1330. *Optical Rotatory Dispersion. Part XXVII.*[1] *The Hudson Lactone Rule*

By W. Klyne, Patricia M. Scopes, and Ann Williams

The Hudson lactone rule is discussed in the light of the optical rotatory dispersion curves of some γ- and δ-lactones and their corresponding non-cyclic reference compounds. It is shown that the difference curve between the rotation of the lactone and that of its reference compound is of the same sign as the lactone Cotton effect at about 225 mμ.

An early attempt to relate the stereochemistry of a lactone to the sign of its optical rotation was made by Hudson,[2] on the basis of studies on five- and six-membered lactones of the sugar series. In his well-known " lactone rule " Hudson suggested that the stereochemistry of the carbon atom carrying the potential hydroxyl group was the dominant feature in determining the rotation of a lactone and that a molecule is dextro-rotatory, if, when drawn in the usual Fischer projection (I), the lactone ring lies to the right. Conversely, if the lactone ring lies to the left the compound is lævo-rotatory.

The absolute configuration (I) may alternatively be represented as in (II) or (III), employing the usual conventions for cyclic structures, and Hudson's rule may then be stated as follows. " If the hydrogen atom at the alkoxy-carbon (C*) in (II) or (III) lies below the plane of the lactone ring then the compound is dextro-rotatory. Conversely if the hydrogen lies above the plane of the ring, the compound will have a negative rotation." In the case of a complex lactone with many asymmetric centres, each centre contributes to the total rotation of the molecule. Therefore, in order to consider only that part of the

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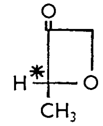
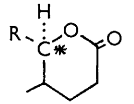
[1] Part XXVI, preceding Paper.

[2] C. S. Hudson, *J. Amer. Chem. Soc.*, 1910, **32**, 338; 1939, **61**, 1525; cf. E. Anderson, *ibid.*, 1912, **34**, 51.

total rotation which is due to lactone formation, it is necessary to *subtract* from the lactone rotation, the rotation of a suitable reference compound, containing all the same asymmetric centres as the parent compound but without a lactone ring. The most suitable non-cyclic reference compounds are the corresponding hydroxy-acid (IV) or hydroxy-ester (V), but the corresponding glycol (VI) and deoxy-acid (VII) have also been used.


(I)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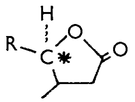
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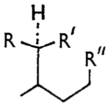
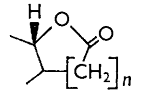
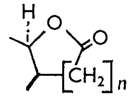


	R'	R''
(IV:	OH	CO_2H)
(V :	OH	CO_2Me)
(VI :	OH	$CH_2{\cdot}OH$)
(VII :	H	CO_2H)

(VIII)



(IX)

Hudson's original rule was later extended[3] to include compounds in which the lactone group is fused to other alicyclic rings as in many groups of natural products—steroids, terpenes, and others; the rotation of the lactone, or, more accurately, the difference between the lactone rotation and that of a suitable non-cyclic reference compound, was again related to the configuration of the alkoxy-carbon (C* in II or III). Many applications of the extended Hudson rule have been made, exceptions have been noted and certain limitations have been suggested.[4]

We have now compared the rotations of some representative lactones and their " ring-opened " reference compounds by means of optical rotatory dispersion (o.r.d.) curves, instead of the monochromatic rotations at 589 mμ used by earlier workers. By subtracting the optical-rotation values of the reference compound from those of the lactone itself one obtains a "difference curve," which is a measure of the rotation caused by the lactone ring in a particular asymmetric environment. Unfortunately, the hydroxy-acids and esters corresponding to many lactones cannot be used as ring-opened reference compounds, owing to the ease with which cyclisation occurs, but in several cases the corresponding glycols are available and have been examined.

