The Molecular Rotations of Polycyclic Compounds. Part III. Polycyclic Alcohols and their Derivatives.*

By W. KLYNE and W. M. STOKES.

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General rules are proposed regarding the molecular-rotation contributions of hydroxyl groups and derived functions in alicyclic compounds. These rules are based on the work of Stokes and Bergmann (*J. Org. Chem.*, 1952, **17**, 1194) and of Mills (*Chem. and Ind.*, 1953, 212). The rules are applied to triterpenoid alcohols and to steroid alcohols carrying hydroxyl groups in ring D.

The molecular-rotation contributions of hydroxyl and derived functions in the steroid side-chain are compared with those for simple aliphatic compounds.

THE previous papers in this series (Klyne, *J.*, 1952, 2916; 1953, 3072) have dealt chiefly with the contributions of ketonic and olefinic groupings to the molecular rotations of polycyclic compounds.

Stokes and Bergmann (*J. Org. Chem.*, 1952, **17**, 1194) have shown that certain general principles may be applied to the rotation contributions of hydroxy-, acetoxy-, and benzoyloxy-groups in steroids. They tried to apply Marker's empirical rules regarding the optical rotations of acyclic compounds (*J. Amer. Chem. Soc.*, 1936, **58**, 976) to steroids and reached the provisional conclusion that the steroid convention for formulæ was opposite to the glyceraldehyde convention.

Mills (*Chem. and Ind.*, 1953, 212) showed by reference to monoterpenoids, whose configurations have been reliably correlated with that of glyceraldehyde, that this application of Marker's rule to cyclic compounds is unjustified and leads to the wrong answer. He produced evidence from the rotations of saturated hydroxy-steroids and hydroxy-monoterpenoids (*loc. cit.*) and from those of their allylic analogues (*J.*, 1952, 4976) that the steroid and the glyceraldehyde convention are in agreement. Prelog and his colleagues (*Helv. Chim. Acta*, 1953, **36**, 308, 320, 325) have confirmed this conclusion by the method of asymmetric synthesis which they have applied to monoterpenoids, triterpenoids, and steroids. Klyne (*J.* 1952, 2916) had previously correlated the triterpenoids with the steroids.

The method of rotational analysis used by Stokes and Bergmann (*loc. cit.*) for steroid alcohols and their derivatives can be applied to triterpenoid alcohols in the light of the later work of Mills (*loc. cit.*, 1953). The results are with few exceptions consistent within themselves and with other evidence regarding the stereochemistry of the triterpenoids.

The value of empirical methods such as these is dependent on their wide applicability. It therefore seems desirable to summarise the data on triterpenoids to provide a firmer foundation for the use of the method in dealing with structural problems. Some further examples from the steroid field are also discussed.

A preliminary communication on this subject has been made (Klyne and Stokes, *Biochem. J.*, 1953, **55**, xxviii).

Conventions.—Molecular rotations and differences are given in parentheses. Values are all for the sodium D line and nearly all for chloroform as solvent. The symbols ΔOH, ΔOAc, and ΔOBz are used as by Klyne and by Stokes and Bergmann (*loc. cit.*). The symbols Δ_1 (ΔOAc − ΔOH) and Δ_2 (OBz − ΔOH) are used as by Barton and Jones (*J.*, 1944, 659).

PRINCIPLES

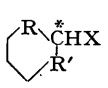
An asymmetric centre C* in a *cyclo*hexane ring system (I) may be represented as (II) where X is a substituent and R and R′ are the ring-members adjacent to C* together with their substituents. If C* is now represented as in (III) by a projection on to a plane at right angles to the bond C*–H, and seen from the side opposite to H (cf. Marker, *loc. cit.*)

* Part II, *J.*, 1953, 3072.

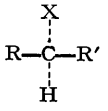
then, if X is hydroxyl, acetoxyl, or benzoyloxy, the magnitude and sign of the rotation contribution of the centre are dependent on the degree of alkyl substitution in R and R'.

(i) If R and R' are both CH_2, the rotation contribution of C* will be small, and attempts to predict its sign are unwise.

(ii) If R is $-CH_2{\cdot}C$ and R' is $-\overset{C}{\underset{C}{\overset{|}{\underset{|}{CH}}}}$ or $-\overset{C}{\underset{C}{\overset{|}{\underset{|}{C}}}}-C$ the rotation contribution of C* will be *negative* (and appreciable). Here the ordinal numbers of the substituents in the Marker system ($R < R' < X$) increase counter-clockwise.



(I)



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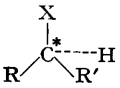


(III)

(iii) If R is $-\overset{C}{\underset{C}{\overset{|}{\underset{|}{CH}}}}$ or $-\overset{C}{\underset{C}{\overset{|}{\underset{|}{C}}}}{\cdot}C$ and R' is $-CH_2{\cdot}C$, the rotation contribution of C* will be *positive* (and appreciable). Here the ordinal numbers in the Marker system increase in a clockwise direction ($R' < R < X$).

ΔOAc and ΔOBz values are generally greater than the corresponding ΔOH values; Δ_1 and Δ_2 values are therefore usually of the signs indicated by the above rules.

The rules do not apply generally to positions adjacent to a ring junction in *cis*-fused polycyclic systems. For example, some of the Δ values for the 6-position in steroids of the 5β-(A–B-*cis*-)series are anomalous. According to the rules it would be expected that Δ values of α- and β-substituents would be positive and negative respectively. The following values are taken from the tables of Barton and Klyne (*Chem. and Ind.*, 1948, 755).

