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

Optical Rotatory Dispersion Studies. LXXXIX.[1] The Octant Rule and the *t*-Butyl Group. Synthesis of Steroidal *t*-Butyl Ketones[2]

BY CARL DJERASSI, P. A. HART,[3] AND E. J. WARAWA[3]

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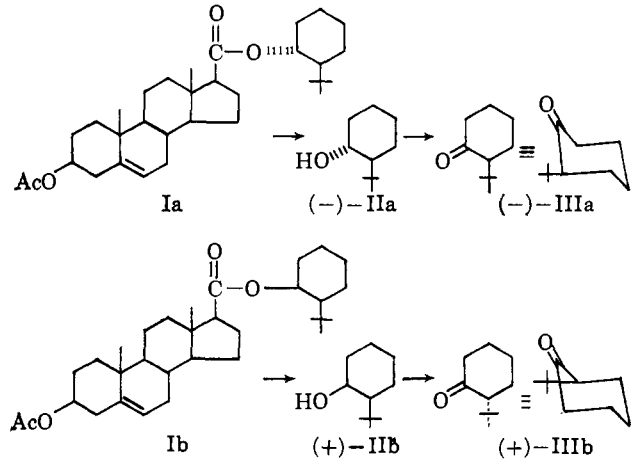
Both antipodes of optically active 2-*t*-butylcyclohexanone (III) were obtained through resolution of *trans*-2-*t*-butylcyclohexyl Δ^5-3β-acetoxyetienate (I), while *trans*- (V) and *cis*- (VI) 2-*t*-butyl-5-methylcyclohexanones were prepared by methylmagnesium iodide addition to (+)-pulegone (IV). In the steroid series, 16-*t*-butyl-Δ^5-androsten-3β-ol-17-one (XIV) was produced in a similar fashion from the 16-isopropylidene-17-ketone and subsequently transformed into 16-*t*-butyltestosterone (XVI), while 2α- (XXIII) and 2β- (XXII) *t*-butylcholestan-3-ones were synthesized by *t*-butylmagnesium chloride addition to cholestan-2-one, followed by dehydration, hydroboration of the olefin, and oxidation of the separated 2α-*t*-butyl-3β-hydroxy- (XX) and 2β-*t*-butyl-3α-hydroxy- (XXI) cholestanes. From the optical rotatory dispersion curves of III, V, and XXIII, a reasonable value for the rotational contribution of the equatorial *t*-butyl group to the Cotton effect amplitude of a cyclohexanone could be calculated. By the use of this amplitude value, it was possible to show the existence of twist conformations (VIc and XXIId) in *cis*-2-*t*-butyl-5-methylcyclohexanone (VI) and in 2β-*t*-butylcholestan-3-one (XXII).

One of the most important applications of the octant rule[4] has been in the field of conformational analysis.[5] In order to be employed for quantitative or even semi-quantitative studies, it is necessary to have available standard values for certain common substituents. As an example, there may be offered the recent[6] attempt to establish a reliable value for the contribution (in terms of rotatory dispersion molecular amplitude) of a methyl group adjacent to the carbonyl group in a cyclohexanone. We now wish to report on similar studies of the *t*-butyl group, which is of particular interest since its bulk requires that it assume an equatorial orientation.[7] We were especially concerned to secure pairs of epimers, differing only in the configuration of the *t*-butyl group; if the *t*-butyl substituent is to retain the equatorial orientation, then one of the two epimers would cause a conformational change in the cyclohexanone ring, which should manifest itself in the optical rotatory dispersion picture.

The relative unavailability of optically active *t*-butylcyclohexanones has so far limited extensive optical rotatory dispersion measurements of such compounds and the only relevant studies which have been recorded in the literature deal with 3-[8] and 4-[6] substituted cyclohexanones. We describe herewith[9] the synthesis of appropriate α-*t*-butylcyclohexanones, followed by a discussion of their optical rotatory dispersion properties.

Synthetic Studies.—As far as possible, it was intended to employ optically active starting materials of known absolute configuration (*e.g.*, terpenes and steroids), but this was not feasible in the case of the parent substance 2-*t*-butylcyclohexanone, which had to be resolved. For this purpose, *trans*-2-*t*-butylcyclohexanol[10] was transformed into the 3β-acetoxy-Δ^5-etienate,[11] which could be separated into its two diastereoisomeric constituents Ia (m.p. 181–182°, $[\alpha]_D$ −45°) and Ib (m.p. 172–174°, $[\alpha]_D$ −9°) by column chromatography. Cleavage of the pure esters with lithium aluminum hydride provided the crystalline antipodes of (−)- (IIa) and (+)- (IIb) *trans*-2-*t*-butylcyclohexanol, the optical purity of the two specimens being assured by the identical magnitude of their rotations ($[\alpha]_D$ −44.4° *vs.* +44.2°). Oxidation by the Jones procedure[12] afforded[13] the required antipodal 2-*t*-butylcyclohexanones (IIIa and IIIb), which exhibited considerable optical stability. Thus, their optical rotatory dispersion curves were unchanged after remaining at room temperature in methanol solution for over 2 months. Addition of concentrated hydrochloric acid to an isopropyl alcohol solution of the ketone did not affect the Cotton effect amplitude and only upon heating the acidified solution did the ketone undergo racemization. The absolute configuration[14] could already be deduced at the alcohol stage (II) by application of the Klyne–Stokes rule[15] and was confirmed further by a consideration (*vide infra*) of the optical rotatory dispersion of the ketones IIIa and IIIb.



Attention has already[16] been directed to the utility of the readily available (+)-pulegone (IV), of known

(1) Paper LXXXVIII: H. Wolf, E. Bunnenberg, and C. Djerassi, *Ber.*, in press.

(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 from portions of the Ph.D. theses of P. A. Hart (1963) and E. J. Warawa (1961).

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

(5) For extensive discussion and leading references see: (a) C. Djerassi and W. Klyne, *J. Chem. Soc.*, 4929 (1962); (b) C. Djerassi and W. Klyne, *Proc. Natl. Acad. Sci. U. S.*, **48**, 1093 (1962); (c) C. Djerassi and W. Klyne, *J. Chem. Soc.*, 2390 (1963).

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

(7) S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, **77**, 5562 (1955).

(8) C. Djerassi, E. J. Warawa, R. E. Wolff, and E. J. Eisenbraun, *J. Org. Chem.*, **25**, 917 (1960).

(9) Some of the present results were announced in a preliminary communication: C. Djerassi, E. J. Warawa, J. M. Berdahl, and E. J. Eisenbraun, *J. Am. Chem. Soc.*, **83**, 3334 (1961).

(10) H. L. Goering, R. L. Reeves, and H. H. Espy, *ibid.*, **78**, 4926 (1956).

(11) For other resolutions with 3β-acetoxy-Δ^5-etienic acid, see R. B. Woodward and T. J. Katz, *Tetrahedron*, **5**, 70 (1959); C. Djerassi and J. Staunton, *J. Am. Chem. Soc.*, **83**, 736 (1961); and ref. 8.

(12) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(13) In our hands, this method of oxidation did not cause any perceptible racemization; see also ref. 6 as well as G. Ohloff, J. Osiecki, and C. Djerassi, *Ber.*, **95**, 1400 (1962), and J. A. Berson, J. S. Walia, A. Remanick, S. Suzuki, P. Reynolds-Warnhoff, and D. Willner, *J. Am. Chem. Soc.*, **83**, 3986 (1961).

(14) All stereoformulas in this paper represent correct absolute configurations using the steroid notation.

