopropylcholestan-3-one (XVIa).—A solution of 100 mg. of 2α-isopropylcholestan-3-one ethylene ketal (XVa) in 10 cc. of acetone containing 15 mg. of *p*-toluenesulfonic acid was kept at room temperature for 4 hr. After pouring into water and extracting with chloroform, evaporation and trituration with methanol led to 80 mg. of the ketone, m.p. 84–89°, $[\alpha]_D$ +17° (*c* 0.59). Further recrystallization provided 47 mg. of an analytical specimen, m.p. 90–91.5°, $[\alpha]_D$ +12° (*c* 0.70), λ_{max}^{KBr} 5.87 μ, which was, however, contaminated by *ca.* 3% of the 2β-isomer XXa as judged by the molecular amplitude $a = +43$.

Anal. Calcd. for $C_{30}H_{52}O$: C, 84.04; H, 12.23. Found: C, 83.99; H, 12.14.

To prepare stereochemically pure 2α-isomer, a sample (150 mg.) of the ketone was reduced with lithium aluminum hydride in ether (2 hr., room temperature) and the product chromatographed carefully on 15 g. of activity II alumina. There was obtained from the benzene fractions 110 mg. of **2α-isopropylcholestan-3β-ol (XVII)**, which was recrystallized from methanol and proved to be homogeneous by thin-layer chromatography; yield 90 mg., m.p. 135–136°, $[\alpha]_D$ −7° (*c* 0.91).

Anal. Calcd. for $C_{30}H_{54}O$: C, 83.65; H, 12.64. Found: C, 83.60; H, 12.64.

A portion (34 mg.) of the alcohol XVII was oxidized at room temperature (1 min.) in acetone solution (5 cc.) with 8 *N* chromium trioxide solution[13] and recrystallized twice from methanol to furnish 25 mg. of pure 2α-isopropylcholestan-3-one (XVIa), m.p. 96.5–97°, the optical rotatory dispersion properties of which are summarized in Table I.

2α-(1-Methyl-1-hydroxy)-ethylcholestan-3-one (XVIII).—A suspension of 0.72 g. of the hydroxy ketal XIIIa in 30 cc. of methanol containing 0.5 cc. of water and 10 drops of concentrated hydrochloric acid was stirred at room temperature until all of the solid had dissolved (2 hr.), whereupon thin-layer chromatography indicated the complete absence of ketal. After seeding with material obtained in an earlier experiment and chilling, crystals separated, which were filtered and washed with methanol; yield 0.54 g., m.p. 63–64°, followed by resolidification and melting at 110–113°, λ_{max}^{KBr} 2.85 and 5.92 μ, $[\alpha]_D$ +27°. The optical rotatory dispersion data in methanol solution are summarized in Table I. In isooctane solution (*c* 0.06), the substance exhibited $[\phi]_{308}^{peak}$ +2080° and $[\phi]_{294}^{trough}$ −2100° corresponding to $a = +5$ as compared to $a = +37$ for cholestan-3 one (VIa) in the same solvent.

Anal. Calcd. for $C_{30}H_{52}O_2$: C, 81.03; H, 11.79. Found: C, 81.07; H, 11.67.

2-Isopropylidenecholestan-3-one (XIXa).—A solution of 0.2 g. of the keto alcohol XVIII in 15 cc. of methanol containing 10 drops of concentrated hydrochloric acid was heated under reflux for 10 min., whereupon thin-layer chromatography disclosed the absence of starting material and the presence of two products. Concentration of the solution and cooling promoted crystallization, and three recrystallizations from methanol of the resulting solid gave 49 mg. of colorless needles of the desired ketone XIXa, which corresponded to the slower moving spot in the thin-layer chromatogram; m.p. 96–97°, $[\alpha]_D$ +22° (*c* 0.41), λ_{max}^{EtOH} 254 mμ, log ε 3.92, $\lambda_{max}^{CHCl_3}$ 6.0 and 6.2–6.33 μ; R.D. in dioxane (*c* 0.12): $[\phi]_{340}^{peak}$ +205°, $[\phi]_{294}^{trough}$ −675°.

