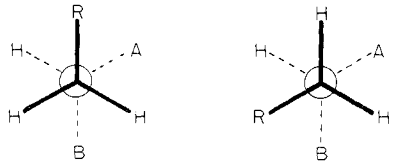

$+k(A - H)(R - H)$ $-k(B - H)(R - H)$

a b

XXIV

Permolecular Asymmetry.—It is to be recognized that additional kinds of screw patterns of polarizability will be possible. Optically active allenes, spiranes and biphenyls show such patterns when viewed along their axes of asymmetry. These screw patterns, in effect, run *through the molecule* and will be called permolecular patterns; such patterns may be important in rigid and cyclic compounds. It is found necessary to invoke this concept in the treatment of carbohydrates (part II).

Acknowledgment.—The author wishes to acknowledge the helpful advice and encouragement given him during the preparation and repeated revisions of this manuscript by Professors H. C. Brown, N. Kornblum, R. A. Benkeser and R. A. Sneen of the Department of Chemistry and by Professor G. N. Wollan of the Department of Mathematics of Purdue University. He is particularly grateful to the Purdue Research Foundation and to the Research Corporation for grants which aided greatly in the preparation of this manuscript; he wishes to express his appreciation to the Department of Chemistry of the University of Wisconsin for its hospitality during the summer of 1957.

LAFAYETTE, IND.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

The Optical Activity of Saturated Cyclic Compounds[1]

BY JAMES H. BREWSTER

RECEIVED SEPTEMBER 2, 1958

It is shown that the principles of conformational asymmetry and the empirical constants used in estimating the sign and magnitude of rotation of acyclic compounds (part I) can also be used in estimating the sign and magnitude of rotation of saturated cyclic compounds.

A flexible chain compound will generally have a relatively small rotation because its molecules can assume many conformations with different and opposed rotatory powers. It was shown in part I that the rotations of many open-chain compounds of known absolute configuration can be estimated by use of a simple system of conformational analysis and a series of empirical rotation constants for asymmetric conformations about individual bonds; this treatment provides an explanation for the regularities observed in the rotations of acyclic compounds.[2] The relatively large rotations of ring compounds can, then, be ascribed to their near rigidity which allows a display of the full rotatory powers of their asymmetric conformations.[3] We may, accordingly, test the rotation constants obtained in part I by determining whether they can be used in estimating the sign and magnitude of rotation of cyclic compounds. It is shown in the present paper that these constants can, indeed, be used for this purpose, whence it follows that indirect support for the system of conformational analysis used in part I has been obtained. An important result of this test is the demonstration that, although the Marker Rules[2] cannot be applied *as such* to cyclic compounds,[4] the principles which lead to rules equivalent to those of Marker can be used successfully in the cyclic series so that the apparent lack of correspondence between the cyclic and acyclic series[4] disappears.[5]

Cyclohexane Derivatives.—Each of the ring bonds of the chair form of cyclohexane is asymmetric, alternating dextro (Ia) and levo (Ib); since these rotatory effects cancel completely, the optical activity of cyclohexane derivatives can be ascribed wholly to the asymmetric conformations made by the substituents with ring atoms or with one another.[6] An isolated equatorial substituent, replacing H* in Ia or Ib, has no effect on the conformational asymmetry of any of the bonds; an isolated axial substituent, replacing H in Ia or Ib, causes equal and opposite changes in the asymmetry of the two nearby ring bonds but should have no effect on more distant bonds. Accordingly the epimers IIa and IIb should have essentially the same rotation and this rotation should be close to

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(1) A Useful Model of Optical Activity, Part II; part I, preceding paper, p. 5475.

(2) R. E. Marker, THIS JOURNAL, **58**, 976 (1936).

(3) W. J. Kauzmann, J. E. Walter and H. Eyring, *Chem. Revs.*, **26**, 338 (1940).

(4) J. A. Mills, *Chemistry & Industry*, 218 (1953).

(5) It should be noted that the present treatment of cyclic compounds was, in many important respects, anticipated by D. H. Whiffen, *ibid.*, 964 (1956), in a discussion of the rotatory properties of the hydroxytetrahydropyrans, the cyclitols and certain of the terpenes. It should also be noted, however, that the present treatment leads to several major simplifications and extensions of Whiffen's work which would have been impossible were *all* of Whiffen's conclusions accepted (see text, below). It is, thus, one of the burdens of this paper to show that the principles presented here and in part I lead to results comparable to those obtained by Whiffen, the net result being to provide a broader justification of the *essential* points of his thesis. The author wishes to make it clear that no part of the present paper is to be regarded as an attack on Whiffen's important pioneering contribution.

(6) Asymmetrically distributed substituents may produce asymmetric distortions of the ring which could make the ring itself optically active. These effects will probably be small but might account for the small rotations observed in compounds otherwise expected to be optically inactive. These possible effects will, for the present, be ignored.

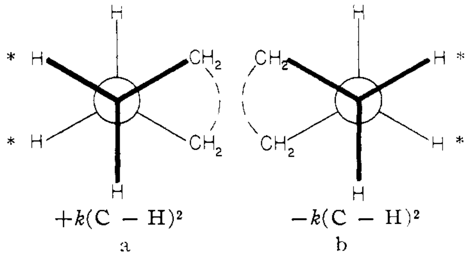
TABLE I

MOLECULAR ROTATIONS OF 3-SUBSTITUTED CHOLESTANES

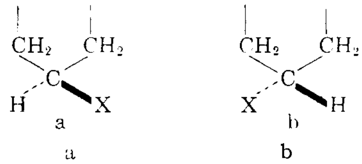
Substituent	α	$[M]_D$	β
	a		
..		93[a]	
F			90[b]
Cl	124[a]		110[a]
Br	129[a]		
NH_2	105[c]		112[c]
NMe_2	91[d]		96[e,f]
OH	97[a]		90[a]
OCH_3	73[a]		85[a]
OBz	$[M]_{578}$ 118[a]		99[a]
CO_2H	100[g]		121[g]
CO_2CH_3	116[g]		128[g]
$CONH_2$	91[g]		109[g]
CN	84[g]		109[g]
CH_2CO_2H	121[g]		99[g]
$CH_2CO_2CH_3$	109[g]		86[g]
CH_2CH_2OH	105[h]		76[h]
$CH_2CH_2CH_3$			103[i]
$CH(CO_2H)_2$	142[h]		
$CH(CO_2CH_3)_2$	100[h]		
$CH_2C(CH_3)_2OH$			102[h]
$CH_2C(C_6H_5)_2OH$			77[h]
$CH{=}C(CH_3)_2$			89[h]
$(OCH_3)_2$		99[j]	
$S_2C_2H_4$		137[k]	
	b		
NHAc	155[c]		52[c,e]
$NMe_3^+I^-$			184[d]
OAc	129[l]		56[a]
CH_3			42[i]
$CH{=}C(C_6H_5)_2$	64[h]		22[h]