	6α			6β		
	ΔOH	ΔOAc	Δ_1	ΔOH	ΔOAc	Δ_1
5α(*trans*)-Series	+ 55°	+210°	+155°	−50°	−110°	−60°
5β(*cis*)-Series	−100	− 87	+ 13	+ 7	− 62	−69

Similar rules may apply for substituents other than hydroxyl and its derivatives, but there is insufficient evidence to extend the principles at present. The data for 7-halogen-substituted steroids (see, *e.g.*, Henbest and Jones, *J.*, 1948, 1798; Schaltegger and Müllner, *Helv. Chim. Acta*, 1951, **34**, 1096), for 7-aminosteroids (Barnett, Ryman, and Smith, *J.*, 1946, 524; Sax and Bernstein, *J. Org. Chem.*, 1951, **16**, 1069), and for the menthylamines (Read, *Trans. Faraday Soc.*, 1930, **26**, 441; Read and Grubb, *J.*, 1934, 314; McNiven and Read, *J.*, 1952, 153) would support this extension.

The above rules probably apply also to *cyclo*pentane rings; values in the steroid skeleton for $C_{(17)}$ (Stokes and Bergmann, *loc. cit.*) and for $C_{(16)}$ (see below, p. 1984) agree with the rules, but more examples are necessary.

Application of principles to triterpenoids

The rotational data for triterpenoid alcohols and their derivatives, which largely support the principles, are summarised in Table 1.

Positions Adjacent to a Bridgehead.—In the pentacyclic triterpenoids of the oleanane (IV), ursane (V), and lupane (VI) series (numbering according to Guider, Halsall, and Jones, *J.*, 1953, 3024), the positions 7, 11, and 16 should resemble steroid positions 4, 7, and 11 (see VII); ΔOH, ΔOAc, ΔOBz, Δ_1, and Δ_2 should be negative for α-substituents and positive for β-substituents.

Triterpenoid positions 1, 6, and 12 or 15 should resemble steroid positions 1, 6, and 12; here Δ values should be positive for α-substituents and negative for β-substituents. Rotation contributions in the lanostane (VIII; R = H) and eburicane (VIII; R = Me) series

TABLE 1. *Δ Values for hydroxyl and related substituents in triterpenoids.*

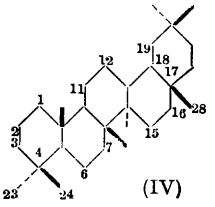
Position considered	Other groups	$[M]_D$ CH_2 [a]	α-Substituents: $[M]_D$ OH	α-Substituents: $[M]_D$ OAc	α-Substituents: Δ values OH	α-Substituents: Δ values OAc	α-Substituents: Δ values Δ_1	β-Substituents: $[M]_D$ OH	β-Substituents: $[M]_D$ OAc	β-Substituents: $[M]_D$ OBz	β-Substituents: Δ values OH	β-Substituents: Δ values OAc	β-Substituents: Δ values OBz	β-Substituents: Δ values Δ_1	β-Substituents: Δ values Δ_2	Refs.
Oleanane series (IV).																
3	None	+41°	—	—	—	—	—	+77°	+99°	—	+36°	+58°	—	+22°	—	1
	12-Ene	+390	+311°	+174° [b]	−79°	−216°	−137°	+379	+384	+530°	−11 *	−6 *	+140°	+5	+151°	
6	3β-OH, 12-ene, 28-CO_2Me	+348	—	—	—	—	—	+228	—	—	−120	—	—	—	—	2
	3β-OAc, ,, ,,	+348	—	—	—	—	—	+211	+142	—	−137	−206	—	−69	—	
	3β-OAc, ,,	+384	—	—	—	—	—	+193	—	—	−191	—	—	—	—	
11	3β-OH, 28-CH_2·OH	+30 [c]	—	—	—	—	—	+88	—	—	+58	—	—	—	—	3
	3β-OAc, 28-CH_2·OAc	+35 [c]	—	—	—	—	—	+168	+322	—	+133	+287	—	+154	—	
12	3β-OH	+77	—	—	—	—	—	+436 [d]	—	—	+359	—	—	—	—	4
	3β-OAc	+99	—	—	—	—	—	—	+226	—	—	+227	—	—	—	
16	3β-OAc, 12-ene	+384	+227 [e]	+58	−157	−326	−169	+406 [f]	+468	—	+22	+84	—	+62	—	5, 6, 7
	3β-OH, 12-ene	+379	+252	—	−127	—	—	+300	—	—	−79 *	—	—	—	—	
Ursane series (V).																
3	12-Ene	+390	—	+182	—	−208	—	+358	+370	+498	−32 *	−20 *	+108	+12	+140	1, 8, 9
Lupane series (VI).																
1 [g]	None	−16 [h]	+163	+111 [i]	+179	+127 [i]	−52 [i] *	−126	−94	—	−110	−78	—	+32 *	—	10
3	None [j]	−16 [h]	—	−230	—	−214	—	−77	−9	+144	−61 *	+7	+160	+68	+251	10, 11
	20(29)-Ene	+115	—	—	—	—	—	+115	+201	+318	0	+86	+203	+86	+203	
Lanostane series (VIII).																
3	None	+145	—	—	—	—	—	+150	+194	—	+5	+49	—	+44	—	12, 13, 14, 15
	8-Ene	+272	—	—	—	—	—	+261	+273	+378	−11 *	+1	+106	+12	+117	
	8 : 24-Diene	+267	—	—	—	—	—	+258	+306	+392	−9 *	+39	+125	+48	+134	
7	3β-OAc, 11β-OH [k]	+113	—	—	—	—	—	—	+392	—	—	+279	—	—	—	12, 16
11	3β-OH [j]	+150	0	—	−150	—	—	+128	—	—	−22 *	—	—	—	—	12, 15, 17
	3β-OAc	+194	—	+69	—	−125	—	+113	—	—	−81 *	—	—	—	—	
12	Four examples [l]	—	—	—	—	+288 to +322	—	—	—	—	—	—	—	—	—	18

