Epoxidation of Lanost-9(11)-enes. The Effect of a β-Carbonyl Group upon the Stereochemistry of Epoxidation

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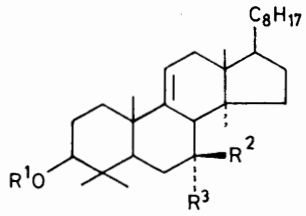
m-Chloroperbenzoic acid epoxidation of 3β-acetoxylanost-9(11)-en-7-one afforded two isomeric epoxides, the β-isomer being the major product. This result is in contrast with the epoxidation of other 9(11)-olefins having no carbonyl group. It is interpreted in terms of the ' directive effect ' of the β-carbonyl group which generally influences the steric course of the epoxidation of β-oxo-olefins and is of polar character.

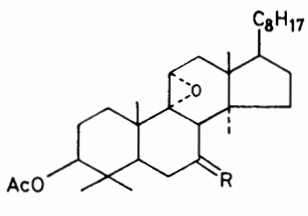
THE formation of epoxides from olefins in steroid and triterpenoid series has been extensively studied, because of the synthetic significance of these compounds. It is generally accepted that peracid epoxidation of all-*trans*-fused unsaturated steroids proceeds with the formation of α-epoxide as a sole or principal product.[1] This results from the steric hindrance caused by angular methyl groups which inhibit the approach of an electrophile from the β-face of the alicyclic skeleton. Extremely hindered double bonds, *e.g.* Δ^{7}- and $\Delta^{9(11)}$-olefins are exclusively attacked from the α-side. Stereochemistry of the epoxidation may be modified by the introduction of suitably located substituents, for example OH, OAc, Cl, through their ' directive effect '.[2] As a consequence, high stereoselectivity may be achieved. Continuing the work on skeletal rearrangements of lanostane derivatives[3] we needed 9,11-functionalized compounds. Therefore, epoxidations of lanost-9(11)-enes were undertaken. The results of this work are presented.

In lanost-8-ene and lanost-9(11)-ene the double bond seems to be extremely hindered, especially on the β-side. Epoxidation of 3β-acetoxylanost-9(11)-ene afforded α-epoxide.[4] The attempted synthesis of 9β,11β-epoxide *via* the bromohydrin route failed.[4] When 3β-acetoxylanosta-7,9(11)-diene was epoxidized with monoperphthalic acid in ether all the possible mono-epoxides, but one, 9β,11β-isomer, were isolated.[5] This indicates that the β-face approach of peracid to the 9,11-double bond is totally inhibited and that it is attacked from the α-side despite the proximity of the 14α-methyl group.

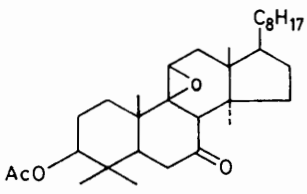
The reaction of the known 3β-acetoxylanost-9(11)-en-7-one (1)[6] with *m*-chloroperbenzoic acid in chloroform gave two epoxides: (4) and (6) in yields of 22 and 69% respectively. The stereochemistry of the epoxides follows from the chemical shift of the 11-proton. A doublet at δ 3.16 and slightly broadened singlet at δ 3.60 were present in the n.m.r. spectra of (4) and (6) respectively. A down-field shift of the analogous hydrogen in steroidal β-epoxides has been previously observed.[7] The corresponding signal in the epoxide (5) is found at δ 3.10. Circular dichroism curves [$\Delta\varepsilon = -0.66$ at 292 nm for (4) and $\Delta\varepsilon = +1.73$ at 298 nm for (6)] were also in agreement with the assigned configuration of the epoxides (*vide infra*). The epoxidation of (1) was a slower reaction when it was carried out in benzene; the yields of (4) and (6) were 29 and 62% respectively.



