180. *Optical Rotatory Power and Structure in Triterpenoid Compounds. Application of the Method of Molecular Rotation Differences.*

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Data on the optical rotatory properties of all known compounds of the triterpenoid class have been collected and analysed by what is probably best known as " the method of molecular rotation differences." This study has made possible a number of useful generalisations which, now that their existence has been revealed, will probably be confirmed and extended by future work in this field.

The molecular rotations of triterpenoid carboxylic acids and their esters are identical. The majority of the well-characterised triterpenoid compounds can be separated, according to their molecular rotation difference values, into two groups, *i.e.*, related to either the α- and β-amyrins or else to lupeol and betulin; the existence of a third, and hitherto unsuspected group, embracing a number of the less well-studied triterpenoids, is suggested. It seems highly probable that α-viscol is identical with β-amyrin, and that gratiolone and betulinic acid are one and the same substance. Very marked anomalies point distinctly to the existence of hydrogen bonding in the α- and β-boswellic acids and in echinocystic acid, and to its absence in siaresinolic acid. Hydrogenation of the easily reducible ethenoid linkage present in certain triterpenes produces characteristic molecular rotation differences and a further classification on this basis seems possible.

Compounds of the polycyclic triterpenoid (C_{30}) type are widely distributed in the vegetable kingdom, especially in resins and plant saps, where they occur in the free state, as esters, or as glycosides (saponins). Although many of them have been studied intensively during the past 15 years, in no case has the structural formula been completely elucidated. Selenium dehydrogenation, which gives mainly a variety of naphthalene compounds, has furnished useful evidence concerning the basic carbon skeletons (for summary, see Haworth, *Ann. Reports*, 1937, **34**, 327), and more recently Ruzicka and his co-workers, by means of elegant interconversions (for summary, see Spring, *ibid.*, 1941, **38**, 192; Ruzicka and Marxer, *Helv. Chim. Acta*, 1940, **23**, 144), have established simple relationships between a number of the more important members. The structural problem has thus been considerably narrowed in scope and may now be said to involve the determination of the structures of the α- and β-amyrins and of lupeol. The establishment by chemical means of the relationship of any triterpenoid compound to these three primary compounds, however, is by no means easy, since it requires a detailed knowledge of the nature and behaviour of the functional groups present. No method is as yet available for the rapid allocation of any new compound to a specific class.

Some years ago one of us observed that acetylation, benzoylation, and oxidation of various compounds derived from the triterpene alcohol, lupeol, produced regular differences in molecular rotatory power, and this suggested that a detailed survey of the literature of the triterpenes might reveal generalisations of value in connection with structural problems.

The relationship between optical rotatory power and structure in compounds of the steroid group has been examined by Wallis and his co-workers (*J. Org. Chem.*, 1941, **6**, 319; 1942, **7**, 103), who have improved upon and extended the work of Callow and Strain (*Proc. Roy. Soc.*, 1936, *A*, **157**, 194). It has been shown that, if a certain change be effected in two different steroid molecules, differing from one another in a portion of the molecule far removed from the reacting centre, then the variation in molecular rotation ($M[\alpha]$) will be approximately the same in each case. This treatment of optical rotatory phenomena in multi-acentred organic molecules is probably best termed " the method of molecular rotation differences." Its usefulness was clearly demonstrated by Wallis and his colleagues, who, by drawing up a series of constants relating each steroid to a basic stereo-skeleton, showed that the optical rotatory powers of many compounds of this group could be calculated, provided only that the relationships to a series of basic substances were known. They were able, by this means, to suggest the inaccuracy of several proposed structures. The success of this method with complex organic molecules containing many centres of asymmetry would appear to depend upon the principle of optical superposition (see, *e.g.*, Read, *Trans. Faraday Soc.*, 1930, **26**, 441), and on the " rule of shift " (Freudenberg, *Ber.*, 1933, **66**, 177; see also Levene and Meyer, *J. Amer. Chem. Soc.*, 1934, **56**, 244), according as to whether the reactions performed do or do not affect the initial molecular asymmetry. Failure to obey these two principles can usually be ascribed to " vicinal action," but Wallis and his co-workers carefully selected conditions under which this is reduced to a minimum, and in this paper also the possible operation of vicinal effects has not been overlooked, particularly where anomalies have been encountered.

Errors in the Observation of Optical Rotatory Power.—It is obviously necessary to form an estimate of the magnitude of the errors involved in routine determinations of optical rotatory power. The purity of the sample is of paramount importance, but the error due to possible impurity cannot be assessed. The actual error in measuring the rotations probably predominates over the other errors involved, *viz.*, weighing, making up of standard solutions, and variations in specific rotation with temperature and concentration. (The variation

of specific rotation with the spectral line employed and with the solvent cannot be neglected and consequently, unless otherwise specified, all values quoted are for chloroform solutions, employing the sodium D line.) A very conservative estimate of the magnitude of error to be expected in observations collected from the literature would appear to be of the order of ±4%. It is to be noted, however, that Plattner and Heusser (*Helv. Chim. Acta*, **1944**, **27**, 748) have recently shown that temperature and concentration variations alone can produce an error of as much as 5%, and the above estimate of ±4% for the overall error may well be too small.

A general search of the literature has been made for the specific rotations of all triterpenoid compounds, the arithmetic means of all the recorded observations (in a few cases certain early determinations which were obviously erroneous have been neglected) have been approximated to the nearest degree, and the molecular rotations (specific rotation × molecular weight) have been rounded off to the nearest 100. (For brevity in the tables, they are divided by 100.)

I. *Triterpenoid Carboxylic Acids and their Esters.*—The molecular rotations ($M[\alpha]$) of these acids and their esters, together with the corresponding molecular rotation differences (Δ) are recorded in Table I and it is at once apparent that there is no appreciable alteration in $M[\alpha]$ on either esterification or hydrolysis. [This is

TABLE I.