Anal. Calcd. for $C_{30}H_{50}O$: C, 84.44; H, 11.81. Found: C, 84.54; H, 12.18.

2β-Isopropylcholestan-3-one (XXa).—Catalytic hydrogenation of 100 mg. of the isopropylidene ketone XIXa in ethyl acetate solution with 20 mg. of 10% palladium-on-charcoal was complete within 10 min. and trituration of the crude product provided 74 mg. of crystals, m.p. 76–81°, changed to m.p. 78–79.5° upon recrystallization from methanol; $[\alpha]_D$ +62° (*c* 0.37), λ_{max}^{KBr} 5.85 μ. The rotatory dispersion results are collected in Table I.

Anal. Calcd. for $C_{30}H_{52}O$: C, 84.04; H, 12.23. Found: C, 83.99; H, 12.06.

Isomerization of either the 2α- (XVIa) or 2β- (XXa) isopropylcholestan-3-ones was effected by heating a 10-mg. sample under reflux for 3 hr. with 2 cc. of 5% sodium methoxide in methanol solution, diluting with water, and extracting with ether. Optical rotatory dispersion measurements on the total residue exhibited

$a = +42$, which—when compared with the values listed in Table I for the pure isomers—corresponds to a 97% (XVIa)–3% (XXa) composition.

19-Nor-Δ^4-androsten-3-one (XXII).—Lithium wire (6 g.) was added in three portions over a 4-hr. period to a stirred and cooled (Dry Ice–acetone) solution of 17 g. of 17-deoxoestrone methyl ether (XXI)[23,24] in 300 cc. of dry tetrahydrofuran, 300 cc. of dry *t*-butyl alcohol, and 1 l. of liquid ammonia (dried and free of iron particles[34]). After an additional 4 hr., methanol was added and the ammonia was allowed to evaporate. Extraction with ether, washing, drying, and evaporation afforded 17 g. of solid, m.p. 70–91°, the ultraviolet absorption spectrum of which indicated the presence of *ca.* 15% of unreduced starting material. No separation was attempted at this stage, but rather the product was heated under reflux for 10 min., with 400 cc. of methanol and 20 cc. of concentrated hydrochloric acid, and, after ether extraction, it was chromatographed on 800 g. of activity II alumina to give 2.5 g. of starting ether XXI in the petroleum ether eluates and 13.2 g. of the desired ketone XXII in the benzene fractions. Recrystallization from methanol–water yielded 10.1 g. of the ketone, m.p. 60–62°, suitable for the next step, while the analytical specimen exhibited m.p. 65–65.5°, $\lambda_{max}^{CHCl_3}$ 6.06 and 6.2 μ, λ_{max}^{EtOH} 240 mμ, log ϵ 4.23, $[\alpha]_D$ +41° (*c* 1.3).

Anal. Calcd. for $C_{18}H_{26}O$: C, 83.66; H, 10.14. Found: C, 83.48; H, 10.06.

19-Nor-5α-androstan-3-one (VIb).—A solution of 10.0 g. of 19-nor-Δ^4-androsten-3-one (XXII) in 500 cc. of dry ether was added over a 15-min. period to 2 l. of refluxing liquid ammonia containing 5 g. of lithium. After stirring for 4 hr., ammonium chloride was added carefully until the blue color was discharged and the ammonia was then allowed to evaporate. The product was isolated by ether extraction and since infrared examination demonstrated the presence of hydroxyl-containing material, it was dissolved in 200 cc. of acetone containing 100 g. of magnesium sulfate; 8 *N* chromium trioxide solution[13] was added at room temperature until an orange color persisted for 5 min. Chromatography of the oxidation product on 500 g. of activity II alumina and elution with petroleum ether (b.p. 60–68°) gave 2.3 g. of recovered starting material (XXII), while elution with benzene provided 7.8 g. of crystals, m.p. 36–40°, raised to m.p. 38–40° after two recrystallizations from methanol–water; $\lambda_{max}^{CHCl_3}$ 5.88 μ $[\alpha]_D$ +50° (*c* 0.66).

Anal. Calcd. for $C_{18}H_{28}O$: C, 83.02; H, 10.84. Found: C, 82.91; H, 10.91.