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

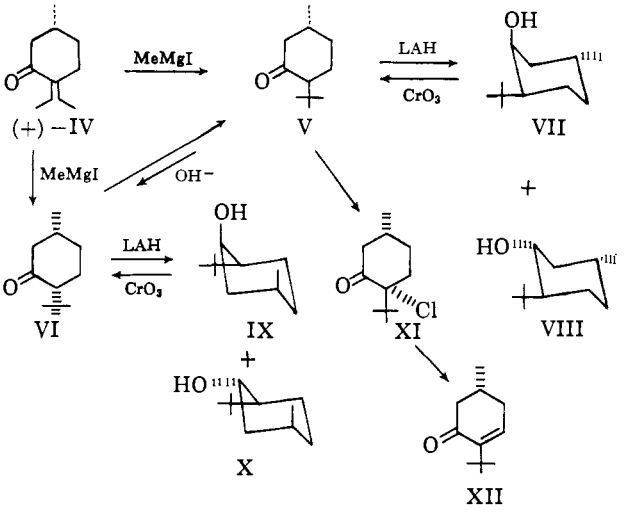
(16) C. Djerassi, J. Osiecki, and E. J. Eisenbraun, *J. Am. Chem. Soc.*, **83**, 4433 (1961).

absolute configuration,[17] for the preparation of optically active, alkylated cyclohexanones. 1,4-Addition[18] of a methyl Grignard reagent to (+)-pulegone (IV) appeared to be a feasible route to 2-*t*-butyl-5-methylcyclohexanones and some effort was expended to develop satisfactory conditions. Using methylmagnesium iodide in tetrahydrofuran solution in the presence of cuprous chloride, there was obtained in over 70% yield a mixture of *trans*- (V) and *cis*- (VI) 2-*t*-butyl-5-methylcyclohexanones. The presence of the *t*-butyl group was established by the n.m.r. signal at 1.00 δ and the isomer composition determined by gas-phase chromatography. The predominant *trans* isomer V was separated by preparative gas-phase chromatography, while the portion enriched in the *cis* isomer VI was reduced with lithium aluminum hydride. Column chromatography provided two crystalline alcohols, one of them (X) in trace amount. The more abundant one was shown to be the all-*cis* 2-*t*-butyl-5-methylcyclohexanol (IX) on the basis of the following evidence:

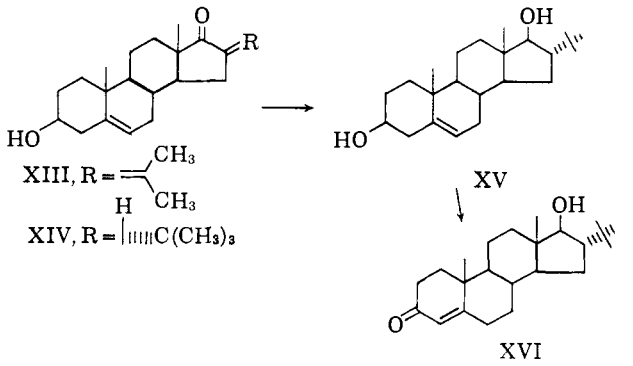
(i) The axial orientation of the hydroxyl group of IX followed from the n.m.r. signal at 4.23 δ (as compared[19] to 4.27 for VII and 3.90 for VIII and X) and its rate of chromium trioxide oxidation,[20] which was identical[21] with that of an axial 11β-hydroxy steroid such as ergostan-11β-ol. (ii) Its negative rotation was in agreement with the Klyne–Stokes rule.[15] (iii) Chromium trioxide oxidation afforded pure *cis*-2-*t*-butyl-5-methylcyclohexanone (VI), which underwent base isomerization to an 80% (V)–20% (VI) equilibrium mixture, identical with that derived by base treatment of the pure *trans*-ketone V.

Reduction of *trans*-2-*t*-butyl-5-methylcyclohexanone (V) with lithium aluminum hydride provided a separable mixture of a crystalline dextrorotatory (VII) and a liquid levorotatory (VIII) alcohol. The axial character of the crystalline alcohol VII was demonstrated by the n.m.r. signal at 4.27 δ,[19] as contrasted with 3.90 δ for the liquid isomer VIII, and by the fact that it was oxidized[20,21] five times as fast as VIII—both alcohols yielding the starting ketone V. The signs of rotation of the two epimers (+)-VII and (−)-VIII were again consistent with the Klyne–Stokes rotation rule.[15] These results, coupled with the optical rotatory dispersion data discussed below, settle the stereochemistry of the 1,4-Grignard addition products to pulegone (IV) in terms of stereoformulas V and VI.

Our interest in the rotatory dispersion behavior of α-halocyclohexanones[22] prompted a study of the halogenation of 2-*t*-butyl-5-methylcyclohexanone. Unstable mixtures were encountered during bromination, but chlorination with sulfuryl chloride[23] provided a crystalline chloroketone, which was shown to possess the constitution XI. The axial orientation of the chlorine atom was proved by the ultraviolet, infrared, and optical rotatory dispersion properties (see Experimental and Tables II and III) and the location of the halogen atom was settled by the n.m.r. spectrum (absence of downfield proton expected from a 6-chloro isomer and shift of *t*-butyl signal from 1.00 (V) to 1.18 p.p.m.) and dehydrochlorination with lithium carbonate–lithium chloride in dimethylformamide[24] to 2-*t*-butyl-5-methylcyclohex-2-en-1-one (XII). Attempts at dehydrochlorination with 2,4-dinitrophenylhydrazine or collidine failed.



The ease of 1,4-Grignard addition to pulegone (IV) prompted an exploration of this route in the steroid series. As a first example, the known[25] 16-isopropylidene-Δ^5-androsten-3β-ol-17-one (XIII) was treated with methylmagnesium bromide in the presence of cuprous chloride to give in over 60% yield the 16α-*t*-butyl-Δ^5-androsten-3β-ol-17-one (XIV).[26] The accessability of this *t*-butyl ketone stimulated us to convert it into the 16-*t*-butyl analog XVI of testosterone by lithium aluminum hydride reduction to the diol XV followed by Oppenauer oxidation. Bioassays by the Endocrine Laboratories (Madison, Wis.) in intact female–castrate male parabiotic rats (subcutaneous administration to castrate member) revealed no inhibition of gonadotrophin activity when examined at a 10 mg./rat level.



The success of these Grignard additions augured well for the synthesis of the important 2-*t*-butyl-3-keto steroids, but numerous attempts[27] to effect this reaction with 2-isopropylidenecholestan-3-one failed completely. Consequently, the following sequence was developed, which had the advantage of affording both isomeric 2-*t*-butylcholestan-3-ones (XXII and XXIII), although

(17) See E. J. Eisenbraun and S. M. McElvain, *J. Am. Chem. Soc.*, **77**, 3383 (1955), and references cited therein.

(18) For earlier attempts see V. Grignard and J. Savard, *Compt. rend.*, **179**, 1573 (1924); H. Rupe, H. Schobel, and E. Abegg, *Ber.*, **45**, 1529 (1912).

(19) See J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958). With tetramethylsilane as internal standard, the equatorial hydrogen attached to the same carbon atom as the hydroxyl group exhibits a signal which is further downfield than that of its axial epimer.

(20) J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta*, **38**, 1529 (1955).

(21) We are greatly indebted to Prof. A. Eschenmoser (E. T. H., Zurich) for these oxidation results, all of which were obtained in his laboratory.

(22) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, Chapter 9.

(23) E. W. Warnhoff and W. S. Johnson, *J. Am. Chem. Soc.*, **75**, 494 (1953); see also E. W. Warnhoff, D. G. Martin, and W. S. Johnson, *Org. Syn.*, **37**, 8 (1957).

(24) R. Joly, J. Warnant, G. Nominé, and D. Bertin, *Bull. soc. chim. France*, 367 (1958).