* Anomalous. [a] At position considered. [b] Klyne, unpublished observation. [c] Estimated from values for erythrodiol and Δ(C:C)12. [d] Obtained from 12-ketone by reduction with sodium and amyl alcohol; presumably equatorial (12β-)hydroxyl. [e] Echinocystic acid derivatives. [f] Maniladiol. [g] Configurations allotted here (see p. 1980). [h] This value appears to be too positive; Δ(C:C)20(29) in all other lupene derivatives is about +190° (cf. Barton and Jones, *loc. cit.*). [i] Propionate, not acetate. [j] $[M]_D$ of 3α-BzO-compound is −176°; ΔOBz, −160°. [k] Acetoxyl and ketone groups at $C_{(7)}$ and $C_{(11)}$ show considerable vicinal action. [l] Derivatives of polyporenic acid A [3α : 12α-dihydroxyeburica-8 : 24(28)-dien-26-oic acid].

References: Many values are taken from the Tables given by Barton and Jones (*loc. cit.*) and Klyne (1952, *loc. cit.*). 1, Ruzicka and Wirz, *Helv. Chim. Acta*, 1941, **24**, 248. 2, Ruzicka, Jeger, Grob, and Hösli, *ibid.*, 1943, **26**, 2283. 3, Barton and Holness, *J.*, 1952, 78. 4, Picard, Sharples, and Spring, *J.*, 1939, 1045. 5, Jeger, Montavon, and Ruzicka, *Helv. Chim. Acta*, 1946, **29**, 1124. 6, Jeger, Nisoli, and Ruzicka, *ibid.*, p. 1183. 7, Meyer, Jeger, and Ruzicka, *ibid.*, 1950, **33**, 687. 8, Ruzicka and Gubser, *ibid.*, 1945, **28**, 1054. 9, Büchi, Jeger, and Ruzicka, *ibid.*, 1946, **29**, 442. 10, Jeger, Montavon, Nowak, and Ruzicka, *ibid.*, 1947, **30**, 1869. 11, Nowak, Jeger, and Ruzicka, *ibid.*, 1949, **32**, 323. 12, Voser, Montavon, Günthard, Jeger, and Ruzicka, *ibid.*, 1950, **33**, 1893. 13, Ruzicka, Rey, and Muhr, *ibid.*, 1944, **27**, 472. 14, Ruzicka, Denss, and Jeger, *ibid.*, 1945, **28**, 759. 15, McGhie, Pradhan, and Cavalla, *J.*, 1952, 3176. 16, Cavalla and McGhie, *J.*, 1951, 834. 17, Mijović, Voser, Heusser, and Jeger, *Helv. Chim. Acta*, 1952, **35**, 964. 18, Curtis, Heilbron, Jones, and Woods, *J.*, 1953, 457; cf. Roth, Saucy, Anliker, Jeger, and Heusser, *Helv. Chim. Acta*, 1953, **36**, 1908.

should follow the same pattern as in the other triterpenoids and steroids. Table 1 shows that, in general, agreement of the predicted signs with those found experimentally is good.

Configurations for 1-substituted triterpenoids (Jeger *et al.*, *Helv. Chim. Acta*, 1947, **30**, 1869) are allotted here on the basis of the ΔOH and ΔOAc values. These allocations are supported by the high positive rotation of lup-2-en-1α-yl propionate (+724°) (cf. Mills, *loc. cit.*, 1952; Klyne, *Helv. Chim. Acta*, 1952, **35**, 1224).



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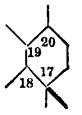

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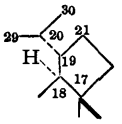

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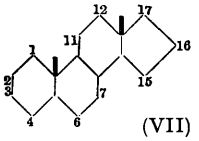

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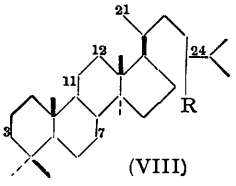

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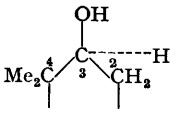


(IX)

Position 3.—$C_{(3)}$ in steroids is flanked by two methylene groups and therefore shows very small Δ values (cf. Stokes and Bergmann, *loc. cit.*). $C_{(3)}$ in triterpenoids, however, is flanked by one methylene group and one CMe_2 group (IX) (3β-hydroxy-compound) and is therefore comparable with positions adjacent to a ring-junction. The Δ values for $C_{(3)}$ for saturated triterpenoids are rather larger than those for $C_{(3)}$ in steroids and their signs (β-groups chiefly positive, α-groups all negative) are in accordance with the principles stated above. Δ Values at $C_{(3)}$ are subject to much vicinal action by other parts of the triterpenoid molecule (cf. Barton and Jones, *loc. cit.*).

3α-Hydroxy-triterpenoids are sufficiently uncommon to warrant special attention. Halsall, Jones, and their colleagues have drawn attention to the large negative Δ_1 values for the 3-hydroxyl groups in polyporenic acid A (3α : 12α-dihydroxyeburica-8 : 24(28)-dien-26-oic acid; *J.*, 1953, 457, 3019) and in hydroxyelemadienic acid (*J.*, 1953, 4139). The epimeric 3β-hydroxy-compounds showed positive Δ_1 values (cf. also Gascoigne, Robertson, and Simes, *J.*, 1953, 1830).