Substance.	General formula of triterpenoid acid.	$10^{-2}M[\alpha]$. Acid.	Ester.		$10^{-2}\Delta$.	Refs.
Amyrin group.						
Ursolic acid	$C_{29}H_{46}(OH)(CO_2H)$: 5R, 1[=]	+319°	Methyl	+324°	+ 5°	1, 2
,, ,, acetate		+319	Ethyl	+321	+ 2	1, 3, 4, 5, 6
			n-Propyl	+319	0	
			n-Butyl	+305	− 14	
			n-Amyl	+307	− 12	
			n-Hexyl	+320	+ 1	
			n-Heptyl	+316	− 3	
			n-Octyl	+317	− 2	
β-Boswellic acid	,,	+949	Methyl	+912	− 37	7, 8, 9
		+543	,,	+522	− 21	
,, ,, acetate		+677	,,	+691	+ 14	,,
		+344	,,	+358	+ 14	
β-Amyrin group.						
α-Boswellic acid	,,	+524	,,	+541	+ 17	9
,, ,, acetate		+324	,,	+353	+ 29	,,
Glycyrrhetic acid	$C_{29}H_{44}(OH)(:O)(CO_2H)$: 5R, 1[=]	+733	,,	+765	+ 32	10, 11, 12, 13, 14, 15
			Ethyl	+757	+ 24	
,, ,, acetate		+742	Methyl	+763	+ 21	10, 11, 12, 13, 14, 15, 16
Deoxoglycyrrhetic acid acetate	$C_{29}H_{46}(OAc)(CO_2H)$: 5R, 1[=]	+578	,,	+614	+ 36	16, 17
Hederagenin	$C_{29}H_{45}(OH)_2(CO_2H)$: 5R, 1[=]	+359	,,	+355	− 4	18, 19, 20, 21
			Ethyl	+365	+ 6	
,, diacetate		+445	Methyl	+433	− 12	,, ,,
			Ethyl	+450	+ 5	
Oleanolic acid	$C_{29}H_{46}(OH)(CO_2H)$: 5R, 1[=]	+356	Methyl	+348	− 8	9, 21, 22, 23, 24, 25, 26, 27, 28, 29
,, ,, acetate		+359	,,	+348	− 11	21, 23, 24, 26, 28, 29
Siaresinolic acid	$C_{29}H_{45}(OH)_2(CO_2H)$: 5R, 1[=]		,,	+224	+ 1	30, 31, 32
			Ethyl	+225		
,, ,, 2-acetate		+252	Methyl	+253	+ 1	31
*iso*Siaresinolic acid diacetate	$C_{29}H_{45}(OAc)_2(CO_2H)$: 5R, 1[=]	+222	,,	+234	+ 12	,,
Sumaresinolic acid	$C_{29}H_{45}(OH)_2(CO_2H)$: 5R, 1[=]	+255	,,	+228	− 27	33
Echinocystic acid [1]	,,	+179	,,	+180	+ 1	34, 35
,, ,, diacetate [1]		− 83	,,	− 86	− 3	34
Lupeol–betulin group.						
Betulonic acid	$C_{29}H_{46}(:O)(CO_2H)$: 5R, 1[=]	+141	,,	+145	+ 4	36
Dihydrobetulonic acid		+ 37	,,	+ 38	+ 1	36. 37
Betulinic acid acetate	$C_{29}H_{46}(OAc)(CO_2H)$: 5R, 1[=]	+100	,,	+ 92	− 8	38, 39
Dihydrobetulinic acid acetate		− 60	,,	− 67	− 7	37
Miscellaneous group.						
*iso*Elemendionolic acid acetate	$C_{29}H_{44}(OAc)(:O)_2(CO_2H)$: 4R, 1[=]	−148	,,	−141	+ 7	40
*iso*Elemenonic acid	$C_{29}H_{47}(:O)(CO_2H)$: 4R, 1[=]	+442	,,	+447	+ 5	41
Pyroquinovic acid	$C_{29}H_{44}(OH)(CO_2H)$: 5R, 1[=]	−271	,,	−279	− 8	42
Exceptions.						
Deoxoglycyrrhetic acid	$C_{29}H_{46}(OH)(CO_2H)$: 5R, 1[=]	+675	,,	+508	−167	17
Oleanonic acid	$C_{29}H_{45}(:O)(CO_2H)$: 5R, 1[=]	+468	,,	+417	− 51	22, 23, 43
*iso*Siaresinolic acid 2-acetate	$C_{29}H_{45}(OH)(OAc)(CO_2H)$: 5R, 1[=]	+206	,,	+259	+ 53	31
Elemadienonic acid	$C_{29}H_{45}(:O)(CO_2H)$: 4R, 2[=]	+209	,,	+154	− 55	44, 45
*iso*Elemadienonic acid	,,	−304	,,	−187	+117	46, 47, 48, 49, 50
Quillaic acid [2]	$C_{28}H_{43}(OH)_2(CHO)(CO_2H)$: 5R, 1[=]	+205	,,	+272	+ 67	51, 52

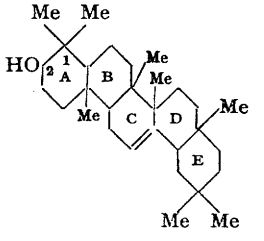
[1] In 95% EtOH; 5460 A. line. [2] In pyridine.

