

**971.** *Correlations between Monocyclic and Polycyclic Unsaturated Compounds from Molecular Rotation Differences.*

By JOHN A. MILLS.

Shifts in molecular rotation caused by epimerisation at one asymmetric centre are compared for unsaturated compounds in the monocyclic terpenoid and steroid groups. There is some evidence that the conventional steroid projection formula conforms to the glyceraldehyde convention.

Relations between structure and molecular rotation are discussed for unsaturated monocyclic terpenoids. An important correlation is established for epimeric allylic alcohols: alcohols derived from the structural unit (I) are always much more levorotatory than their epimers derived from the unit (II).

The present status of the carvotanacetols, *isolimonene*, and the 7-hydroxy-*epicholesterols* is discussed.

THE method of molecular rotation differences has been used very successfully by Barton and his collaborators to elucidate the structure and configuration of steroids (*e.g.*, Barton and Klyne, *Chem. and Ind.*, 1948, 755, and earlier papers), and recently Klyne (*J.*, 1952, 2916) has used it for correlations between steroids and other polycyclic systems. The present paper describes attempts to correlate polycyclic systems with the monocyclic terpenes.

The procedure differs from that usually followed, in that molecular rotation differences between epimeric pairs of unsaturated compounds are compared, rather than differences between saturated structures and their derivatives. The basic assumption is that it should be possible to trace a relation between the rotational shift caused by a configurational change in a monocyclic structure containing only one or two asymmetric centres, and the shift caused by a corresponding change in a complex polycyclic structure. There are several examples from the steroids and the morphine group that seem suitable for comparison with monocyclic terpenes, particularly amongst unsaturated compounds, for which the rotational changes are usually large. Only steroids are considered here.

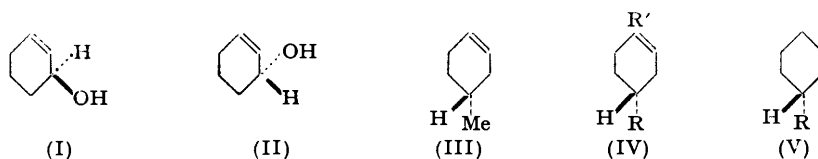
The monocyclic terpenes will be discussed in detail, because enough data are available to permit generalisations about the influence of structure on rotation, and in particular to give all discussions in terms of the glyceraldehyde convention. Fredga has correlated several terpenes with D-glyceraldehyde through the study of "quasi-racemic" compounds (*e.g.*, Fredga and Leskinen, *Arkiv Kemi, Min., Geol.*, 1944, 19, B, no. 1; Fredga, The Svedberg Memorial Volume, 1944, p. 261), and other evidence (which we shall review elsewhere) supports his conclusions. Birch (*Ann. Reports*, 1950, 47, 191) has used Fredga's results, and the extensive configurational relations among terpenes deduced by Huckel (*J. pr. Chem.*, 1941, 157, 225), to compile a list of representative terpenes correctly orientated relatively to D-glyceraldehyde (the sign of rotation for menth-3-ene in his list should be reversed).

In this paper the rotations quoted are all molecular rotations, and, following Klyne (*loc. cit.*), are usually given in parentheses after the name of the substance. Not all of the

rotations compared were taken in the same solvent, but we believe that the errors introduced are small compared with the magnitude of the rotational shifts involved. Data for which no source is given are from Simonsen's "The Terpenes" (Cambridge Univ. Press, 2nd Edn.), and from Fieser and Fieser's "Natural Products Related to Phenanthrene" (Reinhold Publ. Corp., New York, 3rd Edn., 1949).

#### UNSATURATED TERPENOIDS

*Allylic Alcohols.*—Of the possible cyclic, allylic, terpenoid secondary alcohols, epimeric pairs of optically active carveols, cryptols, piperitols, and verbenols have been fully described; the menth-4-en-3-ols and carvotanacetols have not been completely characterised, and the active carvenols are unknown. Table 1 sets out the experimental data for the known epimeric alcohols, their *p*-nitro- and 3 : 5-dinitro-benzoates, the parent ketones, and the corresponding deoxy-compounds (terpene hydrocarbons). According to the evidence available, the configurational assignments are correct, and the projections conform to the glycerinaldehyde convention.



In each optically active epimeric pair, one epimer will be related to the (unknown) optically active *cyclohex-2-en-1-ol* (I), and the other to the enantiomorph (II). All the alcohols derived from the structural unit (I) (third column of Table 1) are more levorotatory than their epimers (fourth column), irrespective of the nature and the position of the alkyl substituents. The differences are greatly enhanced by esterification. In the monocyclic series, the deoxy-compounds tend to have rotations near to the arithmetic mean of the rotations of the derived epimeric alcohols.

One inference which may be drawn is that there is an asymmetric coupling of electronic vibrations in the two strongly polarisable bonds constituting the allylic alcohol system, which produces strong levorotation of polarised sodium light when in the configuration (I) and strong dextrorotation when in configuration (II), independently of other structural features. Models incorporating two coupled oscillators have been used in mathematical treatments of optical rotatory power (cf. Levene and Rothen, in Gilman's "Organic Chemistry," Wiley, New York, 1st Edn., 1938, Vol. II, p. 1791).