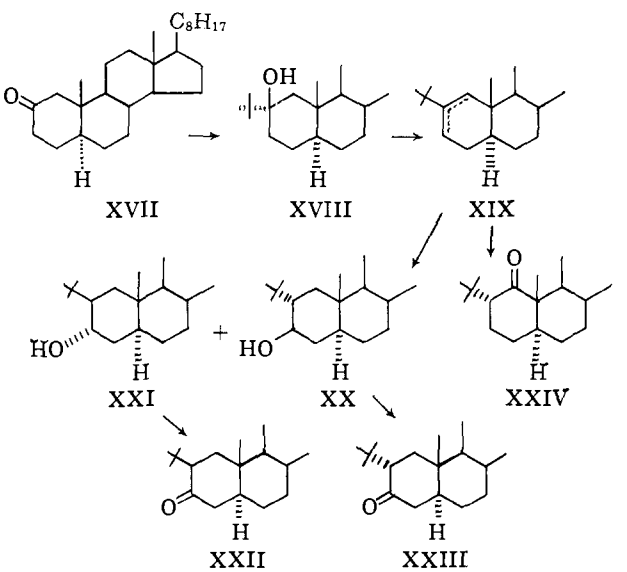
(25) W. C. J. Ross, *J. Chem. Soc.*, 25 (1945).

(26) No attempt was made to establish definitely the configuration of the *t*-butyl function. We are assuming the α-configuration because of the steric interaction of the 16β-isomer with the angular methyl group and because base-catalyzed equilibration of 16-methyl-17-ketones (J. H. Fried, A. N. Nutile, G. E. Arth, and L. H. Sarett, *J. Org. Chem.*, **27**, 682 (1962)) has shown the 16α-methyl isomer to be the energetically preferred one.

(27) For details see Ph.D. thesis of P. A. Hart, Stanford University, 1963.

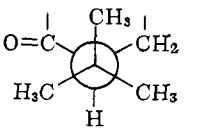
the over-all yield was poor. Cholestan-2-one (XVII) was treated with *t*-butylmagnesium chloride in ether solution and afforded the desired 2α-*t*-butylcholestan-2β-ol (XVIII) together with much recovered starting material (XVII), which could be separated with ease and resubmitted to Grignard addition. In this fashion a 34% yield was realized after three such cycles and the resulting alcohol dehydrated with thionyl chloride in pyridine. The crude olefin (n.m.r. spectrum consistent with structure XIX) was directly hydroborated[28] using the lithium aluminum hydride–boron trifluoride technique.[29] Careful chromatography yielded three alcohols, of which the first two were derived from the Δ^2-component of the olefin mixture (XIX) and the most polar—by exclusion—from the Δ^1-olefin. The hydration of the unsubstituted Δ^2-cholestene yields all four possible isomeric alcohols,[30] with attack from the α-side being favored (75%). In the 2-*t*-butyl analog XIX, the tendency toward such rearward approach should be offset and perhaps even abolished by the consequent generation of an axial *t*-butyl substituent (assuming a chair geometry). In point of fact, both isomers XX and XXI were obtained in pure form and oxidized to the required 2β- (XXII) and 2α- (XXIII) *t*-butylcholestan-3-ones. As was to be anticipated, base equilibration of the pure ketones provided a mixture in which the 2α-isomer XXIII predominated (~95%). In order to prove unambiguously that these two ketones were not the isomeric 2-*t*-butylcholestan-1-ones, a specimen of the 2α-epimer XXIII was equilibrated in deuterium oxide–deuteriomethanol and sodium, whereupon three deuterium atoms were introduced as established by mass spectrometry.

The last and most polar alcohol from the hydration of the olefin mixture XIX was directly oxidized and equilibrated with base, thus yielding a crystalline ketone which is assumed to be 2α-*t*-butylcholestan-1-one (XXIV). Insufficient material was isolated to permit further chemical studies with it.



Discussion of Optical Rotatory Dispersion Results.—For qualitative considerations, the octant rule[4] neglects contributions by equatorial substituents (such as methyl or halogen) adjacent to the carbonyl function, because these lie nearly in one of the symmetry planes of the carbonyl group. As discussed recently[6] in full detail, for quantitative work such an assumption is not necessarily valid and an equatorial α-methyl group in a cyclohexanone makes a small rotatory contribution, most likely due to the fact[31] that it does not lie exactly in the nodal plane.

If the *t*-butyl group were situated exactly in the horizontal nodal plane of the carbonyl function, then the fully staggered rotomer XXV should make no contribution since the effect of the three methyl groups would cancel out.



XXV

In actual fact, optically active 2-*t*-butylcyclohexanone (III) exhibits a very substantial Cotton effect (Table I) of molecular amplitude a[32] ~ 33. We have proposed earlier[9] that this may be due to those rotomers, which depart from the perfect staggered arrangement XXV, because the adjacent C-1 carbonyl and C-3 methylene groups are not sterically equivalent, but another and perhaps more likely explanation is that the substituent is not exactly in the symmetry plane of the carbonyl group. Thus in the (−)-antipode IIIa, the *t*-butyl substituent lies slightly[31] in a negative octant—its much stronger rotatory contribution (a ~ 33) as compared to that[6] (a < 9) of a methyl group then being ascribable to the larger effect of the additional carbon (rather than just hydrogen) substituents.

2α-*t*-Butylcholestan-3-one (XXIII) represents an equatorially substituted α-*t*-butylcyclohexanone derivative of known absolute configuration. When its molecular amplitude, a = +16 (Table I), is subtracted from that (+55) of the unsubstituted cholestan-3-one, there is obtained a second value of a = 39 as the rotatory contribution of an equatorial α-*t*-butyl substituent in a cyclohexanone, which is not too far off from the values deduced from the first two entries in Table I. Furthermore, the sign of this amplitude value from the cholestane series automatically establishes the absolute configuration of the two antipodes of 2-*t*-butylcyclohexanone (III), that of (+)-IIIb corresponding to that of the steroid XXIII.

A third conformationally simple model from which the rotatory contribution of the equatorial *t*-butyl group can be deduced is *trans*-2-*t*-butyl-5-methylcyclohexanone (V), the absolute configuration of which is known because of its origin from (+)-pulegone (IV).[17] Its virtually predominant, if not exclusive, conformation must be that chair form in which both alkyl substituents are equatorially situated. This substance (V) exhibits (Table I) only a very weak, negative Cotton effect (a = −3),[33] and if the molecular amplitude contribution (a = +25) of the methyl group, as derived from (+)-3-methylcyclohexanone (XXVI),[5c] is subtracted, a value of −28 is calculated, which compares favorably with the observed one (Table I) of −33 for (−)-2-*t*-butylcyclohexanone (IIIa). This correspondence in sign and magnitude establishes in a second, independent manner the absolute configuration of the two anti-

(28) H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962.

(29) S. Wolfe, M. Nussim, Y. Mazur, and F. Sondheimer, *J. Org. Chem.*, **26**, 630 (1961).

(30) A. Hassner and C. Pillar, *ibid.*, **27**, 2914 (1962); F. Sondheimer and M. Nussim, *ibid.*, **26**, 630 (1961).

(31) The angle between the horizontal carbonyl plane and the bond connecting the equatorial methyl group in a cyclohexanone (chair form) amounts to 4° 3′ (ref. 4).

(32) As noted in ref. 5a, the molecular amplitude a is defined as the difference between the molecular rotation at the extremum of longer wave length minus the molecular rotation at the extremum of shorter wave length, divided by 100 for convenience—the sign being governed by the sign of the first extremum.

(33) By mistake, a value of −5 rather than −3 was given in ref. 9, since inadvertently the sum, rather than the difference, in molecular rotation of the two negative extrema was listed.