Refs.—(1) Huzii and Osumi, *J. Pharm. Soc. Japan*, 1939, **59**, 176. (2) Simida, *ibid.*, 1939, **59**, 619. (3) Ewen and Spring, J., 1943, 523. (4) Mendive, *J. Org. Chem.*, 1940, **5**, 235. (5) Self and Kremers, *J. Biol. Chem.*, 1938, **125**, 451. (6) Van Haar, *Rec. Trav. chim.*, 1924, **43**, 367. (7) Simpson and Williams, J., 1938, 686, 1712. (8) Trost, *Annali Chim. Appl.*, 1937, **27**, 178. (9) Winterstein and Stein, *Z. physiol. Chem.*, 1932, **208**, 9, 56. (10) Bergman, *Biochem. Z.*, 1933, **267**, 296. (11) Karyone and Nouaka, *J. Pharm. Soc. Japan*, 1937, **57**, 166. (12) Ruzicka and Leuenberger, *Helv. Chim. Acta*, 1936, **19**, 1402. (13) Ruzicka, Furter, and Leuenberger, *ibid.*, 1937, **20**, 312. (14) Takeda, *J. Pharm. Soc. Japan*, 1938, **58**, 731. (15) Voss and Butter, *Ber.*, 1937, **70**, 1212. (16) Ruzicka and Marxer, *Helv. Chim. Acta*, 1939, **22**, 195. (17) Ruzicka, Leuenberger, and Schellenberg, *ibid.*, 1937, **20**, 1271. (18) Kitasato, *Acta Phytochim.*, 1939, **11**, 1. (19) Ruzicka and Giacomello, *Helv. Chim. Acta*, 1937, **20**, 299. (20) Van Haar and Tamburello, *Ber.*, 1921, **54**, 3148. (21) Winterstein and Stein, *Z. physiol. Chem.*, 1932, **211**, 5. (22) Jacobs and Fleck, *J. Biol. Chem.*, 1932, **96**, 341. (23) Kitasato, *Acta Phytochim.*, 1935, **8**, 207. (24) Picard, Sharples, and Spring, J., 1939, 1045. (25) Power and Tutin, J., 1908, 891. (26) Ruzicka and Giacomello, *Helv. Chim. Acta*, 1936, **19**, 1136. (27) Van Haar, *Rec. Trav. chim.*, 1928, **47**, 585. (28) Winterstein and Hämmerle, *Z. physiol. Chem.*, 1931, **199**, 60. (29) Winterstein and Stein, *ibid.*, 1931, **199**, 64. (30) Bilham, Kon, and Ross, J., 1942, 540. (31) Ruzicka, Grob, Egli, and Jeger, *Helv. Chim. Acta*, 1943, **26**, 1218. (32) Winterstein and Egli, *Z. physiol. Chem.*, 1931, **202**, 207. (33) Ruzicka, Jeger, Grob, and Hösli, *Helv. Chim. Acta*, 1943, **26**, 2283. (34) Bergsteinsson and Noller, *J. Amer. Chem. Soc.*, 1934, **56**, 1403. (35) Carson and Noller, *ibid.*, 1941, **63**, 621. (36) Ruzicka and Rey, *Helv. Chim. Acta*, 1941, **24**, 529. (37) Ruzicka, Brenner, and Rey, *ibid.*, 1941, **24**, 515. (38) Robertson, Soliman, and Owen, J., 1939, 1267. (39) Ruzicka, Lamberton, and Christie, *Helv. Chim. Acta*, 1938, **21**, 1706. (40) Ruzicka *et al.*, *ibid.*, 1943, **26**, 1659. (41) Ruzicka *et al.*, *ibid.*, 1943, **26**, 1638. (42) Wieland and Schlenk, *Annalen*, 1939, **539**, 242. (43) Kuwada and Takeda, *J. Pharm. Soc. Japan*, 1939, **59**, 121. (44) Bilham and Kon, J., 1942, 544. (45) Ruzicka and Häusermann, *Helv. Chim. Acta*, 1942, **25**, 439. (46) Lieb and Schwarzel, *Monatsh.*, 1924, **45**, 51. (47) Lieb and Mladenovic, *Monatsh.*, 1932, **59**, 228. (48) Lieb and Mladenović, *ibid.*, 1933, **62**, 232. (49) Mladenović, *ibid.*, 1932, **59**, 7. (50) Ruzicka *et al.*, *Helv. Chim. Acta*, 1932, **15**, 681. (51) Elliott and Kon, J., 1939, 1130. (52) Elliott, Kon, and Soper, J., 1940, 612.

particularly well illustrated by the series of esters of ursolic acid acetate, where M varies from 526 (ethyl ester) to 610 (octyl ester) whilst $M[\alpha]$ remains constant.] On the very reasonable assumption that the specific rotations are susceptible to an error of $\pm 4\%$, the $\Delta_{M[\alpha]}$ values may deviate by some 8% from (say) the arithmetic mean of the $M[\alpha]$'s of the acid and its ester. With two exceptions, all the differences recorded in the first part of Table I are within this 8% limit, and the vast majority are even within 4%. Analysis of these 37 examples by the usual probability expression reveals that the mean error of deviation of each difference from zero is ± 250, which is insignificantly small, and that the $\Delta_{M[\alpha]}$ values are randomised homogeneously about zero.

In the second part of Table I are recorded the only cases which have been encountered where there are serious discrepancies (up to 30%) between the $M[\alpha]$'s of triterpene acids and their esters. It may well be that either the presence of impurities or inaccurate determinations are responsible, but the third alternative, that the structures of the acids and their esters are not comparable, owing possibly to double-bond migration or steric inversion on either esterification or hydrolysis, must not be overlooked. However, recent studies (Plattner and Heusser, *loc. cit.*) in the bile acid series reveal a marked $\Delta_{M[\alpha]}$ between the values for 12-hydroxy-3 : 7-diacetoxycholanic acid and its methyl ester, although special care was taken to ensure the accuracy of the specific rotations. In other similar cases in the bile acid field no appreciable $M[\alpha]$ differences were observed. A general perusal of the literature on optically active carboxylic acids leads to the conclusion that the greater the number of asymmetric centres present in the molecule, the closer becomes the correspondence between the values of $M[\alpha]_{acid}$ and $M[\alpha]_{esters}$.

II. *Triterpenoid Alcohols and their Simple Derivatives.*—As a result of the work of Ruzicka and his associates many of the triterpenoids have now been classified into one of three groups, of which the simplest members ($C_{30}H_{50}O$) are the pentacyclic monoethenoid alcohols, the α- and β-amyrins and lupeol, all three of which almost



(I.) β-Amyrin [formula suggested by Haworth (*loc. cit.*) and now favoured by the Ruzicka school].

certainly contain the secondary alcohol group in the 2-position in ring A (I). The $M[\alpha]$ differences observed with triterpene alcohols of known relative structure, when simple changes (acetylation, benzoylation, and

TABLE II.