If this observation is of general validity it will be of practical value in the assignment of configurations to alcohols, and in correlations with glycerinaldehyde. Two carbohydrates, *D*-xylal and *D*-arabinal, included in Table 1, show a large difference in rotation of the expected sign, but great weight should not be assigned to this, because of the possibility of strong vicinal effects from the adjacent hydroxyl groups, and of electronic interaction with the ring-oxygen atom.

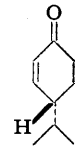
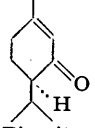
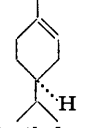
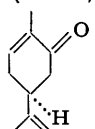
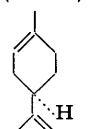
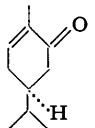
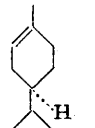
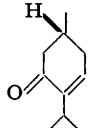
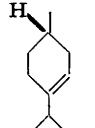


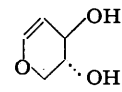
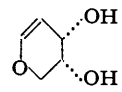
The data of Table 1 are incomplete, and some predictions may be made of probable values for the unknown rotations. These deductions were aided by depicting graphically the data of Table 1, particularly by plotting the values for alcohols, esters, and hydrocarbons related to dextrorotatory ketones.

The structural type is seen to be more important than the nature of the alkyl group (see also the discussion on unsaturated hydrocarbons, below). Carveyl, carvotanacetyl, and menth-4-en-3-yl compounds are of a common structural type, and the alcohols have a common chemical property in ready racemisation by acid-catalysed anionotropic rearrangement (Read and Swann, *loc. cit.*). *trans*-Carveyl and *trans*-menth-4-en-3-yl derivatives have comparable large rotations, and *cis*-carveyl and *cis*-carvotanacetyl derivatives have comparable, much smaller rotations. It is likely that the unknown *cis*-carvotanacetol and *cis*-menth-4-en-3-ol will resemble *cis*-carveol in having quite small rotations, and that *cis*-menth-4-en-3-yl esters will have rotations comparable to those of *cis*-carveyl esters. *cis*-Carvotanacetol has not been isolated in the free state, but the

rotations for its *p*-nitro- and 3:5-dinitro-benzoate reported by Read and Swann are near the expected values.

Read and Swann's values for the rotations of (+)-*trans*-carvotanacetol (+166°) and

TABLE 1. Molecular rotations of allylic terpenoid alcohols.

Ketone	Deoxy-compound	Epimeric alcohols		$\Delta[M]_D$ (II)-(I)	Refs.
		Type (I)	Type (II)		
 Cryptone (-90°)	—	<i>trans</i> -165° NB -494 DNB -500	<i>cis</i> +104° NB +540 DNB +518	269° 1034 1018	1
 Piperitone (-103°)	 Menth-1-ene (-161°)	<i>cis</i> -379 NB -921 DNB -912	<i>trans</i> +43 NB +545 DNB +571	422 1466 1483	2
 Carvone (+94°)	 Limonene (+169°)	<i>cis</i> +35 NB -173 DNB -153	<i>trans</i> +328 NB +800 DNB +807	293 973 960	3
 Carvotanacetone (+90°)	 Menth-1-ene (+161°)	<i>cis</i> < +85 NB -155 DNB -116	<i>trans</i> +166 NB +258 DNB +619	> 81 413 735	3, 4
 Menth-4-en-3-one (-119°)	 Menth-3-ene (-149°)	<i>trans</i> -299 NB -636 DNB -609	<i>cis</i> > -106 DNB > -212	> 193 > 397	5
 Verbenone (+273°)	 $\alpha$ -Pinene (+70°)	<i>cis</i> +100 NB +42	<i>trans</i> +257 NB +593	157 551	6
	 D-Xylal diacetate	-295 -628	 D-Arabinal diacetate	+235 +532	7, 8, 9

Rotations are mainly for the homogeneous state, except for esters (NB = *p*-nitrobenzoate, DNB = 3:5-dinitrobenzoate), which are for chloroform solution. Data from "The Terpenes" and: 1, Gillespie, Macbeth and Mills, *J.*, 1948, 996; 2, Macbeth and Shannon, *J.*, 1952, 2852; 3, Johnston and Read, *J.*, 1934, 233; 4, Read and Swann, *J.*, 1937, 239; 5, Malcolm and Read, *J.*, 1939, 1037; 6, Schulz and Doll, *Schimmel's Ber.*, 1942-43, 50; 7, Gehrke and Obst, *Ber.*, 1931, 64, 1724; 8, Gehrke and Aichner, *Ber.*, 1927, 60, 918; 9, Meisenheimer and Jung, *Ber.*, 1927, 60, 1462.

its *p*-nitrobenzoate (+258°) do not fit the general pattern, being much lower than expected. Johnson and Read (*loc. cit.*) obtained from *trans*-carveol a substance believed to be (+)-*trans*-carvotanacetyl 3 : 5-dinitrobenzoate, that is seen to have a rotation (+619°) of the expected magnitude. Read and Swann's value for (+)-*trans*-carvotanacetyl *p*-nitrobenzoate is near to that to be expected for an equimolecular mixture of (+)-*trans*- and (−)-*cis*-*p*-nitrobenzoates; if this assumption is made, the calculated value for the pure *trans*-ester is +670°.

