551. *The Molecular Rotations of Polycyclic Compounds. Part I. General Principles and the Correlation of the Triterpenoids with the Steroids.*

By W. KLYNE.

The rule of shift is applied in a general form to the molecular optical rotations of polycyclic compounds.

Terminal ring units of the same type make contributions to the molecular rotation which are, very approximately, independent of the nature of the rest of the molecule. Each terminal unit can exist in two enantiomeric types which have rotation contributions of opposite sign.

Evidence for these principles is adduced from the terminal rings of steroids of known structure and configuration, and the principles are then extended to intermediate rings.

The chief use of this general application of the rule of shift will probably be in deciding which of two enantiomeric structures should be allotted to polycyclic natural products.

The principles are used to correlate the stereochemistry of the triterpenoids with that of the steroids. The A–B ring union of the triterpenoids is considered first; then the B-, the C-, and the D-ring of the oleanane (β-amyrane) series, and finally the E-ring. Most rotation values are consistent with the formulæ generally accepted on chemical grounds, but a few anomalies are noted.

THE method of molecular rotation differences has proved of great value in structural problems in the steroid field, largely owing to the work of Barton and his colleagues (Barton, *J.*, 1945, 813, and many subsequent papers). Its application within other groups of polycyclic compounds (*e.g.*, triterpenoids) would no doubt be equally useful (cf. Barton and Jones, *J.*, 1944, 659).

A more general application of the method or of the rule of shift (Freudenberg, *Ber.*, 1933, **66**, 177) lies in correlation of the stereochemistry of one group of polycyclic compounds with that of another. Sufficient data are available to warrant this, and the rule can already be used to correlate the triterpenoids and the diterpenoids with the steroids.

This application will be of particular interest for compounds of biological origin or activity, since the stereochemical relations of biologically active compounds to one another are of fundamental importance in their interaction. For example, it is of little more than academic interest to the structural organic chemist whether the conventions used for representing the formulæ of testosterone and L-alanine agree or not; but it will be quite impossible for a biochemist to give an adequate account of the interaction between steroid hormones and proteins or other asymmetric substances until the stereochemical relations between them are known.

Bijvoet, Peerdeman, and van Bommell (*Nature*, 1951, **168**, 271) have shown that the Fischer conventional formulæ for tartaric acid and related compounds represent the absolute configurations of these compounds. Lardon and Reichstein (*Helv. Chim. Acta*, 1949, **32**, 2003) have produced evidence that the steroid convention may be the converse of the glyceraldehyde convention. As this has not been settled, it seems better in this paper to make the arbitrary assumption that the present steroid formulæ are "correct," since other groups of cyclic compounds will be related to the steroid skeleton.

In this paper the principles on which the rule of shift may be applied to polycyclic compounds are first stated for terminal rings, and evidence in support of the principles is brought forward; they are then extended to intermediate rings. Finally, they are applied to the correlation of the triterpenoids with the steroids.

The present paper deals chiefly with *trans-anti-trans*-fused systems and with the rotational contributions of ketonic and olefinic groupings in these. It is intended that future papers should deal with other substituent groups, with *cis*-fused systems, and with

systems containing aromatic rings fused with alicyclic rings. A preliminary note on this work has already appeared (Klyne, *Chem. and Ind.*, 1952, 172).

Stokes and Bergmann (*J. Org. Chem.*, 1951, **16**, 1817) have recently presented some similar general ideas on the molecular rotations of steroid hydrocarbons; unsaturated compounds are considered as derivatives of enantiomeric 9-methyloctalins. They draw attention to similar suggestions put forward previously by Callow and Young (*Proc. Roy. Soc.*, 1936, *A*, **157**, 194).

Experimental data

Optical Rotations.—All values for optical rotations are molecular rotations $[M] = [\alpha] \times$ mol. wt./100, and are for the sodium-D line at room temperature (15—25°) unless stated otherwise. Nearly all are taken from the literature. To avoid repetition the words "molecular rotation" or "molecular-rotation contribution" are often omitted, and the values given in parentheses; *e.g.*, "cholestane (+91)" indicates $[M]_D = +91°$. Parentheses are used to avoid confusion with square brackets commonly used by Prof. T. Reichstein and other Swiss authors for specific rotations, $[\alpha]_D$.

Concentrations.—These are generally 0·5—2%, rarely up to 5%. Barton and Cox (*J.*, 1948, 783) showed that the rotations of many simple steroids in chloroform are almost independent of concentration.

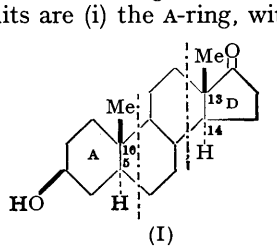
Solvents.—Few deliberate comparisons of rotations for steroids and similar compounds in different solvents have been made (see, *e.g.*, Josephson, *Biochem. J.*, 1935, **29**, 1484; Plattner and Heusser, *Helv. Chim. Acta*, 1944, **27**, 748; Barton, *J.*, 1946, 1116; Barton and Brooks, *J.*, 1949, 2596). These comparisons indicate that rotations in chloroform, ethanol, acetone, and dioxan vary sufficiently (perhaps by $\pm 40°$) to disturb calculations about finer points of structure (*e.g.*, acetylation increments at $C_{(3)}$ of the steroid skeleton). The differences are not, however, sufficiently large to upset qualitative arguments based on the rule of shift where large values of Δ are involved.

Values used for rotations in this paper refer to chloroform solutions wherever possible, otherwise to ethanol, methanol, acetone, or dioxan. Where it is thought necessary to draw attention to the use of an abnormal solvent abbreviations customary in this *Journal* are used, or occasionally special abbreviations such as Di for dioxan.

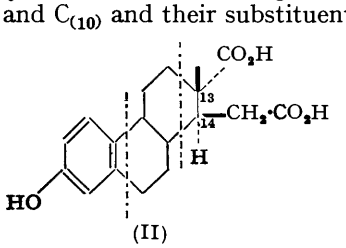
Δ *Values.*—The difference between the molecular rotations of two compounds is called the Δ value. The molecular-rotation contributions of hydroxyl, acetoxyl, ketonic, and olefinic groups [Δ(OH), Δ(OAc), Δ(C:O), and Δ(C:C) values] are the differences: * ($[M]_D$ of compounds with substituent) minus ($[M]_D$ of compound without substituent). The terms Δ_1, Δ_2, Δ_3 are used for the differences (acetoxy — hydroxy) (benzoyloxy — hydroxy) and (ketone — hydroxy) respectively (cf. Barton and Jones, *loc. cit.*).

Definitions and conventions

Terminal Rings and Units.—A terminal ring is one attached to the rest of the system only by two adjacent atoms in common. A terminal unit is defined as (*a*) a terminal ring (with or without substituents) including the two "common" atoms (I) or (*b*) the residues left when such a terminal ring is broken [*e.g.*, by the oxidation of a ring, as in (II)]. In (I) the terminal units are (i) the A-ring, with $C_{(5)}$ and $C_{(10)}$ and their substituents, and (ii) the



(I)



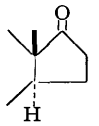
(II)

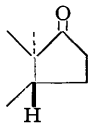
D-ring, with $C_{(13)}$ and $C_{(14)}$ and their exocyclic substituents. In (II) the terminal units are (i) the A-ring and (ii) $C_{(13)}$, $C_{(14)}$ and the residue of the broken ring D.

* These symbols replace ΔO, ΔA, ΔK, and ΔE used previously.

Each terminal unit can exist in two enantiomeric forms, *e.g.*, (III and IV).

(III)
D-Ring of (+)-equilenin





(IV)
D-Ring of (−)-equilenin

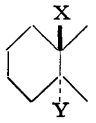
Formulæ.—(1) As stated above, all formulæ are represented arbitrarily in terms of the present steroid convention ($C_{(10)}$-methyl group above the plane of the ring system).

(2) Bonds above and below the plane of the ring system are shown by heavy and broken lines respectively. Bonds whose orientation is uncertain are shown by normal lines.

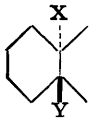
Some of the earlier formulæ in this paper are shown with the rings of the triterpenoid skeleton arranged in the way hitherto customary (rings A and B at the top). Later formulæ [from (XXXVII) onwards] are shown in accordance with the proposals of Ames, Halsall, Jones, and Meakins (*J.*, 1952, 2862), with rings A and B at the bottom to show the formal resemblance to the steroids.

Nomenclature of the triterpenoids and the use of the indices " α," " β," (α), and (β) follow in general the proposals of Ames *et al.* (*loc. cit.*), although some well-established trivial names are used.

(3) The terminal ring under discussion is written with the bridge bond vertical and the substituent at the top of the bridge in front of the general plane of the ring; *e.g.*, (V), but not (VI); (VI) would be written as (VI*A*)



(V)



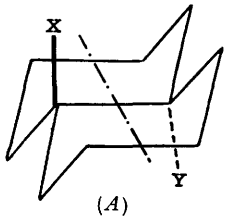
(VI)

(VI*A*)

A-*Type and* D-*Type Rings.*—*trans*-Fused terminal rings which when written in this way resemble (V), with the terminal ring to the left of the bridge bond (like the A-ring of the steroids), will be called *A*-type rings. Those which resemble (VI*A*) (like the D-ring of a D-homo-steroid), with the terminal ring to the right of the bridge bond, will be called *D*-type rings.