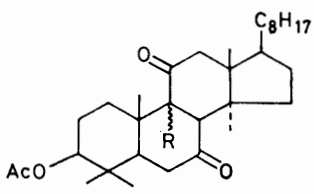
(1) R^1 = Ac R^2, R^3 = O
(2) R^1 = Ac $R^2 = R^3$ = H
(3) R^1 = Ac R^2 = OAc, R^3 = H



(4) R = O
(5) R = H_2



(6)



(7) R = α-H
(8) R = β-H

The following chemical transformations confirmed the stereochemistry of compounds (4) and (6). Treatment of (6) with boron trifluoride–diethyl ether in benzene afforded the known 3β-acetoxy-5α-lanostane-7,11-dione (7),[8] while the α-epoxide (4) was fairly resistant to similar conditions. During the cleavage of the epoxide (6) two unfavourable 1,3-diaxial arrangements are produced, *i.e.* between BF_3-co-ordinated oxygen and two angular methyl groups; however, the reaction is fast. BF_3-catalysed cleavage of the epoxide (5) is also a fast

[1] (*a*) C. Djerassi, ' Steroid Reactions,' Holden-Day, San Francisco, 1963; (*b*) D. N. Kirk, ' Steroid Reaction Mechanism,' Elsevier, Amsterdam, 1968; (*c*) J. Fried and J. A. Edwards, ' Organic Reactions in Steroid Chemistry,' Van Nostrand Reinhold, New York 1972, ch. 9.

[2] ' Rodd's Chemistry of Carbon Compounds,' Elsevier, Amsterdam, 1970, vol. II, part D, p. 85.

[3] O. E. Edwards and Z. Paryzek, *Canad. J. Chem.*, 1973, **51**, 3866; 1975, **53**, 3498; Z. Paryzek, *Tetrahedron Letters*, 1976, 4761.

[4] (*a*) I. C. Guest and B. A. Marples, *J. Chem. Soc.* (*C*), 1971, 1468; (*b*) E. C. Levy and D. Lavie, *Israel J. Chem.*, 1970, **8**, 677.

[5] C. W. Shoppee and J. C. Coll, *J. Chem. Soc.*, (*C*), 1969, 2157.

[6] R. B. Boar, J. F. McGhie, and D. A. Lewis, *J.C.S. Perkin I*, 1972, 2590.

[7] A. D. Cross, *J. Amer. Chem. Soc.*, 1962, **84**, 3206.

[8] (*a*) L. Ruzicka, E. Ray, and A. C. Muhr, *Helv. Chim. Acta*, 1944, **27**, 472; (*b*) C. Doree, J. F. McGhie, and F. Kurzer, *J. Chem. Soc.*, 1948, 988.

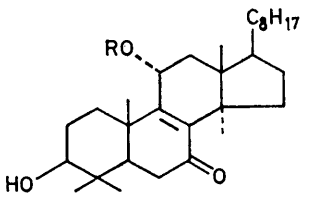
reaction [4a] despite the fact that the product is a thermodynamically less stable ketone having a 9β-configuration. Although the proximity of BF_3-co-ordinated oxygen and a 1α-hydrogen might slow down the reaction of α-epoxides, compound (5) is much more reactive than

(9) (10)

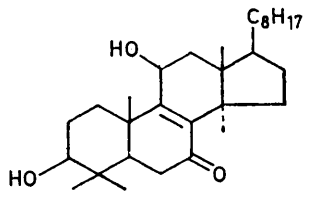
(4). It is assumed, therefore, that the 7-carbonyl group is responsible for the observed difference in the reaction

β-Oxo-epoxides of type (9) are known to undergo ready isomerization to the corresponding α-hydroxy-αβ-unsaturated ketones (10) on treatment with base.[10] The epoxides (4) and (6) were resistant to ethylamine in boiling ethanol, conditions that will effect isomerization of βγ-epoxy-ketones with an easily accessible α-proton.[10] However, when potassium hydroxide in ethanol–benzene was used the isomerizations accompanied by the 3-acetate group hydrolysis proceeded slowly at room temperature. The α-epoxide (4) gave 3β,11α-dihydroxy-5α-lanost-8-en-7-one (11) [11] characterized by its u.v., i.r., and n.m.r. spectra. Acetylation of (11) gave the diacetoxy-derivative (12).[12]

