TABLE XI

MOLECULAR ROTATIONS OF HYDROXYTETRAHYDROPYRANS AND METHYL GLYCOSIDES

Hydroxytetrahydropyran	[M]D Calcd.	[M]D Obsd.[a]	[M]D of methyl glycoside Calcd.	[M]D of methyl glycoside Obsd.[a]
β-D-Ribose	− 45	− 35		
α-D-Xylose	+145	+141	+250	+253
β-D-Xylose	− 45		−150	−108
α-D-Arabinose	−105	−116	0	− 28
β-D-Arabinose	−295	−286	−400	−403
β-D-Lyxose	−105	−109		
1,5-Anhydro-D-arabitol	−150	−132		
2-Deoxy-β-D-xylose	− 45	− 34		
α-D-Glucose	+220	+202	+325	+309
β-D-Glucose	+ 30	+ 34	− 75	− 66
α-D-Mannose	+ 25	+ 53	+130	+154
β-D-Mannose	− 30	− 31	−135	−135
α-D-Galactose	+270	+272	+375	+380
β-D-Galactose	+ 80	+ 95	− 25	0
α-D-Gulose	+135	+115		
β-D-Gulose	− 55		−160	−162
β-D-Allose	+ 30	0		
α-D-Talose	+ 75	+122		
β-D-Talose	+ 20	+ 24		
1,5-Anhydro-D-				
sorbitol	+ 75	+ 70		
galactitol	+125	+126		
mannitol	− 75	− 83		
talitol	− 25	− 19		
2-Deoxy-				
α-D-glucose	+130		+235	+247
β-D-glucose	+ 30		− 75	− 85
α-D-galactose	+180		+285	+303
β-D-galactose	+ 80	+ 67	− 25	0
3-Deoxy-				
α-D-galactose	+180		+285	+254
6-Deoxy-				
α-D-glucose	+195	+120	+300	+271
β-D-glucose	+ 5		−100	− 98
α-D-mannose	0	+ 16	+105	+111
β-D-mannose	− 55	− 63	−160	−170
α-D-galactose	+245	+251	+350	+351
β-D-galactose	+ 55		− 50	− 29
α-D-allose	+195		+302	+ 96
β-D-allose	+ 5	− 20	−100	−109
1,2-Dideoxy-D-				
glucose	+ 30	+ 24		
galactose	+ 80	+ 62		

[a] References given in Whiffen's paper.[5]

These constants have been used to calculate rotations for the fifty-three carbohydrates and derivatives considered by Whiffen[5] (Table XI). The agreement of calculated and observed values is, on the whole, satisfactory; here, as in Whiffen's hands, α-methyl-6-deoxy-D-alloside gave very poor agreement. The average deviation in the present calculations is 14°, roughly 11% of the average rotation of 130°; Whiffen's values give an average deviation of 11.4° which is roughly 9% of the average rotation. It must be concluded that a wide range of constants can be used in this series *when it is considered alone.* Whiffen's constants probably lie at one end of this range and the present constants at the other end; while his constants give somewhat better results than those used here, the use of the present constants allows this series to become a part of the broader picture being developed in these papers.

LAFAYETTE, IND.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

The Optical Activity of Endocyclic Olefins[1]

BY JAMES H. BREWSTER

RECEIVED SEPTEMBER 2, 1958

It is shown that the principles of conformational and atomic asymmetry lead directly to the empirical Mills rules for alkyl- and hydroxycyclohexenes. These rules should be applicable to cyclohexenes with other substituents and to cyclopentenes. The use of three empirical rotation constants (with constants taken from part I) permits calculation of the sign and magnitude of rotation of the terpenes of the cyclohexene and pinene series and permits qualitative predictions of the rotatory effects resulting from introduction of double bonds into the steroid nucleus.

Large rotations and rotational shifts are observed in the cycloölefin series; under the present picture of optical activity the size of these effects is taken as testimony to the high polarizability of the double bond and to the rigidity of asymmetric conformations in ring compounds. It is shown in the present paper that the principles of atomic and conformational asymmetry permit direct prediction of the *sign* of major rotatory effects in this series and allow reasonably close correlation of the *magnitudes* of these effects by use of empirical rotation constants. The fact that principles which can be used to account for the rotatory properties of open-chain compounds (part I) and saturated alicyclic compounds (part II) can be applied successfully to this series is evidence that the present picture of optical activity is not grossly oversimplified.

Cyclopentene is presumably planar and so, of itself, optically inactive.[2] A substituent adjacent to the double bond and in configuration I produces two asymmetric conformations (IIa and IIb) which determine the optical activity of I. Since IIa includes the double bond as an integral part of the conformation, it should have a greater rotatory power than IIb. If the substituent is more polarizable than hydrogen, IIa will be dextro-

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(1) A Useful Model of Optical Activity, Part III.

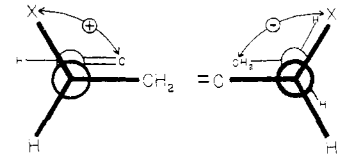
(2) The simplest puckered form of cyclopentene, in which the 4-carbon atom is out of the plane of the other four atoms, is symmetrical and so also optically inactive.

rotatory as, accordingly, will I.[3] This conclusion is supported by the dextrorotation of 3-methylcyclopentene (k in Table I) in this configuration[4] and by the demonstration[5] that (+)-chaulmoogric acid (d, in Table I), (+)a, (+)b and (+)c all have configuration I. It has been suggested[5] that since the other acids of Table I are biologically related to (+)-chaulmoogric acid,[6] they, too, have this configuration. In terms of the present work, any other conclusion would be incredible.

TABLE I

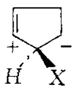
MOLECULAR ROTATIONS OF CYCLOPENTENE DERIVATIVES

	R	$[M]_D$		R	$[M]_D$
a	$-CH_2CH_3$	$+118^5$	g	$-(CH_2)_8CO_2H$	$+173^6$
b	$-CH_2CH_2OH$	$+143^5$	h	$-(CH_2)_6CO_2H$	$+178^6$
c	$-CH_2CO_2H$	$+137^5$	i	$-(CH_2)_4CO_2Et$	$+119^{6}$*
d	$-(CH_2)_{12}CO_2H$	$+173^{5,6}$	j	$-CO_2Et$	$+60^{6}$*
e	$-(CH_2)_{10}CO_2H$	$+174^6$	k	$-CH_3$	$+64^4$
f	$-(CH_2)_6CH{=}CH(CH_2)_4CO_2H$	$+169^6$			