The Conformation and Symmetry of Terminal Rings.—trans-*Fused rings.* Unsubstituted *trans*-fused terminal rings have a two-fold axis of symmetry (see VII and X) (it is assumed here that the bridge substituents X and Y are hydrogen or methyl, which are equivalent for present purposes). This is a result of the conformation of the structures:

(VII)



(*A*)

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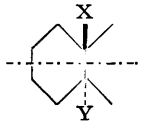

(*B*)

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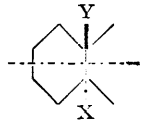
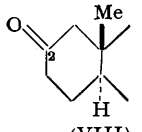
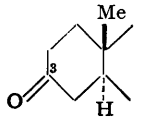


(*C*)

The stable conformation of the terminal *trans*-fused *cyclo*hexane ring in (VII) is a chair form (as shown as VII*A*, where the symmetry is obvious). The formula may be written as



(VIII)



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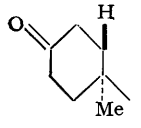
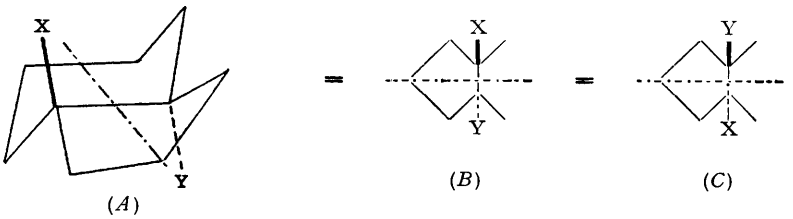


(IX)

(VII*B* or *C*). It is shown below (p. 2924) that the *trans*-2-decalones (VIII) and (IX) (2- and 3-keto-steroids), which are of the same formal type, are indeed of the same character so far as molecular rotations are concerned.

The terminal *cyclo*pentane ring, *trans*-fused to a chair-type *cyclo*hexane ring, as in (X), has a similar two-fold axis of symmetry.

(X) 

cis-*Fused rings*. The available evidence suggests that the terminal ring of a *cis*-decalin probably takes up an asymmetrical conformation in the double-chair form of Bastiansen and Hassel (cf. Barton, *J.*, 1948, 340; *Experientia*, 1950, **6**, 316). Nothing is yet known about the conformations of *cis*-indane types, and in the present paper no assumptions on this point will be made.

Principles

The principles are stated here for terminal rings; their application to intermediate rings is considered later (p. 2924). It seems most convenient to consider the molecular rotation of a complex polycyclic system in terms of contributions made by individual rings (or groups of rings where extended conjugated systems are involved); this treatment seems preferable to that previously employed by some authors (see, *e.g.*, Emde, *Helv. Chim. Acta*, 1930, **13**, 1035; Fieser and Fieser, "Natural Products related to Phenanthrene," Reinhold Publ. Corpn., New York, 3rd. edn., 1949, pp. 211 *et seq.*) in which an attempt is made to allot rotational contributions to individual bridge atoms.

(1) The molecular-rotational contribution of a terminal unit is *very roughly* independent of the nature of the rest of the molecule, provided that the penultimate ring is a saturated unsubstituted *cyclo*hexane ring.

(2) The two enantiomeric forms of a terminal unit A and A' (cf. III and IV) have rotational contributions of opposite sign, often of the same order of magnitude, say, $(\pm a)$. The molecular-rotational difference (Δ value) between two related terminal units A and B (say, $a - b$) is of opposite sign (and usually of the same order of magnitude) as the Δ value between the two enantiomeric units A' and B' (say, $-a + b$).

(3) Unstrained saturated polycyclic hydrocarbons, composed of fused *cyclo*hexane and *cyclo*pentane rings in patterns generally similar to those of the steroids, and with no substituents other than methyl or ethyl groups, have small molecular rotations; for the present purposes these are often negligible.

(4) Replacement of non-angular hydrogen atoms by methyl groups in a polycyclic hydrocarbon makes little difference to the rotational contribution of a terminal unit. Data regarding angular methyl groups are insufficient to permit generalisation, but it appears that the introduction of an angular methyl group does not change the sign of the rotational contribution of a terminal unit.

Application to terminal rings: evidence in support of the principles

Independence of Rotational Contributions of Terminal Units.—The prolonged studies by Barton and his colleagues (*J.*, 1945 to date) and Bernstein, Wallis, and their colleagues (*J. Org. Chem.*, 1941, **6**, 319; 1942, **7**, 103; 1946, **11**, 646) provide a mass of evidence in support of the principles within the group of the steroids. In the present connexion it is appropriate to note that the rotational contributions of groups in the D-ring of the steroids are not greatly altered in the œstrone and the equilenin series, where the A- or (A + B)-rings are aromatic (Table 1).

Further examples may be found in the tricyclic steroid degradation products of the perhydrophenanthrene series (XI; X = Me) studied by Billeter and Miescher (*Helv. Chim. Acta*, 1950, **33**, 388), including Köster and Logemann's acetoxy-ketone (*Ber.*, 1940, **73**, 298) and Reich's diketone (*Helv. Chim. Acta*, 1945, **28**, 892).

TABLE 1. *Rotational differences for the* D*-ring in partially aromatic steroids.*

(Values for the saturated series are for androstan-3β-ol derivatives.)

Substituents in D-ring (at $C_{(17)}$ unless otherwise stated)	Œstrone series	Equilenin series	Saturated series	Refs.
	$[M]_D$ *Values*			
None	+228°	—	0	1, 2
α-OH	+147	—	− 50°	3, 4
β-OH	+218	− 13°	+ 31 *	5, 6, 7
β-OAc	+147	− 48 †	+ 14 *	5, 7
Ketone	+446	+240	+261	8, 9, 10
β-COMe	+474	—	+305	14, 15
α-OH; β-COMe	+264	—	+104	14, 16, 17
16 : 17-ene	+263	—	+ 30	1, 13
D-Homo-series, ketone at $C_{(17a)}$	− 80	—	−200	11, 12
	Δ *Values*			
β-OAc − β-OH	− 71°	− 35°	− 17°	—
Ketone − α-OH	+299	—	+311	—
,, − β-OH	+228	+253	+230	—
,, − CH_2	+218	—	+261	—
β-COMe − CH_2	+246	—	+305	—
α-OH; β-COMe − CH_2	+ 36	—	+104	—
16 : 17-C:C − CH_2	+ 35	—	+ 30	—
D-Homo-17*a*-ketone − 17-ketone	−526	—	−461	—

* Calc. from compounds without 3β-OH.

† Value for 3-acetate; acetylation of a phenolic hydroxyl in this series makes little difference to $[M]_D$.

1, Prelog, Ruzicka, and Wieland, *Helv. Chim. Acta*, 1945, **28**, 250. 2, Ruzicka, Prelog, and Meister, *ibid.*, p. 1651. 3, Whitman, Wintersteiner, and Schwenk, *J. Biol. Chem.*, 1937, **118**, 789. 4, Barton and Klyne, *Chem. and Ind.*, 1948, 755. 5, Djerassi, Rosenkranz, Romo, Kaufmann, and Pataki, *J. Amer. Chem. Soc.*, 1950, **72**, 4534. 6, Wintersteiner, Schwenk, Hirschmann, and Whitman, *ibid.*, 1936, **58**, 2652. 7, Rosenkranz, Kaufmann, and Romo, *ibid.*, 1949, **71**, 3689. 8, Deulofeu and Ferrari, *Z. physiol. Chem.*, 1934, **226**, 192. 9, Sandulesco, Tchung, and Girard, *Compt. rend.*, 1933, **196**, 137. 10, Barton, *J.*, 1946, 1116. 11, Goldberg and Studer, *Helv. Chim. Acta*, 1942, **25**, 1556. 12, Goldberg and Monnier, *ibid.*, 1940, **23**, 376. 13, Prelog, Ruzicka, and Wieland, *ibid.*, 1944, **27**, 66. 14, Djerassi, Rosenkranz, Iriarte, Berlin, and Romo, *J. Amer. Chem. Soc.*, 1951, **73**, 1523. 15, Barton and Cox, *J.*, 1948, 783. 16, Reichstein and Gätzi, *Helv. Chim. Acta*, 1938, **21**, 1497. 17, von Euw and Reichstein, *ibid.*, 1941, **24**, 418.

TABLE 2. *Rotational differences in the perhydrophenanthrene series.*

[All compounds are numbered as for steroids. Refs.: standard values for steroids (4), see Table 1; for perhydrophenanthrenes, (18) Billeter and Miescher, *Helv. Chim. Acta*, 1950, **33**, 388.]