[a] Calculated from average values for specific rotation as cited by J. P. Mathieu and A. Petit, in "Tables de Constantes et Données Numériques. 6. Constantes Sélectionées. Pouvoir Rotatoire Naturel. I. Stéroides," Masson et Cie., Paris, 1956. [b] C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 4813 (1957). [c] C. W. Shoppee, D. E. Evans, H. C. Richards and G. H. R. Summers, *ibid.*, 1649 (1956). [d] R. D. Haworth, J. McKenna and R. G. Powell, *ibid.*, 1110 (1953). [e] D. P. Dodgson and R. D. Haworth, *ibid.*, 67 (1952). [f] L. Lábler, V. Černy and F. Šorm, *Coll. Czech. Chem. Comm.*, 19, 1249 (1954). [g] G. Roberts, C. W. Shoppee and R. J. Stephenson, *J. Chem. Soc.*, 2705 (1954). [h] C. W. Shoppee and R. J. Stephenson, *ibid.*, 2230 (1954). [i] R. H. Baker, L. S. Minckler and Q. R. Petersen, THIS JOURNAL, **77**, 3644 (1955). [j] R. M. Evans, *et al.*, *J. Chem. Soc.*, 1529 (1958). [k] D. K. Fukushima, S. Lieberman and B. Praetz, THIS JOURNAL, **72**, 5205 (1950). [l] C. W. Shoppee, B. D. Agashe and G. H. R. Summers, *J. Chem. Soc.*, 3107 (1957).

that of the compound in which X = H.[7] The relatively small rotations of the 3-methyl cyclohexanols (IIIa and IIIb)[8] are in accord with this prediction. The molecular rotations of a wide variety of 3-substituted cholestanes, as shown in Table I, average to +100°, in good agreement with the value for cholestane itself (+93°). The average deviation (excluding the seemingly anomalous compounds in part b) from +93° is 16°,[9] the largest effects, on the whole, being shown by axial (α) substituents of high polarizability.



I



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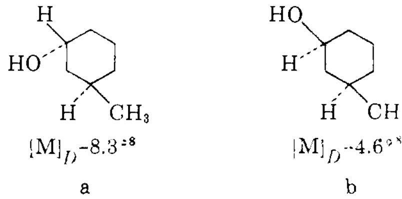
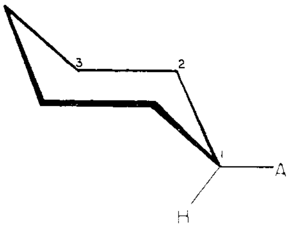
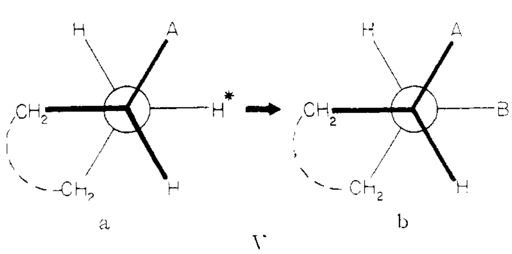


III



IV



V

Adjacent substituents can produce a marked conformational asymmetry; the size of this effect can be estimated by a consideration of the rotational changes which would accompany a stepwise building up of the structure in question from a parent compound which is optically inactive or has a known

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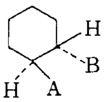
(7) This conclusion was reached earlier by W. M. Stokes and W. Bergmann, *J. Org. Chem.*, **17**, 1194 (1952), and by W. Klyne and W. M. Stokes, *J. Chem. Soc.*, 1979 (1954), on somewhat more intuitive grounds. It would be naive to expect that both epimers would have exactly the same rotation as the parent compound since permolecular asymmetry and second-order atomic asymmetry effects (see part 1) could still be displayed. Indeed these minor effects might most profitably be studied in systems such as these, though such studies could be complicated by the possibility that asymmetric distortions of ring geometry will also produce detectable rotatory effects.[6]

(8) The two (−)-alcohols can be oxidized to the (+)-ketone [G. A. Gough, H. Hunter and J. Kenyon, *ibid.*, 2052 (1926); A. K. Macbeth and J. A. Mills, *ibid.*, 205 (1947)]; the absolute configuration of the ketone is established by its oxidation to β-methyladipic acid (see part III, refs. 11 and 12). Relative configurations (*cis* and *trans*) are assigned in accord with the findings of H. L. Goering and C. Serres, THIS JOURNAL, **74**, 5908 (1952), and of D. S. Noyce and D. B. Denney, *ibid.*, **74**, 5912 (1952).

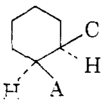
(9) An error of 0.04° in the observed rotation of a 1% solution of a compound with a molecular weight of 400 would produce an error of this magnitude in the molecular rotation.

rotation. Thus, IV is the optically inactive parent compound of the 1,2-disubstituted cyclohexanes having the group A equatorial. Replacement of the equatorial hydrogen at position 2 (H* in Va) by B produces the conformation Vb, which has a rotation $+k(A - H)(B - H)$ higher than Va. The conformation about the bond 2–3 is not altered (see above). Hence diequatorial VI, the product of this transformation, should have the indicated rotation, IV being inactive. Similarly, if the substituent enters axial, to produce VII (C axial), the new substituent produces equal and opposite conformational changes *relative to the ring atoms* but interaction of the substituents make the conformations about bonds 1–2 and 2–3 more levorotatory by a total of $-k(A - H)(C - H)$. The other rotational changes shown in VI–IX can be worked out in a parallel way; these expressions, used in conjunction with the data of Table I, part I, constitute predictions of the sign and magnitude of rotation of the simple compounds shown or of the rotational shifts which should accompany conversion of analogs of IV to the corresponding analogs of VI–IX. *For the most part*, these predictions parallel the empirical conclusion of Klyne and Stokes[7] that X will be dextrorotatory when C* is substituted. Note, however, that in the present picture one form of VI should be inactive and that in some cases VII, VIII and IX could be levorotatory. The present rules should be much more general than that of Klyne and Stokes,[7] which was developed for thepa rticular case where the substituent A (in X) is a hydroxy group.



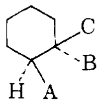
diequatorial:
$+k(A - H)(B - H)$
diaxial: O

VI



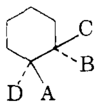
A equatorial:
$-k(A - H)(C - H)$
A axial:
$+k(A - H)(C - H)$

VII



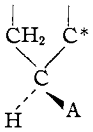
A equatorial:
$+k(A - H)(B - C)$
A axial:
$+k(A - H)(C - H)$

VIII



A equatorial:
$+k(A - H)(B - C)$
$-k(D - H)(B - H)$
A axial:
$+k(A - H)(C - H)$
$+k(D - H)(B - C)$

IX



X

For a test of these predictions we require rotation constants beyond those given in Table I, part I, as, for example, for the conformation XI. Such constants can be obtained by suitable combinations of those given in Table I, part I; thus, from the values given for conformations XII and XIII, we can estimate the value for XI to lie between 36° and 48°.[10]

$$k(O - H)^2 = \frac{[k(O - H)(C - H)]^2}{k(C - H)^2} = \frac{(50 \pm 2.5)^2}{60 \pm 2.5}$$

Whiffen[5] has shown that a value of +45°, which lies in the calculated range, can be used to calculate the sign and magnitude of rotation of eight polyhydroxy cyclohexanes[11]; this value, being suitably rounded, will be used here. It is important to note that estimates of this nature could not possibly be made by use of Whiffen's treatment.