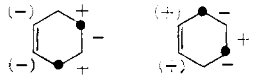


a b

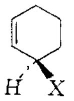
II



I

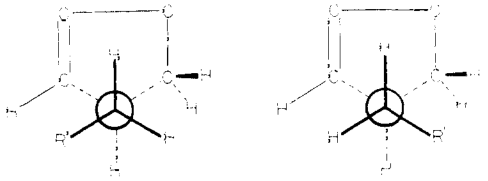


a III b



IV

It is to be expected, from part I, that compounds with flexible chains will have larger rotations than does methylcyclopentene. Of the two "allowed" conformations about the bond linking the chain to the ring, the dextrorotatory one (Va) should have the greater rotatory power. Assuming the two conformations are present in equal amounts, we predict that the ethyl compound (a, Table I) should have a rotation 40° greater than that of the methyl compound (k, Table I) while the carboxymethyl compound (c, Table I) should have a rotation 60° greater. Such deviations from these predictions as are found are consistent with the view that the less crowded conformation (Va) predominates.



a V b

R' = CH_3, $\Delta[M] = +140$ $\Delta[M] = -60$

R' = CO_2H, $\Delta[M] = +210$ $\Delta[M] = -90$

Similar principles should apply in the cyclohexene series, where a 3-substituent in configuration IV produces conformations that are only slightly skewed forms of IIa and IIb.[7] To a first approximation, the rotatory effect of such a substituent will be equivalent to that which it shows in the cyclopentene series.[7] We can predict, thus, that a compound having configuration IV will be more dextrorotatory than its epimer when the substituent is more polarizable than hydrogen.[8] This statement is simply a more general form of one of the empirical rules of Mills.[9] It will be recalled that this rule was invoked in part I to account for the rotatory properties of α-hydroxy and α-amino acids.

The present treatment suggests that this rule should be quantitative. The change in $[M]_D$ accompanying the introduction of a *semi-axial* allylic substituent to form IV can be expressed

$$\Delta_{(X-H)} = k(X - H)(C^*{=}C^* - C) \pm A_X$$

where A_X is the atomic asymmetry contribution (positive except when X is CO_2H or F).[3] When the substituent is semi-equatorial, the change in rotation can be expressed

$$\Delta_{(X-H)} = k'(X - H)(C^*{=}C^* - H) \pm A_X$$

In this case the bond from the ring to the substituent is essentially coplanar with one of the saturated bonds of the ring (hence the term: $C^*{=}C^*$—H) and is nearly coplanar with the double bond (whence the term k'). It is found empirically that a value of +130° is suitable for either case when X = CH_3 (A_X = 0) and is, very roughly, suitable for use with cyclopentene derivatives. On this

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(3) A dextrorotatory atomic asymmetry effect will also occur when the substituent is more polarizable than the vinyl group (*e.g.*, Br, Cl) or less polarizable than the methyl group (*e.g.*, OH, NH_2) (see part I, Table I). Both the conformational and atomic asymmetry effects should be levorotatory when the substituent is less polarizable than hydrogen (*e.g.*, F). The two effects are opposed only when the substituent lies between the vinyl and the methyl group in polarizability (*e.g.*, CO_2H). Throughout this work it is assumed that the phenyl carbon and vinyl carbon will have the same polarizability; on these grounds, the magnitude of the atomic asymmetry effect can be estimated by noting the molecular rotation of the appropriate α-phenylethyl derivative (see part I, Table II).

(4) M. Mousseron, R. Richaud and R. Granger, *Bull. soc. chim. France*, [5] **13**, 222 (1946). Prepared from (+)-3-methylcyclopentanone, which, in turn, has been related to (+)-3-methylcyclohexanone [O. Wallach, *Ann.*, **289**, 337 (1896); **332**, 337 (1904); N. Zelinsky, *Ber.*, **35**, 2488 (1902)].

(5) K. Mislow and I. V. Steinberg, THIS JOURNAL, **77**, 3807 (1955).

(6) H. I. Cole and H. T. Cardozo, *ibid.*, **60**, 612 (1938); **61**, 2349 (1939).

(7) The substituents adjacent to the double bond can assume "semi-equatorial" and "semi-axial" orientations which may be energetically different if the substituent is large enough. In a more refined treatment separate rotation constants would be assigned for the cyclopentenes and the two conformational isomers found in cyclohexene derivatives. This does not seem worthwhile at present.

(8) This generalization is, in principle, subject to three restrictions. An atomic asymmetry effect may oppose the conformational asymmetry effect when C=C > X > CH_3 in polarizability[3]; should this effect be dominant, the rule would be in error. This generalization applies to the rotatory effect of the *attachment atom* of the substituent. If the substituent itself is optically active (because the ring provides a sterically asymmetric environment or because the atom in question is part of a fused ring) then epimerization may produce additional rotatory shifts; it will be seen below that an isopropyl substituent would suffer reversal of its rotatory contribution on such epimerization. Finally the cyclohexene ring itself, in the two semi-chair conformations IIIa and IIIb, is optically active (see below); if the epimerization produces inversion of the ring conformation, the rotational shift can be in the opposite direction. Care should be used, then, when the epimers being compared have carbonyl substituents, have substituents which may show conformational asymmetry of their own, or have enantiomorphic ring conformations.

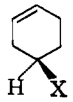
(9) J. A. Mills, *J. Chem. Soc.*, 4976 (1952). The Mills rules, strictly speaking, apply only to cyclohexenes with alkyl, hydroxy or acyloxy substituents, these being the only classes of compound considered by Mills.

basis the predicted rotation change for the formation of IV from cyclohexene becomes

$$\Delta_{(X-H)} = \frac{k(X-H)(C-H)}{k(C-H)(C-H)}\ 130 \pm A_X$$

where the necessary values can be obtained from Tables I and II of part I. The predicted values for $\Delta_{(X-H)}$ are shown in Table II. On the whole, they give satisfactory predictions of rotation changes in allylic steroid derivatives.[10] Major discrepancies are noted with the androst-4-ene-3,-17β-diols (VIII) (which might be due to a low [M]D for androst-4-ene-17β-ol, since the difference in rotation of the epimeric 3-ols is of the right order of magnitude) and the 7β-bromo- and 7-aminocholesterols (X). It is clear, from the discussion of cyclopentenes with flexible chains (see V), that discrepancies are to be expected when the substituent is flexible and especially when it has a highly polarizable group. In general this additional conformational asymmetry will increase the magnitude of $\Delta_{(X-H)}$, particularly when the conformation corresponding to Vb is strained by the presence of a substituent on the ring (as in the 7-substituted cholesterols, X). These effects are strikingly evident throughout this series.