Substance.	General formula of triterpenoid alcohol.	$10^{-2}M[\alpha]$. Alcohol.	Acetate. 1.	Benzoate. 2.	Ketone. 3.	$10^{-2}\Delta_1$.	$10^{-2}\Delta_2$.	$10^{-2}\Delta_3$.	Refs.
α-Amyrin group.[1]									
α-Amyrin	$C_{30}H_{49}(OH)$: 5R, 1|=	+358°	+370°	+498°	—	+ 12°	+140°	—	53, 54, 55, 56, 57
Ursolic acid	$C_{29}H_{46}(OH)(CO_2H)$: 5R, 1|=	+319	+319	—	—	0	—	—	1, 2, 3, 4, 6
β-Amyrin group.[1]									
β-Amyrin	$C_{30}H_{49}(OH)$: 5R, 1|=	+379	+384	+530	+454°	+ 5	+151	+ 75°	16, 54, 57, 58, 59, 60, 61, 62
Glycyrrhetic acid	$C_{29}H_{44}(OH)(CO_2H)(:O)$: 5R, 1|=	+733	+742	—	—	+ 9	—	—	10, 11, 12, 14, 16
Methyl glycyrrhetate		+765	+763	—	—	− 2	—	—	10, 11, 13, 14, 15
Oleanolic acid	$C_{29}H_{46}(OH)(CO_2H)$: 5R, 1|=	+356	+359	—	—	+ 3	—	—	9, 21, 22, 23, 24, 25, 26, 27, 28, 29
Methyl oleanolate		+348	+348	+494	+417	0	+146	+ 69	21, 22, 23, 24, 29
Methyl siaresinolate	$C_{29}H_{45}(OH)_2(CO_2Me)$: 5R, 1|=	+224	+252	—	+276	+ 28	—	+ 52	30, 31, 32, 63
Methyl sumaresinolate	,,	+228	+217	—	—	− 11	—	—	33
Echinocystic acid [4]	$C_{29}H_{45}(OH)_2(CO_2H)$: 5R, 1|=	+179	+190	—	—	+ 11	—	—	34, 64, 65
Methyl 19-ketoechinocystate [5]	$C_{29}H_{44}(OH)(:O)(CO_2Me)$: 5R, 1|= (*a*)	− 48	—	—	+ 10	—	—	+ 58	65
	(*b*)	− 73	− 53	—	− 10	+ 20	—	+ 63	
Lupeol–betulin group.[3]									
Dihydrobetulin	$C_{30}H_{50}(OH)_2$: 5R	− 84	− 24	—	—	+ 60	—	—	37, 66, 67
Betulinaldehyde	$C_{29}H_{46}(OH)(CHO)$: 5R, 1|=	+ 84	+145	—	+232	+ 61	—	+148	36, 67, 68
Methyl betulinate	$C_{29}H_{46}(OH)(CO_2Me)$: 5R, 1|=	+ 33	+ 92	—	+145	+ 59	—	+112	36, 38, 39
Methyl dihydrobetulinate [3]	$C_{29}H_{48}(OH)(CO_2Me)$: 5R	− 90	− 67	—	+ 38	+ 23	—	+128	37
*allo*Betulin	$C_{30}H_{49}(OH)(-O-)$: 5R + Oxide R	+205	+253	+371	+356	+ 48	+166	+151	69
Lupanol	$C_{30}H_{51}(OH)$: 5R	− 77	− 9	+144	+ 68	+ 68	+221	+145	70
Lupanalol	$C_{29}H_{46}(OH)(CHO)$: 5R	+ 18	+ 68	—	—	+ 50	—	—	71
Lupeol	$C_{30}H_{49}(OH)$: 5R, 1|=	+115	+201	+318	+259	+ 86	+203	+144	54, 68, 70, 72, 73, 74, 75, 76, 77, 78
Lupenalol	$C_{29}H_{46}(OH)(CHO)$: 5R, 1|=	+ 4	+ 82	+207	—	+ 78	+203	—	79
Lupeol oxide	$C_{30}H_{49}(OH)(-O-)$: 5R + Oxide R.	+ 40	+116	—	—	+ 76	—	—	71

[1] α- and β-Boswellic acids are discussed separately in Section III. [3] The much smaller $M[\alpha]$ values in this group probably account for less accurate grouping about the mean differences. [3] The value for $M[\alpha]$ Alcohol is possibly in error (see Table VIII). [4] In 95% EtOH; 5460 A. line. [5] In dioxan : (*a*) D line, (*b*) 5460 A. line.

Refs.—(53) Bosrz and Cohen, *Arch. Pharm.*, 1912, **250**, 56. (54) Cohen, *Rec. Trav. chim.*, 1909, **28**, 370, 391. (55) Jungfleisch and Leroux, *Compt. rend.*, 1908, **147**, 862. (56) Ruzicka and Wirz, *Helv. Chim. Acta*, 1939, **22**, 948. (57) Zinke, Friedrich, and Rollett, *Monatsh.*, 1920, **41**, 253. (58) King *et al.*, *J. Amer. Chem. Soc.*, 1943, **65**, 1168. (59) Ruzicka and Schellenberg, *Helv. Chim. Acta*, 1937, **20**, 1553. (60) Ruzicka and Wirz, *ibid.*, 1940, **23**, 132. (61) Ruzicka and Wirz, *ibid.*, 1941, **24**, 248. (62) Ruzicka and Jeger, *ibid.*, 1941, **24**, 1178. (63) Ross, Ph.D. Thesis, University of London, 1943. (64) Noller and Carson, *J. Amer. Chem. Soc.*, 1941, **63**, 2238. (65) White and Noller, *ibid.*, 1939, **61**, 983. (66) Ruzicka and Isler, *Helv. Chim. Acta*, 1936, **19**, 506. (67) R. Vesterberg, *Ber.*, 1927, **60**, 1535. (68) Ruzicka and Brenner, *Helv. Chim. Acta*, 1939, **22**, 1523. (69) Schulze and Pieroh, *Ber.*, 1922, **55**, 2332. (70) Heilbron, Kennedy, and Spring, J., 1938, 329. (71) Ruzicka and Rosenkranz, *Helv. Chim. Acta*, 1939, **22**, 778. (72) Cohen, *Arch. Pharm.*, 1907, **245**, 238. (73) Dieterle, *ibid.*, 1923, **261**, 89. (74) Jungfleisch and Leroux, *Compt. rend.*, 1907, **144**, 1435. (75) Likiernik, *Ber.*, 1891, **24**, 183. (76) Sugii, Sengoku, and Taguchi, *J. Pharm. Soc. Japan*, 1931, **51**, 847. (77) Swift and Walter, *J. Amer. Chem. Soc.*, 1942, **64**, 2539. (78) Van Romburgh, *Ber.*, 1894, **27**, 3441. (79) Jones and Meakins, J., 1940, 1335.