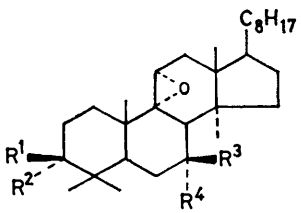
Under similar conditions the β-epoxide (6) gave two



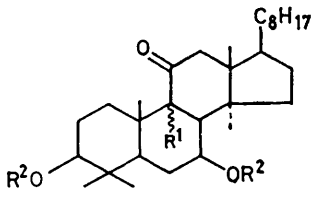
(11) R = H
(12) R = Ac



(13)



	R^1	R^2	R^3	R^4
(14)	OAc	H	OAc	H
(15)	OH	H	OH	H
(16)	OAc	H	OH	H
(17)	O		O	
(18)	O		H	H



(19) R^1 = β-H, R^2 = Ac
(20) R^1 = α-H, R^2 = H

rate of (4), since it may interfere with the Lewis acid approaching from the α-side of the molecule (*vide infra*). In a prolonged reaction (four days) the epoxide (4) was transformed into a mixture of the diketones (7) and (8) in 20 and 66% yield respectively. Chromatographic monitoring of the reaction showed that (8) partially epimerized to (7) in the reaction conditions, as was independently confirmed in the experiment in which pure (8) was subjected to similar conditions. The 9β-configuration of the diketone (8) was assigned on the basis of the high positive Cotton effect in the region of the $n\rightarrow\pi^*$ transition ($\Delta\varepsilon = +3.32$ at 298 nm).[9]

compounds: 3β,11β-dihydroxy-5α-lanost-8-en-7-one (13) and an auto-oxidation product, 3β-hydroxy-5α-lanost-8-ene-7,11-dione, identical with an authentic sample. The configuration of the 11-hydroxy-group in (13) was determined from its n.m.r. spectrum. The 11α-proton resonates at δ 4.52 as a doublet with $w_{1/2}$ 10 Hz, whereas the 11β-proton in (11) resonates at δ 4.49 as a multiplet with $w_{1/2}$ 18 Hz. U.v. spectra of both isomers [(11): $\lambda_{max.}$ 253 nm (ε 9 600); (13): $\lambda_{max.}$ 256 nm (ε 13 850)] were also consistent with the assigned configuration of 11-alcohols.[10] Oxidation of (13) with manganese dioxide in chloroform gave 3β-hydroxy-5α-lanost-8-ene-7,11-dione.

As the β-epoxidation of the 9,11-double bond in

[9] (*a*) P. Crabbé, 'Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry,' Holden-Day, San Francisco, 1965, ch. 7; (*b*) A. D. Cross and P. Crabbé, *J. Chem. Soc.* (*C*), 1969, 329.

[10] D. H. R. Barton and Y. Houminer, *J.C.S. Perkin I*, 1972, 919 and references cited therein.

[11] A. M. Milburn, E. V. Turner, and F. P. Woodford, *J. Chem. Soc.*, 1956, 1740.

[12] M. V. Mijovic, W. Voser, H. Heusser, and O. Jeger, *Helv. Chim. Acta*, 1952, **35**, 964.

lanostane had not been previously reported it appeared that additional stereo-controlling factors might have been involved in the epoxidation under study. Therefore epoxidation of other compounds having a 9,11-double bond was undertaken to check on the role of 7-carbonyl function. The re-examination of the reaction of the olefin (2) with *m*-chloroperbenzoic acid in chloroform revealed that the only product was α-epoxide (5). 3β,-7β-Diacetoxy-5α-lanost-9(11)-ene [13] on similar epoxidation afforded also one epoxide. The chemical shift and the multiplicity of 11-proton signal (δ 3.11, dd,