In Table II are presented the rotatory shifts ($[M]_{OH-H}$) to be expected when a hydroxy group is placed on rings A, B or C of the steroid nucleus[12] (ring D is treated separately below). This table can be used in predicting the rotatory effects of other substituents simply by replacing the numbers ±50 by the value $\pm k(X - H)(C - H)$ as taken from Table I, part I. Additional values must, of course, be used when two adjacent substituents are considered. It is seen that for most cases the rotational difference between epimers is very closely predicted and that, in general, the directions of rotational shifts (relative to the unsubstituted compound) are correctly predicted, indicating the general correctness of this treatment. It will also be noted that sizeable discrepancies occur when predictions of individual rotation shifts are made; *the fact that most of these discrepancies disappear when epimers are compared shows that they are produced by a persistent "anomaly."* A large mass of rotational data which have been accumulated suggests very strongly that this anomaly is produced by a flattening of the rings (to relieve conformational pressure exerted by the angular methyl groups on β-substituents at C_2, C_4, C_6, C_8 and C_{11} and to relieve crowding of 1β-, 7β- and 11α-substituents); these results will be presented in due time. In the meantime, it is of interest to observe the extent to which correct predictions can be made by use of the presently accepted "full-chair" conformation model of the steroid nucleus. In Table II are presented rotations as predicted and as observed for monoamino-, hydroxy- and halo-cholestanes (A/B *trans*) (calculated from [M] +93 for cholestane). Excluding the three italicized values, which are anomalous in magnitude but not in direction of shift, the average deviation from predicted values is 20°. In Table IV are presented predicted and observed values for the hydroxycholanic acids (and their esters) (A/B *cis*); this table includes a

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(10) The rotation constants for conformations XII and XIII are rounded to the nearest five degrees.

(11) See Whiffen's paper[5] for a tabulation of these results. The calculations for the cyclitols are in every respect identical to those that would be made under the present treatment. In his further calculations, however, Whiffen uses an additional value of +32° for XI when it includes a glycosidic hydroxy group, and also a value of +34° for XII (compare the present value of 50°). In these two regards, Whiffen's treatment stands in contradiction to that presented here (see below). It is shown below the present values are adequate for calculating rotations of hydroxytetrahydropyrans and of terpene and steroid alcohols, and are, in most cases, superior to those of Whiffen.

(12) The absolute configuration of the steroid nucleus has been shown to be that given below by tbe work of W. G. Dauben, D. F. Dickel, O. Jeger and V. Prelog, *Helv. Chim. Acta*, **36**, 325 (1953); B. Riniker, D. Arigoni and O. Jeger, *ibid.*, **37**, 546 (1954); J. W. Cornforth, I. Youhotsky and G. Popjak, *Nature*, **173**, 536 (1954); K. Brenneisen, C. Tamm and T. Reichstein, *Helv. Chim. Acta*, **39**, 1233 (1956). This relationship was predicted from rotational analogies with the terpenes by J. A. Mills, *J. Chem. Soc.*, 4976 (1952); ref. 4.

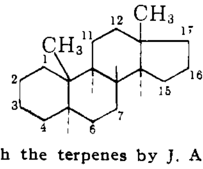


TABLE II

ROTATORY EFFECTS OF HYDROXY GROUPS IN RINGS A, B AND C OF THE STEROID NUCLEUS

	Position	$[M]_{OH-H}$ Calcd.	Obsd.^{a}	$[M]_{\alpha-\beta}$ Calcd.	Obsd.
A/B *trans*	1α	+50	+35		
	β	0	−17	+50	+52
	2α	0	+37		
	β	0	+49	0	−12
	3α	0	+5		
	β	0	−2	0	+7
	4α	−50	−75		
	β	+50	+22	−100	−97
	5α	0	−25^{b}		
	6α	+50	+55		
	β	−50	−50	+100	−105
	7α	−50	−59		
	β	+50	+110	−100	−169
A/B *cis*	1α	0			
	β	−50		−50	
	2α	0			
	β	0		0	
	3α	0	+30		
	β	0	+1	0	+29
	4α	−50			
	β	+50		−100	
	5β	+50			
	6α	−50	−100		
	β	0	+7	−50	−107
	7α	−50	−79		
	β	+50	+95	−100	−174
Both series	8β	+50			
	9α	−50			
	11α	−50	−29		
	β	+50	+96	−100	−125
	12α	+50	+93		
	β	0	+50	+50	+43

[a] Average values as cited 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. [b] See Table V.

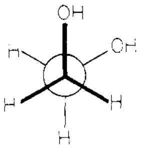
TABLE III

MOLECULAR ROTATIONS OF MONOSUBSTITUTED CHOLESTANES (A/B *trans*)[aa]

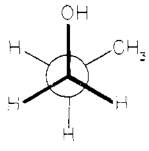
Substituent	Position	$[M]_D$ α Calcd.	α Obsd.	β Calcd.	β Obsd.
None			93		
NH_2	2	93	77^{a}	93	110^{a}
	3	93	105^{b}	93	112^{b}
	4	38	41^{a}	148	*233*^{a}
	6	148	149^{c}	38	24^{c}
	7	38	−*77*^{a}	148	209^{a}
OH	1	143	135^{d}; 128^{e}	93	88^{d}; 76^{e}
	2	93	105^{f}; 101^{a}	93	132^{f}
	3	93	97	93	90
	4	43	23^{g}	143	120^{g}
	6	143	143^{g}	43	31
	7	43	43^{a}	143	202^{a}
F	3			93	90^{h}
Cl	3	93	124	93	110
	6	263	208	−77	−*183*
	7	−77	−86	263	313
Br	3	93	129		
	7	−87	−90		

[aa] All rotations in chloroform. Unless otherwise noted, all rotations calculated from data cited by J. P. Mathieu and A. Petit, ref. *a*, Table I. [a] C. W. Shoppee, R. J. W. Cremlyn, D. E. Evans and G. H. R. Summers, *J. Chem. Soc.*, 4364 (1957). [b] C. W. Shoppee, D. E. Evans, H. C. Richards and G. H. R. Summers, *ibid.*, 1649 (1956). [c] C. W. Shoppee, D. E. Evans and G. H. R. Summers, *ibid.*, 97 (1957). [d] H. B. Henbest and R. A. L. Wilson, *ibid.*, 3289 (1956). [e] P. Striebel and C. Tamm, *Helv. Chim. Acta*, **37**, 1094 (1954). [f] A. Fürst and P. Plattner, *ibid.*, **32**, 275 (1949). [g] D. N. Jones, J. R. Lewis, C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 2876 (1955). [h] C. W. Shoppee and G. H. R. Summers, *ibid.*, 4813 (1957).

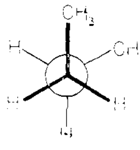
number of vicinal diols. The persistent anomaly shown by 3α-hydroxy compounds in this series has been taken into account by use of the value [M] +138° for 3α-hydroxycholanic acid (to be compared with the value +87° for cholanic acid). Excluding the two italicized values, which appear to be anomalous, the average deviation from the calculated values is 21°. A 5α-hydroxy substituent also produces a small but persistent anomaly; as seen in Table V, rotations for a number of polyhydroxy cholestanes can be calculated (average deviation 15°) when this effect has been taken into account. The data in Table VI provide a striking illustration of the "steroid anomaly" when individual rotations are calculated and an even more striking illustration of the disappearance of this anomaly when rotations of epimers are compared. It seems fair to conclude that the success with which differences in rotation of epimers can be calculated in this series provides strong support for the present treatment of optical activity. It must equally be concluded that the magnitude of individual discrepancies indicates that some persistent factor is not being taken into account in these calculations; this factor could be: (a) an essential error in the present treatment, (b) the occurrence of permolecular asymmetry effects or (c) the use of an incorrect conformational model for the steroid nucleus. As pointed out above, work in progress points strongly to the last-named possibility.