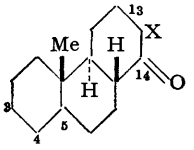
Change	Δ Values in perhydrophenanthrene series (XI; X = Me)	Standard values
5α-*Compounds.*		
3β-OAc − 3β-OH (Δ_1)	−60°, −48° *	− 29°
3CO − 3β-OH (Δ_3)	+62	+ 73
5β-*Compounds.*		
3β-OAc − 3β-OH (Δ_1)	+29, −2 *	+ 17
3CO − 3β-OH (Δ_3)	+62	+ 36
3α-OAc − 3α-OH (Δ_1)	+67, +45 *	+ 82
3CO − 3α-OH (Δ_3)	+12	+ 7
5-*Ene compounds.*		
3β-OAc − 3β-OH (Δ_1)	− 78	− 34
3-CO,4-ene − 3β-OH,5-ene (Δ_3)	+472	+511
3β-OH,5β − 3β-OH,5α	− 25	+ 9
3β-OAc,5β − 3β-OAc,5α	+ 64 †	+ 55
3CO,5β − 3CO,5α	− 25	− 28

* These values are for 12(13)-enes.

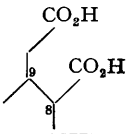
† For compounds of types (XII and XIII), Δ = +74° and +59° respectively.

The data in Table 2 show that complete removal of the D-ring has no major influence on Δ values in the $C_{(3)}$–$C_{(5)}$ area. For convenience in comparison with the steroids, steroid numbering is used for these compounds, as in (XI). [At Pinder and Robinson's suggestion (*J.*, 1952, 1224) these compounds may be called des-D-androstan-14-ones.]

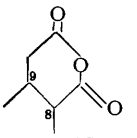
Enantiomeric Units have Rotational Contributions of Opposite Sign.—(*A*) *The* A *and* D-*homo-rings of steroids.* These are enantiomeric units. If we consider A–B-*trans*- and C–D-*trans*-compounds (XIV and XV), 1-keto- and 2-keto-units are the enantiomers of 17*a*-keto-



(XI)

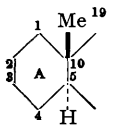


(XII)

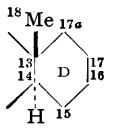


(XIII)

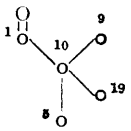
and 17-keto-units respectively. This is seen from (XIV*A*) and (XV*A*) (perspective views from beyond the bonds from $C_{(19)}$ to $C_{(10)}$ and from $C_{(18)}$ to $C_{(13)}$ respectively), or from the Fischer-type projections (XIV*B* and XV*B*).



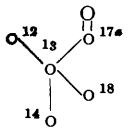
(XIV)



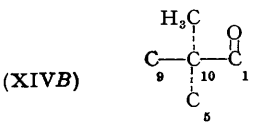
(XV)



(XIV*A*)



(XV*A*)



(XIV*B*) (XV*B*)

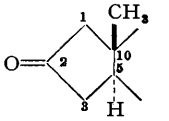
The rotational contributions of the keto-groups concerned are :

Δ(C:O-1)	+67°	Δ(C:O-17*a*)	−153°
Δ(C:O-2)	+98°, +64°	Δ(C:O-17*a*)	−168°

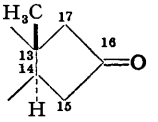
Δ(C:O-1) is of opposite sign to Δ(C:O-17*a*) and of the same order of magnitude; the same is true of Δ(C:O-2) and Δ(C:O-17).

Refs. : cholestan-1-one, Ruzicka, Plattner, and Furrer, *Helv. Chim. Acta*, 1944, **27**, 727; cholestan-2-one, *idem*, *ibid.*, p. 524; Fürst and Plattner, *ibid.*, 1949, **32**, 275; androstane-2 : 17-dione, Djerassi, Yashin, and Rosenkranz, *J. Amer. Chem. Soc.*, 1950, **72**, 5750; D-homo-ketones, Goldberg and Wydler, *Helv. Chim. Acta*, 1943, **26**, 1142 and subsequent references.

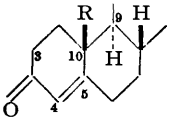
(*B*) *The* A-*nor- and* D-*rings of steroids.* These five-membered rings provide excellent examples in support of the principles. 2-Ketones of the A-norcholestane series (XVI) and 16-ketones of the ordinary *trans*-C–D-series (XVII) are enantiomeric types. The Δ values



(XVI)



(XVII)



(XVIII)

with respect to the corresponding *trans*-indane (or *trans*-decalin) types are of opposite sign and very large (see Table 3). (It is necessary to calculate some of the values with respect to the *trans*-decalin type since few A-nor-hydrocarbons are known. However, evidence given in the following section shows that the differences in rotation between corresponding *trans*-decalin and *trans*-indane types are negligible.)

It may be noted that the two simple (+)- and (−)-*trans*-β-indanones (Barrett and Linstead, *J.*, 1935, 1069; Hückel, Sachs, Yantschulewitsch, and Nerdel, *Annalen*, 1935, **518**, 155) have very large Δ(C:O) values of the same order as the Δ values quoted in Table 3 (*ca.* ±450°).

Rotations of Saturated Polycyclic Hydrocarbons.—Section (*A*) of Table 4 gives rotations of some steroid hydrocarbons, which are saturated and carry no substituents other than methyl groups; all are small values. They show, first, that the difference between *cis*- and

trans-decalin-type terminal rings is negligible, and secondly, that the difference between *trans*-decalin and *trans*-indane types is also negligible.

TABLE 3. *Rotations of* trans-*indan-2-one types.*

[Values are differences between indan-2-one and indane (*a*), decalin (*b*), or decalol (*c*).]

	$[M]_D$					
	Indan-2-one	Indane	Decalin	2-Decalol	Δ Value	Refs.
(i) A-*Nor*-2-*keto-steroids.*						
A-Norandrostan-2-one	+462°	—	+ 5°	+ 3°	+457° (*b*)	2, 13, 2
A-Norergostan-2-one	+417	—	—	+64	+353 (*c*)	19, 20
A-Nor-2-ketone from uzarigenin	+520	—	+83	+72	+437 (*b*)	21
(ii) 16-*Keto-steroids.*						
3β-Hydroxyandrostan-16-one	−464 / −522	0	+ 9	—	−464 / −522 (*a*)	22, 23, 2
3α : 12α-Dihydroxy-5β-androstan-16-one	−330	+134° *	—	—	−464 (*a*)	24, 4
3β : 20β-Diacetoxy-5α-pregnan-16-one	−406	+ 89	—	—	−495 (*a*)	25, 26
3-Hydroxyœstratrien-16-one	−235	+228	—	—	−463 (*a*)	22, 1
(iii) A-*Nor*-2-*keto-triterpenoids derived from* :						
Methyl oleanolate	+762 / +722	—	—	+348	+414 / +374 (*c*)	27, 28, 29
"Oxyallobetulin"	+618 Py	—	—	+218	+400 (*c*)	30
Methyl dihydrobetulinate	+388	—	—	− 90	+478 (*c*)	31
Hedragonic lactone †	+490	—	+120 ‡	—	+370 (*b*)	32, 33
Dihydrolanosterol	+515	—	—	+260	+255 (*c*)	34

* Calc. from tables of standard values (4).

† This compound has only one Me at $C_{(1)}$.

‡ Calc. from hedragonic lactone (+194) by subtraction of Δ(C:O-2) (+74), see Table 7.

1, 2, 13, See Table 1. 19, Reindel, *Annalen*, 1928, **466**, 131. 20, Reindel, Walter, and Rauch, *ibid.*, 1927, **452**, 34. 21, Tschesche, *Z. physiol. Chem.*, 1933, **222**, 50. 22, Huffman and Lott, *J. Amer. Chem. Soc.*, 1951, **73**, 878. 23, Heard and McKay, *J. Biol. Chem.*, 1939, **131**, 371. 24, Marshall and Gallagher, *J. Amer. Chem. Soc.*, 1949, **71**, 2325. 25, Hirschmann, Hirschmann, and Daus, *J. Biol. Chem.*, 1949, **178**, 751. 26, Klyne and Barton, *J. Amer. Chem. Soc.*, 1949, **71**, 1500. 27, Kitasato, *Acta Phytochim., Tokyo*, 1937, **10**, 199. 28, Ruzicka and van der Sluys-Veer, *Helv. Chim. Acta*, 1938, **21**, 1371. 29, Barton and Jones, *J.*, 1944, 659 (summary with full references). 30, Dischendorfer and Polak, *Monatsh.*, 1929, **51**, 43. 31, Ruzicka, Brenner, and Rey, *Helv. Chim. Acta*, 1941, **24**, 515. 32, Ruzicka, Jeger, and Norymberski, *ibid.*, 1944, **27**, 1185. 33, *Idem, ibid.*, 1943, **26**, 2242. 34, Ruzicka, Rey, and Muhr, *ibid.*, 1944, **27**, 472.

Further values, supporting these comparisons, together with a value for a *cis*-indane type, are provided by cholestane and related compounds, including the A-nor-hydrocarbons [section (*B*) of Table 4].

Rotations for some saturated triterpenoid hydrocarbons are given in section (C) of Table 4.