2-Methoxycarbonyl-19-nor-5α-androstan-3-one (VIIIb).—To a solution of 6.1 g. of the ketone VIb in 100 cc. of dry benzene was added 0.58 g. of sodium hydride and 2.75 g. of dimethyl oxalate, and the mixture was stirred at room temperature for 5 hr. The yellow solution was shaken vigorously with two 100-cc. portions of dilute hydrochloric acid and the **glyoxalate VIIb** was isolated with ether and recrystallized from methanol; yield 5.5 g., m.p. 110–113°. The pale yellow analytical specimen exhibited m.p. 114–116°; $\lambda_{max}^{CHCl_3}$ 5.78, 6.2 and 6.4 μ; λ_{max}^{EtOH} 302 mμ, log ϵ 3.94; $[\alpha]_D$ +158° (*c* 1.05).

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.74. Found: C, 72.78; H, 8.78.

Decarbonylation was achieved by heating 5.5 g. of the glyoxalate VIIb to 160° and adding powdered soft glass,[35] effervescence ceasing within 5 min. The resulting β-keto ester VIIIb crystallized from methanol; yield 3.8 g., m.p. 95–96°, $[\alpha]_D$ +127° (*c* 0.67); $\lambda_{max}^{CHCl_3}$ 5.77, 5.86, 6.06, and 6.20 μ.

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.35; H, 9.48.

2α- (IXb) and 2β- (X) Methoxycarbonyl-19-nor-5α-androstan-3-one Ethylene Ketals.—A mixture of 3.7 g. of the β-keto ester VIIIa, 100 cc. of diglyme,[36] 75 cc. of benzene, 20 cc. of ethylene glycol, and 20 mg. of *p*-toluenesulfonic acid was heated under reflux for 3 hr. After pouring into dilute bicarbonate solution, washing, drying, and evaporating, the residue was chromatographed on 100 g. of activity II alumina and eluted with benzene to give 3.4 g. of a mixture of the ketals IXb and X as judged by thin-layer chromatography on silica gel with benzene. Crystallization from methanol at room temperature furnished 0.71 g. of the **2α-epimer IXb** (corresponding to the slower moving t.l.c. spot), m.p. 145–146°, $\lambda_{max}^{CHCl_3}$ 5.79 μ, $[\alpha]_D$ +25° (*c* 1.0).

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.88; H, 9.46. Found: C, 72.54; H, 9.49.

The 2β-epimer X was obtained by chromatographing 1.2 g. of the ketal mixture on 250 g. of Woelm activity I alumina and eluting with ethyl acetate–benzene (5–95%), which gave in order of removal from the column 300 mg. of pure 2β-epimer, 390 mg. of mixture, and 485 mg. of 2α-isomer IXb. One recrystallization of the initially eluted 2β-isomer X led to crystals, m.p. 107–108°, $\lambda_{max}^{CHCl_3}$ 5.81 μ, $[\alpha]_D$ +68° (*c* 1.04).

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.88; H, 9.46. Found: C, 72.58; H, 9.46.

2α- (XIIIb) and 2β- (XI) (1-Methyl-1-hydroxy)-ethyl-19-nor-5α-androstan-3-one Ethylene Ketals.—The Grignard reaction of methylmagnesium bromide with the two ketals XIIIb and XI was performed as described above for the cholestane analog XIIIa. In the **2α-series**, there was obtained 40% of shiny plates (from dilute methanol), m.p. 102–103°, $[\alpha]_D$ +6° (*c* 0.86).

Anal. Calcd. for $C_{23}H_{38}O_3$: C, 76.20; H, 10.57. Found: C, 76.25; H, 10.59.

The 2β-epimer XI was isolated in over 90% yield and exhibited m.p. 89–90°, $[\alpha]_D$ +38° (*c* 0.83) after recrystallization from methanol–water.

Anal. Found: C, 76.14; H, 10.43.