Brein.—The unsaturated diol brein is known to be an urs-12-ene-3 : *x*-diol (Jeger, *Fortschr. Chem. org. Naturstoffe*, 1950, **7**, 1, see p. 57; references there). There has been some confusion regarding the configuration of the hydroxyl group at $C_{(3)}$. Two 3-epimeric hydroxy-*x*-ketones (breinonol A and B, Morice and Simpson, *J.*, 1942, 198; Büchi, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1946, **29**, 442) can be obtained by Meerwein–Ponndorf reduction of the 3 : *x*-dione. Breinonol B must have the same configuration at $C_{(3)}$ as brein because it can also be obtained by oxidation of brein 3-monoacetate with chromic acid (Büchi *et al.*, *loc. cit.*). The same authors claimed that both breinonol acetates on Wolff–Kishner reduction gave " epi-α-amyrin " (urs-12-en-3α-ol) in rather poor yield, and therefore suggested that brein might be a 3α-hydroxy-triterpenoid. However, the catalytic reduction of breindione with platinum oxide in glacial acetic acid yields breinonol B; urs-12-en-3-one in similar circumstances gives the 3β-hydroxy-compound.

Consideration of molecular rotations (Table 2) shows clearly that brein (and breinonol B) are 3β-hydroxy-compounds and that breinonol A is 3α. The Δ_1 values at $C_{(3)}$ for brein and breinonol B agree well with that for urs-12-en-3β-ol (+12°), and that for breinonol A has a large negative value similar to those for 3α-ols (see Table 1). (Isolation of urs-12-en-3α-ol after Wolff–Kishner reduction of " breinonol B " may have been due to contamination of this with the isomer A.)

No conclusions can be drawn from rotations regarding the position or configuration of the second hydroxyl group, at *x*. The data are, however, consistent with its being a

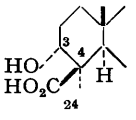
16β-hydroxyl group as in maniladiol (olean-12-ene-3β : 16β-diol), which accompanies brein in Manila elemi resin (cf. Morice and Simpson, *loc. cit.*, 1940).

TABLE 2. *Brein derivatives.*

	Substituents		$[M]_D$		
	3	x	3-OH	3-OAc	Δ_1 at $C_{(3)}$
Brein	β-OH	OH	+292°	+324°	+ 32°
Breinonol B	β-OH	O	+211	+222	+ 11
Breinonol A	α-OH	O	+163	− 63	−226

References : Morice and Simpson, *loc. cit.*, and *J.*, 1940, 795; Büchi *et al.*, *loc. cit.*

α-Boswellic Acid (*3α-Hydroxyolean-12-en-24-oic Acid*, X).—Ruzicka and Wirz (*Helv. Chim. Acta*, 1940, **23**, 132; 1941, **24**, 248) showed that this acid has a 3α-hydroxyl group, and this is confirmed by the reduction of the corresponding 3-ketone by sodium and alcohol to an epimeric (3β-hydroxy-)acid (Meyer, Jeger, and Ruzicka, *ibid.*, 1950, **33**, 672). Evid-



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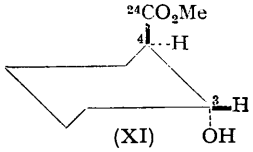

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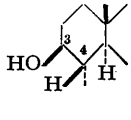
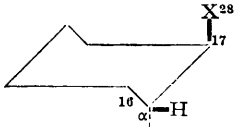


(XII)

ence for the β-orientation of the carboxyl group at $C_{(4)}$ in α-boswellic acid is given by Vogel, Jeger, and Ruzicka (*ibid.*, 1951, **34**, 2321). The Δ values of α-boswellic acid and its derivatives support the allocation of a 3α-configuration; for the methyl esters ΔOH, −80°; ΔOAc, −268°; Δ_1, −188°.

These values are of interest because they show that there is relatively little vicinal action between 4β-methoxycarbonyl groups and 3α-hydroxyl or -acetoxyl groups. Barton and Jones (*loc. cit.*), writing long before anything was known about the stereochemistry of ring A, suggested that hydrogen-bonding between such groups might occur and might be responsible for abnormal Δ values. It is now clear that 3α- and 4β-substituents, being both axial and antiparallel (XI) would be most unfavourably placed for hydrogen bonding. There is, however, serious vicinal action between a 4β-methoxycarbonyl group and a 3-keto-group (ΔC:O for the keto-ester from α-boswellic acid is −114°; standard value for olean-12-en-3-one, +64°). Similar problems in steroid α-ketols have been discussed recently by Norymberski (*J.*, 1954, 762).

Data for the various 3 : 23- and 3 : 24-diols are too incomplete to justify a full discussion, but in general it seems that the ΔOH and ΔOAc values for hydroxyl groups at $C_{(23)}$ and $C_{(24)}$ are small; furthermore the effect of these groups on the rotation contributions of similar groups at $C_{(3)}$ is small.



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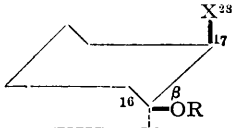

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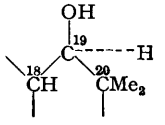


(XV)

β-Boswellic Acid.—This acid is almost certainly the ursane analogue of α-boswellic acid (3α-hydroxyurs-12-en-24-oic acid). There are serious discrepancies in the literature in the rotations quoted for β-boswellic acid and its derivatives (see Elsevier's " Encyclopædia of Organic Chemistry," 1940, Vol. XIV, pp. 559—561; and 1953, Supplement, p. 1087 S). However, the Δ_1 values are all large negative ones, indicating a 3α-hydroxyl group.