$k(O-H)^2 =$
$+45°$
XI



$k(O-H)$
$(C-H) = +50°$
XII



$k(C-H)^2 =$
$+60°$
XIII

These principles can also be applied to the alkyl cyclohexanols, but it must be remembered that some of these compounds can have two conformations of roughly the same energy. Thus, *trans*-2-methylcyclohexanol (in configuration XIVa)[13] has a molecular rotation of +44.2°, in acceptable agreement with the value of +50° predicted for the diequatorial isomer. On the other hand, the related *cis* isomer[13] XIVb has a rotation of −15°,

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(13) Relative configurations are assigned on the ground that sodium reduction of the ketone will give chiefly the diequatorial (*trans*) isomer. Both (+)-XIVa and (−)-XIVb can be oxidized to the (+)-ketone[8]; the toluenesulfonate of (+)-XIVa gives, in hot formamide, a levorotatory olefin,[8] the optical activity of which is *probably* due to the presence of (−)-3-methylcyclohexene. The (+)-form of the olefin has been obtained from (+)-3-methylcyclohexanone [M. Mousseron, R. Richaud and R. Granger, *Bull. soc. chim. France*, [5] **13**, 222 (1946)], the absolute configuration of which has been established (references 11–13 in **part** III).

TABLE IV

MOLECULAR ROTATIONS OF HYDROXYCHOLANIC ACIDS (A/B *cis*)

	$[M]_D$		
Substituents	Calcd.[a]	Acid	Obsd.[b] methyl ester
....	87	80 C	95 A
3α-OH	138	132 E	137 M
3α-OH, 6α-OH	88	33 M	142 M
3α-OH, 6β-OH	138	145 M	
3α-OH, 7α-OH	88	45 E	49 C
3α-OH, 7β-OH	188	224 E	
3α-OH, 11α-OH	88	86 E	88 E
3α-OH, 11β-OH	188	216 M	199 A
3α-OH, 12α-OH	188	208 E	227 A
3α-OH, 12β-OH	138	151 D	176 A
3α-OH, 7α-OH, 12α-OH	138	147 E	
3α-OH, 11α-OH, 12α-OH	93	106 E	
3α-OH, 11α-OH, 12β-OH	133	188 E	
3α-OH, 11β-OH, 12α-OH	238	221 E	
3α-OH, 11β-OH, 12β-OH	143	175 E	
3β-OH	87	97 E	
3β-OH, 6α-OH	37	12 M; 20 E	
3β-OH, 6β-OH	87	58 M	
7α-OH	37	26 C	
7α-OH, 12α-OH	87	106 E	
11α-OH	37		*194* A
11α-OH, 12α-OH	42	13 D	50 M
11β-OH, 12β-OH	92		*227* M
12α-OH	137	164 A	
12β-OH	87	143 A	

[a] Rotations for cholanic acid derivatives containing a 3α-hydroxy group are calculated from the value $[M]_D$ +138 for the parent hydroxy acid; all other rotations are calculated from the value $[M]_D$ +87 for cholanic acid. These values were chosen to give the best fits with the data cited above. In these calculations it is assumed that the acids and methyl esters will have equal molecular rotations. [b] Average values calculated from data taken from the tables of J. P. Mathieu and A. Petit, ref. *a*, Table I: A, acetone; C, chloroform; D, dioxane; E, ethanol; M, methanol.

TABLE V

MOLECULAR ROTATIONS OF CHOLESTAN-5α-OLS

	$[M]_D$	
Additional substituents	Calcd.[c]	Obsd.
....	68	39 C[a,d]
2α-OH	68	79 C[a]
3α-OH	68	69 C[a]
3β-OH	68	77 C[a]
4α-OH	63	57 C[b]
4β-OH	118	109 C[b]
6α-OH	68	61 C[b]
6β-OH	18	−12 C[b]
3α-OH, 4β-OH	118	183 P[a]
3β-OH, 6α-OH	68	88 D[a]
3β-OH, 6β-OH	18	13 E[a]

[a] Calculated from data tabulated by J. P. Mathieu and A. Petit, ref. *a*, Table I. [b] D. N. Jones, J. R. Lewis, C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 2876 (1955). [c] Calculated from the value +68° for cholestan-5α-ol, chosen to give the best fit. [d] C, chloroform; D, dioxane; E, ethanol; P, pyridine.

TABLE VI

EPIMERIC VICINAL *trans*-DISUBSTITUTED CHOLESTANES

		$[M]_D$		$[M]_{aa-ee}$	
Substituent	Conformation	Calcd.	Obsd.	Calcd.	Obsd.
2α-OH, 3β-OH	ee	48	73[a]		
2β-OH, 3α-OH	aa	93	133[a]	+45	+60
2α-Cl, 3β-OH	ee	−24	63[b]		
2β-Cl, 3α-OH	aa	93	166[b]	+117	+103
2α-Br, 3β-OH	ee	−57	56[b]		
2β-Br, 3α-OH	aa	93	205[b]	+150	+149
2α-Cl, 3β-Cl	ee	−235	−27[b]		
2β-Cl, 3α-Cl	aa	93	261[b]	+328	+288
2α-Br, 3β-Cl	ee	−327	−81[b]		
2β-Br, 3α-Cl	aa	93	327[b]	+420	+408
2α-Cl, 3β-Br	ee	−327	−76[b]		
2β-Cl, 3α-Br	aa	93	303[b]	+420	+379
2α-Br, 3β-Br	ee	−447	−152[b]		
2β-Br, 3α-Br	aa	93	404[b]	+540	+556
3β-OH, 4α-OH	ee	88	79[d]		
3α-OH, 4β-OH	aa	143	66[e]	+55	−13
3β-Br, 4α-Br	ee	433	192[b]		
3α-Br, 4β-Br	aa	273	32[b]	−160	−160
5β-OH, 6α-OH	ee	+138	+125[f]		
5α-OH, 6β-OH	aa	+43	−12[f]	−95	−137
5β-Br, 6α-Br	ee	613	261[c]		
5α-Br, 6β-Br	aa	−87	−215[c]	−700	−476

[a] C. W. Shoppee, D. N. Jones and G. H. R. Summers, *J. Chem. Soc.*, 3100 (1957). [b] G. H. Alt and D. H. R. Barton, *ibid.*, 4284 (1954). [c] C. A. Grob and S. Winstein, *Helv. Chim. Acta*, **35**, 782 (1952). [d] L. F. Fieser and R. Stevenson, THIS JOURNAL, **76**, 1728 (1954). [e] P. A. Plattner, H. Heusser and A. B. Kulkarni, *Helv. Chim. Acta*, **31**, 1822 (1948). [f] D. N. Jones, J. R. Lewis, C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 2876 (1955).

intermediate between the value of −50° expected for the conformation having an equatorial methyl group and the value of +50° expected for the conformation with an equatorial hydroxy group (see VII). Indeed, the observed rotation indicates the presence of *roughly* two molecules of the former conformation to one of the latter; conclusions of this nature are, necessarily, very approximate. In the terpene series[14] (Table VII), it is to be expected that the *trans-p*-menthane derivatives will have their alkyl groups essentially completely in the equatorial orientation. If so, the rotational difference between epimeric alcohols, Δ(A − B), should be about 100°. The observed identical values of +108° in the menthol and carvomenthol series indicate that the group R_1 (see figures in Table VII) makes no more contribution to rotatory power than do the substituents in 3-alkylcyclohexanols (see III). *They indicate further that the isopropyl group in the menthol series produces no significant rotatory effect.*[14] In the other *trans*-menthane derivatives, the rotation difference is also close to 100° (observed +102°, +105°); these values are to be compared with the difference of +68° expected from Whiffen's value of +34° for XII.[11] Conformational mixtures are to

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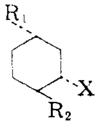
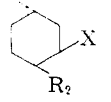
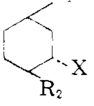
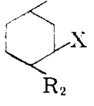
(14) The absolute configurations of the menthones and carvomenthones are established by the work cited in references 11–13 of part III. The relationships of the alcohols and amines to the ketones and their relative configurations are reviewed in J. L. Simonsen "The Terpenes," Vol. I, 1947, Cambridge University Press, Cambridge. The relative and absolute configurations of the dihydrocarveols and their hydrates have been established by the work of H. Schmidt, *Chem. Ber.*, **83**, 193 (1950); **88**, 453 (1955). In menthol and isomenthol, all conformations of the isopropyl groups are "prohibited" by the rules of conformational analysis given in part I; this group may either be free to rotate (and so act as a cylindrically symmetrical substituent) or be frozen in its symmetrical conformation. In the neo-series, the symmetrical conformation of this group is the only one "allowed."