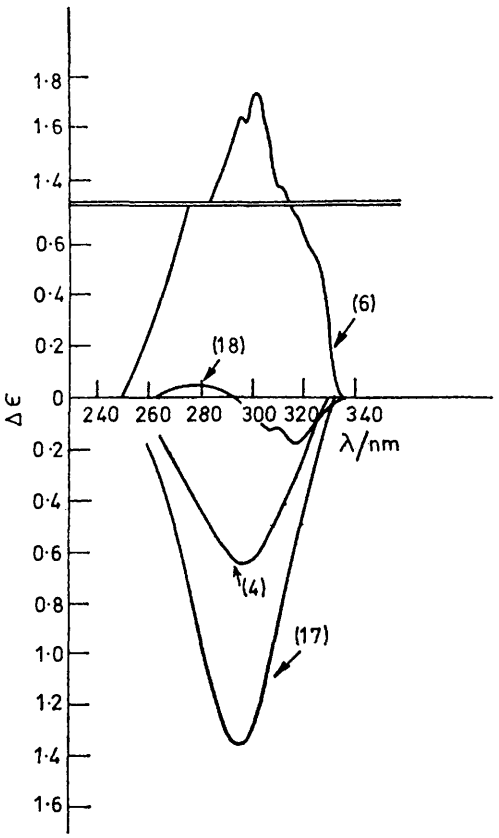


FIGURE 1 C.d. spectra of oxo-epoxides

$J_{11\beta,12\alpha}$ 6 Hz, $J_{11\beta,12\alpha}$ 2 Hz) suggested a 9α,11α-configuration as in (14). This was confirmed as follows. The epoxide (14) was hydrolysed in ethanolic potassium hydroxide to a dihydroxy-derivative (15) which on acetylation in acetic anhydride–benzene mixture gave the 3β-acetoxy-7β-hydroxy-epoxide (16) accompanied by the diacetoxy-epoxide (14). Jones oxidation of (16) afforded the epoxide (4) identical with an authentic sample. Similar oxidation transformed (15) into dioxo-epoxide (17).

BF_3-Catalysed rearrangement of (14) was a slow reaction and a complicated mixture was obtained. The electronegative 7β-substituent markedly inhibited the C(9)–O bond cleavage.[14] Crystallization of the crude product followed by preparative t.l.c. gave 3β,7β-diacetoxy-5α,9β-lanostan-11-one (19) (23% yield) characterized by its high positive Cotton effect ($\Delta\varepsilon = +2.49$ at 297 nm). On treatment with sodium ethoxide in refluxing ethanol, (19) gave a product whose spectral properties were consistent with structure (20); in particular its $\Delta\varepsilon = +0.21$ is compatible with the 9α-configuration. This was confirmed by comparison with an authentic sample.[15]

Circular dichroism spectra of epoxy-ketones are shown in Figure 1. 4,4-Dimethyl-3-oxo- and -7-oxo-steroids exhibit a weak negative Cotton effect in the region of the $n\rightarrow\pi^*$ transition.[16] 9α,11α-Epoxylanostan-3-one (18) [4b] shows a weak, two maxima Cotton effect, similar to the one given by 5α-lanost-8-en-3-one.[16a] A molecular model revealed that introduction of a 9α,11α-epoxy-function into the lanostane skeleton changes its geometry only slightly as compared with that of the 3-ketone, so that the Cotton effect of the oxo-epoxide is of both the same sign and similar magnitude to that of the parent ketone. The same argument applies to the epoxy-ketone (4) ($\Delta\varepsilon = -0.66$). As expected, the 9α,-11α-epoxy-3,7-diketone (17) exhibits a negative Cotton effect, although its amplitude ($\Delta\varepsilon = -1.35$) is higher than would have been expected from the appropriate values for epoxy-monoketones. This is in agreement with the previous finding [17] that the additivity of c.d. and o.r.d. curves is not fulfilled in triterpenoid ketones, presumably because of unpredictable skeletal deformations. The epoxy-ketone (6) exhibits a strong, positive Cotton effect ($\Delta\varepsilon = +1.73$). Introduction of a 9β,11β-epoxy-function into the lanostane skeleton changes significantly the geometry of the molecule and the octant projection of the 7-carbonyl group. It is assumed on the basis of the c.d. curve that ring B adopts a half-chair or boat conformation, while reducing interaction between the oxiran oxygen and the C_{13} methyl group. As a result the spatial arrangement around the 7-carbonyl group is quite different from that of the α-epoxide, thus giving rise to the large Cotton effect of opposite sign.