24-Nor-compounds.—Δ_1 Values for 24-nor-3β-hydroxy-compounds (XII) show the expected positive values; hedragenin (3β-hydroxy-24-norolean-12-en-28-oic acid), +82°; nor-β-amyrin (24-norolean-12-en-3β-ol) +29°.

The " nor-β-boswellenol " of Simpson and Williams (*J.*, 1938, 686, 1712) has Δ_1 (+52°) and must therefore be 24-norurs-12-en-3β-ol (cf. Barton and Jones, *loc. cit.*). The stereo-

isomeric " nor-β-boswellanonols " of the same authors (m. p.s 182—183° and 231—232°) have Δ_1 values of (+86°) and (−65°) and must therefore be 3β- and 3α-hydroxy-compounds respectively.

Position 16.—The Δ_1 values at this position are highly characteristic, those for α- and β-substituents being large negative and positive values respectively, as predicted by the rules. Since 3 : 16 : 28-trisubstituted compounds are common in Nature it is of interest that Δ_1 values at $C_{(16)}$ are not greatly affected by substituents at $C_{(28)}$.

The stereochemical relations between substituents at $C_{(16)}$ and $C_{(28)}$ are similar to those at $C_{(3)}$ and $C_{(24)}$ discussed on p. 1983. The following are Δ_1 values for representative compounds :

Group X at $C_{(28)}$	CH_3	$CH_2{\cdot}OH$	CHO	CO_2H
16α-Series (XIII)	−194°	−297°	—	−232°
16β-Series (XIV)	+138	+175	+228°	—

References : Morice and Simpson, *J.*, 1940, 795; Margot and Reichstein, *Pharm. Acta Helv.*, 1942, **17**, 113; Jeger, Montavon, and Ruzicka, *Helv. Chim. Acta*, 1946, **29**, 1124; Jeger, Nisoli, and Ruzicka, *ibid.*, p. 1183; Jeger, Bischof, and Ruzicka, *ibid.*, 1948, **31**, 1319; Bischof and Jeger, *ibid.*, p. 1760; Djerassi, McDonald, and Lemin, *J. Amer. Chem. Soc.*, 1953, **75**, 5940; Djerassi, Geller, and Lemin, *Chem. and Ind.*, 1954, 161.

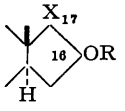
These Δ values are all {$[M_D]$ (fully acetylated compound) *minus* $[M]_D$ (alcohol)}, and most of the compounds have a 3β-hydroxyl group as well as that at $C_{(16)}$. Changes due to acetylation of 3β- and 28-hydroxyl groups are, however, small; Δ_1 for 3β-hydroxyl is +5° (see Table 1). Δ_1 for 28-hydroxyl is about −30° [olean-12-en-3β : 28-diol (erythrodiol) +330°; 3-acetate +344°; 3 : 28-diacetate, +310°].

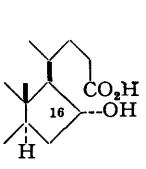
Djerassi, Geller, and Lemin (*loc. cit.*) have drawn attention to the fact that Δ(16β-acetoxy *minus* 16α-acetoxy) is constant in spite of substitution at $C_{(28)}$. (The authors are indebted to Prof. C. Djerassi for a copy of this paper before publication.)

Position 19.—This position is peculiar in that it is flanked in the oleanane series by a tertiary and a quaternary carbon atom (XV; 19β-OH); the rules therefore cannot be applied. Δ(OH) values for α- and β-substituents in the 18α-(D–E-*trans*)-series are both negative, α being greater than β (see Klyne, Part II, *loc. cit.*, Table 11).

Further applications to steroids

Stokes and Bergmann (*loc. cit.*) have discussed the rotational contributions of hydroxyl and related groupings in rings A, B, and C of the steroid nucleus. Groups in ring D and in the side-chain will be considered here.

(XVI) 



(XVII)

Position 16.—In C_{19} steroids (XVI; X = H) this position is flanked by two methylene groups, and small Δ values would be expected. No values are at present available, but values for 2-substituted A-norsteroids, which are of enantiomeric type (cf. Klyne, Part I, *J.*, 1952, 2916), may be considered instead. The epimeric A-norandrostan-2-ols (Ruzicka, Meister, and Prelog, *Helv. Chim. Acta*, 1945, **28**, 1651) both have very small rotations (2α, +5°; 2β, +8°). A-Norandrostane is not known, but since A-norcholestane and cholestane have almost identical rotations (cf. Klyne, *loc. cit.*, Table 4), A-norandrostane would be expected to have a negligible rotation, like androstane (+5°). The ΔOH values for the 2-hydroxyl groups are therefore almost zero.

In C_{21} steroids position 16 is flanked by one methylene group and one tertiary carbon atom (XVI; X = CHMe·OR') and, as expected, Δ values are considerable. The values for α-substituents are negative and for β-substituents positive, in agreement with the rules stated above (p. 1980).

A summary, including Δ values for 16α- and 16β-acetoxyl and 16α-methoxyl groups, is given by Fukushima and Gallagher (*J. Amer. Chem. Soc.*, 1951, **73**, 196: see also Hirschmann and Hirschmann, *J. Biol. Chem.*, 1950, **184**, 259; Hirschmann, Hirschmann, and

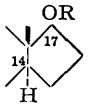
Farrel, *J. Amer. Chem. Soc.*, 1953, **75**, 4862; Vischer, Schmidlin, and Wettstein, *Helv. Chim. Acta*, 1954, **37**, 321). Δ(OH)16α is −64° for 5α-pregnane-3β : 16α : 20β-triol (Brooks, Klyne, Miller, and Paterson, *Biochem. J.*, 1952, **51**, 694); Δ(O·CH_2Ph)16α is −194° (Hirschmann, Hirschmann, and Daus, *J. Amer. Chem. Soc.*, 1952, **74**, 539).