Further tests of this point can be made by use of rotatory data for the olefinic terpenes. Assignments of absolute configuration to the monocyclic terpenes depend, first, on a demonstration that menthone has a *trans* configuration,[11] next, on a correlation of one of the asymmetric centers with glyceraldehyde[12]; and, finally, on a network of correlations within the terpene series itself.[13] We require first an estimate of the rotatory properties of the two semi-chair forms of cyclohexene (IIIa, IIIb).[14] The sign of the expected rotatory contribution of each bond is shown in IIIa and IIIb.[15] The principles presented in part II suggest that an empirical estimate of the magnitude of this ring asymmetry effect can be made. A 4-alkylcyclohexene in configuration XII will exist mainly with the substituent in the equatorial orientation[14] and, therefore, with the ring in conformation IIIa. *Since an equatorial substituent will have virtually no other rotatory effect* (see part II), *the rotations of such compounds should be equivalent simply to that of IIIa and should be essentially independent of the nature of the substituent.* As seen in Table II, a number of terpenes are strongly dextrorotatory in configuration XII and have very nearly the same rotation despite an appreciable variation in the nature of the substituent. The rounded average of these values, +160°, will therefore be taken as the empirical rotation of IIIa[16]; this value is reasonable in size.[15]



XII

When the 4-substituent is axial in configuration XII it forms a dextrorotatory conformation with the nearest unsaturated atom ([M]D +140°) and a levorotatory conformation with a saturated atom on the other side ([M]D −60°) (see Table I, part I). The net rotatory change resulting from the introduction of this substituent is thus Δ[M]D +80°. It follows that a compound having a substituent in configuration XII will be more dextrorotatory than its epimer (*when the ring conformation is the same in both compounds* (substituent effect) or *when the substituent is equatorial in both compounds*) (see Fig. 1). This statement (without the parenthetical qualifications) is equivalent to the

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(10) The configurations of the alcohols appear to be rigorously established (see H. Schaltegger and F. X. Müllner, *Helv. Chim. Acta*, **34**, 1096 (1951), H. Heymann and L. F. Fieser, *ibid.*, **35**, 631 (1952) and W. Klyne, *ibid.*, **35**, 1224 (1952) for references). It should be noted that the trivial indices applied to the 7-substituted cholesterols in earlier papers are to be reversed in accord with the findings of Heymann and Fieser. Schaltegger and Müllner showed that the more levorotatory of the 7-bromocholesterols is the more stable and suggested on these grounds that it has the β (equatorial) configuration. An inspection of models shows, however, that an equatorial bromine atom is badly crowded by C_{15}, this crowding being absent in the axial isomers. On these grounds, the assignments of configuration by Schaltegger and Müllner should be reversed, as shown in X.

(11) This relationship was first deduced by use of the Auwers–Skita rules and from data on the relative stability of the epimeric menthones and carvomenthones [for a review see N. L. McNiven and J. Read, *J. Chem. Soc.*, 153, 159 (1952)] and was placed on a firmer basis by studies of the quasi-racemates formed in the mono-alkyl succinic acid series [A. Fredga and J. K. Miettinen, *Acta Chem. Scand.*, **1**, 371 (1947); A. Fredga, *ibid.*, **3**, 208 (1949)]. The issue was settled by direct chemical correlation of the optically active β-alkyl adipic acids derived from pulegone and 1-menthene [K. Freudenberg and W. Lwowski, *Ann.*, **587**, 213 (1954)].

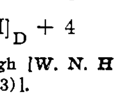
(12) This relationship was deduced by J. F. Lane, *Science*, **113**, 577 (1951), on mechanistic grounds and by Fredga[11] by studies of quasi-racemates. An unequivocal relationship has been established *via* degradations of *cis*-3-hydroxycyclohexanecarboxylic acid [D. S. Noyce and D. B. Denney, THIS JOURNAL, **74**, 5912 (1952); **76**, 768 (1954); D. S. Noyce and J. H. Canfield, *ibid.*, **76**, 3630 (1954); see also H. L. Goering and C. Serres, *ibid.*, **74**, 5908 (1952)].

(13) *Cf.* W. Hückel, *J. prakt. Chem.*, **157**, 225 (1941) (the absolute configurations shown by Hückel must be reversed) and A. J. Birch, *Ann. Reports* (*Chem. Soc.*), **47**, 191 (1950); see also J. L. Simonsen, "The Terpenes," Cambridge University Press, Cambridge, Vol. I, 1947; Vol. II, 1949, for individual correlations within this series.

(14) The dark circles represent axial and semi-axial hydrogen atoms above the plane of the ring. It is important to note that ring atoms 4 and 5 have essentially the geometry of cyclohexane ring atoms, while atoms 3 and 6 more closely resemble the ring atoms of cyclopentene and can at most be described as having semi-axial and semi-equatorial substituents. It is assumed that the rotatory effects of semi-axial and semi-equatorial substituents are identical but that a large substituent will show some preference for a semi-equatorial orientation.

(15) A ring bond next to the double bond is only slightly skewed, but the double bond itself is part of the asymmetric conformation. The sign of rotation can be predicted, but not the magnitude, hence the parentheses. The next most distant bonds are strongly skewed and, assuming the equivalence of phenyl and vinyl carbon atoms,[8] should have rotatory powers of +140° in IIIa and −140° in IIIb (see Table I, part I). Note the presence of two such bonds in each ring conformation. The remaining bond is equivalent to a ring bond of cyclohexane and should contribute −60° to the rotation of IIIa, +60° to that of IIIb. These three bonds contribute, then, +220° to the rotation of IIIa and −220° to IIIb; since it is doubtful that the other bonds will be strongly optically active it seems safe to predict that IIIa will be dextrorotatory, possibly strongly so, and that IIIb will be correspondingly levorotatory.

(16) In the present picture a saturated substituent attached to one of the unsaturated atoms will have little effect on the rotatory properties *of the ring itself*. This point requires further study, however, since sylvesterpineol is reported to have a very low rotation even though



$[M]_D + 4$

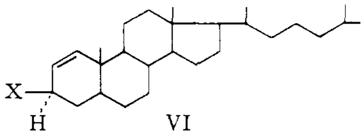
its optical purity is quite high [W. N. Haworth and W. H. Perkin *J. Chem. Soc.*, **103**, 2225 (1913)].

TABLE II

PREDICTED ROTATORY EFFECT OF ALLYLIC SUBSTITUENTS IN THE CONFIGURATION

X	$\frac{k(X-H)(C-H)}{k(C-H)(C-H)}$ 130[a]	A_x[b]	Δ(X − H)[c]
I	542	250 (est.)	790
Br	390	184	570
SH	379	146	530
Cl	369	144	510
C=C	303	0	300
CO_2H	195	−122	70
CH_3	130	0	130
NH_2	119	49	170
OH	108	53	160

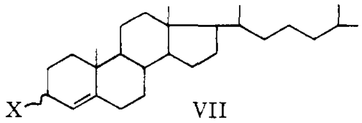
[b] [a] Values for k(X − H) (C − H) from Table I, part I. Values for appropriate α-phenethyl derivatives; from Table II, part I. [c] Rounded to nearest 10.°



VI

X	[M]D (chf.) Obs.	[M]D (chf.) Calcd.[a]
H	+44,[b] +48[c]	
3β-OH	+212[c]	+206
-OAc	+248[c]	
−OBz	+465[c]	
3β-Cl	+405[c]	+556

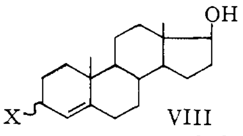
[a] By addition of values from Table II to +46, the mean of the two values cited for cholest-1-ene. [b] R. B. Turner, W. R. Meador and R. E. Winkler, THIS JOURNAL, **79**, 4122 (1957). [c] H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 3289 (1956).