oxidation) are effected at this 2-position, are given in Table II, and on using these criteria, two main groupings are clearly discernible :

	$\Delta_{acetyl.}$	$\Delta_{benzoyl.}$	$\Delta_{ketone.}$
α- and β-Amyrin group	+ 600°	+14,500°	+ 6000°
Lupeol–betulin group	+7000	+20,000	+14,000

The almost complete identity of the $\Delta_{M[\alpha]}$ values in the α- and β-amyrin series suggests that, identical carbon skeletons being assumed (which is by no means certain), the ethenoid linkages in both series are sufficiently far removed from ring A so that " vicinal action " with the 2-hydroxyl group cannot occur. In the steroid field, Bernstein, Wilson, and Wallis (*J. Org. Chem.*, 1942, **7**, 103) observed a negligible influence of ethenoid linkages in the 8 : 14- and the 14 : 15-position on the C_3 centre, whereas 7 : 8- and 8 : 9-bonds appeared to exert an appreciable effect. On this basis it might be suggested that in neither α- nor β-amyrin can the double bond be located in ring A or B, a suggestion which is in accord with the bulk of the chemical evidence.

Table III gives the data for triterpenoids whose inter-relationships have yet to be established, grouped

TABLE III.

Substance.	General formula of triterpenoid alcohol.	$10^{-2}M[\alpha]$. Alcohol.	Acetate.	Benzoate.	Ketone.	$10^{-2}\Delta_1$.	$10^{-2}\Delta_2$.	$10^{-2}\Delta_3$	Refs.
			1.	2.	3.				
Amyrin type.									
α-Viscol	$C_{30}H_{49}(OH)$: 5R, 1|=	+362°	+374°	—	—	+ 12°	—	—	80
Lanosterol	$C_{30}H_{49}(OH)$: 4R, 2|=	+247	+262	+392°	+307°	+ 15	+145°	+ 60°	81, 82, 83
Lupeol–betulin type.									
Gratiolone methyl ester	$C_{29}H_{46}(OH)(CO_2Me)$: 5R, 1|=	+ 24	+100 [1]	—	—	+ 76	—	—	84
Polyporenic acid A methyl ester	$C_{29}H_{45}(OH)_2(CO_2Me)$: 4R, 2|=	+374	+465	—	—	+ 91	—	—	85
Possible new type.									
Euphol	$C_{30}H_{49}(OH)$: 4R, 2|=	+136	+192	—	—	+ 56	—	—	86
Germanicol	$C_{30}H_{49}(OH)$: (?) 5R, 1|=	+ 26	+ 84	+207	—	+ 58	+181	—	87
Scandol	$C_{30}H_{49}(OH)$: (?) 5R, 1|=	+243	+286	+392	—	+ 43	+149	—	88
Skimmiol	$C_{30}H_{49}(OH)$: 5R, 1|=	+ 13	+ 66	+191	—	+ 53	+178	—	89
Taraxasterol	,,	+409	+473	+567	+466	+ 64	+158	+ 57	90, 91, 92
ψ-Taraxasterol	,,	+200	+248	+371	—	+ 48	+171	—	90, 93
Cryptosterol	$C_{30}H_{49}(OH)$: 4R, 2|=	+251	+300	+376	+322	+ 49	+125	+ 71	94
Miscellaneous.									
Agnosterol	$C_{30}H_{47}(OH)$: 4R, 3|=	+301	+424	+549	—	+123	+248	—	82, 83
Basseol	$C_{30}H_{49}(OH)$: 4R, 2|=	− 51	+ 94	—	—	+145	—	—	95, 96
Elemadienolic acid	$C_{29}H_{46}(OH)(CO_2H)$: 4R, 2|=	−105	−209	—	+209	−104	—	+314	44, 45, 97
*epi*Elemadienolic acid	,,	+ 46	+130	—	+209	+ 84	—	+163	44, 45
Elemenolic acid	$C_{29}H_{48}(OH)(CO_2H)$: 4R, 1|=	− 73	−160	—	+169	− 87	—	+242	44, 45, 47, 98, 99
Euphorbol	$C_{30}H_{49}(OH)$: 4R, 2|=	0	0	—	—	0	—	—	86
Taraxol	$C_{30}H_{47}(OH)O_2$: 5R, 1|=	+359	+466	—	—	+107	—	—	90
β-Viscol	$C_{30}H_{49}(OH)$: 5R, 1|=	+239	+201	—	—	− 38	—	—	80

[1] Value for gratiolone acetate.

Refs.—(80) Bauer and Gerloff, *Arch. Pharm.*, 1936, **274**, 473. (81) Doree and Garrett, *J. Soc. Chem. Ind.*, 1933, **52**, 141, 355. (82) Ruzicka, Rey, and Muhr, *Helv. Chim. Acta*, 1944, **27**, 472. (83) Windaus and Tschesche, *Z. physiol. Chem.*, 1930, **190**, 51. (84) Maurer, Meier, and Reiff, *Ber.*, 1939, **72**, 1870. (85) Cross, Eliot, Heilbron, and Jones, J., 1940, 632. (86) Newbold and Spring, J., 1944, 249. (87) Simpson, J., 1944, 283. (88) Cook *et al.*, *J. Amer. Pharm. Assoc.*, 1944, **33**, 15. (89) Takeda, *J. Pharm. Soc. Japan*, 1941, **61**, 63. (90) Burrows and Simpson, J., 1938, 2042. (91) Power and Browning, J., 1912, 2411. (92) *Idem*, J., 1914, 1829. (93) Morice and Simpson, J., 1940, 795. (94) Wieland *et al.*, *Annalen*, 1937, **529**, 68. (95) Beynon, Heilbron, and Spring, J., 1937, 989. (96) Heilbron, Moffett, and Spring, J., 1934, 1583. (97) Lieb and Mladenovič, *Monatsh.*, 1932, **61**, 274. (98) Lieb and Mladenovič, *ibid.*, 1931, **58**, 59. (99) Ruzicka *et al.*, *Helv. Chim. Acta*, 1932, **15**, 1454.