RESULTS AND DISCUSSION

The data for some lactones of general type (VIII) are collected in Table 1.† According to the extended Hudson rule,[3] the difference in rotation between these lactones and their reference compounds should be negative, and this prediction is borne out by the compounds examined (both for five- and for six-membered lactone rings). The o.r.d. curves for lactones and reference compounds were measured from 400—270 mμ, and the difference curve for a given lactone, was then obtained by subtracting the o.r.d. curve of the reference compound from that of the lactone. In all cases the o.r.d. difference curve was plain negative in the wavelength region examined; the sign of the difference curve and typical values at 300 mμ, are given in Table 1.†

Similar data are collected in Table 2 † for compounds of general type (IX) for which the extended Hudson rule would predict a positive rotation difference between lactone and reference compound. Again, the sign of the difference curve and selected values at 300 mμ quoted in Table 2 † show the expected results. It should be noted that the difference between

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† To avoid reproducing a large number of structural formulæ, the individual compounds in Tables 1 and 2 are described by Roman numerals which refer to Part XXIV (*J.*, 1965, 7211), where full formulæ, sector diagrams, and experimental details are given.

[3] W. Klyne, *Chem. and Ind.*, 1954, 1198.

[4] V. Sykora and M. Romanuk, *Coll. Czech. Chem. Comm.*, 1957, **22**, 1909; P. Vlad and M. Souček, *ibid.*, 1962, **27**, 1726; J. Křepinsky, M. Romaňuk, V. Herout, and F. Šorm, *ibid.*, 1963, **28**, 3122; M. Romaňuk and J. Křepinsky, *ibid.*, 1964, **29**, 830; B. Witkop, *Experientia*, 1957, **12**, 372; J. W. Clark-Lewis and P. I. Mortimer, *J.*, 1961, 4268; W. Cocker and M. A. Nisbet, *Chem. and Ind.*, 1962, 2121; G. Fodor, I. W. Vincze, and J. Tóth, *J.*, 1961, 3219; G. Fodor and F. Sóti, *Tetrahedron Letters*, 1964, 1917.

6-oxa-7-oxo-17β-hydroxy-5β-androstane and its reference compound in fact gives a plain postive curve, although the actual value at 300 mμ is negative.

Tetrahydroalantolactone (X), although of general type (IX), shows a plain negative o.r.d. curve at low wavelength. This lactone and similar related compounds are now being investigated in collaboration with Professor W. Cocker (Trinity College, Dublin).

Lactone Cotton Effects.—Developments in instrumentation have now made it possible to measure o.r.d. curves down to about 210 mμ, and it has been shown that compounds containing the carboxyl or related chromophores show Cotton effects in this low-wavelength region, corresponding to the absorption band at about 220 mμ.[5] In particular, most lactones show Cotton effects with a first extremum between about 233 and 225 mμ.[1,6,7] We have measured Cotton effects for all the lactones mentioned in this Paper and the values of the molecular rotations at the first extremum or at 227 mμ, are quoted in the final columns of Table 1 and 2. (Cf. details in ref. 6.)

It can be seen that, in every case, there is agreement between the sign of the Cotton effect of the lactone and that of the plain difference curve, to 270 mμ. Compounds of type (VIII) (Table 1) have negative Cotton effects and negative difference curves, while compounds of type (IX) (Table 2) have positive Cotton effects and positive difference curves.

This agreement would be expected, since both the "difference curve" and the lactone Cotton effect are measures of the rotation contribution of a lactone group to the total rotation of a molecule. The "difference curve" approach attempts to do this by subtracting from the lactone rotation, the rotation of a reference compound containing all the same asymmetric features apart from a lactone ring. The lactone Cotton effect measures directly the rotation of the lactone chromophore in its asymmetric environment and at the wavelength of its characteristic ultraviolet absorption.