VII

X	[M]D 3α Obsd.	3α Calcd.[e]	3β Obsd.	3β Calcd.[e]
H	+244[a]		+244[a]	
OH	+445[b]	+404	+177[b]	+ 84
OAc	+760[b]		+ 43[b]	
OCH_3	(+280)[b]		+164[b]	
NH_2		+414		+ 74
NHAc	+400[d]		+ 26[c]	
Cl		+754	−110[b]	−266

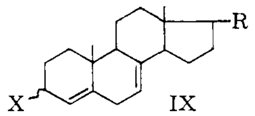
[a] See VIb. [b] C. W. Shoppee, B. D. Agashe and G. H. R. Summers, *J. Chem. Soc.*, 3107 (1957). [c] R. A. B. Bannard and A. F. McKay, *Can. J. Chem.*, **33**, 1166 (1955). [d] C. W. Shoppee, D. E. Evans, H. C. Richards and G. H. R. Summers, *J. Chem. Soc.*, 1649 (1956). [e] By addition of values from Table II to +244, the [M]D of cholest-4-ene. [f] Probably not pure (*b*).



VIII

X	[M]D Obsd.	[M]D Calcd.
H	129[a] (alc.)	
3α-OH	543[b] (pyr.)	289
3β-OH	141[b] (alc.)	−31
Δα − β	402	320

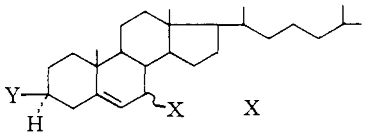
[a] Huang-Minlon, THIS JOURNAL, **71**, 3301 (1949). The present treatment suggests that this value is much too low and should be about 340. This product may contain some (? much) Δ^3-17β-ol: *cf.* G. Lardelli and O. Jeger, *Helv. Chim. Acta*, **32**, 1817 (1949). The value 129 is used in the calculations. [b] A. Butenandt and A. Heusner, *Ber.*, **71**, 198 (1938).



IX

X	[M]D R = C_8H_{17} Obsd.	R = C_8H_{17} Calcd.	R = $C_9H_{17}(\Delta^{22})$ Obsd.	R = $C_9H_{17}(\Delta^{22})$ Calcd.
3α-OH	308[a]		151[b]	
3β-OH	38[a]		−143[c]	
Δα-β	270	320	294	320

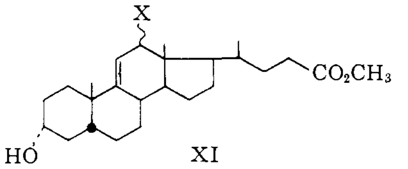
[a] A. Windaus and O. Kaufmann, *Ann.*, **542**, 218 (1939). [b] A. Windaus and K. Buchholz, *Ber.*, **71**, 576 (1938). [c] *Idem.*, *ibid.*, **72**, 597 (1939).



Y	X	[M]D 7α Obsd.	7α Calcd.[aa]	7β Obsd.	7β Calcd.[aa]
OH	H	− 154[a]		−154[a]	
	OH	− 351[b]	− 364	+ 28[b]	+ 56
	OCH_3	− 530[b]		+ 96[b]	
	OAc	− 860[b]		+325[b]	
	OC_6H_5			+532[b]	
	OBz	−1017[b]		+563[b]	
	NH_2	−1350[c]	− 379	+727[c]	+ 71
		−1395[d]		+822[d]	
	NHAc	− 860[c]		+377[c]	
		− 797[d]		+359[d]	
	SH	− 763[e]	− 859		+551
	SCN	−1330[f]		−292[f]	
OAc	H	− 188[a]		−188[a]	
	OH	− 392[b]	− 398	− 22[b]	+ 22
	OCH_3	− 569[b]		+ 83[b]	
	OAc	− 857[b]		+253[b]	
	OC_6H_5			+433[b]	
	OBz	− 968[b]		+450[b]	
	Cl	− 765[b]	− 868		
	Br	−1245[b]	− 938		
	I	−2015[b]	−1228		
OBz	H	− 74[a]		− 74[a]	
	OH	− 258[b]	− 284	+ 71[b]	+136
	OCH_3	− 177[b]		+203[b]	
	OAc	− 665[b]		+417[b]	
	OC_6H_5			+665[b]	
	OBz	− 649[b]		+575[b]	
	Cl	− 625[b]	− 754	+320[b]	+606
	Br	− 983[b]	− 824		
		−1050[g]		+114[g]	+676
	I	−1670[b]	−1114		
Cl	H	− 107[h]			
	Cl	− 725[i]	− 787		
	Br	−1080[i]	− 857		
Br	H	− 103[h]			
	Br	−1050[i]	− 853		

[aa] Values for Δ_{X-H} obtained by adding appropriate values from Table I, part I, to values in Table II to take into account asymmetric conformations with C_{14}. [a] D. H. R. Barton and J. D. Cox, *J. Chem. Soc.*, 783 (1948). [b] H. B. Henbest and E. R. H. Jones, *ibid.*, 1798 (1948). [c] J. Barnett, B. E. Ryman and F. Smith, *ibid.*, 524 (1946). [d] C. W.

Shoppee, R. J. W. Cremlyn, D. E. Evans and G. H. R. Summers, *ibid.*, 4364 (1957). [e] E. Frederiksen and S. Liisberg, *Chem. Ber.*, **88**, 684 (1955). [f] K. Abildgaard-Elling, British Patent 714,624 (1954) [*C.A.*, **49**, 14042 (1955)]. [g] H. Schaltegger and F. X. Müllner, *Helv. Chim. Acta*, **34**, 1096 (1951). [h] A. F. Wagner, N. E. Wolff and E. S. Wallis, *J. Org. Chem.*, **17**, 529 (1952). [i] S. Bernstein, K. J. Sax and Y. SubbaRow, *ibid.*, **13**, 837 (1948).

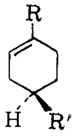

XI

X	$[M]_D$			
	3α-OH		3α-OAc	
	Obsd.	Calcd.[a]	Obsd.	Calcd.[a]
H	+179 (MeOH)		+240	
α-OH	+400 (MeOH)	+389	+446 (MeOH)	+450
α-Cl	+640	+859	+717	+920
α-Br	+985	+929		
β-OH	+125[b] (MeOH)	+ 19		

[a] A 12α-substituent is semi-axial and shows positive conformational asymmetry with C_{17}; the calculated $\Delta(X-H)$ values are, then: OH +210, Cl +680, Br +750. A 12β-substituent should show only the effects given in Table II. [b] V. R. Mattox, R. B. Turner, B. F. McKenzie, L. L. Engel and E. C. Kendall, *J. Biol. Chem.*, **173**, 283 (1948); all other data: V. R. Mattox, R. B. Turner, L. L. Engel, B. F. McKenzie, W. F. McGuckin and E. C. Kendall, *ibid.*, **164**, 569 (1946). See also, B. F. McKenzie, V. R. Mattox and E. C. Kendall, *ibid.*, **175**, 249 (1948).