The assumption of an equimolecular mixture to reconcile the data is not dictated solely by mathematical considerations. It is quite reasonable that an equimolecular mixture of diastereoisomeric esters should form a compound not resolvable by recrystallisation; such a compound would represent a limiting case of quasi-racemic compound formation in which the sets of groups about the centres of opposite configuration are structurally identical. The possibility that such equimolecular diastereoisomeric compounds may be formed from esters of cyclic terpene alcohols does not seem to have been explored, but it is known that epimeric *p*-nitrobenzoates of cyclic alcohols have a tendency to form mixed crystals (*e.g.*, the cryptols; Gillespie, Macbeth, and Mills, *loc. cit.*).

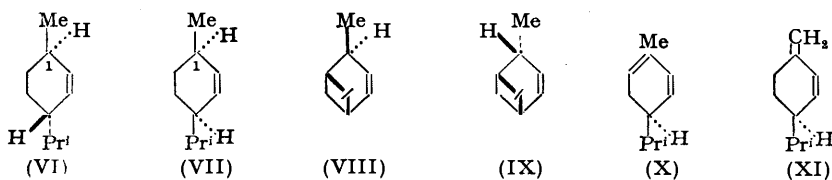
Read and Swann found that their crude carvotanacetyl mixture (+143°) (which should have contained comparable amounts of the epimers, since it was obtained by aluminium *isopropoxide* reduction; cf. Jackman, Macbeth, and Mills, *J.*, 1949, 2641) gave the supposedly pure *p*-nitrobenzoate rather easily, with only a small change in rotation (+166° for the regenerated alcohol), but did not afford a crystallisable 3 : 5-dinitrobenzoate; this suggests that the crude alcohol was far from optically pure. The *cis*-carvotanacetyl esters, which have the expected rotations, were isolated from an abnormal batch of crude carvotanacetyl (+85°) that appears to have contained a preponderance of *cis*-epimer.

The unknown carvenols should show optical rotations similar to those of the piperitols, and, like the piperitols and other allylic alcohols with branching at the  $\gamma$ -carbon atom, be very susceptible to acid-catalysed 1 : 4-dehydration. In piperitols, two asymmetric centres are adjacent, and the enhanced rotational differences noted are probably due to stronger vicinal action than in the other alcohols of Table 1.

*Unsaturated Hydrocarbons.*—Data for the hydrocarbons in Table 1, and other available examples, show that a double bond may cause large rotational shifts when introduced into a cyclohexane ring at a position either 2 : 3 or 3 : 4 to an alkyl group.

Consideration of 4-methylcyclohex-1-ene (III; +97°) (Mousseron, *Bull. Soc. chim.*, 1946, 218) and, in Table 1, limonene (+169°), menth-1-ene (+161°), and menth-3-ene (−149°) suggests the generalisation that the projection (IV), in which the hydrogen atom at the asymmetric centre is two places removed from the double bond in a clockwise direction and orientated above the plane of the ring, will represent a dextrorotatory compound when R, R' are simple alkyl groups; when R' is present the rotation is likely to be of the order of +150°, but probably less when R' = H.

The structure (V), in which the hydrogen atom is orientated above the plane at an asymmetric centre one place clockwise from the double bond, is also associated with dextrorotation. 3-Methylcyclohex-1-ene (V; R = Me; +74°) (Mousseron, *loc. cit.*) is the only simple representative of the class, but the rotational differences between (+)-*trans*-menth-

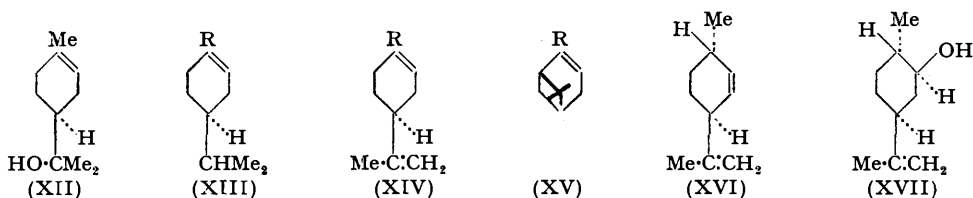


2-ene (VI; +182°) and (+)-*cis*-menth-2-ene (VII; +63°) (Hückel and Wagner, *Ber.*, 1941, 74, 657), and between (+)-*cis*- $\delta$ -pinene (VIII; +80°) and (−)-*trans*- $\delta$ -pinene (IX; −146°) (Schmidt, *Chem. Ber.*, 1947, 80, 520), are doubtless due largely to the epimerisation of the hydrogen atom at one asymmetric centre; the sign of the difference is the same as for transformation of (V; R = Me) into its enantiomorph, and a difference of the same

sign is obtained by epimerisation at  $C_{(1)}$  only in (VI) or (VII). The four molecular rotation differences ( $148^\circ$ ,  $119^\circ$ ,  $226^\circ$ ,  $245^\circ$ ) obtainable by epimerisation of one C-H group in the structures (V; R = Me) to (IX) differ considerably, although the signs conform; evidently strong vicinal effects are introduced even when the two centres are separated as in menth-2-ene.