TABLE IV.

Substance.	α-Viscol. M. p.	α-Viscol. [α]D.	β-Amyrin. M. p.	β-Amyrin. [α]D.	Ref.
Alcohol	200°	+85°	201—203°	+89°	16
			198—199		59
			199—200		58
Acetate	241	+80	241—242	+82	16
			240—241		59
			242		60
			241—242		62
			238—239 }		58
			238—240 }		
Benzoate	240	—	233—234	—	16
			235—236		60
			223—224 }		58
			232—233 }		
Ketone	181°	—	178—180°	—	100
			177—179		101
			177—178		102
			186		60
Ketone oxime	256	—	262—263	—	100
			265—267		101
Ketone semi-carbazone	245	—	244—245	—	103
			244—245		102
			248—249		60
Diene (from alcohol with PCl_5)	169	+120° [1]	175—178	+112° [1]	104
			173—175		105
			170—175		106

[1] In C_6H_6; other rotations in $CHCl_3$.

Refs.—(100) A. Vesterberg, *Ber.*, 1891, **24**, 3837. (101) Rollett, *Monatsh.*, 1923, **43**, 413. (102) Ruzicka, Schellenberg, and Goldberg, *Helv. Chim. Acta*, 1937, **20**, 791. (103) Hormann and Firzlaff, *Arch. Pharm.*, 1930, **268**, 64. (104) A. Vesterberg, *Ber.*, 1887, **20**, 1245. (105) Ruzicka, Silbermann, and Furter, *Helv. Chim. Acta*, 1932, **15**, 482. (106) Winterstein and Stein, *Annalen*, 1933, **502**, 223.

TABLE V.

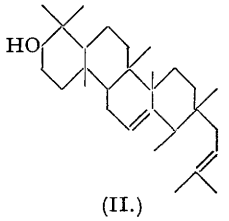
	Gratiolone (Ref. 84). M. p.[1]	Gratiolone (Ref. 84). [α]D.	Betulinic acid. (Ref. 39). M. p.[2]	Betulinic acid. (Ref. 39). [α]D.	Betulinic acid. (Ref. 38). M. p.[4]	Betulinic acid. (Ref. 38). [α]D.	Betulinic acid. (Ref. 107). M. p.[5]
Acid	311—312°	+ 6° [6]	295—297°	—	316—318°	+ 8° [6]	315—317°
Acetate	268 [1]	+20	288—290	+20°	289—291	+ 8	290—292
Methyl ester	220	+ 5	224—225	+ 5	223—224	+ 8	223—225
Methyl ester acetate	197	—	200—202	+17	201—202	+18	202—203
Acetate bromolactone	186	+13	—	—	290 (d.)	—	293—296 (d.)

[1] The low m. p. is almost certainly due to contamination with the mixed anhydride, known to be readily formed from betulinic acid unless special precautions are taken. [2] Presumably uncorrected. [3] Corrected. [4] Uncorrected. [5] Probably uncorrected. [6] In pyridine.

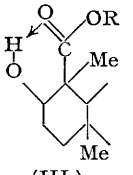
Ref.—(107) Kawaguti and Kim, *J. Pharm. Soc. Japan*, 1940, **60**, 343.

according to the magnitude of their $M[\alpha]$ differences. α-Viscol falls into the amyrin group, and a careful comparison (Table IV) with β-amyrin indicates that the two substances must almost certainly be identical. Rather surprisingly, the possibility of this identity does not appear to have been considered by the original investigators (Bauer and Gerloff, *Arch. Pharm.*, 1936, **274**, 473), although the reactions of α-viscol and β-amyrin are more or less identical. Again, gratiolone, which falls into the lupeol–betulin group, is almost certainly identical with betulinic acid (Table V)—the one or two reported discrepancies between the two substances would probably be eliminated on more deliberate investigation.

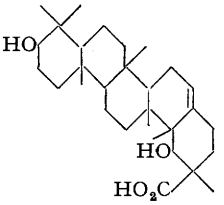
It is difficult to believe that the close agreement between the $M[\alpha]$ differences of lanosterol and those of the amyrins is entirely fortuitous. It seems reasonable to suppose that if ring E of the pentacyclic (say) β-amyrin system were opened (as in II), this change would have comparatively little effect on the $M[\alpha]$ differences produced by reactions at the remote 2-position, and formulations such as (II), which explain many of the reactions of lanosterol, might be considered.



(II.)



(III.)



(IV.)

The $M[\alpha]$ difference data also suggest a relationship between polyporenic acid A (Cross, Eliot, Heilbron, and Jones, J., 1940, 632; Cross and Jones, *ibid.*, p. 1491) and the lupeol–betulin group. This is by no means unlikely, for the acid is obtained from a fungus parasitic on the birch tree, the bark of which contains a high proportion of betulin

As is indicated in Table III, some 6 triterpenoids have $M[\alpha]$ differences of the same order, but yet entirely distinct from those of the amyrin and the lupeol group (Δ_{acetyl} 5500°; $\Delta_{benzoyl}$ 16,000°; Δ_{ketone} 6500°), and, although future investigations may require a revision of some of the values, it seems reasonable to suggest that we have here an entirely new group of triterpenoids.