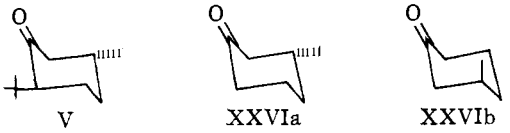
TABLE I

SUMMARY OF OPTICAL ROTATORY DISPERSION DATA

Compound	Extrema of O.R.D. Cotton effects (MeOH) [ϕ]	λ, mμ	[ϕ]	λ, mμ	Amplitude (a)[32]
(−)-2-*t*-Butylcyclohexanone (IIIa)	−1650°	317	+1670°	275	−33
(+)-2-*t*-Butylcyclohexanone (IIIb)	+1690	317	−1720	275	+34
(+)-3-Methylcyclohexanone (XXVI)[5c]					+25
trans-2-*t*-Butyl-5-methylcyclohexanone (V)	−384	300	−106	275	−3
cis-2-*t*-Butyl-5-methylcyclohexanone (VI)	+2150	316.5	−2650	277	+48
Cholestan-3-one[a]					+55
2α-*t*-Butylcholestan-3-one (XXIII)	+857	314	−765	270	+16
2β-*t*-Butylcholestan-3-one (XXII)	+6150	313	−2210	270	+84
Δ^5-Androsten-3β-ol-17-one[b]	+5920	312	−8350	275	+143
16α-*t*-Butyl-Δ^5-androsten-3β-ol-17-one (XIV)[26]	+5980	330	−6820	290	+128

[a] Average value of 15 determinations performed on the same instrument as measurements of XXII and XXIII. [b] W. Klyne, cited on p. 47 of ref. 22.

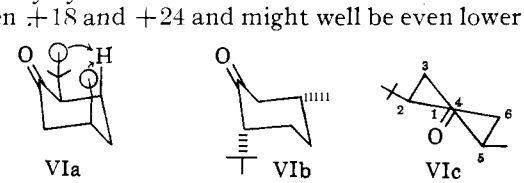
podes IIIa and IIIb. The somewhat low value (−28 *vs.* −33) derived from this calculation is to be expected since the rotatory contribution of the methyl group (a = +25) is taken from the experimentally observed amplitude of (+)-3-methylcyclohexanone (XXVI), which at room temperature contains[34] a small amount of a negatively rotating conformer (XXVIb or appropriate twist form) in addition to the predominant and positively rotating form XXVIa.



V XXVIa XXVIb

Using either 2-*t*-butylcyclohexanone (III) or the difference between cholestan-3-one and its 2α-*t*-butyl derivative XXIII as reference points (Table I), the rotatory contribution of an equatorial *t*-butyl substituent adjacent to a carbonyl group in a cyclohexanone (chair form) can safely be assumed to lie between a = 33–39. This range is sufficiently small to permit its semiquantitative use in conformational analysis as illustrated for *cis*-2-*t*-butyl-5-methylcyclohexanone (VI) and 2β-*t*-butylcholestan-3-one (XXII).

If we consider only chair forms, there is no doubt that conformer VIa is the preferred one over VIb, where the bulky *t*-butyl group would have to assume an axial orientation, which is prohibitively expensive from an energetic viewpoint.[7] If conformer VIa is the correct representation, then its molecular amplitude should approximately equal the sum of the individual rotatory contributions of the equatorial α-*t*-butyl and axial β-methyl substituents. For the former, we can employ the above cited value of +33 to +39. According to the tenets of the octant rule,[4] the contribution of the axial β-methyl group of VIa must equal that of conformer XXVIb of 3-methylcyclohexanone, and while its precise magnitude is not known, it must be negative and amount at least to a = −15 (see first entry in Table 4 of ref. 5c). We conclude, therefore, that the molecular amplitude of chair form VIa of *cis*-2-*t*-butyl-5-methylcyclohexanone should be no more than between +18 and +24 and might well be even lower.



VIa VIb VIc

The experimentally determined value (Table I) of a = +48 precludes the possibility that the chair form VIa constitutes the only conformer of this substance and demonstrates that another conformational representation must make a partial or exclusive contribution. In searching for energetically plausible reasons for a departure from the chair conformation VIa, it seems most likely to ascribe this to the buttressing to which the axial C-3 hydrogen atom is exposed on the part of the two axially situated methyl groups (see arrows in VIa). This steric interaction would be completely relieved in the twist[35] form VIc, which offers the additional advantage that the axial methyl group of VIa now assumes the equatorial orientation. Such a twist form would be expected[5b] to exhibit a very strongly positive Cotton effect, since carbon atoms 3 and 5, as well as the larger portion of the *t*-butyl substituent, are located in positive octants. Whether this twist form VIc contributes predominantly or only partly to the conformer equilibrium cannot be judged on the basis of the available evidence, but the present rotatory dispersion results point definitely toward its participation. It is pertinent to note that the existence of twist forms has recently been invoked in other α-*t*-butylcyclohexanone derivatives.[36]

The position of the equilibrium between the *trans*- (V) and *cis*- (VI) 2-*t*-butyl-5-methylcyclohexanones was established by heating each isomer under reflux with methanolic potassium hydroxide solution. The rotatory dispersion curves of the two isomerized samples were virtually identical. By utilizing three wave lengths (335, 350, and 375 mμ) of these dispersion curves and comparing them with those of the pure isomers, values of 83.6, 79.4, and 79.7% *trans* isomer V were obtained, indicating that the energy difference between the favored *trans* isomer V and the less stable *cis* form VI amounts to slighly less than 1 kcal./mole.

We now turn to a discussion of a second pair of ketones which are isomeric at the *t*-butyl center, namely 2α- (XXIII) and 2β- (XXII) *t*-butylcholestan-3-ones. There is little doubt that the equatorial isomer exists essentially in the standard chair conformation, which is substantiated by the fair agreement (Table I) of its molecular amplitude increment (as compared to cholestan-3-one) with that of 2-*t*-butylcyclohexanone (III). It is equally certain that 2β-*t*-butylcholestan-3-one (XXII) does not exist in a chair form, since this would subject the ketone to a 1,3-diaxial interaction between the *t*-butyl and the angular methyl substituents. It was of interest, therefore, to determine whether optical rotatory dispersion could shed some light on its preferred conformation.

The classical boat form XXIIa, with C-3 and C-10 representing the prow and stern, can be excluded immediately on the basis of the observed (Table I) am-

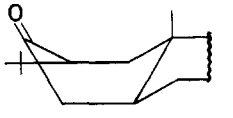
(34) Experimental verification has been provided by low-temperature circular dichroism measurements (K. M. Wellman, E. Bunnenberg, and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 1870 (1963)).

(35) See W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. H. Drieger, and W. N. Hubbard, *ibid.*, **83**, 606 (1961).

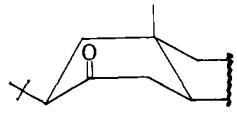
(36) R. D. Stolow and C. B. Boyce, *ibid.*, **83**, 3722 (1961); B. Rickborn, *ibid.*, **84**, 2414 (1962).

plitude $a = +84$. Even if the *t*-butyl function is assumed to be in a positive octant, thus contributing +32 to +39 to the molecular amplitude, rings B and D are in negative octants, while the ring C carbon atoms cancel out. The evaluation of the alternate boat XXIIb (C-5 and C-2 at prow and stern) is less clear-cut, since C-1 is now in a positive octant and carbon atoms 5, 6, and 7 in the horizontal carbonyl plane. The C-19 methyl group, on the other hand, is in a negative octant and the *t*-butyl group seems to be essentially in the horizontal plane. It seems unlikely, therefore, that this conformer would exhibit such a strong positive Cotton effect, but its presence cannot be excluded.