(-)- $\alpha$ -Phellandrene (X;  $-241^\circ$ ) (Hancox and Jones, *Univ. Queensland Papers*, 1939, 1, 14) and (-)- $\beta$ -phellandrene (XI;  $-101^\circ$ ) (Berry, *J. Proc. Aust. Chem. Inst.*, 1947, 14, 387) are included to show that large molecular rotations are associated with monocyclic conjugated dienes, but nothing is known about the effect of altering the nature and degree of alkylation of the diene system.

Altering the polarity of alkyl substituents has surprisingly little effect on rotation, provided the structural type remains constant. The various combinations of methyl, isopropyl, and isopropenyl in Table 1 have very similar rotations, and this is generally true if one of the alkyl groups is hydroxylated; e.g., (-)- $\alpha$ -terpineol (XII;  $-155^\circ$ ), (-)-menth-1-ene (XIII; R = Me;  $-161^\circ$ ), and (-)-limonene (XIV; R = Me;  $-169^\circ$ );



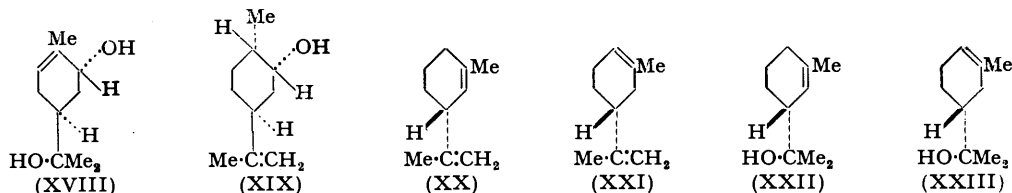
phellandrol (XIII; R =  $\text{CH}_2\cdot\text{OH}$ ;  $-167^\circ$ ) and phellandryl esters [*p*-nitrobenzoate ( $-182^\circ$ ), 3:5-dinitrobenzoate ( $-173^\circ$ ), hydrogen phthalate ( $-164^\circ$ ), phenylurethane ( $-164^\circ$ ),  $\alpha$ -naphthylurethane ( $-170^\circ$ ); Human, Macbeth, and Rodda, *J.*, 1949, 350]; perillyl alcohol (XIV; R =  $\text{CH}_2\cdot\text{OH}$ ;  $-148^\circ$ ) and perillyl acetate ( $-147^\circ$ ) (Schmidt, *Chem. Ber.*, 1950, 83, 193). Fuller and Kenyon (*J.*, 1924, 125, 2304) found that aliphatic esters of  $\alpha$ -terpineol have rotations very similar to that of  $\alpha$ -terpineol itself, but divergence occurs for more complex esters, e.g., the hydrogen phthalate ( $-124^\circ$ ) and phenylurethane ( $-112^\circ$ ). In the dicyclic series,  $\alpha$ -pinene (XV; R = Me;  $+70^\circ$ ), myrtenol (XV; R =  $\text{CH}_2\cdot\text{OH}$ ;  $+76^\circ$ ) and various myrtenyl esters ( $+64^\circ$  to  $+76^\circ$ ; Akermann, *Annalen*, 1920, 420, 1) also show little change in rotation as the alkyl group is altered. Free rotation of the substituents can reduce the effects of differing polarity, but not abolish them. As expected, introducing conjugation has a marked effect, as in phellandral (XIII; R = CHO;  $-243^\circ$ ), perilla aldehyde (XIV; R = CHO;  $-220^\circ$ ), and myrtenal (XV; R = CHO;  $+23^\circ$ ).

One reported variant on the structural type (VI) deserves comment. By the thermal decomposition of a dihydrocarveyl methyl xanthate, Tschugaev (*J. Russ. Phys. Chem. Soc.*, 1904, 36, 993) obtained a product, (-)-isolimonene ( $-191^\circ$ ), to which he assigned the structure of a mentha-2:8(9)-diene. Some doubt has been expressed about this formulation ("The Terpenes," Vol. I, p. 214), although support for it has been forthcoming (Pigulevski and Gorbunova, *Chem. Abs.*, 1947, 41, 6551). The magnitude and sign of rotation indicate that (-)-isolimonene is in fact (-)-*trans*-mentha-2:8(9)-diene (XVI), and the *trans*-configuration is also indicated by the method of preparation. The dihydrocarveol from which it was made apparently is the chief product from the reduction of (+)-carvone with sodium in alcohol (cf. Johnston and Read, *loc. cit.*), and is therefore the thermodynamically most stable isomer (XVII), with all-equatorial substituents (Barton, *Experientia*, 1950, 6, 316). However, the decomposition of the methyl xanthate appears to produce far more of (XVI) than would be expected, in view of the preferential elimination towards a tertiary carbon atom when this is possible (Barton, *J.*, 1949, 2174).

One allylic alcohol with a hydroxyalkyl substituent is known. Sobrerol ( $-240^\circ$ ; Wallach, *Annalen*, 1918, 414, 195) must be represented by (XVIII), the *trans*-configuration following from its correlation with neodihydrocarveol (XIX) (Schmidt, *loc. cit.*, footnote 4). Sobrerol has a rotation of the same sign as, but rather less than, the configurationally

related carveol ( $-328^\circ$ ) and menth-4-en-3-ol ( $-299^\circ$ ). *cis*-Sobrerol apparently has not been described; its rotation probably would be quite small.