Some of these values are subject to vicinal action by the substituents at $C_{(20)}$, but they include examples from both 20α- and 20β-substituted compounds.

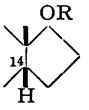
The bile acid, pythocholic acid, isolated by Haslewood and Wootton (*Biochem. J.*, 1950, **47**, 584; 1951, **49**, 67) has been shown by these authors to be a 3α : 12α : *x*-trihydroxycholanic acid where *x* is 16 (or 15). Position 15 is excluded since the *x*-oxo-derivatives show large negative rotational contributions, which are compatible with that from a 16-ketone but not with that from a 15-ketone. Δ(C:O)15 is (+106°) (Barnes, Barton, and Laws, *Chem. and Ind.*, 1953, 616; Barton and Laws, *J.*, 1954, 52). The Δ(OH) value for the third hydroxyl (*x*) is +123° − 195° = −72°. This negative value indicates a 16α-hydroxyl group (XVII).

Rotational contributions at $C_{(16)}$ in the cardiac aglycones and toad poisons cannot be treated as reference values because of vicinal action by the unsaturated lactone rings in the side chain and by the 14β-hydroxyl group.

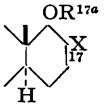
Position 17.—The data collected by Stokes and Bergmann (*loc. cit.*) show that for 17-substituted steroids of the normal C–D-*trans*-series (*e.g.*, XVIII), the general principles



(XVIII)



(XIX)



(XX)

stated on p. 1980 are applicable, although the substituents are in a *cyclo*pentane and not a *cyclo*hexane ring. Values are now available for 17-epimeric steroids of the 14β-(C–D-*cis*-) series (XIX) (St. André, MacPhillamy, Nelson, Shabica, and Scholz, *J. Amer. Chem. Soc.*, 1952, **74**, 5506). The values for $\{[M]_D(17\beta) - [M]_D(17\alpha)\}$ are of the expected sign. Since the corresponding compounds unsubstituted at $C_{(17)}$ are unknown, ΔOH and ΔOAc values cannot be calculated.

	$[M]_D$ 17α	$[M]_D$ 17β	Δ(17β−17α)
14β-Androstane-3β : 17-diol	+105°	+111°	+ 6°
,, ,, diacetate	+ 87	+132	+45
(14α)-Androstane-3β : 17-diol	− 29	+ 12	+41
,, ,, diacetate	− 67 *	0	+67

* Estimated from values in the Tables of Barton and Klyne (*Chem. and Ind.*, 1948, 755) and the value for 17α-acetoxy-5β-androstan-3α-ol (Gallagher and Kritchevsky, *J. Amer. Chem. Soc.*, 1950, **72**, 882).

Position 15.—The above data seem to justify the application of the rules to the 15(?α)-substituted steroids recently prepared by Barton and Laws (*J.*, 1954, 52). (The authors are grateful to Prof. D. H. R. Barton, F.R.S. for an advance copy of this paper.) These compounds show ΔOAc +184°, and ΔOBz +365°, which support the allotment of the 15α-configuration.

Position 17α *in* D-*Homosteroids*.—The Δ values at this position (XX; X = H) are in accordance with the rules above (except for the one acetate value), α-substituents being negative and β-substituents positive. The indices α and β are allotted according to Goldberg, Sicé, Robert, and Plattner (*Helv. Chim. Acta*, 1947, **30**, 1441). Representative values are as follows :

Position	ΔOH	ΔOAc	ΔOBz	Δ_1	Δ_2
17*a*α	−38°	—	−190°	—	−152°
17*a*β	+90	−27° *	+321	−117° *	+231

* Anomalous.

References : Goldberg *et al.*, *loc. cit.*; Goldberg and Wydler, *Helv. Chim. Acta*, 1943, **26**, 1142.

For the 17*a* position in ursanediol derivatives (17α-methyl-3β : 17*a*β-diol series (XX; X = Me), Brooks *et al.* (*loc. cit.*) give Δ_1 −104°, Δ_2 +100°. Here the 17*a*-position somewhat resembles 19 in the 18α-oleanane series (cf. p. 1984).

THE STEROID SIDE CHAIN

Now that the stereochemistry of the steroid nucleus has been related to glyceraldehyde,* and the stereochemistry of $C_{(20)}$ to $C_{(17)}$ (Fieser and Fieser, *Experientia*, 1948, **4**, 285; for a recent review see Klyne, *Chem. and Ind.*, 1951, 426; also Prelog and Tsatsas, *Helv. Chim. Acta*, 1953, **36**, 1178), it seems appropriate to compare the rotational contributions of $C_{(20)}$ and other side-chain centres with those of the corresponding atoms in simple aliphatic compounds.

(XXI) (XXII)

Position 20.—The contributions of hydroxyl and derived groups at $C_{(20)}$ may be compared with the rotations of other alcohols where the CH·OH group is flanked by a methyl group and a tertiary carbon atom X (Table 3). It is seen that the contributions of $C_{(20)}$ in the steroids, where X is a substituted *cyclo*pentyl group, are of the same sign as the rotations of the simpler *iso*propyl and *cyclo*hexyl compounds.

TABLE 3. *Molecular rotations and Δ values for $C_{(20)}$ and simpler reference compounds.*

Values shown in the columns headed OBz are for benzoates in the steroid series and for hydrogen phthalates in the aliphatic compounds. Values for the benzoates and hydrogen phthalates of the same alcohol are very similar (Kenyon and Pickard, *J.*, 1915, **107**, 121).