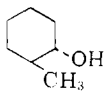
TABLE VII

MOLECULAR ROTATIONS OF TERPENE ALCOHOLS AND AMINES

									
			[M]D						
						iso C		neoiso D	
			A	neo B	Δ(A − B)	R_1 eq.	R_1 ax	R_1 eq.	R_1 ax
Predicted: R_2 = alkyl									
X = OH			+50	−50	+100	0	+50	+50	−50
X − NH_2			+55	−55	+110	0	+55	+55	−55
Observed[a]									
R_1	R_2	X							
$-CH_3$	$-CH(CH_3)_2$	-OH	+77	−31	+108	+42		+ 0.21	
$-CH_3$	$-CH(CH_3)_2$	$-NH_2$	+69	−23	+ 92	+45		+ 3.6	
$-CH(CH_3)_2$	$-CH_3$	-OH	+43	−65	+108	+28		+55	
$-CH(CH_3)_2$	$-CH_3$	$-NH_2$	+20	−42	+ 62	+22			
CH_2 ‖ $-C-CH_3$	$-CH_3$	-OH	+52	−50	+102	+43			
$-C(CH_3)_2$ | OH	$-CH_3$	-OH	+36	−69	+105	+41		+45	

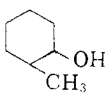
[a] Data from references cited in footnote 14.

be expected in those members of the *cis*-menthane series in which the two small substituents could be equatorial when the large one is axial. Thus, the rotation of neoiso-menthol (+0.21°) suggests that the two forms are present in nearly equal amounts as does the rotation of iso-carvomenthol (+28°). The rotations of iso-dihydrocarveol (+43°) and its hydrate (+41°) are out of line, being considerably larger than expected. The present analysis indicates that the rotations of the amines should be parallel to those of the corresponding alcohols as, on the whole, they are.



[M]D +44.2°[8]

a



[M]D −15°[8]

b

XIV

A stringent test of the utility of the present treatment is provided by its application to the prediction of the rotatory effects of substituents in ring D of the steroids. The five-membered ring is forced into a puckered conformation by fusion to ring C; its most probable conformation is one in which C_{13}, C_{14} and C_{16} are coplanar, with C_{15} above and C_{17} below the plane.[15] This conformation is awkward to handle under the present treatment but we may approximate it by noting that it is intermediate between the two simpler conformations, XVa, in which C_{13} is the only non-planar atom, and XVb, in which C_{14} is the non-planar atom. Rotatory effects will then be the average of those predicted from these two conformations. The bond conformations are as shown in XVI–XXIII. In Table VIII are summarized the rotatory changes to be expected when a hydrogen atom at C_{14}, C_{15}, C_{16} or C_{17} is replaced by a simple substituent.[16,17] A comparison of predicted with observed values for the insertion of *single* substituents on the otherwise unsubstituted D ring of steroids is provided by the data in Table IX; on the whole the agreement is satisfactory. It is a simple matter to extend this treatment to more highly substituted compounds, such as estriols and androstan-3,16,17-triols (XXIV), where excellent agreement is observed.

Monocyclic cyclopentanes are, in principle, more complex to analyze since ten puckered conformations (of possibly unequal energy) should be considered. A major simplification is provided by the assumption that the average conformation will be equivalent to the fully planar conformation. To illustrate the utility of this approach, let us consider the nepetic acids,[18] having the relative and

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[15] See C. W. Shoppee, R. H. Jenkins and G. H. R. Summers, *J. Chem. Soc.*, 3048 (1958), for a review of this point.

[16] More complex substituents, as found in the etio acids, the pregnan-20-ones, the cholestanes and the cholanic acids, show additional conformational asymmetry effects as a result of the sterically asymmetric environment produced by the angular methyl group at C_{13}. These effects will be considered in more detail in a more complete review of rotatory effects in the steroid series.

[17] These calculations can only be made by assuming that the rotatory power of the skew chain of four atoms, X-C-C-Y, increases with angular separation to 90° and then decreases to zero at 180°, in the *trans* conformation, as, for example, in the simple expression

$$[M] = +\sin \phi \cdot k'XY$$

which will be used here. For correlation with values presented in Table I, part I, this expression becomes

$$[M] = \frac{2}{\sqrt{3}} \sin \phi \cdot kXY$$

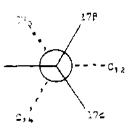
The values used for commonly observed angular separations are then

ϕ	[M]
0°, 180°	0
30°, 150°	$\frac{k}{\sqrt{3}}XY$
60°, 120°	kXY
90°	$\frac{2k}{\sqrt{3}}XY$

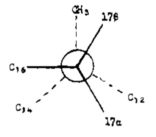
On this basis, corresponding staggered and eclipsed conformations should have the same rotatory power.

[18] S. M. McElvain and E. J. Eisenbraun, THIS JOURNAL, **77**, 1599 (1955); E. J. Eisenbraun and S. M. McElvain, *ibid.*, **77**, 3383 (1955); R. B. Bates, E. J. Eisenbraun and S. M. McElvain, *ibid.*, **80**, 3413, 3420 (1958).

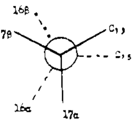
a XV b



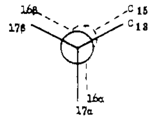
C_{17}–C_{13} (XVa)
XVI



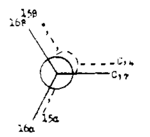
C_{17}–C_{13} (XVb)
XVII



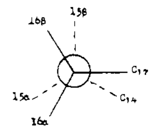
C_{17}–C_{16} (XVa)
XVIII



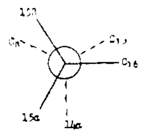
C_{17}–C_{16} (XVb)
XIX



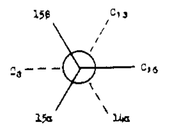
C_{16}–C_{15} (XVa)
XX



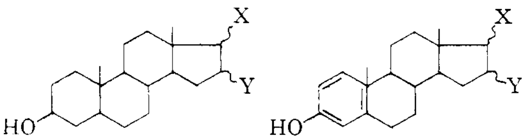
C_{16}–C_{15} (XVb)
XXI



C_{15}–C_{14} (XVa)
XXII



C_{15}–C_{14} (XVb)
XXIII

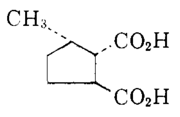


X	Y	[M]D Calcd.	[M]D Obsd.	[M]D Calcd.	[M]D Obsd.
H	*H*		0		226 E[c]
α-OH	α-OH	−56	−59 E[a]	170	167 E[a]
α-OH	β-OH	−34		192	
β-OH	α-OH	−24	−6 E[b]	202	190 E[d]
β-OH	β-OH	+39	+40 E[b]	265	254 E[e]

[a] L. Ruzicka, V. Prelog and P. Wieland, *Helv. Chim. Acta*, **28**, 1609 (1945); **28**, 250 (1945). [b] N. S. Leeds, D. K. Fukushima and T. F. Gallagher, THIS JOURNAL, **76**, 2943 (1954). [c] A. Butenandt and U. Westphal, *Z. physiol. Chem.*, **223**, 147 (1934). [d] A. Butenandt and J. S. L. Browne, *ibid.*, 216, 49 (1933). [e] M. N. Huffman and H. H. Darby, THIS JOURNAL, 66, 150 (1944).