An interesting and important example is found in the 1:3-menthane series. (+)-

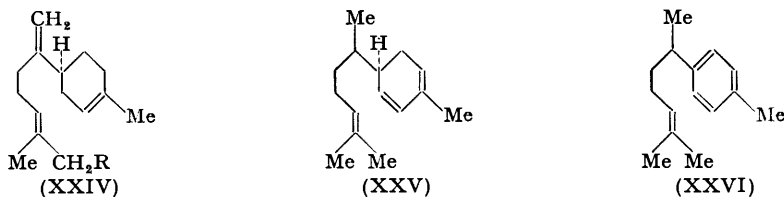


Sylvestrene is believed to be a mixture of (XX) and (XXI), the correlation with glyceraldehyde following from the relation to (+)-car-3-ene and (+)-car-4-ene (cf. Birch, *loc. cit.*). The individual rotations of (XX) and (XXI) are not known, but the related sylveterpineols (XXII) and (XXIII) are known in practically pure forms (Haworth and Perkin, *J.*, 1913, 103, 2225). Isomer (XXII) is strongly dextrorotatory ( $+71^\circ$ ), and therefore conforms to the general behaviour of analogous 1:4-menthane derivatives, but (XXIII) is slightly laevorotatory ( $-4^\circ$ ). The latter differs from (+)- $\alpha$ -terpineol in having the methyl group at the opposite end of the double bond; this will reverse the preferred direction of polarisation of the double bond, and this suffices to annul the strong dextrorotation of  $\alpha$ -terpineol. Data for the unmethylated analogue of (XXIII) would be of interest.

These examples from the monoterpenoids provide enough working rules to be of use in assigning configurations to, and assessing optical purity of, other terpenes, and should provide an interesting testing ground for theories on the origin of optical rotatory power. Their application to configurational problems in more complex unsaturated structures is discussed below, and the example of the sylveterpineols shows that the application should be carried out with discretion.

Reference may be made to a method which is sometimes used to assess the rotatory contributions of individual asymmetric centres in a complex structure (cf. Fieser and Fieser, *op. cit.*, pp. 26, 211). It has been assumed that if, for example, the introduction of a double bond near to one asymmetric centre causes a strong dextrorotatory shift, the contribution of the asymmetric centre is dextrorotatory in the saturated structure. This argument is quite fallacious, as the direction of the shift on introduction of unsaturation will be largely determined by the spatial arrangement of the double bond and the asymmetric centre, and the degree of alkylation of the double bond.

*Unsaturated Sesquiterpenes.*—No sesquiterpene appears to have been correlated with glyceraldehyde, but firm correlations may now be advanced in at least two cases. The environment of the sole asymmetric centre in lanceol (XXIV; R = OH) (Birch and Murray, *J.*, 1951, 1888; Eschenmoser, Schreiber, and Keller, *Helv. Chim. Acta*, 1951, 34, 1667) and  $\beta$ -bisabolene (XXIV; R = H) is comparable to that in limonene (XIV; R = Me),



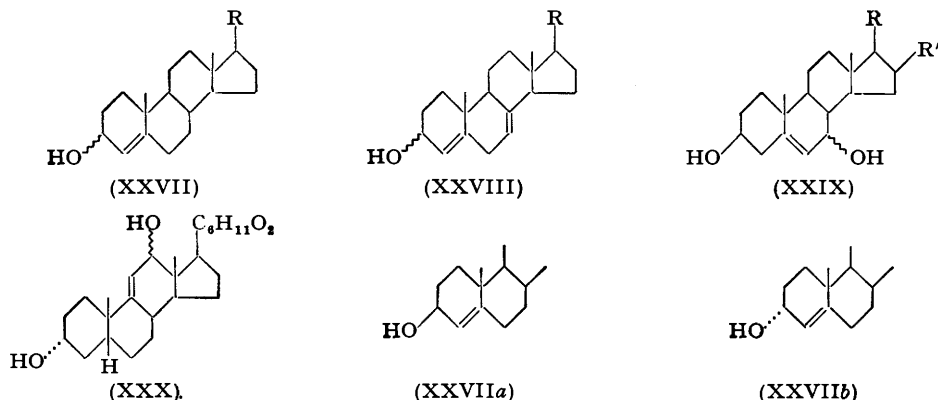
therefore projection (XXIV) should represent the (–)-forms. For natural lanceol ( $-152^\circ$ ) and the derived  $\beta$ -bisabolene ( $-157^\circ$ ) Birch and Murray observed relations similar to that of limonene ( $-169^\circ$ ).

Zingiberene (XXV) contains the elements of  $\alpha$ -phellandrene (X) (Eschenmoser and Schintz, *ibid.*, 1950, 33, 171), with an additional asymmetric centre in the side chain. The configuration at the latter centre is unknown, but its contribution to the total activity of zingiberene is not likely to exceed the rotation of  $\alpha$ -curcumene (XXVI;  $[M]_{5461} \pm 84^\circ$ ). The sign of rotation for zingiberene should be determined by the configuration of the

$\alpha$ -phellandrene portion, and natural zingiberene ( $-150^\circ$ ), which has not been obtained demonstrably pure, is probably one of the diastereoisomers represented by (XXV). The complete configuration of zingiberene would be of interest, because it is related to that of some dicyclic sesquiterpenes (cf. Soffer, Steinhardt, Turner, and Stebbins, *J. Amer. Chem. Soc.*, 1944, **66**, 1520; Eschenmoser and Schintz, *loc. cit.*).