TABLE 4. *Rotations of saturated hydrocarbons.*

	$[M]_D$	Refs.
(*A*) *Steroids carrying only methyl groups.*		
Androstane	+ 5°	13
5β-Androstane	+ 11	35
D-Homoandrostane	− 9	36
(*B*) *Cholestane and related hydrocarbons.*		
Cholestane	+ 91	15
5β-Cholestane	+ 93	37
A-Norcholestane	+ 90	38
5β-A-Norcholestane	+119	38
(*C*) *Triterpenoid hydrocarbons.*		
Oleanane (β-amyrane)	+ 41°	39
Heterolupane	+ 50	40
α-Lupane	− 16	41
Lupane-I	+107	42, 43
Zeorinane	+ 49	44

For the *trans*-indanes Barrett and Linstead (*loc. cit.*) found +15°.

13, 15, See Table 1. 35, Shoppee, *Helv. Chim. Acta*, 1944, **27**, 246. 36, Goldberg and Wydler, *ibid.*, 1943, **26**, 1142. 37, Mauthner, *Monatsh.*, 1909, **30**, 635. 38, Lettré, *Z. physiol. Chem.*, 1933, **221**, 73. 39, Ruzicka and Jeger, *Helv. Chim. Acta*, 1945, **28**, 1178. 40, Jeger and Lardelli, *ibid.*, 1947, **30**, 1020. 41, Jeger, Montavon, Novak, and Ruzicka, *ibid.*, p. 1869. 42, Heilbron, Kennedy, and Spring, *J.*, 1938, 329. 43, Ames, Halsall, and Jones, *J.*, 1951, 450. 44, Barton and Bruun, *J.*, 1952, 1683.

Effect of Methyl Groups.—(*A*) *Non-angle methyl groups.* Evidence from many types of compounds shows that the substitution of hydrogen (not at a ring-junction) by methyl makes little difference to the molecular rotations of hydrocarbons and ketones. Data are summarized in Table 5. Consideration of the effect of methyl groups on the rotational contributions of hydroxy- and acetoxy-groups is not simple (cf. Barton and Jones, *loc. cit.*), but it is hoped to deal with this in a subsequent paper.

TABLE 5. *Effect of non-angular methyl groups on rotations.*

Type and compound	Position of substituent Me	$[M]_D$ values: with Me (*a*)	$[M]_D$ values: without Me (*b*)	Δ (*a* − *b*)	Refs.
Androstane :					
Androstan-3α-ol	17	+ 29°	+ 10°	+19°	45, 2
Androstan-3β-ol	17	+ 17	0	+17	45, 2
Androstan-3-one	17	+ 91	+ 76	+15	45, 2
D-Homoandrostane	17*a*	− 9	− 9	0	36, 46
Cholesta-3 : 5-diene	3	−493	−453	−40	47, 48
17-Keto-steroid :					
3β-Acetoxyandrost-5-en-17-one	16	0	+ 6	− 6	49, 15
17*a*-Keto-D-homo-steroid :					
D-Homoandrostane-3 : 17*a*-dione	17	− 66	− 81	+15	50, 51, 36
3β-Acetoxy-D-homoandrostan-17*a*-one	17	−107	−156	+49	52, 53
Perhydrophenanthrenes [see formula XI; steroid numbering; *A*(−)-series] :					
3-ol-14-one	13	−108	− 91	−17	54
3 : 14-dione	13	− 50	− 33	−17	54

2, 15, See Table 1. 36, See Table 4. 45, Ruzicka, Meister, and Prelog, *Helv. Chim. Acta*, 1947, **30**, 867. 46, Ruzicka and Meldahl, *ibid.*, 1940, **23**, 364. 47, Musgrave, *J.*, 1951, 3121. 48, Schoenheimer and Evans, *J. Biol. Chem.*, 1936, **114**, 567. 49, Julian, Meyer, and Printy, *J. Amer. Chem. Soc.*, 1948, **70**, 3872. 50, Klyne, *Biochem. J.*, 1948, **43**, 611. 51, *Idem*, *Nature*, 1950, **166**, 559. 52, Prins and Shoppee, *J.*, 1946, 494. 53, Goldberg and Monnier, *Helv. Chim. Acta*, 1940, **23**, 376. 54, Cornforth and Robinson, *J.*, 1949, 1855.

(*B*) *Angle (ring-junction) methyl groups.* The following facts indicate that the rotational contributions of ketone and similar groups retain the same sign when an angle methyl group (*i.e.*, a methyl group at a ring-junction) is replaced by a hydrogen atom of the same configuration.

19-Nor-analogues (XVIII; R = H) of the hormones testosterone and progesterone (XVIII; R = Me) have recently been prepared (Birch, *J.*, 1950, 367; Birch and Smith, *J.*, 1951, 1882; Miramontes, Rosenkranz, and Djerassi, *J. Amer. Chem. Soc.*, 1951, **73**, 3540). All the available evidence suggests that the 19-nor-compounds are true analogues of the common Δ^4-steroids, *i.e.*, that the $C_{(10)}$-H is β. Birch and Smith point out that the 19-nor-compounds, which are formed under conditions of reversible proton addition, must be the isomers at $C_{(10)}$ of lower energy-level, and therefore presumably the $C_{(10)}$-H is *trans* to the $C_{(9)}$-H, *i.e.*, is β.

Furthermore, the nor-compounds have physiological activity similar to that of the natural hormones, from which it seems very probable that the molecular configuration is essentially the same as that of the natural products. The molecular model of a 10α-19-nor-Δ^4-steroid differs greatly in the shape of the A–B-rings from that of the natural Δ^4-steroids; it seems most improbable that the 10α-19-nor-compounds could have the physiological activities for which the Δ^4-3-ketone grouping is essential.

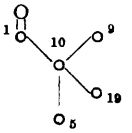
The rotations are as follows :

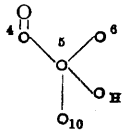
	αβ-Unsaturated ketones (XVIII): natural, R = Me	αβ-Unsaturated ketones (XVIII): 19-nor, R = H	Compounds with saturated hydrocarbon grouping at $C_{(3)}$–$C_{(5)}$ and 19-methyl
Testosterone	+340°	+184°	+ 33°
Progesterone	+631	+441	+302

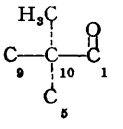
Refs. : Birch, Miramontes *et al.*, *locc. cit.*; Barton and Cox, *loc. cit.*; Romo, Romero, Djerassi, and Rosenkranz, *J. Amer. Chem. Soc.*, 1951, **73**, 1528; Rosenkranz, Kaufmann, and Romo, *ibid.*, 1949, **71**, 3689.

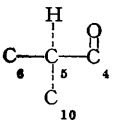
19-Nor-Δ^4-3-ketones, like the ordinary Δ^4-3-ketones, have a positive rotational contribution for the 4-en-3-one grouping, although it is only about one-half as large as in the natural 10-methyl series.

Further evidence may be obtained from the A-ring ketones of the common A–B-*trans*-steroids. If a 4-ketone and a 1-ketone of the cholestane series (XIV*A* and XIX*A*; XIV*B* and XIX*B*) are compared, it is seen that (except for the methyl group in the 1-ketone) they are of the same enantiomeric type. In fact the rotational contributions of 1- and 4-keto-


(XIV*A*)


(XIX*A*)


(XIV*B*)


(XIX*B*)

groups are of the same sign; this is also true of the similarly related pair of 2- and 3-keto-groups.

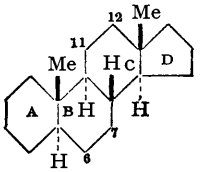
Δ(C:O-1)	+67°	Δ(C:O-4)	+25°
Δ(C:O-2)	+98, +64	Δ(C:O-3)	+71

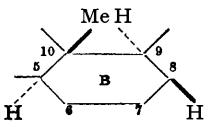
Refs.: 1- and 2-ketones, see p. 2921; 3-ketones, Barton and Cox, *loc. cit.*; 4-ketones, Ruzicka, Plattner, and Furrer, *Helv. Chim. Acta*, 1944, **27**, 727.

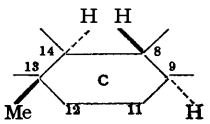
Application of the Rule of Shift to Intermediate Rings

When it had been found that the rule of shift could be applied to the enantiomeric terminal rings of steroids and that its application to the triterpenoids (see p. 2919) gave four mutually consistent pieces of evidence linking the stereochemistry of these compounds with that of the steroids, attention was turned to the intermediate or middle rings of these compounds.

No true enantiomeric types exist in the B- and the C-ring of the steroids (XX), since the D-ring is five membered and the A-ring six-membered. However, these rings are of somewhat similar but enantiomeric types. This is seen if rings B and C are placed with their CH_2–CH_2 groups in corresponding positions (XXI and XXII).


(XX)


(XXI)


(XXII)

The Δ values for the introduction of ketonic and olefinic groupings into rings B and C are of opposite sign, although quantitatively the agreement is poor (see Table 6).

TABLE 6. *Comparison of molecular rotation differences in the* B- *and the* C-*ring of the steroids.*

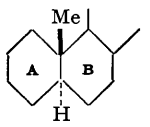
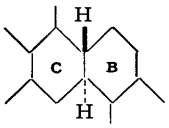
(Values in the B-ring are for A–B-*trans*-compounds.)