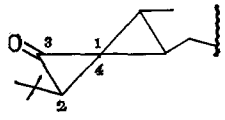
Of the two twist forms XXIIc and XXIId, the former does not appear very likely, since the only close substituent in a positive octant is C-1. The *t*-butyl group lies either in the horizontal plane or even slightly in a negative octant. In the twist form XXIId, with C-3 and C-10 the "points"[5b] of the twist, C-1, C-5, the *t*-butyl group, and ring B are in positive octants, the C-19 angular methyl function being the only negative contributor in the vicinity of the carbonyl group. An important participation by such a conformation (XXIId), or one closely approximating it, seems to be most consistent with the rotatory dispersion evidence (Table I).



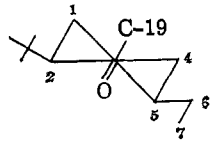
XXIIa



XXIIb



XXIIc



XXIId

The last two entries in Table I pertain to the situation existing in a fused cyclopentanone. It is premature to generalize from this single example and we note only that while the *t*-butyl function does not contribute to a very pronounced extent to the molecular amplitude of the 17-keto steroid, it produces a marked bathochromic shift in the position of the extrema. This single example seems to confirm that the asymmetry of the cyclopentanone ring[37] represents the controlling factor in the Cotton effect of such ketones,[38] the slight negative contribution of the *t*-butyl group being reasonable since the 16α-substituent in XIV projects into a negative octant.

Experimental[39]

Resolution of *trans*-2-*t*-Butylcyclohexanol.—3β-Acetoxy-Δ^5-etienic acid[40] (30 g.), 300 cc. of benzene, and 50 g. of oxalyl chloride was left at room temperature for 22 hr., the relatively insoluble acid gradually dissolving during the course of the reaction. The benzene and excess oxalyl chloride were removed under reduced pressure, dry pyridine (300 cc.) was added to the residual acid chloride, followed (with cooling) by a solution of 9.3 g. of *trans*-2-*t*-butylcyclohexanol[10] in 50 cc. of pyridine. After 30 hr. at room temperature, the reddish violet suspension was poured into 1 l. of cold 3 *N* hydrochloric acid, the solid collected and washed with dilute acid. The air-dried material was extracted with ether and the insoluble unreacted etienic acid removed by filtration. Evaporation of the ether left a solid, which was dissolved in 100 cc. of chloroform, mixed with 100 g. of activity II neutral alumina (E. Merck, Darmstadt), and the chloroform removed under reduced pressure. The dried material was applied to the top of a column of 2 kg. of similar alumina packed in 40% benzene–hexane, the same solvent being used for elution, and each fraction (55 cc.) analyzed by thin-layer chromatography (silica gel G with 1% ethyl acetate in benzene). The initially eluted diastereoisomer Ia (11.6 g., m.p. 177–181°) was recrystallized from methanol–methylene chloride to afford an analytical specimen of the **etienate Ia**, m.p. 181–182°, $[\alpha]_D$ −45°.

Anal. Calcd. for $C_{32}H_{50}O_4$: C, 77.06; H, 10.11. Found: C, 76.98; H, 10.06.

The second isomer was eluted with a larger proportion of benzene, giving 7.3 g. of **etienate Ib**, m.p. 163–171°, which exhibited m.p. 172–174°, $[\alpha]_D$ −9° (*c* 0.75) after recrystallization from methanol–methylene chloride.

Anal. Found: C, 76.79; H, 10.14.

The appropriate etienate (1.5 g.) was heated under reflux for 1 hr. with lithium aluminum hydride (1.0 g.) in ether solution and the mixture worked up by the sodium sulfate technique. The ether was removed by careful distillation through a tantalum wire column, leaving a white, solid residue which was sublimed at a bath temperature of 30–60° (0.1 mm.) to afford star-like crystals (370 mg.). Starting with the higher melting etienate Ia, the (−)-**antipode IIa** of *trans*-2-*t*-butylcyclohexanol, m.p. 50–52°, $[\alpha]_D$ −44.4° (*c* 0.76), was obtained, while from the diastereoisomer Ib, the (+)-**antipode IIb** (m.p. 50–52°, $[\alpha]_D$ +44.2° (*c* 0.79)) was isolated.

Anal. Calcd. for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.80; H, 12.71.

Optically Active 2-*t*-Butylcyclohexanone (III).—To an ice-cooled solution of 97 mg. of the optically active alcohol (IIa or IIb) in purified acetone was added dropwise a standardized solution[12] of chromium trioxide together with occasional small portions of anhydrous magnesium sulfate. When the orange color appeared permanent (*ca.* 10 min.), stirring was continued for an additional 3 min., solid sodium bicarbonate was added, and the solution was filtered. The acetone was removed under reduced pressure, using a rotary evaporator; hexane was added to the liquid residue and the evaporation process repeated. The flask was then connected to a high vacuum system, the sample cooled in liquid nitrogen, and a vacuum of 3×10^{-5} mm. applied. The liquid nitrogen was removed and placed under the receiver and distillation was effected at room temperature under high vacuum, approximately 40 mg. of pure distilled ketone being recovered. The rotatory dispersion constants of the two antipodes (−)-IIIa and (+)-IIIb are collected in Table I and these values remained unchanged for 64 days for a methanol solution of the ketone kept at room temperature. Addition of 1 drop of concentrated hydrochloric acid to an isopropyl alcohol solution of the ketone at room temperature did not affect the amplitude of its Cotton effect, but this dropped rapidly upon heating at 65°: $[\alpha]_{317}$ −1089° (25°) → $[\alpha]_{317}$ −447° (6 min. at 65°) → $[\alpha]_{317}$ −102° (14 min. at 65°).

Anal. Calcd. for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.81; H, 11.78.

(−)-*trans*-2-*t*-Butyl-5-methylcyclohexanone (V).—Into a 300-cc. three-necked round-bottomed flask, equipped with magnetic stirring bar and condenser set downward for distillation, was placed 60 cc. of 1.69 *N* ethereal methylmagnesium iodide solution. To this was added 125 cc. of tetrahydrofuran, freshly distilled from lithium aluminum hydride, which resulted in formation of a suspension. The solvents were removed by distillation until the temperature reached 50°, whereupon the flask was cooled to 0° in an ice–salt bath, the condenser (with drying tube) placed in an upright position, and a dropping funnel, containing 10 g. of (+)-pulegone (IV)[41] in 50 cc. of tetrahydrofuran, was attached. To the Grignard solution was added 200 mg. of cuprous chloride and the pulegone solution was dropped in slowly over a period of 1.5 hr. while maintaining the temperature at 0–5°. The resulting bright yellow suspension was stirred for 1 hr. at ice-bath temperature and for an additional 5 hr. at room tem-

(37) See W. Klyne, *Tetrahedron*, **13**, 29 (1961); *Bull. soc. chim. France*, 1396 (1960).

(38) See also Table I in C. Beard, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, in press.

(39) All melting points were determined on a Kofler hot stage and are uncorrected. Rotations (chloroform solution, unless specified otherwise) and infrared and ultraviolet spectra were determined by Mrs. D. Aguilar on a Zeiss Model 50-370 polarimeter, Perkin–Elmer 421 grating spectrophotomer, and Cary Applied Physics Model 14 spectrophotometer, respectively. The rotatory dispersion curves were obtained by Mrs. R. Records with a Nippon Bunko (Japan Spectroscopic Manufacturing Co., Ltd.) recording spectropolarimeter. Mass spectra were determined by Drs. H. Budzikiewicz, M. Ohashi, and J. M. Wilson with a CEC mass spectrometer Model 21-103C, while n.m.r. measurements (deuteriochloroform solution with tetramethylsilane as internal standard) were performed by Dr. L. J. Durham on a Varian A-60 n.m.r. spectrometer. All microanalyses are due to Messrs. E. Meier and J. Consul of the Stanford Microanalytical Laboratory.

(40) J. Staunton and E. J. Eisenbraun, *Org. Syn.*, **42**, 4 (1962).