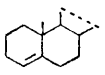
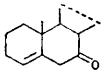
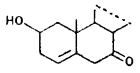
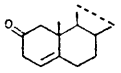
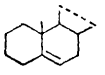
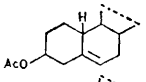
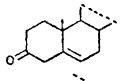
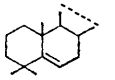
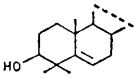
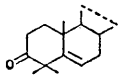
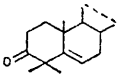
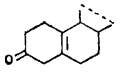
Given the structure of $\Delta^{9(11)}$-olefins it is reasonable to assume that in compound (1) the carbonyl group does not influence significantly the conformation of rings B and C which should, therefore, be the same as in the olefin (2); at most, slight changes of the torsion angles are expected. β-Epoxidation of the $\Delta^{9(11)}$-olefin requires some conformational change in the C ring of the molecule. Moreover, additional crowding is produced in the product as a consequence of the *cis*-fusion of rings B and C (oxiran oxygen is in a *cis*-relation to the 10β- and 13β-methyl

[13] (*a*) W. Voser, M. Montavan, H. Günthard, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta*, 1950, **33**, 1893; (*b*) J. F. Cavalla and J. F. McGhie, *J. Chem. Soc.*, 1951, 834.
[14] I. G. Guest and B. A. Marples, *J.C.S. Perkin I*, 1973, 900.
[15] C. W. Shoppee, N. W. Hughes, and R. E. Lack, *J. Chem. Soc.*, (*C*), 1966, 2359.
[16] (*a*) L. Velluz, M. Legrand, and M. Grosjean, 'Optical Circular Dichroism,' Academic Press, New York, 1965, ch. 4; (*b*) P. Crabbè, 'An Introduction to the Chiroptical Methods in Chemistry,' Universidad Iberoamericana, Mexico, 1971, ch. 2.
[17] J. Sliwowski and Z. Kasprzyk, *Tetrahedron*, 1972, **28**, 991.

groups and to the 8β-hydrogen). Despite these unfavourable effects the β-epoxide (6) is the predominant product of epoxidation of (1) in non-polar solvents. This suggests that besides the usual steric factors influencing the direction of peracid attack upon a 9,11-double bond

TABLE 1

Stereochemistry of epoxidation of selected steroidal olefins and oxo-olefins

	Type of structure	Orientation of carbonyl group *	Reported yield of epoxides α	β	Proportion of epoxides α	β	Ref.
(21)			51	32	61	39	18
(22)		'α'	34	26	57	43	10
(23)		'α'	17	56	23	77	10
(24)		'β'	Only		>95		10
(25)			72	19	79	21	18
(26)			90		>95		*a*
(27)		'α'	58	23	72	28	18
(28)			Only		>95		*b*
(29)			90		>95		*c*
(30)		'α'	46	30	61	39	*c*
(31)		'α'	26	18	59	41	*c*
(32)		'α'		65			*d*

* 'α' and 'β' mean that carbonyl oxygen lies respectively below or above the mean plane of the alicyclic ring. [a] R. Villotti, C. Djerassi, and H. J. Ringold, *J. Amer. Chem. Soc.*, 1959, **81**, 4566. [b] J. W. Blunt and M. P. Hartshorn, *J. Chem. Soc.* (*C*), 1968, 635. [c] T. C. Halsall, E. R. H. Jones, E. L. Tan, and G. R. Chandry, *J. Chem. Soc.* (*C*), 1966, 1374. [d] J. P. Ruelas, J. Iriarte, F. Kincl, and C. Djerassi, *J. Org. Chem.*, 1958, **23**, 1744.

an additional 'derivative effect' associated with the 7-carbonyl group which is unsymmetrically disposed with respect to the olefinic double bond, operates.