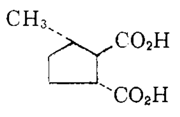
XXIV

absolute configurations shown in XXV. It is seen, from these calculations that, given the relative configurations, the absolute configurations could be assigned simply from the signs of rotation. Alternatively, given the absolute orientation of the methyl group and the *cis*, *trans* relationships of the carboxy groups, the remaining stereochemical relationship (of the methyl group and the adjacent carboxy group) could, in each case, be decided from the sign and magnitude of rotation. Similarly,



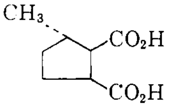
Predicted: $+k(CO_2H - H)^2$; +135°
Observed: $[M]_D$ + 150°[18]

a



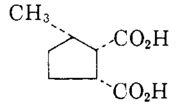
Predicted: $+k(C - H)(CO_2H - H) - k(CO_2H - H)^2$; −45°
Observed: $[M]_D$ −60°[18]

b



Predicted: $+k(C - H)(CO_2H - H)$; +90°
Observed: $[M]_D$ +120°[18]

c

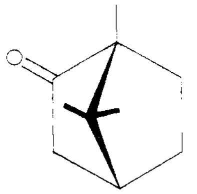


Predicted: 0

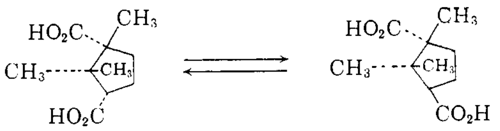
d

XXV

given the relative configurations of the camphoric acids (XXVII),[19] their absolute configurations can be assigned, this leading to an absolute configuration for (+)-camphor (XXVI) in agreement with the conclusions of Fredga.[20]



(+)
XXVI



Predicted: $+k(C - H)^2$; +60°
Observed: $[M]_D$ +95.5°
XXVIIa

Predicted: $+k(C - H)^2 - 2k(C - H)(CO_2H - H)$; −120°
Observed: $[M]_D$ −97.2°
XXVIIb

Absolute configurations can now readily be assigned to a number of other dibasic acids (XXVIII–XXXI).[21–25] The configuration assigned to (−)-*trans*-caronic acid (XXXI) is consistent with its formation from (+)-*trans*-chrysanthemic acid,[21] the configuration of which has been established[22]; note particularly the important rotatory effect of the *gem*-dimethyl group. Barton and Nickon[26] have assigned the absolute configuration XXXII to caryophyllene, basing their conclusions on the rotational properties of rearrangement products and the rules of Stokes and Bergmann and of Klyne and Stokes.[7] The same conclusion is reached somewhat more directly by noting that the

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(19) O. Aschan, *Ann.*, **316**, 209 (1901); W. Hartmann, *Ber.*, **21**, 221 (1888).

(20) A. Fredga and J. K. Miettinen, *Acta Chem. Scand.*, **1**, 371 (1947).

(21) H. Staudinger and L. Ruzicka, *Helv. Chim. Acta*, **7**, 201 (1924).

(22) L. Crombie and S. H. Harper, *J. Chem. Soc.*, 470 (1954).

(23) L. J. Goldsworthy and W. H. Perkin, *ibid.*, **105**, 2639 (1914).

(24) L. J. Goldsworthy, *ibid.*, **125**, 2012 (1924).

(25) E. Buchner and R. v. d. Heide, *Ber.*, **38**, 3112 (1905).

(26) D. H. R. Barton and A. Nickon, *J. Chem. Soc.*, 4665 (1954)

TABLE VIII

CALCULATION OF ROTATORY SHIFTS FOR SUBSTITUTION IN RING D

Substituent	Bond	$[M]_{(X-H)}$ XVa	$[M]_{(X-H)}$ XVb	Average
17β	C_{17}–C_{18}	0	0	
	C_{17}–C_{16}	$\frac{k}{\sqrt{3}}(X-H)(C-H)$	$k(X-H)(C-H)$	$+0.8k(X-H)(C-H)$
17α	C_{17}–C_{18}	0	0	
	C_{17}–C_{16}	$\frac{-2k}{\sqrt{3}}(X-H)(C-H)$	$-k(X-H)(C-H)$	$-1.1k(X-H)(C-H)$
16β	C_{17}–C_{16}	$\frac{-2k}{\sqrt{3}}(X-H)(C-H)$	$-k(X-H)(C-H)$	
	C_{16}–C_{15}	$+k(X-H)(C-H)$	$\frac{+k}{\sqrt{3}}(X-H)(C-H)$	$-0.3k(X-H)(C-H)$
16α	C_{17}–C_{16}	$\frac{+k}{\sqrt{3}}(X-H)(C-H)$	$+k(X-H)(C-H)$	
	C_{16}–C_{15}	$-k(X-H)(C-H)$	$\frac{-2k}{\sqrt{3}}(X-H)(C-H)$	$-0.3k(X-H)(C-H)$
15β	C_{16}–C_{15}	$-k(X-H)(C-H)$	$\frac{-2k}{\sqrt{3}}(X-H)(C-H)$	
	C_{15}–C_{14}	$\frac{+k}{\sqrt{3}}(X-H)(C-H)$	0	$-0.8k(X-H)(C-H)$
15α	C_{16}–C_{15}	$+k(X-H)(C-H)$	$\frac{+k}{\sqrt{3}}(X-H)(C-H)$	
	C_{15}–C_{14}	$\frac{+k}{\sqrt{3}}(X-H)(C-H)$	$+k(X-H)(C-H)$	$+1.6k(X-H)(C-H)$
14α	C_{15}–C_{14}	$\frac{+2k}{\sqrt{3}}(X-H)(C-H)$	$+k(X-H)(C-H)$	
	C_{14}–C_{13}	0	0	
	C_{14}–C_{8}	0	0	$+1.8k(X-H)(C-H)$

TABLE IX

ROTATORY SHIFTS FOR SUBSTITUTION IN RING D OF STEROIDS

Substituent	$\Delta[M]_{X-H}$ α Calcd.	α Obsd.	β Calcd.	β Obsd.
14-CH_3	+108	+73 ± 17[a]		
15-OH	+80	+73[b]	−40	−110[b]
16-OH	−15	−36[c]	−15	−20[c]
17-OH	−55	−50[d]	+40	+20[d]
17-CH_3	−66		+48	+20 ± 10[e]