TABLE III

MOLECULAR ROTATIONS OF 4-ALKYLCYCLOHEXENES



	R	R′	$[M]_D$	Ref.
1-Menthene	$-CH_3$	$-CH(CH_3)_2$	+161°	[a]
3-Menthene	$-CH(CH_3)_2$	$-CH_3$	+153	[b]
Limonene	$-CH_3$	$-\overset{\overset{\textstyle CH_2}{\|}}{C}-CH_3$	+169	[c]
α-Terpineol	$-CH_3$	$-C(OH)(CH_3)_2$	+155	[d]
Phellandrol	$-CH_2OH$	$-CH(CH_3)_2$	+167	[e]
Perillyl alcohol	$-CH_2OH$	$-\underset{\underset{\textstyle CH_2}{\|}}{C}-CH_3$	+148	[f]

[a] Prepared by catalytic hydrogenation of (+)-limonene [G. Vavon, *Bull. soc. chim. France*, [4] **15**, 282 (1914); J. von Braun and G. Werner, *Ber.*, **62**, 1057 (1929)] and by sodium reduction of (+)-α-phellandrene [F. W. Semmler, *ibid.*, **36**, 1033, 1749 (1903)]; the (−)-isomer has been prepared from (+)-carvone *via* (−)-carvomenthone and (−)-neocarvomenthylamine [W. Huckel and E. Wilip, *J. prakt. Chem.*, **158**, 21 (1941)]. Both (+)-1-menthene and (+)-α-phellandrene have been degraded to (+)-isopropylsuccinic acid [*cf.* A. Fredga, ref. 11; T. A. Henry and H. Paget, *J. Chem. Soc.*, 70 (1928)]; (+)-1-menthene has been degraded to (+)-β-isopropyladipic acid [*cf.* J. von Braun and G. Werner, above], the absolute configuration of which has been established by the work cited in ref. 11 and 12. [b] Prepared from (−)-menthone [*cf.* N. L. McNiven and J. Read, *J. Chem. Soc.*, 153 (1952), for a review], in turn prepared from (+)-pulegone [E. Beckmann and M. Pleissner, *Ann.*, **262**, 1 (1891)], from which (+)-3-methylcyclohexanone and (+)-β-methyladipic acid [O. Wallach, *Ann.*, **289**, 337 (1896)] can be obtained. The absolute configuration of the last named substance is shown by the work cited in ref. 12. [c] The absolute configuration of this substance follows from its relation to (+)-1-menthene (see *a*). [d] Prepared by hydration of (+)-limonene; can be dehydrated to (+)-limonene [*cf.* A. T. Fuller and J. Kenyon, *J. Chem. Soc.*, **125**, 2304 (1924)]. The following derivatives have been prepared by these workers; formate, $[M]_D$ +161°; acetate, $[M]_D$ +157°; propionate, $[M]_D$ +158°; butyrate, $[M]_D$ +158°; valerate, $[M]_D$ +155° (all homogeneous); phenylurethan, $[M]_D$ +112°; hydrogen phthalate, $[M]_D$ +110° (both in chloroform.) [e] The (−)-alcohol is formed by reduction of the (−)-aldehyde; the (−)-aldehyde has been oxidized to (−)-β-isopropyladipic acid (see *a*) [G. Burger and A. K. Macbeth, *ibid.*, 145 (1946)]. The following derivatives have been prepared from the (−)-alcohol: *p*-nitrobenzoate, $[M]_D$ −172°; 3,5-dinitrobenzoate, $[M]_D$ −173°; hydrogen phthalate, $[M]_D$ −164°; phenylurethane, $[M]_D$ −164°; α-naphthylurethan, $[M]_D$ −170° [J. P. E. Human, A. K. Macbeth and H. J. Rodda, *ibid.*, 350 (1949)]. [f] The (+)-alcohol is formed by selenium dioxide oxidation of (+)-limonene [H. Schmidt, *Chem. Ber.*, **83**, 193 (1950)]. The (−)-alcohol is formed by Ponndorf reduction of (−)-perilla aldehyde and forms a (−)-acetate ($[M]_D$ −146°) (Schmidt). The (−)-chloride, from alcohol with $[M]_D$ −103°, has a reported $[M]_D$ −101° [F. W. Semmler and B. Zaar, *Ber.*, **44**, 52 (1911)]; using Schmidt's value for the alcohol, this corresponds to $[M]_D$ −145°. The (−)-chloride has been reduced to (−)-limonene, $[M]_D$ −70°; this corresponds to a rotation of $[M]_D$ −350° for the chloride, which seems high.

second of Mills' empirical rules,[9] but more general. The qualifications given suggest that some caution be used in applying this rule to enantiomorphs and even to epimers if it is likely that the substituent is axial in both compounds.

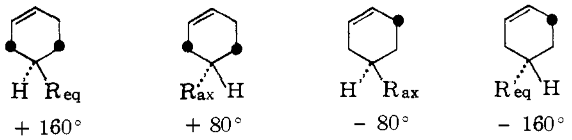
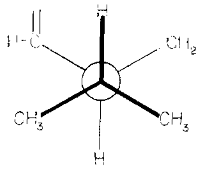


Fig. 1.—Estimated molecular rotations of individual conformations of 4-alkylcyclohexenes.

We are now in a position to attempt to calculate the sign and magnitude of rotation of the terpene olefins having two asymmetric centers. The 2-menthenes (*trans*, XIV; *cis*, XV) are shown with their rings in conformation IIIb (−160°) and the isopropyl groups in the semi-equatorial orientation.[17] In the *trans* isomer shown, the two alkyl groups make similar dextrorotatory contributions (+130° each) while in the *cis* isomer these contributions are opposed and cancel. Models show clearly that the isopropyl group will be predominantly in the conformation shown in XIII and so contribute +80° in each case. Here, where configurations are reliably established,[17] there is excellent agreement of calculated and observed results. The cryptols (XVI, XVII)[18] should be

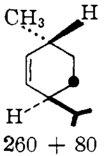
(17) The (+) *trans* olefin has been obtained from (−) menthone *via* (−) menthylamine, while the (−) *trans* olefin has been obtained from (−) carvomenthone. The (+) *cis* olefin has been obtained from (−) piperitone *via* (+) *iso*menthone and (+) *iso*menthylamine [(+) isomenthone and (−) menthone are C_4 epimers]. [N. L. McNiven and J. Read, *J. Chem. Soc.*, 153, 159 (1952).] The absolute configurations of the menthones and carvomenthones have rigorously been established (references 11, 12).