## UNSATURATED STEROIDS

*Allylic Alcohols.*—While this paper was being written, Klyne (*Helv. Chim. Acta*, 1952, **35**, 1224) pointed out that the large rotational shifts associated with epimerisation of the hydroxyl group in some allylic steroid alcohols (cf. Schaltegger and Müllner, *ibid.*, 1951, **34**, 1096; Heymann and Fieser, *ibid.*, 1952, **35**, 631; Henbest and Jones, *J.*, 1948, 1798)



are rationally explained in three cases if the spatial dispositions of the hydroxyl group and the double bond are taken into account. Altogether, there are at least seven epimeric pairs of homoannular allylic alcohols (see Table 2) which show a uniformity of molecular

TABLE 2. Molecular rotations of allylic steroid alcohols.

Structure	Epimer of type (I)	Epimer of type (II)	$\Delta[M]_D$ (II) - (I)	Deoxy-compound	Refs.
<i>Ring A</i>					
Cholest-4-en-3-ol (XXVII; R = C <sub>8</sub> H <sub>17</sub> )	3 $\beta$ , + 170°	3 $\alpha$ , +467°	+ 297°	+248°	1
Androst-4-en-3 : 17 $\beta$ -diol (XXVII; R = OH)	3 $\beta$ , + 142	3 $\alpha$ , +545	+ 403	+136	2, 3
Cholesta-4 : 7-dien-3-ol (XXVIII; R = C <sub>8</sub> H <sub>17</sub> )	3 $\beta$ , + 38	3 $\alpha$ , +307	+ 269	—	4
acetate	3 $\beta$ , - 239	3 $\alpha$ , +538	+ 777	—	
3 : 5-dinitrobenzoate	3 $\beta$ , - 454	3 $\alpha$ , +919	+1373	—	
Ergosta-4 : 7 : 22-trien-3-ol (XXVIII; R = C <sub>9</sub> H <sub>17</sub> )	3 $\beta$ , - 143	3 $\alpha$ , +150	+ 293	—	5
acetate	3 $\beta$ , - 339	3 $\alpha$ , +405	+ 744	—	
<i>Ring B</i>					
Cholest-5-ene-3 $\beta$ : 7-diol (XXIX; R = C <sub>8</sub> H <sub>17</sub> , R' = H)	7 $\alpha$ , - 351	7 $\beta$ , + 29	+ 380	-151	1
7-monoacetate	7 $\alpha$ , - 851	7 $\beta$ , +322	+1179	-151	
diacetate	7 $\alpha$ , - 847	7 $\beta$ , +252	+1099	-184	
dibenzoate	7 $\alpha$ , - 641	7 $\beta$ , +573	+1214	- 74	
22-isoSpirost-5-ene-3 $\beta$ : 7-diol (XXIX; RR' = C <sub>8</sub> H <sub>14</sub> O <sub>2</sub> )	7 $\alpha$ , - 690	7 $\beta$ , -323	+ 367	-534	6
dibenzoate	7 $\alpha$ , -1068	7 $\beta$ , +166	+1234	-472	
<i>Ring c</i>					
Methyl 3 $\alpha$ : 12-dihydroxychol-9(11)-enate (XXX)	12 $\beta$ , + 110	12 $\alpha$ , +407	+297	+175	1
diacetate	12 $\beta$ , + 15	12 $\alpha$ , +976	+991	+271	

Refs. : 1, Klyne, *loc. cit.*; 2, Butenandt and Heusner, *Ber.*, 1938, **71**, 198; 3, Huang-Minlon, *J. Amer. Chem. Soc.*, 1949, **71**, 3301; 4, Windaus and Kaufmann, *Annalen*, 1939, **542**, 218; 5, Windaus and Buchholz, *Ber.*, 1938, **71**, 576; 1939, **72**, 597; 6, Ringold, Rosenkranz, and Djerassi, *J. Amer. Chem. Soc.*, 1952, **74**, 3318.

rotation differences comparable to that of the terpenes. Further, the magnitude of the differences for the alcohols, and the enhanced differences for the esters, are similar in the two series and have presumably a common cause. Again, too, the differences for the allylic steroid alcohols (min. 269°; mean *ca.* 330°) are far greater than those found on epimerisation of analogous saturated steroid alcohols (max. 181°; mean *ca.* 50°; cf. Fieser and Fieser, *op. cit.*, Table XV).

The most striking feature is that all these pairs of alcohols, of very diverse structural types, conform to the pattern noted by Klyne for three of them, and, furthermore, when the usual steroid projection is used it is the same pattern as is shown by the monoterpenoids when they conform to the glycerinaldehyde convention: the more lævorotatory epimers are built up from the *cyclohex-2-en-1-ol* projection (I), and the more dextrorotatory from the enantiomorphous projection (II) [cf. steroid  $-4\text{-en-}3\beta\text{-ols}$  (XXVIIa) and  $-4\text{-en-}3\alpha\text{-ols}$  (XXVIIb)]. These facts suggest that the usual steroid projection conforms to the glycerinaldehyde convention, in contradiction to Bergström, Lardon, and Reichstein (*Helv. Chim. Acta*, 1949, **32**, 3, 1613, 1617, 2003). Other evidence in favour of this new correlation is presented below.