B-Ring		C-Ring		Refs.
Δ(C:O-6)	−110°	Δ(C:O-12)	+270°	4
Δ(C:O-7)	−230	Δ(C:O-11)	+ 80	4
Δ(C:C-5)	−300	—		4
Δ(C:C-6)	−440,-415	Δ(C:C-11)	+ 30	55, 56, 60*a*, 4
Δ(C:C-7)	− 70	Δ[C:C-9(11)]	+50, +100	4
Δ[C:O-7; C:C-8(9)]	−190 to −270	Δ[C:O-11; C:C-8(9)]	+380, +500	57, 58, 59, 60

4, See Table 1. 55, Barton and Rosenfelder, *J.*, 1949, 2459. 56, Wintersteiner and Moore, *J. Amer. Chem. Soc.*, 1950, **72**, 1923. 57, Fieser, Herz, and Huang, *ibid.*, 1951, **73**, 2397. 58, Djerassi, Mancera, Stork, and Rosenkranz, *ibid.*, p. 4496. 59, Heusser, Eichenberger, Kurath, Dällenbach, and Jeger, *Helv. Chim. Acta*, 1951, **34**, 2106. 60, Heusser, Heusler, Eichenberger, Honegger, and Jeger, *ibid.*, 1952, **35**, 295. 60*a*, Fischer, Lardelli, and Jeger, *ibid.*, 1951, **34**, 1577.

Each intermediate ring (in an angular *trans-anti-trans*-linked array of *cyclo*hexane rings) may be considered as of *A* or *D* type with respect to its two neighbours. Steroid ring B is of *D* type with respect to A, and also of *D* type with respect to C (see XXIII and XXIV). Steroid ring C is of *A* type with respect to B and to D.

All *A*-type *trans*-decalones and *trans*-octalins have positive Δ values, and the corresponding *D*-type compounds (where known) have negative Δ values (reference values in

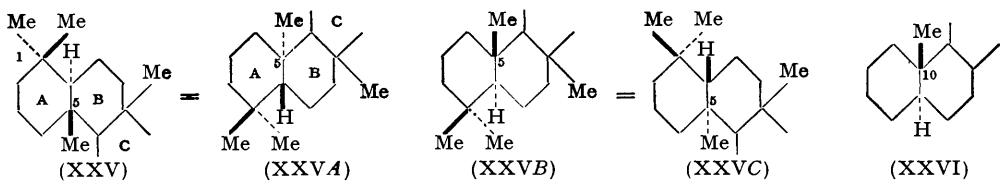
(XXIII)   (XXIV)

Barton and Klyne, *loc. cit.* and p. 2921). The values in Table 6 are all in agreement with these (cf. Stokes and Bergman, *loc. cit.*).

It therefore seems permissible to extend the rule of shift to intermediate rings if true analogies are available and if no substituents likely to cause serious vicinal action are present. This means that the linking of the ring or rings under consideration with their neighbours must be of the same type (*trans-anti-trans* in most cases) and that the only substituents in the neighbouring rings should be alkyl radicals or other groups which make only small contributions to the molecular rotation.

Correlation of the Stereochemistry of the Triterpenoids with that of the Steroids

The A and *the* B *Rings.*—Evidence for the *trans*-fusion of the A and the B ring in the triterpenoids has recently been summarized by Barton and Holness (*J.*, 1952, 78). The formula of the A and the B ring of the triterpenoids resembles closely that of the same area in the steroids; compare the oleanane (β-amyrane) structure (usually written, in part, as XXV; may be rewritten as XXV*A*) with the androstane skeleton (XXVI). The ring union

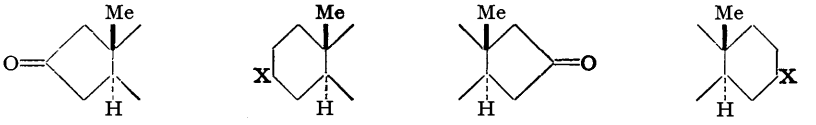


(XXV) (XXV*A*) (XXV*B*) (XXV*C*) (XXVI)

is *trans* in each case, the angle methyl group on this bridge is in a similar position, and the only essential difference is the *gem*-dimethyl group at $C_{(1)}$ in the triterpenoid (XXV).

The question remains whether the triterpenoid is to be represented by (XXV*A*; with $C_{(5)}$-methyl behind the plane of the ring system), or its enantiomer (XXV*B*; with $C_{(5)}$-methyl in front of the plane). On the assumption that the usual steroid convention ($C_{(10)}$-methyl in front of the ring system) is "correct," the rule of shift as discussed in the preceding sections of this paper shows that (XXV*B* = *C*) is "correct." The evidence is as follows.

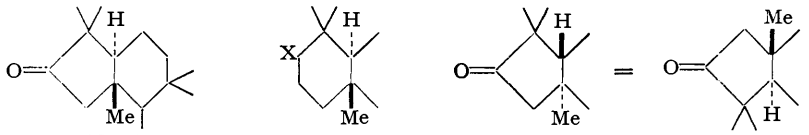
Comparison of trans-*indan-2-one types.* The keto-groups in steroids of these types (*A* and *D*) have large positive and negative rotations respectively (see p. 2922). It has also been shown (p. 2922) that there is no significant difference between *trans*-indane and *trans*-decalin types as reference substances; furthermore, the rotational contribution of a hydroxyl group at $C_{(2)}$ (ΔOH-2) in the triterpenoid skeleton is small (mean of 5 values, 0; range −32 to +36).



(XXVII*A*) (XXVIII*A*; X = H or OH) (XXVII*D*) (XXVIII*D*; X = H or OH)

We may therefore say that the Δ value of (XXVII*A* — XXVIII*A*) has a large positive value (*ca.* +400), whilst the Δ value of (XXVII*D* — XXVIII*D*) has a large negative value (*ca.* −500). 2-Keto-A-nor-triterpenoids of type (XXIX) have been obtained by oxidation of 2-ketones to 2 : 3-*seco*-acids, and ring-closure of these. Table 3 (part iii) shows that the

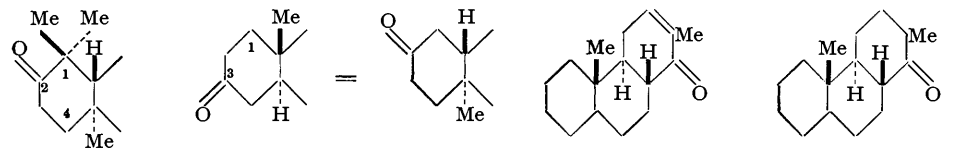
Δ values between these 2-keto-A-nor-compounds and the triterpenoid hydrocarbons or alcohols of type (XXX; X = H or OH) are all very large positive values, of the same order as the difference for 2-keto-A-nor-steroids. Thus the A-nor-triterpenoids (XXIX) are compounds of the enantiomeric type (*A*); (XXIX) should therefore be written as (XXXI), or as (XXXII), if steroid conventions are followed.



(XXIX) (XXX) (XXXI) (XXXII)

The A–B-ring union in the natural triterpenoids should therefore be written as in (XXV*B* or *C*), and not as in (XXV) or (XXV*A*).

trans-*Decalone types.* 2-Ketones of the triterpenoid series (XXXIII) are analogous to 3-keto-steroids (A–B-*trans*; XXXIV), except for the *gem*-dimethyl group at $C_{(1)}$. Similarly 4-keto-triterpenoids are analogous to 1-keto-steroids. The Δ(C:O) values of these compounds are compared in the first two sections of Table 7.



(XXXIII) (XXXIV) (XXXV) (XXXVI)

trans-Δ^2-*Octalin types.* Δ^2-Triterpenoids may be compared with cholest-2-ene (third section of Table 7).

αβ-*Unsaturated ketone types.* A further comparison may be made between the unsaturated ketones of the type studied by Billeter and Miescher (*loc. cit.*) and the lup-2-en-4-one of Jeger, Montavon, Novak, and Ruzicka (*Helv. Chim. Acta*, 1947, **30**, 1869). The Δ values for the change (XXXV → XXXVI) are given in the last section of Table 7.