Although there is a large body of literature concerned with epoxide formation from steroidal olefins, accurately estimated yields of α- and β-isomers have been reported in only a few cases; literature data are given in Table 1. Although these data refer to epoxidations which were carried out under different reaction conditions, we believe that they are comparable because: (i) the stereochemistry of the reaction seems not to be significantly affected by the solvent and peracid used (perbenzoic, *m*-chloroperbenzoic, and monoperphthalic acid,[18] in ether, benzene, or chloroform) and (ii) the results of each group of workers were usually obtained by using similar reaction conditions. In the work described here it has been found that, while the rate of epoxidation depends to some extent on the nature of the solvent (*vide infra*), the ratio of α : β epoxide is only slightly solvent-dependent provided solvents of similar polarity are considered. In the case studied it changes from 68 : 32 in benzene to 74 : 26 in chloroform. However, the β-epoxide predominates in both solvents.

The results summarized in Table 1 support our observation concerning the role of the carbonyl group. Thus it seems to be a general rule that a carbonyl group in the β-position to the olefinic double bond has a pronounced 'directive effect' upon peracid epoxidation, provided that these two functionalities are not co-planar. In all cases a higher ratio of the epoxide '*trans*' to the

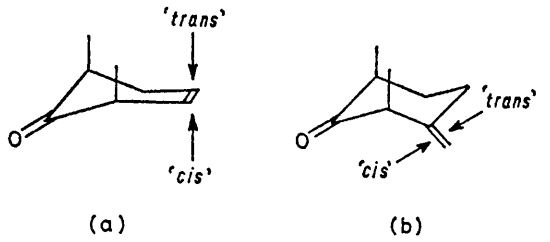


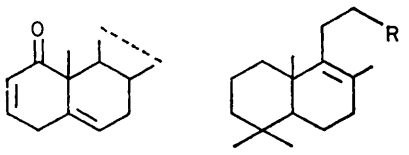
FIGURE 2 Two possible modes for the peracid molecule approach to the double bond in the rigid, non-planar β-oxo-olefin; (a) endocyclic double bond, (b) exocyclic double bond

carbonyl group (Figure 2) is obtained compared with the isomer ratio for the olefin without the carbonyl.

Epoxidation of cholest-4-ene (21), in which the double bond is relatively accessible for β-attack, gives a 61 : 39 ratio of α- and β-epoxides. Introduction of a 7-carbonyl group ('α' carbonyl) as in (22) slightly enhances β-epoxidation, while the 2-carbonyl group in (24) ('β' carbonyl) opposes β-attack leading, consequently, to α-epoxide formation. The influence of the carbonyl group in the β position is significant in Δ^5-unsaturated steroids. In epoxidations of 4,4-dimethyl-3-ketones, (30) and (31), the ratio of epoxides may be partially ascribed to the flattening of ring A as a result of 4β- and 10β-methyl interaction, although this effect does not seem to be of primary importance, since compound (28) gives only the α-epoxide. The 'α' orientation of the 3-carbonyl group in compound (32) may well account for the predominant β-epoxidation of the 5(10)-double bond. Epoxidation of withanolides having the partial structure (33), as well as their 2,3-dihydro-derivatives, proceeded with the formation of 5β,6β- and 5α,6α-isomers. The β-epoxide was often the predominant product despite the

[18] Y. Houminer, *J.C.S. Perkin I*, 1975, 1663.