III. *Hydrogen Bonding in Triterpenoid Carboxylic Acids.*—Ruzicka has converted the α- and β-boswellic acids into the β- and α-amyrins respectively, but the $M[\alpha]$ difference data recorded in Table VI reveal, instead of the expected small increases, large *decreases* in $M[\alpha]$ on acetylation, benzoylation, and oxidation of the boswellic acids and their esters. These anomalies can almost certainly be attributed to the existence of hydrogen bonding, as indicated in (III), in the acids and esters, and the inhibition of this bonding on esterification or oxidation of the 2-hydroxyl group. It is to be noted that normal $M[\alpha]$ differences are observed with the decarboxylated β-boswellic acid derivatives (nor-β-boswellenol, etc.) in which hydrogen bonding is, of course, impossible. Echinocystic acid (IV, according to Kon) is also known to contain a hydroxyl group in the β-position to the carboxyl group, and White and Noller (*J. Amer. Chem. Soc.*, 1939, **61**, 983) have already tentatively suggested the existence of hydrogen bonding. This is clearly indicated by the large decreases in $M[\alpha]$ both on acetylation and on oxidation of the second hydroxyl group (Table VI). Similar effects will

TABLE VI.

Substance.	General formula of triterpenoid alcohol.	$10^{-2}M[\alpha]$. Alcohol.	Acetate. 1.	Ketone. 2.	$10^{-2}\Delta_1$.	$10^{-2}\Delta_2$.	Refs.
α-Amyrin group.							
β-Boswellic acid	$C_{29}H_{46}(OH)(CO_2H)$: 5R, 1|=	+949°	+677°	+577°	−272°	−372°	7, 8, 9
		+543	+344	—	−199	—	
Methyl β-boswellate		+912	+691	—	−221	—	7, 9
		+522	+358	—	−164	—	
Nor-β-boswellenol	$C_{29}H_{47}(OH)$: 5R, 1|=	+461	+495	+525	+ 34	+ 64	7, 8
β-Amyrin group.							
α-Boswellic acid	$C_{29}H_{46}(OH)(CO_2H)$: 5R, 1|=	+524	+324	—	−200	—	9
Methyl α-boswellate		+541	+353	—	−188	—	9
Echinocystic acid acetate [1]	$C_{29}H_{45}(OH)(OAc)(CO_2H)$: 5R, 1|=	+190	− 83	—	−273	—	34, 64, 65
,, methyl ester [2]		(*a*) +148	—	− 53	—	−201	,,
		(*b*) +174	− 86	− 95	−260	−269	

[1] In 95% EtOH; 5460 A. line. [2] In dioxan: (*a*) D line, (*b*) 5460 A. line.

TABLE VII.

Substance.	General formula of triterpenoid alcohol.	$10^{-2}M[\alpha]$. Alcohol.	Diacetate. 1.	Diketone. 2.	$10^{-2}\Delta_1$.	$10^{-2}\Delta_2$.	Refs.
Methyl echinocystate [1]	$C_{29}H_{45}(OH)_2(CO_2Me)$: 5R, 1|=	+180° [2]	—	− 73° [2]	—	−253°	34, 35, 64, 65
Methyl siaresinolate	,,	+224	—	+665	—	+441	30, 31, 32
Echinocystic acid 2-acetate [1]	$C_{29}H_{45}(OH)(OAc)(CO_2H)$: 5R, 1|=	+190 [2]	− 83° [2]	—	−273°	—	34, 64, 65
*iso*Siaresinolic acid 2-acetate	,,	+206	+222	—	+ 16	—	31
Methyl echinocystate 2-acetate [1]	$C_{29}H_{45}(OH)(OAc)(CO_2Me)$: 5R, 1|=	+148 [3]	—	(ketoacetate) − 53 [3]	—	−201	34, 64, 65
Methyl *iso*siaresinolate 2-acetate	,,	+259	—	(ketoacetate) +326	—	+ 67	31

[1] 5460 A. line. [2] In 95% EtOH. [3] In dioxan.

undoubtedly be observed with quillaic acid (which is closely related to echinocystic acid) when sufficient data are available.

Two alternative formulations for siaresinolic acid have been put forward, by Ruzicka and Kon respectively, and in that due to the latter, hydrogen bonding between the second hydroxyl group and the carboxyl group would certainly be expected. The comparison given in Table VII of the $M[\alpha]$ differences in the siaresinolic and echinocystic acid series does not indicate any hydrogen bonding in the former case, and suggests that in respect of the relative positions of the second hydroxyl and carboxyl groups, the Ruzicka formulation is preferable, although the possible interference by steric factors cannot be overlooked entirely.

It should be noted, in connection with this postulation of the existence of hydrogen bonding in the triterpene series, that Rule and his collaborators (J., 1929, 401, 2516) made a similar suggestion to explain abnormal optical rotatory phenomena observed with the *l*-menthyl esters of salicylic and 1-hydroxy-2-naphthoic acids and their methyl ethers.

IV. *Triterpenoids with Easily Reducible Ethenoid Linkages.*—Triterpenes of the lupeol–betulin group and also the majority of the tetracyclic triterpenes possess, in striking contrast to those of the amyrin type, a readily reducible double bond. The $M[\alpha]$ differences consequent upon hydrogenation of this ethenoid linkage are quoted in Table VIII, from which it is immediately apparent that the $\Delta_{M[\alpha]}$ value of about −19,000° for lupeol

TABLE VIII.

Substance.	General formula of triterpenoid.	$10^{-2}M[\alpha]$. Triterpene.	Dihydro.	$10^{-2}\Delta$.	Refs.
Basseol acetate	$C_{30}H_{48}(OAc)$: 4R, 2|=	+ 94°	+155°	+ 61°	95, 96
Betulin	$C_{30}H_{48}(OH)_2$: 5R, 1|=	+ 66	− 84	−150	66, 67
,, diacetate		+116	− 37	−153	66, 67, 69
Methyl betulinate [1]	$C_{29}H_{46}(OH)(CO_2Me)$: 5R, 1|=	+ 24	− 90	−114	37, 39
,, ,, acetate		+ 87	− 67	−154	,,
Betulonic acid	$C_{29}H_{46}(:O)(CO_2H)$: 5R, 1|=	+141	+ 37	−104	36
Methyl betulonate		+145	+ 38	−107	36, 37
Lupadiene	$C_{30}H_{48}$: 5R, 2|=	+102	− 81	−183	70
Lupeol	$C_{30}H_{49}(OH)$: 5R, 1|=	+115	− 77	−192	68, 70, 72, 74, 75, 76, 77, 78
,, acetate		+201	− 9	−210	68, 70, 73, 76, 77
,, benzoate		+318	+144	−174	54, 68, 70, 76
Lupeone	$C_{30}H_{48}(:O)$: 5R, 1|=	+259	+ 68	−191	68, 70, 76
α-Lupene [2]	$C_{30}H_{50}$: 5R, 1|=	+115	− 4	−119	70, 108
Lupenalol	$C_{29}H_{46}(OH)(CHO)$: 5R, 1|=	+ 4	+ 18	+ 14	71, 79
,, acetate		+ 82	+ 68	− 14	,,
Lupenediol [2]	$C_{30}H_{48}(OH)_2$: 5R, 1|=	− 18	+ 22	+ 40	109