The agreement in sign for all Δ values in the two series [all Δ(C:O) and Δ(C:C) values

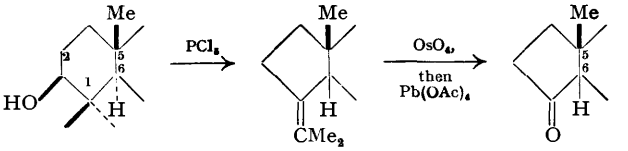
TABLE 7. *Other Δ values in the A-rings of the triterpenoids and steroids.*

	Triterpenoids $[M]_D$ with substituent	Triterpenoids $[M]_D$ without substituent	Δ value	Refs.	Steroids (comparable structures; refs. in parentheses)
trans-2-*Decalones.*					
α-Amyrone	+465°	+390°	+ 75°	61, 63	Cholestan-3-one, Δ(C:O-3), +70° (4)
β-Amyrone (olean-12-en-2-one)	+454	+390	+ 64	29, 62	
Lupan-2-one	+ 68	− 16	+ 84	29, 41	
Lupenone	+259	+115	+144	29	
Methyl betulonate	+150	+ 9	+141	64	
2-Keto-oleanan-28-oic acid	+160	+ 35	+125	66	
trans-1-*Decalone.*					
Lupan-4-one	+149	− 16	+165	41	Cholestan-1-one, Δ(C:O-1), +67° (65)
trans-Δ^2-*Octalins.*					
α-Amyrilene-II	+572	+390	+182	62, 63	Cholest-2-ene, Δ(C:C-2), +139° (55)
β-Amyrilene-II (olean-2 : 12-diene)	+580	+390	+190	62	
Lup-2-ene	+ 57	− 16	+ 73	41	
αβ-*Unsaturated ketones.*	(αβ-Unsatd.)	(Satd. ketone)			Perhydrophenanthrenes (XXXV—XXXVI); 6 examples, mean Δ value, +43° (range +5° to +74°) (18)
Lup-2-en-4-one	+195	+149	+ 46	41	

4, See Table 1. 18, See Table 2. 29, See Table 3. 41, See Table 4. 55, See Table 6. 61, Barton and de Mayo (unpublished). 62, Winterstein and Stein, *Annalen*, 1933, **502**, 223. 63, Ruzicka, Muller, and Schellenberg, *Helv. Chim. Acta*, 1939, **22**, 758. 64, Ruzicka and Rey, *ibid.*, 1941, **24**, 529. 65, Ruzicka, Plattner, and Furrer, *ibid.*, 1944, **27**, 727. 66, Dietrich and Jeger, *ibid.*, 1950, **33**, 711.

positive] confirms the allotment of configurations made for the triterpenoids on the basis of the previous argument.†

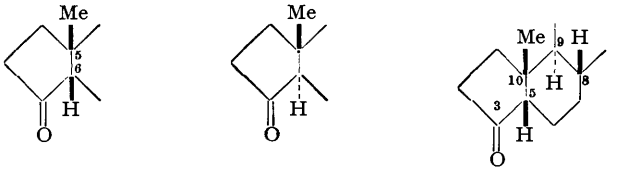
Indan-1-one types in the triterpenoids. Proof of cis-*union.* Ruzicka, Jeger, and their colleagues (Ruzicka, Montavon, and Jeger, *Helv. Chim. Acta*, 1948, **31**, 819 and



(XXXVII) (XXXVIII) (XXXIX)

earlier papers) have developed a general method by which the six-membered A-ring of a triterpenoid may be changed to a five-membered ring, with the loss of the *gem*-dimethyl group (represented by XXXVII, XXXVIII, XXXIX).

It has never been stated whether the indan-1-ones of type (XXXIX) have a *cis*-A–B-union, which would involve epimerization at $C_{(6)}$ at some stage. Analogy with simpler



(XL) (XLI) (XLII)

compounds suggests that the *cis*-union would be stable here (cf. Hückel *et al.*, *loc. cit.*); Barton and Thomas (personal communication) have recently shown that the indan-1-one prepared thus from dihydrolanosterol is indeed stable to alkali.

The rule of shift shows that (XXXIX) must be a *cis*-compound (XL) and not the *trans*-isomer (XLI). The latter is the *A*-type analogue of a 17-keto-steroid [*D*-type; Δ(C:O),

TABLE 8. *Rotations of* cis-*indan-1-one types.*

[Δ Values are differences between *cis*-indan-1-one and *trans*-decalin (*a*) or *trans*-2-decalol (*b*).]

	$[M]_D$				
	cis-Indan-1-one	*trans*-Decalin	*trans*-2-Decalol	Δ Value	Refs.
Steroids					
A-Nor-compounds from :					
Androstan-3β-ol	+387°	+ 5°	0°	+382° (*a*) +387 (*b*)	2, 13
3α-Hydroxy-12-ketocholanic acid	+665	+344 *	—	+321 (*a*)	67, 4
Triterpenoids					
A-Nor-compounds from :					
α-Amyrenonol	+925	—	+480	+445 (*b*)	68, 69
Dihydrolanosterol	+768	—	+260	+508 (*b*)	70, 34
Lupan-2" β "-ol	+410	− 16	− 77	+426 (*a*) +487 (*b*)	71, 41, 42
18(α)-Oleanolic lactone	+503	—	+ 59	+444 (*b*)	72, 73

* Calc. from tables of standard values (ref. 4).

2, 4, 13, See Table 1. 34, See Table 3. 42, See Table 4. 67, Wieland and Kulenkampff, *Z. physiol. Chem.*, 1919—20, **108**, 295. 68, Ruzicka, Jeger, and Volli, *Helv. Chim. Acta*, 1945, **28**, 767. 69, Spring and Vickerstaff, *J.*, 1937, 251. 70, Ruzicka, Montavon, and Jeger, *Helv. Chim. Acta*, 1948, **31**, 818. 71, Ruzicka, Jeger, and Huber, *ibid.*, 1945, **28**, 942. 72, Ruzicka, Rudowski, Norymberski, and Jeger, *ibid.*, 1946, **29**, 210. 73, Barton and Holness, *J.*, 1952, 78.

+250] and would have a large negative Δ(C:O) value. The isomer (XL) is, so far as its A- and B-rings are concerned, the same as the A-nor-3-keto-steroids of the A–B-*cis*-series (XLII) and so, whatever conformation is favoured for such a structure, the two types of

† [*Added in proof.*] Voser, White, Heusser, Jeger, and Ruzicka (*Helv. Chim. Acta*, 1952, **35**, 830) have prepared from lanostadienol an unsatuated ketone of 2-keto-$\Delta^{1(6)}$-type without the *gem*-dimethyl group in ring A, which is exactly analogous to a 3-keto-Δ^4-steriod and shows the expected large positive rotation.

TABLE 9. *Rotational differences for the intermediate rings of the triterpenoids and steroids.*

References for the saturated triterpenoids are: oleanan-2-ol and acetate, 39; oleanan-2-ol-28-oic acid and derivatives, 66. References for steroid Δ values, 4; 55, 56, 60*a* for Δ(C:C-6). $[M]_D$ Values for triterpenoid acids are for methyl esters, except where marked (*a*). Barton and Jones (29) have shown that the difference in $[M]_D$ between an acid and its methyl ester is negligible. All oleanane derivatives are 18(β) unless stated otherwise; all 2-hydroxy-groups are 2" β."

Triterpenoids (XLV)					Steroids (XLVI)	
	$[M]_D$					
Type and compound	with substituent	without substituent	Δ Value	Refs.	Type	Δ Value
10-*Ene*					7-*Ene*	−70°
Olean-10-en-2-yl acetate	+360°	+ 99°	+261°	74, 75	Enantiomeric type; Δ values, opposite sign	
Olean-10-en-2-ol-28-oic acid	+193	+ 80	+113	76		
,, acetate	+226	+ 87	+139	76, 73		
12-*Ene*					5-*Ene*	−300
Olean-12-en-2-ol	+379	+ 77	+302	29	Enantiomeric type; Δ values, opposite sign	
,, acetate	+384	+ 99	+285			
Olean-12-en-2-ol-28-oic acid	+348	+ 80	+268			
,, acetate	+348 *	+ 87	+261			
15-*Ene*					6-*Ene*	−440
Oleane-12 : 15-dien-2-ol-28-oic acid	+ 84	+348	−264	86	Same type; Δ values, same sign	
,, ,, acetate	+102	+348	−246			
10 : 12-*Diene*					5 : 7-*Diene*	−540
Oleane-10 : 12-dien-2-yl acetate	+1540	+ 99	+1441	77, 78	Enantiomeric type; Δ value, opposite sign	
Oleane-10 : 12-dien-2-ol-28-oic acid	+920 (*a*)	+ 69 (*a*)	+851	76, 77		
	+950	+ 80	+870			
11 : 13(18)-*Diene*					3 : 5-*Diene*	−550
Oleane-11 : 13-(18)-dien-2-ol ‡	−305	+ 77	−382	80, 75	Same type; Δ values, same sign	
,, ,, acetate ‡	−289	+ 99	−388			
Oleane-11 : 13(18)-dien-2-ol-28-oic acid	−645	+ 80	−725	84		
Oleane-11 : 13(18)-dien-2-ol-28-oic acetate	−653	+ 87	−740			
11-*One*					7-*One*	−230
2-Acetoxyoleanan-11-one	+ 33	+ 99	− 66	74	Enantiomeric type, but Δ values same sign *Anomalous*	
2-Acetoxyoleanan-11-on-28-oic acid	+ 25	+ 87	− 62	73		
12-*One*					6-*One*	−110
Oleanan-2-ol-12-one	−115	+ 77	−192	75	Enantiomeric type, but Δ values same sign *Anomalous*	
,, acetate	− 73	+ 99	−172			
Oleanan-2-ol-12-on-28-oic acid	− 95	+ 80	−175	82, 83		
,, acetate	− 53	+ 87	−140			
16-*One*					7-*One*	−230
Olean-12-en-2 : 16-dion-28-oic acid	+ 10	+417	−407	87	Same type; Δ values, same sign	
2-Acetoxyolean-12-en-16-one	+125	+384	−259	88		
Olean-12-ene-2 : 16-dione	+236	+454	−218			
12-*En*-11-*one*					5-*En*-7-*one*	−500
Olean-12-en-11-on-2-ol	+448	+ 77	+371	77, 81	Enantiomeric type; Δ values, opposite sign	
	+498		+421			
,, acetate	+762	+ 99	+663			
Olean-12-en-11-on-2-ol-28-oic acid acetate	+520 †	+ 87	+433	85		
10-*En*-12-*one*					5-*En*-7-*one*	−500
2-Acetoxyolean-10-en-12-on-28-oic acid	+279	+ 87	+192	73	Enantiomeric type; Δ values, opposite sign	

* The corresponding 18-(α)-compound (D–E trans) has +226° (ref. 73).