2α-Isopropenyl-19-nor-5α-androstan-3-one Ethylene Ketal (XIVb).—Dehydration of 180 mg. of 2α-(1-methyl-1-hydroxy)-ethyl-19-nor-5α-androstan-3-one ethylene ketal (XIIIb) was effected at room temperature (4 hr.) with 0.5 cc. of phosphorus oxychloride and 3 cc. of pyridine as described above in the cholestane series. Recrystallization from methanol provided 125 mg. of dimorphic crystals, m.p. 87° and 97–98°, $\lambda_{max}^{CHCl_3}$ 6.13 μ, $[\alpha]_D$ +25° (*c* 0.87).

Anal. Calcd. for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 80.24; H, 10.50.

2α- (XVIb) and 2β- (XXb) Isopropyl-19-nor-5α-androstan-3-ones.—The hydrogenation of the ketal XIVb (120 mg.) was performed in cyclohexane solution (10 cc.) with 15 mg. of 10% palladium-on-charcoal catalyst and the total product (XVb) was directly cleaved by keeping in acetone solution at room temperature for 3 hr. in the presence of a few crystals of *p*-toluenesulfonic acid. The product was a clear oil, which could not be crystallized, but its mass spectrum (molecular ion at *m/e* 302) demonstrated that it consisted of only one molecular species ($C_{21}H_{34}O$). Thin-layer chromatography demonstrated that it was contaminated by a small amount of the 2β-isomer XXb.

As an alternate route to both isomeric ketones XVIb and XXb, an approximately 1:1 mixture of the ketals XI and XIIIb (1.0 g.) was dissolved in 30 cc. of methanol, 8 drops of concentrated sulfuric acid was added, and the solution kept at room temperature for 4 hr. Dilution with water and extraction with chloroform gave 0.85 g. of yellowish sirup, thin-layer chromatography (benzene) of which indicated the presence of one major fast moving spot and one minor more polar one. Chromatography of a 200-mg. aliquot on 40 g. of activity II alumina and elution with benzene–petroleum ether (1:1) yielded 35 mg. of nearly homogeneous (by t.l.c.) **2-isopropylidene-19-nor-5α-androstan-3-one (XIXb)**, which could not be crystallized and which was used in the next step; λ_{max}^{EtOH} 253 mμ, log ϵ 3.77.

The unsaturated ketone XIXb (175 mg.) was hydrogenated in ethyl acetate solution as described for the cholestane analog XIXa, thin-layer chromatography of the crude hydrogenation product showing the presence of three equally spaced spots of nearly equal intensity. The least polar one was not characterized further. A preparative thin-layer chromatogram using silica gel G (E. Merck, Darmstadt) as adsorbent, benzene as the solvent, and ceric sulfate solution for detection afforded 50 mg. of the **2α-isopropyl ketone XVIb** from the most mobile fraction and 30 mg. of the **2β-ketone XXb** from the intermediate one, the empirical formula of each fraction being determined by mass spectrometry (mol. ion at *m/e* 302 = $C_{21}H_{34}O$). The rotary dispersion characteristics of the two isomeric ketones are summarized in Table I. The 2α-isomer XVIb could not be crystallized, but the 2β-epimer XXb exhibited m.p. 65–67° after recrystallization from aqueous methanol.

Equilibration of the two pure isomeric ketones with sodium methoxide was performed as described above in the cholestane series. The rotatory dispersion amplitude of the mixture amounted to $a = +59$, corresponding to an 83% XVIb–17% XXb equilibrium when compared with the values for the two pure epimers listed in Table I. Alternatively, the circular dichroism was also measured and yielded the following molecular ellipticity values[37]: 2α-ketone XVIb, $[\theta]_{300}$ +2200; 2β-ketone XXb, $[\theta]_{296}$ +11,000; equilibration mixture, $[\theta]_{298}$ +3430, the latter figure corresponding to an 82% XVIb–18% XXb mixture.

(34) See H. L. Dryden, G. M. Webber, R. R. Burtner, and J. A. Cella, *J. Org. Chem.*, **26**, 3237 (1961).

(35) See W. E. Bachmann, W. Cole, and A. L. Wilds, *J. Am. Chem. Soc.*, **62**, 824 (1940).

(36) The reaction proceeded in much poorer yield when the ketalization was attempted in the conventional manner without added diglyme.

(37) For circular dichroism nomenclature see C. Djerassi and E. Bunnenberg, *Proc. Chem. Soc.*, 299 (1963).