For comparison, the o.r.d. curves of a few selected reference compounds have been examined in the low-wavelength region (see Table 3). Acids and esters containing the -CO·O- chromophore have Cotton effects at about 227 mμ but they are smaller than those for the corresponding lactones. This is as would be expected, since the acids have a less-rigid conformation than the cyclic lactones. Glycols show no Cotton effects in this region and their rotations are numerically small.

The direct measurement of lactone Cotton effects at low wavelengths has advantages over the older difference method (whether applied through monochromatic rotations or o.r.d. curves). One lactone o.r.d. curve measured to low wavelengths not only gives more information that was previously available from measurements on two or more compounds, but the necessity of obtaining suitable reference compounds (which may not be easy) is removed.

The extended Hudson rule[3] permitted conclusions to be drawn regarding the stereochemistry of a single centre of asymmetry [the alkoxy-carbon atom, C*, in (I)] in a limited range of optically active lactones, namely, those in which the alkoxy-carbon was asymmetric. The extended Hudson rule could not be used for any other type of optically active lactone in which the alkoxy-carbon atom is not asymmetric (*i.e.*, it is of the type -CH_2·O·CO-).

The sector rule[6] correlates the absolute stereochemistry of a lactone with the sign and magnitude of the o.r.d. curve in the low-wavelength region. In contrast to Hudson's rule, the sector rule can be applied to any type of lactone, not only those with an asymmetric alkoxy-carbon of the type (VIII) or (IX). It would therefore appear that the sector rule

[5] J. P. Dirkx and F. L. Sixma, *Rec. Trav. chim.*, 1964, **83**, 522; W. Gaffield, *Chem. and Ind.*, 1964, 1460; J. P. Jennings, W. Klyne, and P. M. Scopes, *J.*, 1965, 294; A. Fredga, J. P. Jennings, W. Klyne, P. M. Scopes, B. Sjoberg, and S. Sjoberg, *J.*, 1965, 3928; A. Kjaer, W. Klyne, P. M. Scopes, and D. R. Sparrow, *Acta Chem. Scand.*, 1964, **18**, 2412; J. Cymerman Craig and S. K. Roy, *Tetrahedron*, 1965, **21**, 391, for circular-dichroism results see M. Legrand and R Viennet, *Bull. Soc. chim. France*, 1965, 679.

[6] J. P. Jennings, W. Klyne, and P. M. Scopes, *Proc. Chem. Soc.*, 1964, 412; *J.*, 1965, 7211.

[7] H. Wolf, *Tetrahedron Letters*, 1965, **16**, 1075; T. Okuda, S. Marigaya, and A. Kiyomoto, *Chem. and Pharm. Bull.* (*Japan*), 1964, **12**, 504.

TABLE 1

Compounds for which the Hudson rule predicts a negative rotation

	General formula †	[ϕ] at 300 mμ	$\Delta[\phi]$ at 300 mμ	Sign of difference curve	Lactone Cotton effect (first extremum or 225 mμ)	
					[ϕ]	λ (mμ)
Five-membered lactone rings						
2α,3β,15β,16β-Tetrahydroxy-23,24-dinor-5α-cholan-22-oic acid 22 ⟶ 16β-lactone	(XXXV)	−1160	−1030	—	−3360 *	225
Corresponding glycol (16β,22-diol)		−130				
3β-Acetoxy-16β-hydroxy-23,24-dinor-5α-cholan-22-oic acid lactone	(XXXV)	−940	−1230	—	−3300 *	225
Corresponding glycol (16β,22-diol) ‡		+290				
8β-Hydroxy-(8α-methyl)iresan-11-oic acid lactone	(XXX)	−450	−590	—	−1540 *	225
Corresponding glycol (8β,11-diol)		+140				
4,5,α(H),8,11β(H)-Eudesman-8,13-olide	(XXIII)	−220	−460	—	−2820 tr	233
Corresponding hydroxy-acid		+240				
1ξ-Acetoxy-4,5,11α(H),8β(H)-eudesman-8,13-olide	(XXII)	−1050	−1850	—	−2450 infl	225
Corresponding hydroxy-acid ‡		+800				
(−)-α-Desmotroposantonin	(XXVII)	−650	−1020	—	−3100!	233
Corresponding 6-deoxy-acid		+370				
(−)-β-Desmotroposantonin	(XXVII)	−2810	−3060	—	−2740!	260
Corresponding 6-deoxy-acid		+250				
Six-membered lactone rings						
4-Oxa-3-oxo-5β-cholestane	(XVII)	+340	−480	—	−1400 tr	225
Corresponding glycol (3,5-seco-A-nor-3,5-diol)		+820				
6-Oxa-7-oxo-5α-cholestane	(XV)	−630	−1490	—	−2840!	233
Corresponding glycol (5,7-seco-B-nor-5,7-diol)		+860				
17a-Oxa-17-oxo-3β-hydroxy-D-homo-5α-androstane	(XII)	−560	−640	—	−3460 *	225
Corresponding glycol (13,17-seco-13,17-diol)		+80				