(41) The (+)-pulegone (IV) was isolated from oil of pennyroyal (Fritzsche Bros.) by preparative gas-phase chromatography at 180° using a Beckman Megachrom equipped with 6-ft. columns of Apiezon J substrate on Chromosorb support, the purity of the material being checked by analytical gas-phase chromatography at 160° using a Craig polyester column.

perature, at which time the yellow color had faded almost completely. The mixture was poured onto 100 g. of ice containing 20 g. of ammonium chloride and the product isolated by ether extraction and distilled to afford 8.32 g. of a colorless liquid, b.p. 45–55° (0.1 mm.), which contained only about 5% of unreacted pulegone, the remainder representing a 65–35% mixture of *trans*- (V) and *cis*- (VI) 2-*t*-butyl-5-methylcyclohexanone as determined by gas-phase chromatography at 150° on an analytical 5-ft. phenyldiethanolamine succinate–firebrick column.

A sample of the ketone mixture was transformed into its **2,4-dinitrophenylhydrazone** and recrystallized from ethanol to provide the analytical specimen, m.p. 144–146°, $[\alpha]_D$ +122° (*c* 0.55), $\lambda_{max}^{CHCl_3}$ 368 mμ, log ε 4.40, which showed only one spot in a paper chromatogram on Whatman No. 1 paper with the system 40% Phenyl Cellosolve–heptane.

Anal. Calcd. for $C_{17}H_{24}N_4O_4$: C, 58.60; H, 6.94; N, 16.09. Found: C, 57.99; H, 6.97; N, 16.00.

A **semicarbazone** was prepared in aqueous ethanol solution, using semicarbazide hydrochloride and sodium acetate, and after recrystallization from aqueous ethanol, it exhibited m.p. 188–189° dec., $[\alpha]_D$ +12° (*c* 0.50).

Anal. Calcd. for $C_{12}H_{23}N_3O$: C, 63.96; H, 10.29; N, 18.65. Found: C, 64.00; H, 10.25; N, 18.17.

Regeneration of the ketone from the semicarbazone by steam distillation in the presence of oxalic acid followed by optical rotatory dispersion measurement (a = −1.5) and comparison with the data of the pure isomers collected in Table I indicated that the resulting ketone represented *ca.* 97% pure *trans* isomer V.

From the standpoint of convenience, the pure *trans*-ketone V was isolated by preparative gas-phase chromatography on a 12-ft. 20% Ucon Polar–Chromosorb column using helium (10 p.s.i.), the *trans* isomer showing a retention time at 150° of 32 min. as compared to 35 min. for the *cis*-ketone VI, incomplete separation at the base line making the isolation of the latter more difficult. The purity of the *trans*-ketone V was established by analytical gas chromatographic analysis. The optical rotatory dispersion, and infrared and ultraviolet spectral properties are collected in Tables I–III; in the infrared fingerprint region, the *trans* isomer V showed peaks at 8.03, 8.25, and 10.10 μ, which are absent in the *cis* isomer VI.

Anal. Calcd. for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.57; H, 11.91.

TABLE II

POSITIONS OF INFRARED ABSORPTION CARBONYL MAXIMA

Solvent	*trans*-2-*t*-Butyl-5-methylcyclohexanone (V) λ_{max}, μ	*cis*-2-*t*-Butyl-5-methylcyclohexanone (VI) λ_{max}, μ	2-Chloro-*trans*-2-*t*-butyl-5-methylcyclohexanone (XI) λ_{max}, μ
Chloroform	5.89	5.90	5.84
Isooctane	5.84	5.85	5.82
Dioxane	5.85	5.87	5.82
Methanol			5.85

TABLE III

POSITIONS OF ULTRAVIOLET ABSORPTION CARBONYL MAXIMA

Solvent	*trans*-2-*t*-Butyl-5-methylcyclohexanone (V) λ_{max}, mμ	log ε	*cis*-2-*t*-Butyl-5-methylcyclohexanone (VI) λ_{max}, mμ	log ε	2-Chloro-*trans*-2-*t*-butyl-5-methylcyclohexanone (XI) λ_{max}, mμ	log ε
Isooctane	293	1.33	293	1.36	308	1.47
Chloroform	290	1.39	290	1.47	307	1.52
Dioxane	290	1.33	292	1.33	307	1.45
Methanol	288	1.33	290	1.42	303	1.47

Lithium Aluminum Hydride Reduction of *trans*-2-*t*-Butyl-5-methylcyclohexanone (V).—*trans*-2-*t*-Butyl-5-methylcyclohexanone (V, 1.06 g.) was reduced with lithium aluminum hydride in ether solution by heating under reflux for 1 hr. The mixture was decomposed by the sodium sulfate technique and the resulting liquid alcohol (1.02 g., no infrared carbonyl band) was chromatographed on 87 g. of activity III neutral alumina. Elution with low-boiling petroleum ether provided 107 mg. of the alcohol VII (m.p. 34–36°), the axial nature of the hydroxyl group being demonstrated by n.m.r. and quantitative oxidation measurements as outlined in the Discussion section. The analytical specimen (100 mg.) was obtained by sublimation at 0.1 mm., m.p. 36–36.5°, $[\alpha]_D$ +34° (*c* 0.70). Jones oxidation[12] regenerated the starting ketone V.

Anal. Calcd. for $C_{11}H_{22}O$: C, 77.57; H, 13.02. Found: C, 78.00; H, 12.86.

Continued elution with petroleum ether yielded oils which were shown to be mixtures of the epimeric alcohols VII and VIII by thin-layer chromatography on silica gel (5% ether–petroleum ether). Eventually, 32 mg. of the pure equatorial alcohol VIII was obtained as a liquid, $[\alpha]_D$ −28° (*c* 0.60), the homogeneity of which was established by thin-layer chromatography. The evidence for the equatorial orientation is summarized in the Discussion section.

Anal. Found: C, 77.12; H, 12.81.

***cis*-2-*t*-Butyl-5-methylcyclohexanone (VI).**—A ketone fraction, enriched in the *cis* isomer VI by gas-phase chromatography, was reduced with lithium aluminum hydride and chromatographed on alumina exactly as described above the the *trans*-ketone V. The predominant alcohol, eluted with hexane, was the all-*cis*-alcohol IX, m.p. 45–46°, $[\alpha]_D$ −37° (*c* 0.75) with an axial hydroxyl group (for n.m.r. and oxidation evidence, see Discussion section).

Anal. Calcd. for $C_{11}H_{22}O$: C, 77.58; H, 13.02; O, 9.40. Found: C, 77.34; H, 12.78; O, 9.61.

From the later benzene–hexane eluates, there was isolated 5 mg. of an alcohol, m.p. 104.5–105.5°, the n.m.r. spectrum of which indicated the presence of an equatorial hydroxyl group. By exclusion, we attribute structure X to this alcohol.

Oxidation of the pure crystalline alcohol IX, m.p. 45–46°, by the Jones[12] procedure led to *cis*-2-*t*-butyl-5-methylcyclohexanone (VI), b.p. 40–45° (0.2 mm.), which was uncontaminated by the *trans* isomer V as demonstrated by analytical gas-phase chromatography. The pertinent physical constants are collected in Tables I, II, and III; in the infrared fingerprint region, the *cis*-ketone VI exhibited peaks of medium intensity at 8.10, 8.20, 9.11, and 9.27 μ, which are absent in the *trans* isomer V.

Anal. Calcd. for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.56; H, 12.07.

When either pure ketone V or VI was heated under reflux for 2 hr. with 5% methanolic potassium hydroxide solution, there was obtained the identical equilibrium mixture as evidenced by infrared and optical rotatory dispersion measurements. Its composition (*ca.* 80% V–20% VI) was determined from the optical rotatory dispersion curves (see Discussion) of the two pure isomers and the equilibrium mixture.