[a] Calculated from data for 14 α-methylcholestan-3β-ol, its acetate and ketone (D. H. R. Barton, D. A. J. Ives and B. R. Thomas, *Chemistry & Industry*, 1180 (1953)) and for 4,4,14α-trimethylcholestanol derivatives (D. H. R. Barton, J. E. Page and E. W. Warnhoff, *J. Chem. Soc.*, 2715 (1954); D. H. R. Barton and B. R. Thomas, *ibid.*, 1842 (1953); W. Voser, M. Montavon, H. H. Günthard, O. Jeger and L. Ruzicka, *Helv. Chim. Acta*, **33**, 1893 (1950)). [b] Single compounds in methanol; reference compound in dioxane; data of S. Bernstein, L. I. Feldman, W. S. Allen, R. H. Blank and C. E. Linden, *Chemistry & Industry*, 111 (1956). [c] Values cited by C. W. Shoppee, R. H. Jenkins and G. H. R. Summers, *J. Chem. Soc.*, 3048 (1958). [d] Average values as cited by W. Klyne, ref. *a*, Table II. [e] Average of three values; data of L. Ruzicka, P. Meister and V. Prelog, *Helv. Chim. Acta*, **30**, 867 (1947); S. A. Julia and H. Heusser, *ibid.*, **35**, 2080 (1952).

dimethyl esters of the degradation products: *trans-nor*-caryophyllenic acid (XXXIIIa),[27] *trans*-caryophyllenic acid (XXXIIIb)[27] and *trans*-homocaryophyllenic acid (XXXIIIc)[27] are all strongly dextrorotatory while *cis*-homocaryophyllenic acid (XXXIV)[27e] is distinctly less dextrorotatory. It will be noted that the rotations predicted on the assumption that the ring is planar do not agree well with those observed, but that rotations predicted on the assumption that the rings are puckered, as shown in XXXIII and XXXIV, agree quite well.[28]

As a final example of the application of this treatment to alicyclic compounds, consider the two alcohols (+)-borneol and (−)-isoborneol formed by reduction of (+)-camphor (XXVI).[29] The parent hydrocarbon is optically inactive, as is the conformation about the bond between C_1 and C_2 in each alcohol; the bond between C_2 and C_3 is, however, asymmetric in opposite senses in the two alcohols and is the sole conformational source of optical activity. On this basis, all derivatives of (+)-camphor having the relative configuration XXXVa should have $[M]_D = +k(X-H)(C-H)$ while those having configuration XXXVb should have an equal but opposite rotation. The assignment of configuration XXXVa to (+)-borneol is consistent with the conclusion reached by Asahina, *et al.*[30] on chemical grounds. Since

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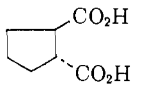
[27] (a) W. C. Evans, G. R. Ramage and J. L. Simonsen, *J. Chem. Soc.*, 1806 (1934); (b) G. R. Ramage and J. L. Simonsen, *ibid.*, 532 (1935); (c) T. L. Dawson and G. R. Ramage, *ibid.*, 3523 (1950); (d) H. N. Rydon, *ibid.*, 593 (1936); 1340 (1937); (e) V. Jarolim, M. Streibl, L. Dolejs and F. Sorm, *Coll. Czech. Chem. Comm.*, **22**, 1266 (1957).

[28] Electron diffraction studies indicate puckered structures for octafluorocyclobutane [H. P. Lemaire and R. L. Livingston, *J. Chem. Phys.*, **18**, 569 (1950)] and for cyclobutane [J. D. Dunitz and V. Schomaker, *ibid.*, **20**, 1703 (1954)]; X-ray studies indicate a similar structure for octachlorocyclobutane [T. B. Owen and J. L. Hoard, *Acta Cryst.*, **4**, 172 (1951)]. In each case dihedral angles of about 20° have been suggested. In the present system, one puckered form, in which a methyl group and the carbomethoxy group across the ring are crowded together, should be much less stable than the other puckered form, in which these two groups are quite far apart. The diagrams XXXIII and XXXIV show the more stable puckered forms.

[29] A. Haller, *Ann. chim.*, [VI] **27**, 392 (1892).

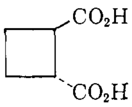
[30] Y. Asahina, M. Ishidate and T. Sano, *Ber.*, **69**, 343 (1936).



Predicted: $-k(CO_2H - H)^2$; $-135°$

Observed: $[M]_D$ $-138°$[23]

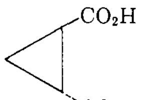
XXVIII



Predicted: $-k(CO_2H - H)^2$; $-135°$

Observed: $[M]_D$ $-179°$[24]

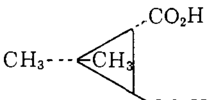
XXIX



Predicted: $-k(CO_2H - H)^2$; $-135°$

Observed: $[M]_D$ $-110°$[25]

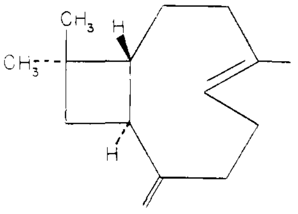
XXX



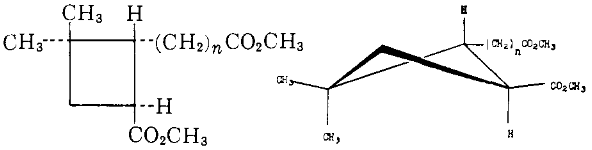
Predicted: $k(CO_2H - H)^2 - 2k(C - H)(CO_2H - H)$; $-45°$

Observed: $[M]_D$ $-52.5°$[21]

XXXI

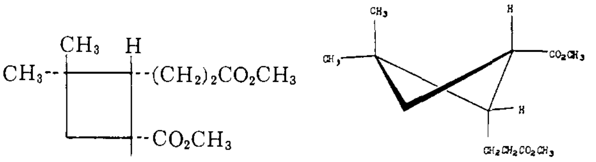


XXXII



		$[M]_D$ Predicted Planar	Puckered	Observed
	n			
a	0	+45°	+135°	+119°(MeOH)[27]
b	1	+30°	+90°	+95°(MeOH)[27]
c	2	+30°	+90°	+99°[27e]

XXXIII



Predicted $[M]_D$ Planar	Puckered	Observed
−60°	+30°	+35°[27e]

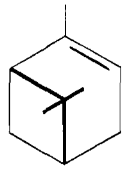
XXXIV

the reduction of camphor with sodium gives predominantly borneol,[31] it is to be expected that the predominant products of reduction of the oxime[32] or thio derivative[33] with active metals will be bornyl derivatives; configurations assigned in this way are in agreement with the present rule. Since (+)-bornyl acetate is formed by addition of acetic acid to (+)-pinene[34] (XXXVI), the (+)-halides formed by addition of HX to (+)-pinene[35,36] are assigned bornyl configurations (XXXVa). The (−)-halides formed by addition of HX to (+)-camphene[37] (XXXVII) are assigned isobornyl configurations (XXXVb) in analogy with the formation of (−)-isobornyl acetate from (+)-camphene.[38] These conclusions are consistent with the present rule and with the views of Nevell, de Salas and Wilson[39] on the stereochemistry of these additions.

a b

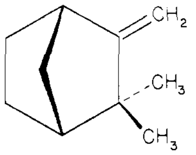
X	$[M]_D$ a	b
-OH	+ 58 (toluene)[29]	− 33 (toluene)[40]
-SH	+ 36 (EtOAc)[33]	
-NH₂	+ 73 (alc)[41]	− 67 (alc)[32]
-Cl	+ 58 (alc)[35]	− 72 (ether)[37]
-Br	+ 67 (alc)[36]	−135[37]
-I	+ 96[36]	

XXXV



(+)

XXXVI



(+)

XXVII

Tetrahydropyran Derivatives.—The principles which permit the present major simplification and extension of Whiffen's treatment of conformational asymmetry[5] appear to be contradicted at three important points by Whiffen's work. These contradictions can be met only by showing that the present treatment allows a satisfactory calculation of the rotations of the pyranose sugars and their methyl glycosides by use of empirical rotation constants consistent (as some of Whiffen's are not) with the principles used here. It is shown below that these rotations can, indeed, be calculated using *six* such constants (*rounded to the nearest five degrees*); Whiffen used *seven* unrelated and unrounded constants in the same calculations.