tr = trough; infl = inflection; ! = lowest wavelength measured; * = value at 225 mμ, extremum not reached. † See footnote on p. 7238. ‡ No acetoxy-group.

TABLE 2

Compounds for which the Hudson rule predicts a positive rotation

	General formula †	[ϕ] at 300 mμ	$\Delta[\phi]$ at 300 mμ	Sign of difference curve	Lactone Cotton effect (first extremum or 225 mμ)	
					[ϕ]	λ (mμ)
Five-membered lactone rings						
3β-Acetoxy-16α-hydroxy-23,24-dinor-5α,17α-cholan-22-oic acid lactone	(XXXVI)	+510	+600	+	+2660 pk	227
Corresponding glycol (16α,22-diol)		−90				
3β,17β-Dihydroxy-5α-androstan-16β-ylacetic acid lactone	(XXXVII)	+410	+650	+	+2200 pk	230
Corresponding hydroxy-acid (3β,17β-diacetate) ‡		−240				
3β,17β-Dihydroxyandrost-5-en-16β-ylacetic acid lactone	(XXXVII)	−230	+1200	+	+1050 pk	226
Corresponding hydroxy-acid (3β,17β-diacetate) ‡		−1430				
3β,17β-Dihydroxy-5α-androstan-16β-ylpropionic acid lactone		+1970	+1820	+	+6150 pk	226
Corresponding hydroxy-acid		+150				

TABLE 2 (*Continued*)

	General formula †	$[\phi]$ at 300 mμ	$\Delta[\phi]$ at 300 mμ	Sign of difference curve	Lactone Cotton effect (first extremum or 225 mμ) $[\phi]$	λ (mμ)
Five-membered lactone rings						
8α-Hydroxy-(8β-methyl)iresan-11-oic acid lactone	(XXVI)	+900	+960	+	+5100 pk	228
Corresponding glycol (8,11-diol)		−60				
5α(H),4,6,11β(H)-Eudesman-6,13,-olide	(XXI)	+400	+320	+	+2250 pk	230
Corresponding glycol (6α,13-diol)		+80				
3α-Acetoxy-4,5α(H),6,11β(H)-eudesman-6,13-olide	(XXI)	+330	+ 610	+	+2340 pk	231
Corresponding glycol (6α,13-diol) §		−280				
3-Oxo-5α(H),4,6,11β(H)-eudesman-6,13-olide 3-ethylene ketal	(XXI)	+400	+580	+		
Corresponding glycol (6α,13-diol)		−180				
Six-membered lactone rings						
4-Oxa-3-oxo-17β-hydroxy-5α-androstane	(XI)	+1380	+1130	+	+6250 pk	226
Corresponding glycol (3,5-seco-A-nor-3,5-diol)		+250				
4-Oxa-3-oxo-17β-hydroxy-17α-methyl-5α-androstane	(XI)	+490	+630	+	+4670 pk	227
Corresponding glycol (3,5-seco-A-nor-3,5-diol)		−140				
6-Oxa-7-oxo-17β-hydroxy-5β-androstane	(XVIII)	−280	−90	+	+3120 pk	233
Corresponding glycol (5,7-seco-B-nor-5,7-diol)		−190				
3α,12β-Dihydroxy-23,24-dinor-5β-cholan-22-oic acid 22 ⟶ 12β-lactone	(XIV)	+960	+350	+	+3760 *	225
Corresponding hydroxy-acid		+610				
3β-Acetoxy-12β-hydroxy-20-iso-23,24-dinor-5β-cholan-22-oic acid lactone	(XIV)	+1380				
Corresponding hydroxy-acid §		+190	+1190	+	+5150 *	225
Corresponding hydroxy-acid methyl ester §		+160	+1220			