(18) Ponndorf reduction of (−)-cryptone gives (−)-*trans*- and (+)-*cis*-cryptol (the enantiomorphs of XVI and XVII, respectively). Relative configurations were assigned by reduction of these alcohols to the corresponding 4-isopropylcyclohexanols, configurations being assigned here on the basis of the Auwers–Skita rule, relative rates of saponification of esters (*trans* > *cis*) and the formation of the *trans*-alcohol by sodium–alcohol reduction of the ketone [R. G. Cooke, D. T. C. Gillespie and A. K. Macbeth, *ibid.*, 518 (1939); D. T. C. Gillespie, A. K. Macbeth and J. A. Mills, *ibid.*, 996 (1948)]. (−)-Cryptone has been oxidized to (+)-α-isopropylglutaric acid [A. R. Penfold and J. L. Simonsen, *ibid.*, 403 (1930)] which has been related to (−)-isopropylsuccinic acid [A. Fredga and J. K. Miettinen, *Acta Chem. Scand.*, **1**, 371 (1947)] whence, from the work cited in ref. 11 and 12, the absolute configuration at C_4 is established.

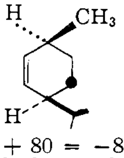


$$\Delta[\mathrm{M}] = k(\mathrm{C}-\mathrm{H})(\overset{\mathrm{C}}{\overset{\|}{\mathrm{C}}}-\mathrm{H}) - k(\mathrm{C}-\mathrm{H})^2 = 140 - 60 = +80°$$

XIII

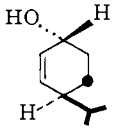


−160 + 260 + 80 = +180°
Obsd. [M]D +185°[17]
XIV

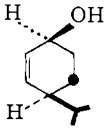


−160 + 80 = −80°
Obsd. [M]D −64°[17]
XV

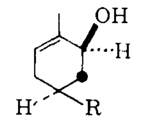
altogether analogous. The agreement of calculated and observed values is reasonably close. The allylic alcohols which have a 1-menthene ring structure (XVIII-XXI) are all shown with the ring in conformation IIIa (+160°) and the alkyl group in the equatorial orientation. The hydroxy group makes contributions of ±160° depending on its orientation relative to the double bond and of ±50° (see Table I, part I; part II) depending on its orientation relative to the methyl group. These effects are opposed in the six alcohols shown in XVIII and XIX. On this basis, the three *cis* isomers XVIII should have [M]D +50° and the three *trans* isomers XIX [M]D +270°. Of these six compounds, four, the carveols (XVIIIb, XIXb) and the sobrerols (XVIIIc, XIXc), have been prepared in apparently pure state and have been assigned reliable configurations[19]; the calculated and observed rotations are in reasonable agreement. The reduction of (+)-carvotanacetone (from (+)-carvone) gives a carvotanacetol (XVIIIa, XIXa)[20] whose rotation suggests that it may be a 1:1 mixture of the *cis* and *trans* form[9] (calculated for such a mixture, [M]D + 160°; observed [M]D +166°). The piperitols (XX, XXI)[21] show a much greater difference in rotation than do the foregoing alcohols, reflecting the fact that here the two conformational asymmetry contributions of the hydroxy group (±160°, ±50°) have the same sign. The two 4-menthene-3-ols (XXII, XXIII)[22] should be analogous in rotation to the 1-menthenes XVIII and XIX, since models indicate that the isopropyl group will straddle the double bond and make little or no contribution to optical activity. The agreement of calculated and observed values is good enough that absolute or relative configurations could have been assigned on this basis.



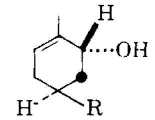
−160 + 130 + 160 + 80 = +210°
Obsd. [M]D +165°[18]
XVI



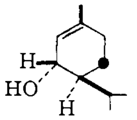
−160 + 130 − 160 + 80 = −110°
Obsd. [M]D −104°[18]
XVII



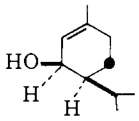
+160 − 160 + 50 = +50°
a, R = −CH(CH$_3$)$_2$ (see text)
b, R = $-\overset{\mathrm{CH_2}}{\overset{\|}{\mathrm{C}}}-\mathrm{CH_3}$, [M]D +35°[19]
c, R = $-\overset{\mathrm{OH}}{\overset{|}{\mathrm{C}}}(\mathrm{CH_3})_2$, [M]D +26°[19]
XVIII



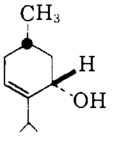
+160 + 160 − 50 = +270°
a, R = −CH(CH$_3$)$_2$ (see text)
b, R = $-\overset{\mathrm{CH_2}}{\overset{\|}{\mathrm{C}}}-\mathrm{CH_3}$, [M]D +324°[19]
c, R = $-\overset{\mathrm{OH}}{\overset{|}{\mathrm{C}}}(\mathrm{CH_3})_2$, [M]D +255°[19]
XIX



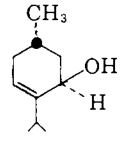
+160 − 160 − 50 = −50°
Obsd. [M]D −43°[21]
XX



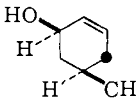
+160 + 160 + 50 = +370°
Obsd. [M]D +379°[21]
XXI



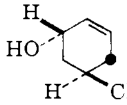
+160 − 160 + 50 = +50°
Obsd. [M]D +117° (impure)[22]
XXII



+160 + 160 − 50 = +270°
Obsd. [M]D +255°[22]
XXIII



−160 + 160 = 0°
Obsd. [M]D +8°[23]
XXIV



−160 − 160 = −320°
Obsd. [M]D −185°[23]
XXV

It is important to note that calculations such as those described above can safely be used only with

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(19) Reduction of the (+)-hydrate of (+)-carvone by the Ponndorf method gives (+)-*cis*- and (+)-*trans*-sobrerol (XVIIIc, XIXc); these products were reduced to, respectively, (+)-dihydrosobrerol and (−)-neodihydrosobrerol (2,8-*trans*-*p*-menthanediols) [H. Schmidt, *Chem. Ber.*, **88**, 453 (1955)]. These products have in turn been dehydrated to (+)-dihydrocarveol and (−)-neodihydrocarveol; (+)-dihydrocarveol is formed by sodium–alcohol reduction of (+)-carvone and so probably has the all-equatorial configuration [H. Schmidt, *ibid.*, **83**, 193 (1950)]. (+)-Dihydrocarveol has been reduced to (+)-carvomenthol and (−)-neodihydrocarveol to (−)-*neo*carvomenthol (both related to (−)-carvomenthone[17]) [R. G. Johnston and J. Read, *J. Chem. Soc.*, 233 (1934)]. (+)-*trans*-Sobrerol has been dehydrated to (+)-*trans*-carveol (XIXb) and (+)-*cis*-sobrerol to (+)-*cis*-carveol (XVIIIb) some racemization occurring in each case [H. Schmidt, *Chem. Ber.*, **86**, 1437 (1953)]; these substances have been prepared by Ponndorf reduction of (+)-carvone (Johnston and Read, above). All of these assignments are in accord with the Auwers–Skita rules.