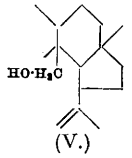
[1] It has been suggested (Table III) that the $M[\alpha]$ value for methyl dihydrobetulinate is erroneous. A correction to −12,000° results in uniformity both here and in the previous table.

[2] In view of the good agreement between other values in this series it seems probable that one of the rotation values is incorrect. [3] In pyridine.

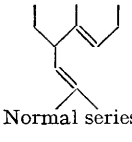
Refs.—(108) Ruzicka and Rosenkranz, *Helv. Chim. Acta*, 1940, **23**, 1311. (109) Meakins, Ph.D. Thesis, University of London, 1941.

and most of its derivatives is highly characteristic. Exceptions are observed only in those compounds where the methyl group in the α-position to the olefinic linkage in the *iso*propenyl side chain (–CMe:CH_2) is substituted, as in lupenalol, –C(CHO):CH_2, and in lupenediol, –C(CH_2OH):CH_2. This profound discrepancy may find interpretation either in (*a*) the asymmetric synthesis consequent upon the introduction of a new asymmetric centre upon reduction of the olefinic linkage or in (*b*) the operation of a " vicinal effect."

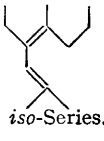
The $\Delta_{M[\alpha]}$ values for betulin and its derivatives range around −15,000°, and the difference from the lupeol value may also be attributed to a " vicinal effect " between the primary carbinol group and the olefinic linkage, the possibility of which is clearly apparent in the partial formulation (V) for betulin (Ruzicka and Rey, *Helv. Chim. Acta*, 1943, **26**, 2143).



(V.)



Normal series.



iso-Series.

(VI.)

According to the data in Table IX for triterpenoids of unknown and as yet unrelated structure, there is a distinct similarity between agnosterol, lanosterol, and cryptosterol. The first two have been correlated (Markes, Wittle, and Mixon, *J. Amer. Chem. Soc.*, 1937, **59**, 1368) and the last two are already known to possses

TABLE IX.

Substance.	General formula of triterpenoid.	$10^{-2}M[\alpha]$. Triterpene.	Dihydro.	$10^{-2}\Delta$.	Refs.
Agnosterol	$C_{30}H_{47}(OH)$: 4R, 3|=	+301°	+260°	− 41°	82, 83
,, acetate		+424	+393	− 31	82, 83
Cryptosterol	$C_{30}H_{49}(OH)$: 4R, 2|=	+251	+231	− 20	94
,, acetate		+300	+249	− 51	,,
,, benzoate		+376	+383	+ 7	,,
Lanosterol	,,	+247	+223	− 24	81, 82, 83
,, acetate		+262	+249	− 13	81, 83
Polyporenic acid A methyl ester	$C_{29}H_{45}(OH)_2(CO_2Me)$: 4R, 2|=	+374	+371	− 3	85
Elemadienolic acid	$C_{29}H_{46}(OH)(CO_2H)$: 4R, 2|=	−105	− 73	+ 32	44, 47, 97, 98, 99
*epi*Elemadienolic acid	,,	+ 46	+ 64	+ 18	45
Elemadienonic acid	$C_{29}H_{45}(:O)(CO_2H)$: 4R, 2|=	+209	+169	− 40	44, 45
*iso*Elemadienonic acid	,,	−304	−427	−123	41, 46, 49, 50, 97

many similarities, and both yield acetone as an ozonolysis product; possibly agnosterol will likewise be found to contain an *iso*propylidene grouping.

The marked distinction between the $\Delta_{M[\alpha]}$ values in the elemadienolic acid series is doubtless related to the position of the second, non-reducible double bond (see VI), and may well be due to the operation of a " vicinal effect."

V. *Triterpenoid Diols and their Simple Derivatives.*—Although a detailed examination of the literature on these compounds has been made, sufficient data are not yet available on the mono- and di-esters and similar derivatives for any relationships which might exist to become apparent.

Conclusions.—In view of the multiplicity and possible magnitude of the sources of error inherent in routine specific rotation determinations, and also of the many experimental difficulties encountered in obtaining triterpenoid compounds in an analytically pure condition, the regularities now brought to light are remarkable. Just as in the steroid field, $M[\alpha]$ differences appear to be characteristic of the basic stereo-skeleton of the molecule, and by careful determinations of the molecular rotations of the simple derivatives obtained in the preliminary stages of routine structural investigations, determinations which result in only a negligible consumption of material, much information concerning the fundamental structural unit involved may be forthcoming. The possible identities of α-viscol and gratiolone with β-amyrin and betulinic acid, respectively, only became apparent after these compounds had been classified according to their $M[\alpha]$ differences, and these cases provide good examples of the general usefulness of this new method of attack. The constancy of molecular rotations on esterification and hydrolysis of triterpene acid derivatives, the relatively facile diagnosis of hydrogen bonding in hydroxy-acids, and the characteristic $M[\alpha]$ differences observed on hydrogenation of lupeol and elemadienolic acid derivatives, all represent useful additions to the present state of knowledge of triterpene chemistry. It seems certain that future observations in this field will confirm, extend, and more completely systematise the regularities already brought to light in the present investigation, and that further rules relating structure to optical rotatory properties will undoubtedly emerge.

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