pk = peak; * = value at 225 mμ, extremum not reached. † See footnote on p. 7238. ‡ With diacetate. § No acetoxy-group.

TABLE 3

Optical rotatory dispersion of some reference compounds at low wavelengths

	Cotton effect of acid $[\phi]$	Cotton effect of acid λ (mμ)	Cotton effect of lactone $[\phi]$	Cotton effect of lactone λ (mμ)	General formula of lactone †
Hydroxy-acids and esters					
8α-Hydroxy-4,5α(H),8,11β(H)-eudesman-13-oic acid	−1408 tr	229	−2820 tr	223	(XXIII)
3α,12β-Dihydroxy-23,24-dinor-5β-cholan-22-oic acid	+750!	222	+3760 *	225	(XIV)
3β,12β-Dihydroxy-20-iso-23,24-dinor-5β-cholan-22-oic acid	+970 pk	226	+5150 *	225	(XIV)
3β,12β-Dihydroxy-20-iso-23,24-dinor-5β-cholan-22-oic acid methyl ester	+1070 pk	226	+5150 *	225	(XIV)
Glycols					
3β,13α,17-Trihydroxy-13,17-seco-5α-androstane	−60!	213	−3460 *	225	(XII)
5β,7-Dihydroxy-5,7-seco-B-nor-5α-cholestane	+1690!	223	−2840!	233	(XV)
3,5β,17β-Trihydroxy-3,5-seco-A-nor-5α-androstane	+570!	222	+6250 pk	226	(XI)
8β,11-Dihydroxy-(8α-methyl)iresane	−270!	210	−1540 *	225	(XXX)
3α,6α,13-Trihydroxy-4,5α(H),6,11β(H)-eudesmane	−700!	227	+2340 pk	231	(XXI)

tr = trough; pk = peak; * = value of $[\phi]$ at 225 mμ, extremum not reached; ! = lowest wavelength measured. † See footnote on p. 7238.

has a much more general application than the extended Hudson rule and is likely to supersede the older work in discussions of lactone stereochemistry.

The recent work of Okuda *et al.*,[7] has been concerned with the o.r.d. of carbohydrate lactones, for which Hudson's rule was originally developed, and it has been shown that some of these compounds, which obey Hudson's rule at the *D*-line, have Cotton effects of *opposite* sign. It should be borne in mind that these carbohydrate lactones are α-hydroxy-lactones; our treatment of lactones using the sector rule has so far been concerned only with alkyl substituents and additional carbocyclic rings, and has not been extended to α-hydroxy-substituents.

EXPERIMENTAL

Optical rotatory dispersion curves were measured on the Rudolph photoelectric spectropolarimeter (down to 270 mμ) and in the low-wavelength region, on the modified [5] Bellingham and Stanley/Bendix-Ericsson automatic recording spectropolarimeter, Polarmatic '62. Detailed experimental data for o.r.d. curves are given in ref. 6. Solvent; methanol; $l = 0{\cdot}1$ dm.; $t = 20$—$25°$; $t = 1$ mg./ml. or less.

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