† The corresponding 18-(α)-compound (D–E trans) has +442° (ref. 73).

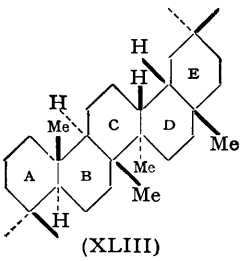
‡ Δ Values for these compounds may also be calculated from 18-(α)-oleanan-2-ol and its acetate as reference compounds. For $[M]_D$ of these, see Table. 11. Δ values are −459°, −491°.

4, See Table 1. 29, See Table 3. 65, 66, See Table 7. 73, See Table 8. 74, Jeger and Ruzicka, *Helv. Chim. Acta*, 1945, **28**, 209. 75, Budziarek, Johnston, Manson, and Spring, *J.*, 1951, 3019. 76, McKean, Manson, and Spring, *J.*, 1952, 432. 77, Beynon, Sharples, and Spring, *J.*, 1938, 1233. 78, Picard, Sharples, and Spring, *J.*, 1939, 1045. 79, Kitasato, *Acta Phytochim., Tokyo*, 1935, **8**, 315. 80, Ruzicka, Müller, and Schellenberg, *Helv. Chim. Acta*, 1939, **22**, 767. 81, *Idem, ibid.*, p. 758. 82, Kitasato, *Acta Phytochim., Tokyo*, 1934—5, **8**, 207; 1936—7, **9**, 43. 83, Ruzicka and Cohen, *Helv. Chim. Acta*, 1937, **20**, 804. 84, Barton and Brooks, *J.*, 1951, 257. 85, Ruzicka, Cohen, Furter, and van der Sluys-Veer, *Helv. Chim. Acta*, 1938, **21**, 1735. 86, Frazier and Noller, *J. Amer. Chem. Soc.*, 1944, **66**, 1267. 87, White and Noller, *ibid.*, 1939, **61**, 983. 88, Jeger, Montavon, and Ruzicka, *Helv. Chim. Acta*, 1946, **29**, 1124.

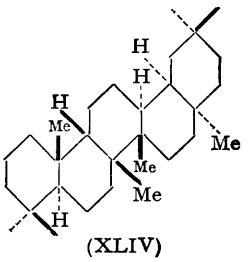
compound should have Δ(C:O) values of the same sign. The A-nor-3-keto-steroids (A–B *cis*; XLII) have large positive Δ(C:O) values, and so have the triterpenoid compounds, which are therefore of type (XL), with a *cis*-union (see Table 8).

It may be pointed out that the agreement between the Δ value for the nor-ketone from dihydrolanosterol and those for other A-nor-triterpenoid ketones indicates that the stereochemistry of the A–B-ring area in the lanosterol group is the same as in the pentacylic triterpenoids.

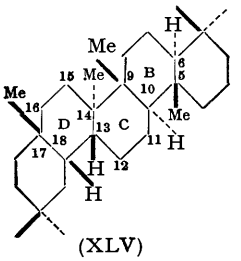
The Intermediate Rings of the Oleanane Triterpenoids.—Recent work has shown that the ring unions of the oleanane (β-amyrane) group of triterpenoids are either (more probably) *trans-anti-trans-anti-trans-syn-cis* (as XLIII) or (less probably) *trans-syn-cis-syn-trans-syn-cis* (as XLIV) (Barton and Holness, *loc. cit.*, *q.v.* for other references).



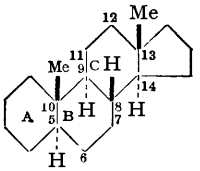
(XLIII)



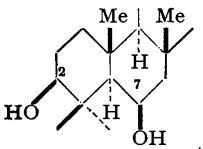
(XLIV)



(XLV)



(XLVI)



(XLVII)

The C- *and the* D-*ring of the triterpenoids.* Oleanane (XLIII) may be rewritten (XLV), in which rings DCB are of enantiomeric type to rings ABC of the steroids (A–B *trans*-series) (XLVI). Comparison of molecular rotation differences for many olefinic, ketonic, and conjugated groups in the two series shows that, in all but two cases, the Δ values in the triterpenoid series are of the sign which would be predicted for (XLV) from the known Δ values for steroids (see Table 9). Often the Δ values in the two series are of the same order of magnitude. There is at present no explanation for the anomalous Δ values for 11- and 12-keto-triterpenoids.

Triterpenoids of the ursane (α-amyrane) series are not treated in the present paper. It is hoped to consider them later and to discuss the recent structural proposals of Tschesche and Fugmann (*Chem. Ber.*, 1951, **84**, 810).

The B-*ring of the triterpenoids.* Further comparisons may be made between the ABC ring system of the triterpenoids and the ABC rings of the steroids. If formula (XLIII = XLV) is correct, then the B-rings of the two series are of the same enantiomeric type (cf. XLIII and XLVI). Here $C_{(7)}$ in the triterpenoid is equivalent to $C_{(6)}$ in the steroid. The experimental data of Table 10 support this view. The triterpenoid values are for derivatives of sumaresinolic acid. Barton (1950, *loc. cit.*) has produced evidence for the "β"-configuration of the 7-hydroxyl group in this acid (XLVII). The steroid values (for 6β-substituted 5α-compounds) are from the tables of Barton and Klyne (*loc. cit.*).

TABLE 10. Δ *Values for 7-substituted triterpenoids.*

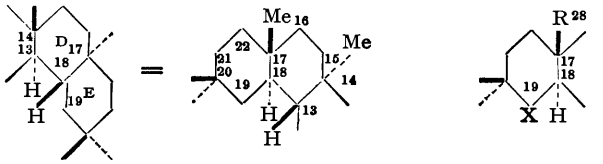
	Δ(C:O)	Δ(OH)	Δ(OAc)	Δ_1	Δ(C:C) †
Triterpenoids * (changes at $C_{(7)}$) ...	−112°, −84°	−137°, −191°	−206°	−69°	−103°
Steroids (changes at $C_{(6)}$)	−113	− 50	−110	−60	−298

* Refs.: Ruzicka, Jeger, *et al.*, *Helv. Chim. Acta*, 1943, **26**, 2283; 1945, **28**, 380; 1948, **31**, 1205.
† Δ(C:C-6) in triterpenoid, Δ(C:C-5) in steroid.

Ring E *of the triterpenoids.* The rule of shift may be applied to several groups of triterpenoids having a six-membered terminal ring E. The results support the formula

(XLIII) for oleanane given above, except for those referring to the olefinic grouping at $C_{(18)}$–$C_{(19)}$ in germanicol, moradiol, and morolic acid. The Δ values for this olefinic linkage are anomalous and cannot at present be explained, since the chemical evidence for the location of the double bond at $C_{(18)}$–$C_{(19)}$ is extensive and convincing (David, *Bull. Soc. chim.*, 1949, **16**, 155; Barton and Brooks, *J.*, 1951, 257; Barton, Brooks, and Holness, *ibid.*, p. 278; Barton and Holness, *J.*, 1952, 78; Davy, Halsall, and Jones, *J.*, 1951, 2696; Davy, Halsall, Jones, and Meakins, *ibid.*, p. 2702).

(*a*) 19-*Substituted* 18(α)-*oleananes*. 19-Substituted 18(α)-compounds (D–E *trans*) have recently been prepared by Ames, Davy, Halsall, Jones, and Meakins (*Chem. and Ind.*, 1951, 741; cf. *J.*, 1952, 2862) and by Budziarek, Johnston, Manson, and Spring (*Chem. and Ind.*, 1951, 478; *J.*, 1951, 3336). If formula (XLIII) is correct for the 18(β)-oleanane series, then 18(α)-oleanane is (XLVIII = XLIX) and the E-ring is of *A*-type.



(XLVIII) (XLIX) (L)

If 18(β)-oleanane were (XLIV), the E-ring of the 18(α)-compound would be of *D*-type. The Δ values for the 19-substituted 18(α)-oleananes (L; R = Me) are all of the same sign as those for 4-substituted steroids (see Table 11). This evidence supports the formulation of 18(β)-oleanane as (XLIII) and its 18(α)-compound as (XLVIII = XLIX).

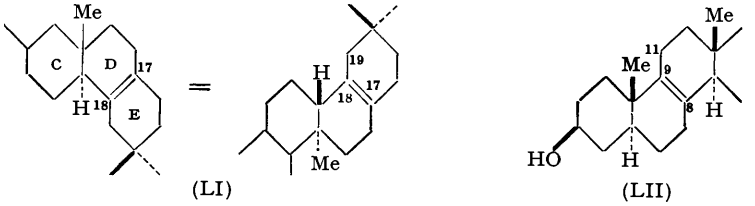
TABLE 11. *Rotations of* 18(α)-*oleanane derivatives.*

[Configurations at $C_{(19)}$ allotted following Ames *et al.* (90); configurations at $C_{(4)}$ in steroids following ref. 93.]