(+)-2-Chloro-2-*t*-butyl-5-methylcyclohexanone (XI).—A mixture (4.0 g.) of *trans*- (V) and *cis*- (VI) 2-*t*-butyl-5-methylcyclohexanone in 20 cc. of dry carbon tetrachloride was stirred for 12 hr. at room temperature with 2.2 cc. of redistilled sulfuryl chloride with protection from atmospheric moisture. The reaction mixture was poured into saturated sodium chloride solution and the product extracted with carbon tetrachloride. After washing with dilute sodium bicarbonate solution and water, drying, and evaporating, there was obtained a liquid residue which was chromatographed on 50 g. of silicic acid (Mallinckrodt analytical grade, washed with water and activated by heating for 24 hr. at 125°). Elution with pentane provided 356 mg. of solid, m.p. 56.5–58.5°, raised to 57–58.5° after sublimation at 0.1 mm. The infrared and ultraviolet properties, summarized in Tables II and III, clearly demonstrate the axial nature of the chlorine atom, as does the location[42] of the optical rotatory dispersion extrema (*c* 0.145 in methanol): $[\alpha]_{589}$ +162°, $[\alpha]_{335}$ +3980°, $[\alpha]_{287.5}$ −4323°, $[\alpha]_{260}$ −3056°. The n.m.r. spectrum showed no downfield proton signal, as would be expected from a 6-chloro isomer, while the position of the *t*-butyl signal was shifted from 1.00 p.p.m. in the halogen-free ketone to 1.18 p.p.m., thus showing that the chlorine atom was attached to the same carbon as the *t*-butyl group.

Anal. Calcd. for $C_{11}H_{19}ClO$: C, 65.13; H, 9.46; Cl, 17.51; O, 7.88. Found: C, 65.33; H, 9.43; Cl, 17.89; O, 8.19.

Dehydrochlorination was effected by heating for 19 hr. at 100° in a current of nitrogen in dimethylformamide solution with lithium bromide and lithium carbonate[24] and purifying the crude product by chromatography on silicic acid. Elution with hexane and sublimation at 0.1 mm. led to colorless crystals of **2-*t*-butyl-5-methylcyclohex-2-en-1-one (XII)**, m.p. 47–48.5°, $\lambda_{max}^{CHCl_3}$ 6.00 and 6.08 μ, λ_{max}^{MeOH} 234 mμ, log ε 4.00. The n.m.r. spectrum supported structure XII, since the *t*-butyl signal was shifted from 1.00 p.p.m. in the saturated ketone to 1.15 p.p.m., as would be expected if the *t*-butyl group were located on the double bond.

Anal. Calcd. for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.46; H, 11.11.

The red **2,4-dinitrophenylhydrazone of XII** was recrystallized from ethanol, whereupon it exhibited m.p. 150–152°, $[\alpha]_D$ −180° (*c* 0.01), $\lambda_{max}^{CHCl_3}$ 383 mμ, log ε 4.37.

Anal. Calcd. for $C_{17}H_{22}N_4O_4$: C, 58.94; H, 6.40. Found: C, 58.65; H, 6.83.

Attempts to effect dehydrochlorination of XI by heating for 20 min. in acetic acid with 2,4-dinitrophenylhydrazine[43] or for 7 min. at 150° with γ-collidine proved abortive.

(42) See C. Djerassi, J. Osiecki, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **80**, 1216 (1958).

(43) See C. Djerassi, *ibid.*, **71**, 1003 (1949).

16α-*t*-Butyl-Δ⁵-androsten-3β-ol-17-one (XIV).[26]—To 50 cc. of dry tetrahydrofuran was added 10.8 cc. of 3 *M* methylmagnesium bromide in ether and 10 mg. of cuprous chloride. To the stirred mixture cooled in ice was added a solution of 0.36 g. of 16-isopropylidene-Δ⁵-androsten-3β-ol-17-one (XIII) in 15 cc. of tetrahydrofuran at such a rate that the temperature of the reaction mixture did not rise above 4°. After stirring for an additional hour at 0° and for 5 hr. at room temperature, the mixture was poured into 100 cc. of 5% ammonium chloride and extracted with ether. Evaporation of the washed and dried ether extract, followed by crystallization from 95% ethanol, provided 0.23 g. of white shiny plates melting at 174–176° after structure change starting at 105°. One additional recrystallization provided the analytical specimen melting at 178° after crystal structure change accompanied by effervescence beginning at 109°; $\lambda_{max}^{CHCl_3}$ 2.8 and 5.83 μ, $[\alpha]_D$ +3° (*c* 1.1).

Anal. Calcd. for $C_{23}H_{36}O_2 \cdot {}^1/_2C_2H_5OH$: C, 78.42; H, 10.69. Found: C, 78.83; H, 10.61; mol. wt., 344 (mass spec. corresponding to unsolvated $C_{23}H_{36}O_2$).

Recrystallization from methanol provided the hemi-methanolate, m.p. 185–187°, with prior crystal change at 135°. The substance was unchanged after being heated under reflux for 1 hr. in 5% methanolic sodium methoxide, thus suggesting the α-configuration of the *t*-butyl substituent.[26]

Anal. Calcd. for $C_{23}H_{36}O_2 \cdot {}^1/_2CH_3OH$: C, 78.28; H, 10.62. Found: C, 77.95; H, 10.50.

16α-*t*-Butyl-Δ⁵-androstene-3β,17β-diol (XV).[44]—The above ketone XIV (0.3 g.) in 10 cc. of tetrahydrofuran was stirred at room temperature for 1 hr. with 0.25 g. of lithium aluminum hydride and the mixture was then heated under reflux for an additional hour. The excess reagent was decomposed by the cautious addition of water; dilute hydrochloric acid was then added and the aqueous phase was decanted from the resulting gum. Trituration of this gum with acetone effected crystallization and the rather insoluble solid was recrystallized from pyridine–water to give 0.18 g. of crystals, m.p. 265–266°, $[\alpha]_D$ −91° (*c* 0.65 in pyridine), which exhibited no carbonyl absorption in the infrared region.

Anal. Calcd. for $C_{23}H_{38}O_2$: C, 79.73; H, 11.06. Found: C, 79.75; H, 11.05.

16α-*t*-Butyltestosterone (XVI).[26,44]—The diol XV (0.41 g.), dry benzene (80 cc.), and aluminum isopropoxide (0.56 g.) were heated under reflux with stirring for 30 min.; acetone (8 cc.) was added and heating was continued overnight. Dilution with ether, washing with water, and evaporation gave an oily solid, which yielded 54 mg. of recovered starting diol XV upon trituration with acetone. The acetone-soluble fraction represented a mixture of two components, as determined by thin-layer chromatography, and was purified by chromatography on 20 g. of activity II neutral alumina. Elution with 10% ethyl acetate–90% benzene provided 160 mg. of solid, m.p. 200–205°, while the analytical specimen crystallized from dilute methanol, had m.p. 205–207°, $[\alpha]_D$ +72 (*c* 0.91 in pyridine), λ_{max}^{EtOH} 240 mμ, log ε 4.20; $\lambda_{max}^{CHCl_3}$ 2.85, 6.02, and 6.20 μ.

Anal. Calcd. for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 79.81; H, 10.59.