(20) J. Read and G. Swann, *J. Chem. Soc.*, 239 (1937). The product was purified *via* the *p*-nitrobenzoate, the rotation of which ([M]D +258°) is near enough to the average of the rotations of the *p*-nitrobenzoates of the carveols (*cis*, [M]D −173; *trans*, [M]D +800) [Johnston and Read, ref. 19] to suggest that it may be a sharp melting 1:1 mixture. This point has been discussed in more detail by Mills.[9]

(21) The enantiomorphic forms of the alcohols shown above were prepared by lithium aluminum hydride reduction of (−)-piperitone. The (−)-*cis* isomer was hydrogenated to (−)-neomenthol and the (+)-*trans* isomer to (+)-isomenthol; A. K. Macbeth and J. S. Shannon, *ibid.*, 2852 (1952).

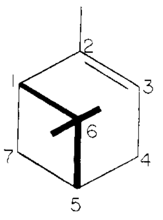
(22) Ponndorf reduction of (−)-4-menthene-3-one gave (−)-*trans*- and (−)-*cis*-4-menthene-3-ol, the latter substance not being obtained pure. These products were reduced to (+)-isomenthol and (−)-menthol and are, accordingly, enantiomorphs of the compounds shown in XXII and XXIII; D. Malcolm and J. Read, *J. Chem. Soc.*, 1037 (1939).

compounds of large rotation or of known epimeric relationships to one another. Thus, one can clearly decide which of the epimeric 3-hydroxy-5-methylcyclohexenes, XXIV and XXV, is *cis* and which *trans* from the observed magnitudes of rotation[23] and, equally clearly, assign the indicated absolute configuration to XXV. Note, however, that no assignment of configuration could be made on the basis of the *sign* of rotation of XXIV. A possible explanation for the discrepancies found here is that the methyl group may adopt an axial orientation to some extent. The diaxial form of XXIV would have a rotation of about +240°; the observed rotation would obtain if the sample contained about 3% of this form. In the case of the *trans* isomer, the form in which the methyl group is axial would have a rotation of about −80°; it would require about 55% of this form to bring the rotation down to that observed.

The rotatory properties of many compounds of the pinene series[24] are consistent with the treatment given here. It is assumed, so that calculations can be made at all, that atoms 1-5 of (+)-α-pinene (XXVI) are coplanar; this plane includes the methyl group at position 2. On this basis, the optical activity of XXVI derives wholly from conformational asymmetry about the four bonds of the cyclobutane ring, the *net* effect being

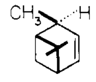
$$[M]_D = k(C - H)(\overset{\overset{C}{\|}}{C}{}^* - H) - k(C - H)^2$$
$$= 140 - 60 = +80°$$

(as with an axial substituent β to the double bond in XII). This value is a reasonable approximation to that observed ([M]D +69°; see Table IV); the rotations of the other compounds in Table III are also close to this value *if they have short chains at position 2.*[25]



XXVI

The δ-pinenes (XXVII, XXVIII)[26] have ring configurations enantiomorphic to that of XXVI.



cis

−80 + 130 = +50°

Obsd. [M]D +80°[26]

XXVII

trans

−80 − 130 = −210°

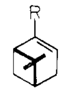
Obsd. [M]D −146°[26]

XXVIII

The methyl groups at position 2 are in essentially the environment of 3-methylcyclohexene, *with the*

TABLE IV

MOLECULAR ROTATIONS OF α-PINENE DERIVATIVES



R	[M]D	Ref.	R	[M]D	Ref.
$-CH_3$	+69°	a	$-(CH_2)_4CH_3$	+39°	b
$-CH_2CH_3$	+51	b	$-(CH_2)_2C_6H_5$	+37	b
$-CH_2OH$	+72.5	c	$-(CH_2)_3C_6H_5$	−37	b
$-CH_2Cl$	+41	c	$-(CH_2)_4C_6H_5$	+12.5	b
$-CH_2Br$	+69.5	b	$-CH_2CH{=}CHC_6H_5$	+31	b
$-CH_2C_6H_5$	+62.5	b	$-CH_2C{\equiv}CC_6H_5$	+44	b
$-(CH_2)_2CH_3$	+36	b	$-(CH_2)_2\overset{\overset{O}{\|}}{C}CH_3$	+51	b
$-(CH_2)_2OH$	+63	d	$-\overset{\overset{O}{\|}}{C}H$	+24	b

[a] F. H. Thurber and R. C. Thielcke, THIS JOURNAL, **53**, 1030 (1931). [b] H. Rupe and A. Heritier, *Ann.*, **459**, 171 (1927). [c] F. W. Semmler and K. Bartelt, *Ber.*, **40**, 1363 (1907). [d] J. P. Bain, THIS JOURNAL, **68**, 638 (1946).

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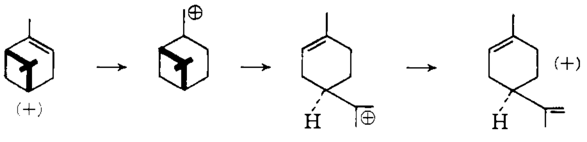
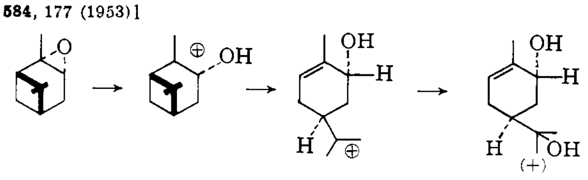
(23) The two alcohols shown can be oxidized to the corresponding (−)-ketone which, in turn, can be reduced to (+)-3-methylcyclohexanone (which has been related to (+)-pulegone and (−)-menthone); XXIV has been reduced to (−)-*cis*-3-methylcyclohexanol; H. L. Goering and E. F. Silversmith, THIS JOURNAL, **77**, 5172 (1955).

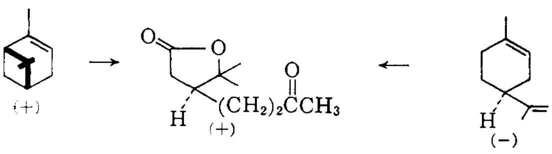
(24) Three separate lines of evidence indicate that (+)-α-pinene has the configuration shown in XXVI; the configurations of most of the other bicyclic terpenes follow from their relationship to α-pinene. Treatment of (+)-α-pinene with dilute sulfuric acid [F. Flavitzky, *Ber.*, **12**, 1022, 1406, 2354 (1879); **20**, 1956 (1887)] or benzoic acid [M. Delepine, *Bull. soc. chim. France*, [4] **35**, 1463 (1924)] gives (+)-limonene; this reaction presumably occurs by a carbonium ion mechanism



Second, the epoxide of (+)-α-pinene gives (+)-*trans*-sobrerol[19] on treatment with acid [G. O. Schenck, H. Eggert and W. Denk, *Ann.*, **584**, 177 (1953)]



Finally (+)-homoterpenyl methyl ketone is formed by oxidative degradation of (+)-α-pinene [E. Gildemeister and H. Köhler, *Ber.*, *Schimmel and Co.*, 125 (1909); *Chem. Zentr.*, **80**, II, 2158 (1909)] and of (−)-limonene [T. A. Henry and H. Paget, *J. Chem. Soc.*, 70 (1928)]

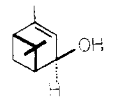


The configurations of the compounds in Table III follow from their preparation from (+)-myrtenyl chloride, which has been reduced to (+)-α-pinene [F. W. Semmler and K. Bartelt, *Ber.*, **40** 1363 (1907)].