			Type XXI			Type XXII			
Value	X	OR :	OH	OAc	OBz	OH	OAc	OBz	Refs.
$[M]_D$	$CHMe_2$		+ 4°	—	+ 98°	− 4°	—	− 98°	a
$[M]_D$	*cyclo*Hexyl		+ 7	− 5°	+150	− 7	+ 5°	−150	a, b
			←	(20α)	→	←	(20β)	→	
Δ for $C_{(20)}$	$_{17}C---H$		+15	−22	+130	−43	+68	−150	c

References: a, See summary in Freudenberg, "Stereochemie," Vol. II, facing p. 696, Deuticke, Leipzig and Vienna. b, Levene and Harris, *J. Biol. Chem.*, 1936, **113**, 55. c, ΔOH and ΔOAc from Barton and Klyne, *loc. cit.* ΔOBz from Brooks, Klyne, and Miller, *Biochem. J.*, 1953, **54**, 212. These benzoate contributions are subject to much vicinal action.

It therefore seems justified to apply these values to deduce the configurations of carbinol groups in similar structures. This is virtually the same as applying Marker's rule in its original form for acyclic compounds.

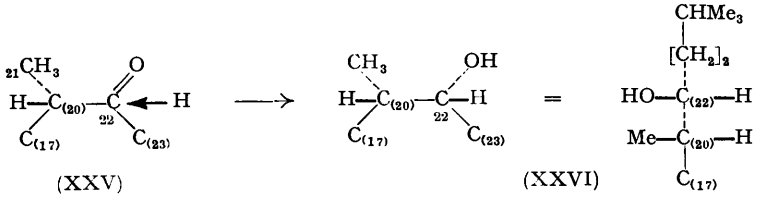
(XXIII) (XXIV)

The bisnorcholanic acids (XXIII) and their 20-epimers may now be compared with the α-*cyclo*hexylpropionic acids [XXIV, (+)-acid] recently described by Cram and Greene (*J. Amer. Chem. Soc.*, 1953, **75**, 6005). $[M]_D$ of (XXIV) is +30°; Δ(XXIV — its enantiomer) is therefore +60°. Δ Values for the 20-*n*-bisnorcholanic esters (XXIII; R = Me) *minus* the corresponding 20-*iso*-bisnorcholanic esters are, with one exception, positive (+103°, +72°, +181°, −60°, +36°, +25°) (Fieser and Fieser, "Natural Products related to Phenanthrene," Reinhold Publ. Corp., New York, 3rd edn., 1949, p. 418; Sorkin and Reichstein, *Helv. Chim. Acta*, 1944, **27**, 1631; 1945, **28**, 875).

Position 22.—Fieser and Wei-Yuan Huang (*J. Amer. Chem. Soc.*, 1953, **75**, 5356) have reduced 22-oxocholestan-3β-ol with lithium aluminium hydride and obtained (apparently)

* A direct correlation of the configuration of $C_{(20)}$ with that of asymmetric carbon atoms in the branched-chain aliphatic series has recently been achieved by Cornforth, Youhotsky, and Popják (*Nature*, 1954, **173**, 536) and by Riniker, Arigoni, and Jeger (*Helv. Chim. Acta*, 1954, **37**, 546).

only one of the two possible cholestane-3β : 22-diols. Application of Cram's rule of steric control of asymmetric induction (*ibid.*, 1952, **74**, 5828) to a 22-oxo-steroid (XXV) indicates that the 22" β "-isomer (XXVI) should preponderate in the reduction products. (The index " β " is allotted according to the convention proposed by Plattner for side-chain isomers, *Chem. and Ind.*, 1951, SN 1; *Helv. Chim. Acta*, 1951, **34**, 1693. This convention is not generally accepted; indices are therefore given in quotation marks.) The cholest-5-ene-3β : 16β : 22 : 26-tetrol obtained by Sandoval, Romo, Rosenkranz, Kaufmann, and Djerassi (*J. Amer. Chem. Soc.*, 1951, **73**, 3820) by reduction of the corresponding 16 : 22-dione can therefore also be allotted the 22" β "-configuration.

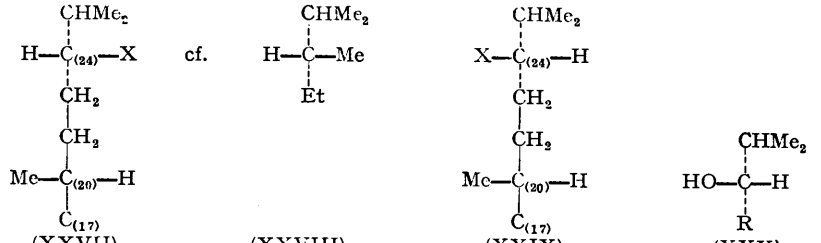


(XXV) (XXVI)

Stabursvik (*Acta Chem. Scand.*, 1953, **7**, 1220) has isolated from *Narthecium ossifragum* Huds. a cholest-5-ene-3β : 22ξ-diol, which on catalytic hydrogenation yields a saturated diol different from Fieser's 3β : 22" β "-diol. Stabursvik's natural product must therefore be the 22" α "-isomer.

The " rule of shift " cannot be applied at present to the molecular rotations of the cholestane-3β : 22-diols and their derivatives because adequate reference values for branched chain alcohols of the type R·$[CH_2]_2$·CH(OH)·CHMeR′ are not available.

Position 24.—Alkyl substituents. The application of Marker's rule to $C_{(24)}$ has been discussed by Stokes and Bergmann (*J. Org. Chem.*, 1951, **16**, 1817). In view of the confusion which has arisen regarding the relation of steroids to glyceraldehyde, it seems desirable to indicate projection formulæ for the 24-substituted hydrocarbons (XXVII, XXIX) in the light of the latest knowledge. The reference compound (XXVIII) has (+28°) (Levene and Marker, *J. Biol. Chem.*, 1935, **111**, 299).