2α-*t*-Butylcholestan-2β-ol (XVIII).—A solution of 6.0 g. of cholestan-2-one (XVII) in 100 cc. of dry ether was added dropwise with stirring to 20 cc. of a 2.58 *M* ethereal solution of *t*-butylmagnesium chloride, which had been prepared from 7.2 g. of magnesium and 27.6 g. of *t*-butyl chloride and standardized by titration with hydrochloric acid. All operations were performed with exclusion of atmospheric moisture. At the end of the addition, the solution was poured into 100 cc. of 10% ammonium chloride solution, the ether phase drawn off and washed with water. Evaporation to dryness and chromatography of the residue on 275 g. of activity II alumina provided 0.812 g. of the desired alcohol XVIII (m.p. 129–133°) in the benzene eluates and 4.9 g. of recovered cholestan-2-one (XVII), which was removed subsequently with benzene. The above procedure was repeated twice with the recovered ketone to yield a total of 2.4 g. of addition product, which was recrystallized from acetone to give an analytical specimen melting at 136–137°, $[\alpha]_D$ +22° (*c* 1.1).

Anal. Calcd. for $C_{31}H_{56}O$: C, 83.71; H, 12.69. Found: C, 83.92; H, 12.57.

Dehydration of 2α-*t*-Butylcholestan-2β-ol (XVIII).—Thionyl chloride (0.2 cc.) was added to the tertiary alcohol XVIII (40 mg.) in 2 cc. of pyridine and the solution was left at room temperature for 3 hr., whereupon it was poured onto crushed ice and the product extracted with ether; yield 38 mg. Thin-layer chromatography indicated the absence of any starting material, the product moving with the solvent (benzene) front. No further purification was attempted, but the n.m.r. spectrum exhibited signals at 0.66 (C-18 methyl), 0.8 (C-26 and C-27), 0.9 (C-21), and especially at 1.0 p.p.m. (*t*-butyl group and C-19 methyl function) as well as olefinic proton signals at 5.35 and 5.62 p.p.m. all of them consistent with a mixture of Δ¹- and Δ²-*t*-butylcholestene (XIX).

Hydroboration of the Olefin Mixture XIX.—The crude olefin mixture XIX (450 mg.) was dissolved in 40 cc. of ether containing 1.5 g. of boron trifluoride etherate (47%) and a slurry of 0.3 g. of powdered lithium aluminum hydride in 20 cc. of ether was added dropwise. After stirring at room temperature for 1.5 hr., excess hydride was decomposed by the addition of a saturated, aqueous sodium sulfate solution, followed by anhydrous solid sodium sulfate. The mixture was filtered, the cake washed well with ether, and the filtrate evaporated to give 0.66 g. of a gum, which was stirred for 3 hr. in 20 cc. of 95% ethanol with 0.6 g. of sodium hydroxide and 1.3 cc. of 30% hydrogen peroxide. Dilution with water, extraction with ether, thorough washing with water, drying, and evaporation left 0.47 g. of gummy material, which was purified by chromatography on 50 g. of activity II alumina, elution being effected with benzene and each 5-cc. fraction being examined separately. The initially eluted oil (62 mg.) was not further examined, but subsequent fractions gave 240 mg. of crystals, m.p. 82–112°, which were rechromatographed on 60 g. of activity II alumina, elution being effected with 1:1 petroleum ether (b.p. 60–68°)–benzene, and 2-cc. fractions being collected.

The first crystalline material (10 mg.) represented thin-layer chromatographically pure **2β-*t*-butylcholestan-3α-ol (XXI)**, m.p. 129–131°, which furnished an analytical specimen upon recrystallization from methanol; m.p. 135–136°, $[\alpha]_D$ +74° (*c* 0.52).

Anal. Calcd. for $C_{31}H_{56}O$: C, 83.71; H, 12.69. Found: C, 83.90; H, 12.68.

Continued elution with the same solvent combination yielded a two-component mixture followed by 52 mg. of chromatographically pure **2α-*t*-butylcholestan-3β-ol (XX)**, m.p. 118–122°. Recrystallization from methanol led to solvated needles, m.p. 83–85° (effervescence), which resolidified and melted at 120–121°, $[\alpha]_D$ −1° (*c* 1.0).

Anal. Calcd. for $C_{31}H_{56}O \cdot {}^1/_2CH_3OH$: C, 82.11; H, 12.67. Found: C, 81.97; H, 12.38.

Finally, there was eluted 83 mg. of sirup, which crystallized from methanol to give 52 mg. of blunt prisms, m.p. 84–105°, which were presumed to be the isomeric 2-*t*-butylcholestan-1-ols. This material was oxidized directly in acetone solution[12] with chromium trioxide and the resulting gum heated under reflux for 3 hr. with 5% methanolic sodium methoxide solution. Crystallization from methanol provided 20 mg. of colorless needles which are assumed to be **2α-*t*-butylcholestan-1-one (XXIV)**, m.p. 133–135° (with sintering at 130°), $\lambda_{max}^{CHCl_3}$ 5.90 μ, $[\alpha]_D$ +36° (*c* 0.25); R.D. (*c* 0.063 in methanol): $[\Phi]_{589}$ +141°, $[\Phi]_{310}$ −774°, $[\Phi]_{270}$ +4770° (infl.), $[\Phi]_{240}$ +5200°; C.D.[45] in methanol (1.62 g./l.): $[\theta]_{350}$ 0, $[\theta]_{305}$ −2540, $[\theta]_{250}$ 0.

Anal. Calcd. for $C_{31}H_{54}O$: C, 84.09; H, 12.29. Found C, 83.90; H, 12.37.

2β-*t*-Butylcholestan-3-one (XXII).—To a solution of 10 mg. of 2β-*t*-butylcholestan-3α-ol (XXI) in 3 cc. of acetone was added dropwise 8 *N* chromium trioxide reagent[12,13] until the orange color persisted for 1 min. The mixture was then poured into saturated aqueous sodium bicarbonate solution and the product extracted with benzene. Evaporation of the washed benzene solution led to 8 mg. of crystalline solid, m.p. 119–122°, which was recrystallized from methanol to furnish colorless needles of the ketone XXII, m.p. 120–121.5°, $\lambda_{max}^{CHCl_3}$ 5.90 μ, $[\alpha]_D$ +146° (*c* 0.14 in methanol). Its n.m.r. spectrum exhibited methyl proton signals at 0.68, 0.81, 0.91, and 0.98 p.p.m., the latter also including the *t*-butyl protons.

Anal. Calcd. for $C_{31}H_{54}O$: mol. wt., 442. Found: mol. wt., 442 (mass spec.).

2α-*t*-Butylcholestan-3-one (XXIII).—Similar oxidation of the 2α-*t*-butyl-3β-alcohol XX led to the 2α-*t*-butyl-3-ketone XXIII, which could be obtained more conveniently by oxidizing the unseparated mixture of alcohols XX and XXI from the hydroboration and equilibrating by heating under reflux with methanolic sodium hydroxide solution. Recrystallization from methanol gave colorless needles, melting at 131–132°, $\lambda_{max}^{CHCl_3}$ 5.92 μ, $[\alpha]_D$ +3° (*c* 1.0); n.m.r. methyl proton signals at 0.68, 0.81, 0.91, 0.98 (*t*-butyl), and 1.03 (C-19 methyl) p.p.m.

Anal. Calcd. for $C_{31}H_{54}O$: C, 84.09; H, 12.29. Found: C, 84.24; H, 12.20.

(44) We are assuming the 17β-orientation of the alcohol function by analogy to the course of the lithium aluminum hydride reduction of ordinary 17-keto steroids. It is conceivable, however, that the bulky 16α-*t*-butyl substituent (ref. 26) may direct approach of the reagent from the top side, in which case the diol XV and the testosterone derivative XVI actually possess the α-configuration.

(45) For circular dichroism nomenclature and mode of recording results, see C. Djerassi and E. Bunnenberg, *Proc. Chem. Soc.*, 299 (1963).

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 $[\Phi]_{313}^{trough}$ +1230°, $[\Phi]_{274}^{trough}$ −856°, while that from the 2α-isomer showed $[\Phi]_{315}^{trough}$ +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.

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[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

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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).

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(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).