	19-Substituted 18(α)-triterpenoids			4-Substituted steroids (A–B *trans*).
	$[M]_D$	Δ values		Δ Values
18(α)-Oleanan-2"β"-ol	+154°	—		—
,, acetate	+202	—		—
18(α)-Oleanan-2"β"-ol-19-one	+170	+ 16°	Δ(C:O-19)	+25°, Δ(C:O-4)
,, acetate	+237	+ 35		—
18(α)-Oleanane-2"β":19(α)-diol	− 22	−176	Δ[OH-19(α)]	−75, Δ(OH-4α)
,, 2-acetate	+ 34	−168		—
18(α)-Oleanane-2"β":19(β)-diol	+111	− 43	Δ[OH-19(β)]	−22, Δ(OH-4β)
,, 2-acetate	+160	− 42		—

Refs: 89, Ames, Davy, Halsall, Jones, and Meakins, *Chem. and Ind.*, 1951, 741. 90, *Idem*, *J.*, 1952, 2862. 91, Budziarek, Johnston, Manson, and Spring, *Chem. and Ind.*, 1951, 478. 92, Budziarek, Manson, and Spring, *J.*, 1951, 3336. 93, Barton and Rosenfelder, *ibid.*, p. 1048.

Other 19-substituted 18(α)-compounds are available for consideration, *viz.*: the 28-acetoxy-compounds obtained by Barton and Holness (*loc. cit.*) and Davy, Halsall, Jones, and Meakins (*loc. cit.*). 2"β": 28-Diacetoxy-18(α)-oleanan-19(β)-ol (L; R = CH_2·OAc, X = H, OH; "betulin triol diacetate") has (+119°, +136°); the corresponding 19-ketone has (+200°, +222°). Thus Δ_3 is +83°; for the compounds considered in Table 11, Δ_3 is +58°, +67°; for cholestan-4β-ol, it is +47°.



(LI) (LII)

(*b*) "*Oleanol*" *and derivatives* (28-*nor*-Δ^{17}-*compounds*). "Oleanol" (LI; 28-norolean-17-en-2"β"-ol) resembles cholest-8(9)-en-3β-ol ("δ-cholestenol"; LII). The Δ values for

the bridge double bonds are as follows: Δ(C:C-17) in the triterpenoids is +77°, +16° (Barton and Brooks, *loc. cit.*; Winterstein and Stein, *Z. physiol. Chem.*, 1931, **202**, 222); Δ[C:C-8(9)] in the steroids (cholestane and ergostane derivatives) is +100° (mean of 5 values, range +83° to +115°; Barton, *Angew. Chem.*, 1949, **61**, 57). Both sets of Δ(C:C) values are positive.

2"β"-Acetoxy-28-norolean-17-en-19-one resembles the steroid 8(9)-en-11-ones [cf. (LI) and (LII) with keto-groups at $C_{(19)}$ and $C_{(11)}$ respectively]. The triterpenoid (+645°; Barton and Brooks, *loc. cit.*, 1951, p. 257) shows a large positive Δ(C:C·C:O), +443°. Two steroid 8(9)-en-11-ones recently prepared by Heusser *et al.* (*Helv. Chim. Acta*, 1951, **34**, 2106; 1952, **35**, 295) show Δ(C:C·C:O) values of +493° and +376°.

(*c*) *Triterpenoids unsaturated in the* 13(18)*-position and in ring* E. Most of the triterpenoids carrying an olefinic linkage in the 13(18)-position or in ring E show Δ(C:C) values which are compatible with the formulation of 18(α)-oleanane as (XLVIII = XLIX); however, one group, the 18(19)-unsaturated compounds (germanicol, moradiol, morolic acid), show anomalous values which cannot at present be explained. Molecular rotations and Δ values are summarized in Table 12.

TABLE 12. *Rotational differences for olefinic linkages at* 13(18) *and in ring* E *of the triterpenoids.*

Oleanane series.

	$[M]_D$ Values				Δ(C:C) Values			
	Satd. 18(β)	Satd. 18(α)	13(18)-Ene	18-Ene	13(18)-Ene-18(β)	13(18)-Ene-18(α)	18-Ene-18(β)	18-Ene-18(α)
Oleanane	+41°	—	−135°	+ 12°	−176°	—	− 29°	—
Oleanan-2"β"-ol	+77	+154°	−216[a]	+ 17[b]	−293	−370°	− 60	−137°
Oleanan-2"β"-yl acetate	+99	+202	−161	+ 84	−260	−363	− 15	−118
Oleanane-2"β": 28-diol	—	—	−212	− 49[c]	—	—	—	—
Oleanane-2"β": 28-diol diacetate	—	—	−281	+125	—	—	—	—
Oleanan-2"β"-ol-28-oic acid *	+80	—	—	+122[d]	—	—	+ 42	—
Oleanan-2"β"-ol-28-oic acid acetate *	+87	—	−346	+192	−433	—	+105	—
Refs.	39	91	43, 84	84				
	66	92	94, 99	95				

[a] δ-Amyrin; [b] germanicol; [c] moradiol; [d] morolic acid.
* Methyl ester.

Lupene-I and ψ-taraxasterol series.

Substituent in ring A	$[M]_D$ Values: Satd., Lupane-I	20-Ene (?), Lupene-I	Satd., Heterolupane	19-Ene (?), ψ-Taraxasterol	Δ Values: Δ(C:C-20)	Δ(C:C-19)
None	+107°	+418°	+ 50°	+197°	+311°	+147°
2-OH	—	+400	+ 47	+200	—	+153
2-OAc	—	+444	+108	+248	—	+140
2-Ketone	—	+534	+190	—	—	—
Refs.	43, 90	43, 90	40, 97	98, 100, 101		

Steroid Δ(C:C) values for comparison: Δ(C:C-2), +153°; Δ(C:C-3), +149°; Δ(C:C-4), +194°; Δ(C:C-5), −298°. Refs. 4, 93, 96.

4, See Table 1. 39, 40, 43, See Table 4. 66, See Table 7. 84, See Table 9. 90—93, See Table 11. 94, Ruzicka and Jeger, *Helv. Chim. Acta*, 1941, **24**, 1243. 95, Simpson, *J.*, 1944, 283. 96, Lardelli and Jeger, *Helv. Chim. Acta*, 1949, **32**, 1817. 97, *Idem, ibid.*, 1948, **31**, 813. 98, Jeger, Krüsi, and Ruzicka, *ibid.*, 1947, **30**, 1048. 99, Jeger, Norymberski, and Ruzicka, *ibid.*, 1944, **27**, 1532. 100, Burrows and Simpson, *J.*, 1938, 2042. 101, Morice and Simpson, *J.*, 1940, 795.

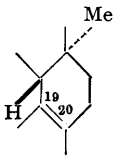
If 18(α)-oleanane is (XLIX), the D-ring is of *D*-type with respect to ring C and to ring E. The negative Δ(C:C) values for 13(18)-enes support this formulation.

The E-ring should be of *A*-type with respect to ring D and it would be expected that Δ(C:C) values in ring E would be positive. ψ-Taraxasterol has an olefinic double bond in ring E, now thought to be at $C_{(19)}$–$C_{(20)}$ (LIII) (Ames, Halsall, Jones, and Meakins, *J.*, 1952, 2862. Its Δ(C:C) value as expected is positive.

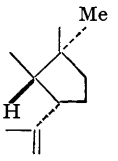
(*d*) *Lupene-I derivatives.* These compounds have recently been prepared by Jones and his colleagues (Ames, Halsall, and Jones, *J.*, 1951, 450; Ames, Davey, Halsall, Jones, and

Meakins, *J.*, 1952, 2862) by isomerization of lupene (LIV) and its derivatives. The structure (LV) with a double bond at $C_{(20)}$–$C_{(21)}$ has been proposed for the lupene-I series. This formula is compatible with the rotations of the compounds, which have large positive Δ(C:C) and $[M]_D$ values, as would be expected for analogues of cholest-2-ene.

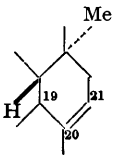
(*e*) *The germanicol–morolic acid series.* The work of Barton and his colleagues, supported by additional evidence from Jones and his school (for references see p. 2930), has resulted in the formula (LVI) for these compounds (R = Me, germanicol; R = CH_2·OH,



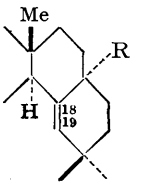
(LIII)



(LIV)



(LV)



(LVI)

moradiol; R = CO_2H, morolic acid); the compounds are thus Δ^{18}-triterpenoids, and are formally analgous to Δ^4-steroids. The Δ(C:C) values of germanicol and its derivatives, with reference to 18(β)(D–E *cis*)- and 18(α)(D–E *trans*)-saturated compounds are, however, *negative*, and not positive as expected. The Δ(C:C) value for morolic acid with reference to the 18(β)-saturated compound is indeed positive, but vicinal action by the carboxyl group on the double bond may occur here.

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