(25) A chain length greater than two permits steric interactions with the *gem*-dimethyl group; this will introduce an element of conformational asymmetry and produce deviations from the calculated value (see the second column of Table III).

(26) Absolute configurations can be assigned to the *rings* of the δ-pinenes on the grounds that the pinocampheols from which they are obtained can also form (+)-α-pinene. Both δ-pinenes are reduced to (+)-pinane as is (+)-α-pinene. It is highly probable that the levorotatory δ-pinene has the *trans* configuration since it is formed by dehydration of (+)-pinocampheol. Pinocampheol is the most stable of the alcohols of this series and is related to pinocamphone, the most stable ketone; these facts suggest that the methyl group is *trans* to the *gem*-dimethyl group [H. Schmidt, *Chem. Zentr.*, **113**, I, 2531 (1942); *Ber.*, **77**, 544 (1944); *Chem. Ber.*, **80**, 520 (1947)]. These assignments are not controverted by the arguments of A. K. Bose, *J. Org. Chem.*, **20**, 1003 (1955), who disputes some of Schmidt's assignments of configuration.

cyclobutane ring having virtually no effect beyond this, and so should make rotatory contributions of ±130°. The calculated rotations are reasonably close to those observed considering the assumptions used in the calculations. The predicted difference in rotation of the epimers (Δ[M] −260°) should be compared with that observed (−226°). Rotations can be calculated for the verbenols (XXIX, XXX)[27] in a similar way. The value calculated for the *trans* isomer XXX is in good agreement with that found for the isomer to which a *trans* configuration has been assigned. The observed value for the presumed *cis*-verbenol is badly out of line with that calculated; it is, however, quite close to that expected for a 1:1 mixture of the two isomers (+80°, observed +100°). This case is to be compared with that of the carvotanacetols (above).



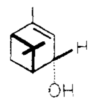
cis

+80 − 160 = −80°

"Obsd. [M]D" +100°[27]

(see text)

XXX



trans

+80 + 160 = +240°

Obsd. [M]D +257°[27]

XXXI

It might, at first thought, be expected that one could calculate the rotatory effects resulting from the introduction of a double bond into the steroid nucleus. An inspection of models suggests, however, that a fused cyclohexene ring may prefer a conformation in which five of the ring atoms are planar and in which three atoms have true axial and equatorial bonds (XXXII). It is to be noted that this form is only slightly altered, relative to the semi-chair form; it would be expected to have the same sign of rotation as the corresponding semi-chair form, but a different magnitude of rotation. Conversely, if the cyclohexene ring has the semi-chair conformation it may distort the ring fused to it and produce an additional rotatory shift. Accordingly, predictions in this series can be expected to be only rough and approximate.[28] As seen in Table V, the present simple treatment gives correct predictions of the *sign* of rotatory change in every case, but the predictions of magnitude are, more often than not, rather poor. In the case of the Δ^4-steroids, ring A can assume either of the two ring conformations IIIa or IIIb; the observed value is close to that calculated on the assumption that the two forms are present in equal amounts. The results suggest that caution be used in this application of the present method to fused ring compounds.

TABLE V

CHANGES IN MOLECULAR ROTATION ON INTRODUCTION OF A DOUBLE BOND INTO THE STEROID NUCLEUS

Position of C=C		Rotatory contributions Ring	α-Substituent	β-Substituent Endo	β-Substituent Exo	Δ(C=C) − (CH–CH) Calcd.	Obsd.
A/B *trans*							
1:2		−160	0	0	+80	− 80	− 47[c]
2:3		+160	0	−80	0	+ 80	+167[c]
3:4		−160	+130	+80	0	+ 50	+124[c]
6:7		+160	−260	−80	−80	−260	−402[c]
8:9		0	+130	+80	0	+210	+ 96[d]
A/B *cis*							
1:2		+160	0	0	+80	+240	
2:3		−160	0	+80	0	− 80	− 24[d]
3:4		+160	−130	−80	0	− 50	− 44[d]
6:7		+160	0	−80	−80	0	
8:9		0	+130	0	0	+130	
Both series							
4:5	a	+160	+130	0	0	+130	+153[c]
	b	−160	+130	0	0		
5:6		−160	−130	0	0	−290	−294[c]
11:12[a]		−160	+130	0	+80	+ 50	+33[d]
15:16[a]		0	0	0	0	0	
16:17[b]		0	0	0	0	0	+ 31[d]

[a] Substituent at C_{17}. [b] No substituent at C_{17}. [c] Data for cholestenes; Δ-values calculated from [M]D for cholestane. +91; data of R. B. Turner, W. R. Meador and R. E. Winkler, THIS JOURNAL, **79**, 4122 (1957). [d] Average Δ-values as tabulated by W. Klyne in E. A. Braude and F. C. Nachod, "Determination of Organic Structures by Physical Methods," Academic Press, Inc., New York, N. Y., 1955, p. 111.

XXXII

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(27) One isomer, having a high rotation, is obtained by autoxidation of (+)-α-pinene and isolated *via* the *p*-nitrobenzoate. Another material, presumed to be isomeric, was obtained *in an impure state* from the *p*-nitrobenzoate of the product of Ponndorf reduction of verbenone. Both products could be oxidized to the same verbenone, *but there is no evidence that the last named alcohol was not a mixture of epimers.* Relative configurations were assigned by use of the Auwers-Skita rules and by a comparison of rates of esterification [H. Schmidt, L. Schulz and W. Doll, *Chem. Zentr.*, **111**, II, 3038 (1940); L. Schulz and W. Doll, *ibid.*, **115**, II, 755 (1944).]

(28) The empirical constants used to this point do not allow prediction of the rotation shift for introduction of a double bond at 7:8, 9:11 or 14:15. Uncertainty as to the conformation of ring D prevents a prediction for introduction of a double bond at 8:14.

LAFAYETTE, IND.

[CONTRIBUTION FROM THE RESEARCH DIVISION, PARKE, DAVIS & COMPANY]

Chemistry of Streptimidone, A New Antibiotic

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RECEIVED APRIL 17, 1959

A new antibiotic, streptimidone ($C_{16}H_{23}NO_4$), has been obtained from the culture filtrates of a *Streptomyces*. The characteristic physical properties of the antibiotic have been determined. Degradative studies have demonstrated that streptimidone is 3-(2-hydroxy-7-methyl-5-methylene-4-oxo-6-nonenyl)-glutarimide. A novel cross-conjugated chromophore is proposed for the dienone.