Table 2 shows that in several cases the corresponding deoxy-compound has a rotation intermediate between those of the epimeric alcohols. It is even less likely for the steroids than for the terpenoids that the rotation of the deoxy-compound should be the arithmetic mean of those for the alcohols, because of the likelihood of complex vicinal actions.

One pair of substances alleged to be epimeric allylic alcohols does not conform to the pattern of Table 2. Windaus and Naggatz (*Annalen*, 1939, **542**, 204), by aluminium *isopropoxide* reduction of 7-keto*epi*cholesteryl acetate, obtained two compounds which they called " $\alpha$ - and  $\beta$ -7-hydroxy*epi*cholesterol." Barton (*J.*, 1949, 2174) pointed out that the evidence from pyrolysis of the dibenzoates indicated that the trivial indices were correctly assigned, and that the alcohols in question were therefore cholest-5-ene-3 $\alpha$ :7 $\alpha$ - and -3 $\alpha$ :7 $\beta$ -diol (XXXI and XXXII). The validity of this argument is weakened by the



admission by Windaus and Naggatz that they could not obtain the  $\beta$ -dibenzoate properly crystalline. By analogy with the other two ring-B allylic alcohols of Table 2, the  $\alpha$ -diol should be the more lævorotatory by about 350°, but Windaus and Naggatz found it to be rather more dextrorotatory. Table 3 shows the rotational data for the two alcohols in

TABLE 3. *Cholest-5-ene-3:7-diols and their derivatives.*

Derivative	7-Hydroxycholesterols <sup>1</sup>		"7-Hydroxy <i>epi</i> cholesterols" <sup>2</sup>	
	3 $\beta$ :7 $\alpha$	3 $\beta$ :7 $\beta$	"3 $\alpha$ :7 $\alpha$ "	"3 $\alpha$ :7 $\beta$ "
Diol .....	-351°	+29°	+153°	+36°
Diacetate .....	-847	+252	+97	+340
Dibenzoate .....	-641	+573	+573	+61
Cholesterol .....	-151° <sup>3</sup>	<i>epi</i> Cholesterol .....	-145° <sup>3</sup>	
acetate .....	-184 <sup>4</sup>	acetate .....	-54 <sup>5</sup>	
benzoate .....	-64 <sup>5</sup>	benzoate .....	-142 <sup>6</sup>	

<sup>1</sup> Table 2. <sup>2</sup> Windaus and Naggatz, *loc. cit.* <sup>3</sup> Fieser and Fieser, *op. cit.*, Table XV. <sup>4</sup> Barton, *J.*, 1945, 813. <sup>5</sup> Plattner and Lang, *Helv. Chim. Acta*, 1944, **27**, 1872. <sup>6</sup> Barnett, Heilbron, Jones, and Verrill, *J.*, 1940, 1390.

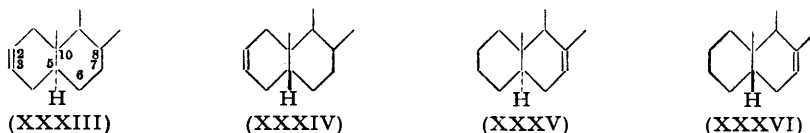
question, for the 7-hydroxycholesterols, and for cholesterol and *epi*cholesterol. The data for the " $\beta$ -7-hydroxy*epi*cholesterol" and its diacetate agree well with what would be expected for a substance of structure (XXXII), but the  $\alpha$ -diol isolated by Windaus and Naggatz certainly is not (XXXI). If it is a pure compound, it may have resulted from a shift of the double bond. Windaus and Naggatz obtained the  $\alpha$ -diol in greater yield (25%) than would be expected if it were genuinely (XXXI); under similar conditions,



7-ketocholesteryl acetate affords only about 7% of the  $3\beta:7\alpha$ -diol (Wintersteiner and Ruigh, *J. Amer. Chem. Soc.*, 1942, **64**, 2453), and structures of this type are very likely to suffer ionic dehydration.

*Unsaturated Hydrocarbons.*—Few pairs of unsaturated steroids are known differing only in configuration at  $C_{(5)}$ , but the standard tables of Barton and Klyne (*loc. cit.*) may be used to calculate molecular rotation differences for epimerisation at  $C_{(5)}$  in several structural types.

Saturated steroid hydrocarbon pairs epimeric at  $C_{(5)}$  (cholestane, coprostane, etc.) show rotation differences of only about  $6^\circ$ . When a double bond is introduced at the 2:3-position in a saturated 5-*allosteroid* ( $5\alpha$ ; rings A/B *trans*), the molecular rotation changes by about  $+152^\circ$ , whereas introducing 2:3-unsaturation into a saturated 5-*n-steroid* ( $5\beta$ ; rings A/B *cis*) causes a molecular rotation shift of about  $-41^\circ$ . Therefore, the molecular rotation shift caused by epimerisation of  $C_{(5)}$  from the  $5\alpha$ -structure (XXXIII) to the  $5\beta$ -structure (XXXIV) is about  $-190^\circ$ .