One of the present constants [$k(C - H)(O - H) = +50°$] corresponds in form to Whiffen's constant *H*,[5] for which he gives a value of +34°[42]; as shown above and in part I, the present value is suitable for use with acyclic alcohols and is generally

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[31] E. Beckmann, *J. prakt. Chem.*, [ii] **55**, 31 (1897).

[32] M. O. Forster, *J. Chem. Soc.*, **73**, 386 (1898); M. O. Forster and J. Hart-Smith, *ibid.*, **77**, 1152 (1900).

[33] H. Wuyts, *Ber.*, **36**, 863 (1903).

[34] G. Bouchardat and J. Lafont, *Ann. chim.*, [vi] **16**, 236 (1889).

[35] F. H. Thurber and R. C. Thielke, THIS JOURNAL, **53**, 1030 (1931).

[36] J. L. Kondakov and S. Saprikin, *Bull. soc. chim. France*, [iv] **37**, 726 (1925).

[37] Pariselle, *Compt. rend.*, **180**, 1832 (1925).

[38] J. Bertram and H. Walbaum, *J. prakt. Chem.*, [ii] **49**, 1 (1894).

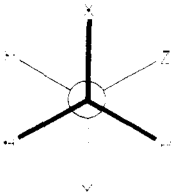
[39] T. P. Nevell, E. de Salas and C. L. Wilson, *J. Chem. Soc.*, 1188 (1939).

[40] R. H. Pickard and W. O. Littlebury, *ibid.*, **91**, 1973 (1907).

[41] P. F. Frankland and F. Barrow, *ibid.*, **95**, 2017 (1909).

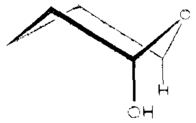
[42] Whiffen's value, together with the value for his constant *F* (+45°) [$k(O - H)^2$], presents several contradictions with the present work. If the numerical manipulations used here are allowed, these two values lead to: $k(C - H)^2 = +25°$, which is badly out of line with the value of +60° used in part I and suggests that carbon is less polarizable than oxygen. Acceptance of Whiffen's value, then, would require abandonment of the numerical manipulations or of the value $k(C - H)^2 = +60°$.

better than Whiffen's value when terpene and steroid alcohols are considered. The second of the present constants [$k(O - H)^2 = +45°$] corresponds in form and magnitude to Whiffen's constant *F* and is, as Whiffen has shown,[5,11] suitable for calculating the rotations of the cyclitols; as shown above, it forms a consistent series with the values for $k(C - H)(O - H)$ and $k(C - H)^2$ used in part I. This constant will also be used to compute the rotation of asymmetric conformations about bond $C_1 - C_2$, where one of the hydroxy groups is glycosidic. Whiffen has used a constant *G* (+32°) for this purpose; acceptance of his value would require a repudiation of the central principle that the rotatory power of the asymmetric conformation XXXVIII is independent of the nature of Y.

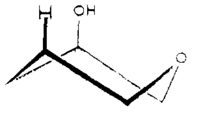


$$[M] = k(X - H)(Z - H)$$
XXXVIII

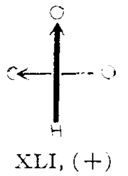
The tetrahydropyran ring, in contrast to cyclohexane, has an axis of polarizability difference (between O and C_4). If the axial substituents at C_1 and C_5 are different (as in XXXIX), they will form an axis of polarizability difference which will form a screw pattern of polarizability with the ring axis. This pattern, as seen in projection in XLI, has the character of a left-handed screw and should (part I) be dextrorotatory. Since the conformational asymmetry effect of the hydroxy group is $+ -k\mathrm{H}(O - H)$, we may expect XXXIX to be strongly dextrorotatory; the empirical value used here is +100°, to be compared with Whiffen's value $J = +113°$. An axial hydroxy group at C_2 or C_4 as shown in XL produces the same permolecular pattern XLI, here opposed by the weak net levorotatory conformational effect: $-k(C - O)(O - H) = ca.\ -5°$. The total rotatory effect of XL is estimated here to be +60°; Whiffen's constant *I* (+43°) fills the corresponding role in his calculations.[43] An additional constant is required for the hexoses since the hydroxy methyl group is in a sterically asymmetric environment; the two "allowed" conformations of this group as found in D-hexoses are seen in XLII. The empirical value +25° is used here for this system; Whiffen uses a value of +30°. The positive sign of this value is consistent with the smaller size of the ether oxygen as compared to C_4 *and its substituents;* the magnitude of this constant cannot be predicted. A final constant is required for calculations of the rotation of methyl glycosides. This constant reflects the fact that the methoxy group is in a sterically asymmetric environment. In the β-D-hexosides (XLIII), for example, the asymmetric conformation XLV should predominate; this conformation should be levorotatory but its magnitude of rotation cannot be predicted. A value of −105° is used here (Whiffen uses −100°); a value of +105° is, then, required for α-D-hexosides (XLIV).



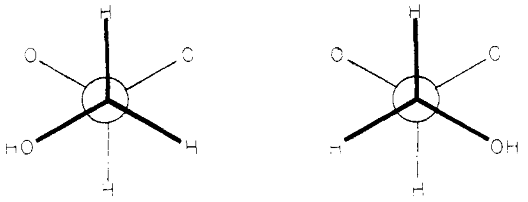
XXXIX, +100°



XL, +60°



XLI, (+)



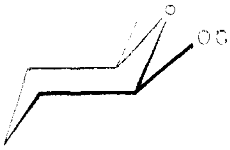
$$\underbrace{+k(O - H)^2 = +45° \qquad -k(C - H)(O - H) = -50°}_{+25°}$$
XLII

TABLE X

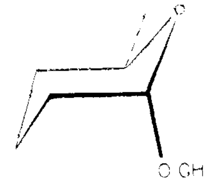
ROTATION CONSTANTS FOR USE WITH CARBOHYDRATES

Notation		Δ[M]	
Present	Whiffen[5]	Whiffen[5]	Present
$k(O - H)(O - H)$	F G	+45° +32°	+45°
$k(C - H)(O - H)$	H	+34°	+50°
XXXIX[a]	J	+113°	+100°
XL[a]	I	+43°	+60°
XLII		+30°	+25°
XLV[a]		−100°	−105°

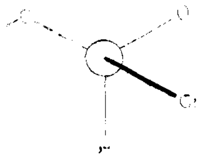
[a] These values can be, roughly, calculated by letting the permolecular effect be +65° and by assigning the value: $k(E - H)(C - H) = -50°$, where E represents an unshared pair of electrons on oxygen. On this basis XXXIX becomes: $65 + k(C - E)(O - H) - k(O - H)(C - H) = +107$; XL becomes: $65 - k(C - O)(O - H) = 60$ (using the value $k(O - H)^2 = 45$) and XLV becomes: $-k(C - E)(O - H) = -92°$. The empirical values give better fits and are used in Table XI.



XLIII, β



XLIV, α



XLV, $-kC(O - H) = -105°$

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(43) Acceptance of Whiffen's *interpretation* of this constant as being due wholly to conformational asymmetry effects would be altogether inconsistent with the present treatment.

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.