(XXVII) (XXVIII) (XXIX) (XXX)

24"α"-Series (formerly 24*a*)
Campestanol, X = Me
Poriferastanol, X = Et

24"β"-Series (formerly 24*b*)
Ergostanol, X = Me
Stigmastanol, X = Et

Hydroxy-compounds. Ercoli, Di Frisco, and de Ruggieri (*J. Amer. Chem. Soc.*, 1953, **75**, 3289; *Gazzetta*, 1953, **83**, 78) have isolated from brain tissue a cholest-5-ene-3β : 24-diol (cerebrostenediol) and have synthesised this compound and its 24-epimer. Comparison of the molecular rotations of these compounds with reference values for *n*-alkyl*iso*propylcarbinols permits the allotment of configurations at $C_{(24)}$. The natural isomer (ξ^1) is thus shown to be 24" β " (XXIX; X = OH) (Plattner convention).

$[M]_D$ Values for *n*-alkyl*iso*propylcarbinols of the type (XXX) are: R = Et −17°, Pr^n −27°, Bu^n −36°, C_5H_{11} −38° (Freudenberg, *op. cit.*). If, in accordance with Stokes and Bergmann's suggestions (*loc. cit.*, 1951), the steroid nucleus *plus* side-chain as far as $C_{(23)}$ is considered as being similar to an ethyl group, the 24-hydroxyl compounds which show negative ΔOH values (the natural series) must be of the same enantiomeric type as (XXX).

No clear evidence can be obtained from the rotations of the acetates and benzoates of the $C_{(24)}$-isomers, because the acetates of the simple optically active carbinols (XXX) are

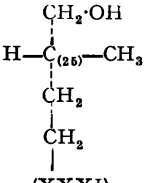
unknown, and the phthalates (= benzoates) show a change in sign of rotation between (XXX, R = Et; phthalate −10°) and (XXX, R = Pr^n; phthalate +22°).

	$[M]_D$				
	24-CH_3	24-CH·OH "α" (epi)(ξ^2)	24-CH·OH "β" natural (ξ^1)	Δ OH "α"	Δ OH "β"
Cholest-5-en-3β-ol	−151°	−108°	−195° *	+43°	−44°
Cholestan-3β-ol	+ 89	—	+ 97 †	—	+ 8
Cholest-4-en-3-one	+342	+375	+319	+33	−23

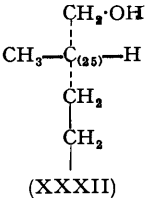
* Hey, Honeyman, and Peal (*J.*, 1952, 4836) give − 160°.

† All values in chloroform, except for this, which is in dioxan; the anomalous Δ value is probably due to a solvent difference.

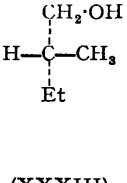
Position 25.—Recent work on the stereochemistry of $C_{(25)}$ in the sapogenins (Scheer, Kostic, and Mosettig, *J. Amer. Chem. Soc.*, 1953, **75**, 4871; James, *Chem. and Ind.*, 1953, 1388) permits an independent check on the applicability of the rule of shift to positions in the steroid side chain, by using reference values from simple aliphatic compounds. These authors have shown that $C_{(25)}$ in dihydrosmilagenin (and the corresponding derivatives of tigogenin and hecogenin) must be represented as in (XXXI) (Fischer projection), whilst



(XXXI)



(XXXII)



(XXXIII)

$C_{(25)}$ in dihydrosarsasapogenin is as in (XXXII). (These may be called 25*D*- and 25*L*-methyl compounds, following Linstead, Lunt, and Weedon, *J.*, 1950, 3333.)

If the rotation differences between 25*D*- and 25*L*-methyl compounds are compared with the molecular rotations of a simple α-methyl substituted primary alcohol (*e.g.*, 2-methyl-

TABLE 4. $C_{(25)}$-*Methyl-substituted compounds and simple analogues.*

	Group at $C_{(26)}$	$[M]_D$ *D* series	$[M]_D$ *L* series	Δ (*D* − *L*)
Genin derivatives.				
ψ-Genin [furost-20(22)ene-3β : 26-diol]	CH_2·OH	+100°	+ 50°	+50°
Dihydrogenin (furostan-3β : 26-diol)	CH_2·OH	+ 13	− 17	+30
Dihydrogenin diacetate	CH_2·OAc	− 5	− 15	+10 *
Dihydrogenin dibenzoate	CH_2·OBz	+ 12	+ 19	− 7
ψ-Genin bis-3 : 5-dinitrobenzoate	CH_2·OAcyl	+116	+177	−61
Aliphatic analogues (XXXIII).				
2-Methylbutanol	—	+ 5	− 5	+10
,, acetate	—	− 4	+ 4	− 8
,, hydrogen 3-nitrophthalate	—	−17	+17	−34

* Anomalous. References: Derivatives of genins, Scheer *et al.*, *loc. cit.* 2-Methylbutanol and derivatives, Marckwald and McKenzie, *Ber.*, 1901, **34**, 485. Guye and Chavanne, *Bull. Soc. chim.*, 1896, **15**, 280; Guye, *ibid.*, 1901, **25**, 549.

butanol, XXXIII) (see Table 4), the signs of the Δ values are as expected in all cases but one.

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POSTGRADUATE MEDICAL SCHOOL, DUCANE ROAD,
LONDON, W.12.
PROVIDENCE COLLEGE, PROVIDENCE 8, RHODE IS., U.S.A. [*Received, January 29th*, 1954.]