If the double bond,  $C_{(5)}$ , and the  $C_{(6)}-CH_2$  group are alone considered, the transformation of (XXXIII) into (XXXIV) is analogous to the transformation of (+)-4-methylcyclohex-1-ene (III) into its enantiomorph, which causes a rotational shift of  $-194^\circ$ . The close correspondence of these two values may be presented as evidence for the identity of the glyceraldehyde and steroid conventions, provided two objections can be met: the double bond may not have a constant influence in (XXXIII) and (XXXIV) on asymmetric centres other than  $C_{(5)}$ , because of the different shape of the A/B section in the two structures; and the vicinal effects between  $C_{(5)}$  and  $C_{(10)}$  may be much greater in the unsaturated compounds.

The standard rotational increments for the introduction of 7:8-unsaturation are approximately  $-68^\circ$  for the  $5\alpha$ -series and  $+119^\circ$  for the  $5\beta$ -series, therefore the shift on epimerising (XXXV) to (XXXVI) is about  $+193^\circ (\pm 30^\circ)$ . The formally analogous transformation among the terpenes is the conversion of (-)-menth-3-ene into (+)-menth-3-ene, which causes a shift of  $+298^\circ$ . As evidence of the correctness of the current steroid convention, this is open to the same objections as the preceding case.

These objections cannot be met in detail, because there are no suitable data for structures intermediate between monoterpenoids and steroids. Interaction between  $C_{(5)}$  and  $C_{(10)}$  is not likely to be greatly increased by 2:3- or 7:8-unsaturation, because neither centre is in an allylic position. The different shape of the A/B portion of  $5\alpha$ - and  $5\beta$ -steroids does not seem likely to cause marked alterations in the contributions from asymmetric centres other than  $C_{(5)}$  or  $C_{(10)}$ : for 7:8-unsaturation the relation of these other centres to the double bond is apparently the same; for 2:3-unsaturation it is not, but the double bond is now at a greater distance from the other centres than that (*ca.* 3.5 Å) at which vicinal action between an asymmetric centre and a double bond seems to become negligible for our purpose (Stokes and Bergmann, *J. Org. Chem.*, 1951, **16**, 1817).

The most valid objection we have encountered is that cyclohexene rings in monocyclic and polycyclic systems may exist in conformations sufficiently different to vitiate comparisons between unsaturated hydrocarbons, or even allylic alcohols. We believe this can be met, at least in a general way. The basic assumption behind all the above correlations is that the large rotations associated with these unsaturated systems arise mainly from interaction between two electric fields, one associated with the double bond, the other with the asymmetric centre; this seems to be consistent with some modern views on optical rotatory power (Levene and Rothen, *op. cit.*; Kauzmann, Walter, and Eyring, *Chem. Reviews*, 1940, **26**, 338). It is then logical to assign greater weight to a reversal of the asymmetric centre than to possible small angular displacements of it relative to the double bond.

Effects due to possible differences of conformation should be least when the asymmetric centre is in an allylic position, because of the restraint of the double bond on extensive atomic displacements in its vicinity. Allylic pinene derivatives are discussed along with monocyclic compounds (Table I and p. 4979) because the relevant parts of the bicyclic and monocyclic structures must be of nearly the same shape: ring fusion will constrain five ring atoms of (VIII) to a plane, and in (VII) four ring atoms will be at or near coplanarity because of the presence of the double bond. The slight displacements resulting from strain in the former are unlikely to introduce disturbances sufficient to mask the effect due to epimerisation of the asymmetric centre.

In the comparison of (XXXIII) and (XXXIV) with 4-methylcyclohexenes, it is assumed that in the steroids the shift expected from the epimerisation of  $C_{(5)}$  is great enough to predominate over the sum of the effects due to the altered relations between the other asymmetric centres (these effects would have to amount to about  $400^\circ$  to reverse the correlation), and that the same relation between the C-H bond at the asymmetric centre and rotational shift will hold as holds in monocyclic compounds. 4-Methylcyclohexene is the closest monocyclic model available, but the quantitative agreement is probably fortuitous; a decisive shift in the same direction in each case was all that was expected.

Stokes and Bergmann (*loc. cit.*) have discussed rotational shifts in unsaturated steroid hydrocarbons, and developed ideas with which we agree in principle. Their detailed discussion is based on the steroid correlation of Bergström, Lardon, and Reichstein (*loc. cit.*), but if the above ideas are correct the observed shifts at nuclear centres seem to be explicable on the current steroid convention.

The data for allylic alcohols show by their quantity and variety that there are grounds for believing in the correctness of the current steroid convention. The correlation through unsaturated hydrocarbons is presented as a tentative new approach to the problem of correlation through molecular rotation differences; at present it suffers from paucity of examples and the necessity for considering asymmetric centres which are also ring junctions. Deductions from optical data can never prove a correlation, but we feel that those above deserve some weight, in view of the experimental difficulties encountered by Bergström *et al.* The most decisive proof of steroid configuration would be the isolation of a degradation product containing a quaternary carbon atom of known configuration.

I thank the Australian National University for the award of a Scholarship, and Dr. W. Klyne for some helpful criticism.