steric effect of the angular methyl group in the 10β-position.[19,20] Striking differences in the course of epoxidation of the non-rigid system of 14,15-bisnorlabd-8-enes, is noteworthy.[21] The 13-acetoxy-compound



(33) (34)

[34; R = CH(OAc)Me] afforded a 2 : 1 mixture of α- and β-epoxide, while the 13-ketone (34; R = Ac) gave, exclusively, the α-epoxide. This fact may suggest that the C_9 side-chain adopts a preferential conformation with the 13-carbonyl group on the β-face of the molecule. A similar ' directive effect ' was observed in the alkaline epoxidation of 3-oxo-Δ^4-androstanes [22] which in the absence of a carbonyl group at position 11 or 17 proceeded with the formation of the β-epoxide. If polar C-17 substituents were present up to 30% of the α-epoxide was formed. In the presence of an 11-carbonyl group (' β ' oriented) the epoxidation gave 86% of the α-epoxide. It does not seem reasonable to consider the relief of compression as the only stereo-controlling factor. Alternatively, the interaction between anionic transition state and carbonyl group, although situated in the γ-position with respect to the double bond, is responsible for the steric course of the epoxidation. The remarkable enhancement of electrophilic β-attack in cholest-5-en-3-one

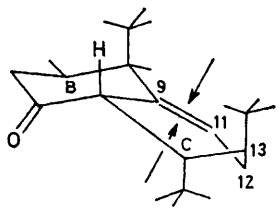


FIGURE 3 Partial structure of 3β-acetoxylanost-9(11)-en-7-one (1)

in comparison with 3β-substituted Δ^5-olefins was interpreted recently in terms of geometric factors in the neighbourhood of the double bond.[23] We assume that a considerable contribution to β-attack is largely because of the ' directive effect ' of the 3-carbonyl group which has an ' α ' orientation.

In compound (1) since the carbonyl group is ' α ' oriented (Figure 3), β-epoxidation should be enhanced; this was indeed observed experimentally.

The polarity of the reaction medium strongly affects the proportion of epoxides (4) and (6) (Table 2). In non-polar solvents, *e.g.* benzene or chloroform, the β-epoxide (6) is the major product, while in the polar solvent

TABLE 2

Solvent-dependence of the ratio of epoxides

Solvent	Ratio of (6) : (4)
$CHCl_3$	72 : 28 [a]
	76 : 24 [b]
C_6H_6	67.5 : 32.5 [a]
	68.5 : 31.5 [b]
CH_3CN–CH_2Cl_2 (2 : 1)	48 : 52 [a]
CH_3NO_2–CH_2Cl_2 (2 : 1)	53 : 47 [a]

[a] Estimated from the integration of 11-proton signals in the n.m.r. spectrum. [b] Determined by t.l.c.

systems, *e.g.* acetonitrile–methylene chloride (2 : 1) or nitromethane–methylene chloride (2 : 1), an approximately 1 : 1 mixture of the epoxides (4) and (6) is obtained. Since the olefin (1) was insoluble in acetonitrile or nitromethane a mixture of these solvents with methylene chloride had to be used. It is reasonable to assume that the epoxidation in pure acetonitrile or nitromethane would give the α-epoxide (4) as the major product. Kinetic studies of the epoxidation of the olefins (1), (2), and (3) (Table 3) shows that the reactivity of the 9(11)-double bond is remarkably decreased if an electronegative substituent is present in the β-position. α-Epoxidation of the unsubstituted olefin (2) in chloroform is *ca.* 10 times faster than epoxidation of the 7β-acetoxyolefin (3) and *ca.* 300 times faster than that of the 7-oxo-olefin (1). It is apparent from a comparison of the epoxidation rates k_α and k_β that the rate of α-epoxidation of (1) is selectively reduced, consequently β-epoxidation is the faster reaction. This cannot be interpreted in terms of the inductive effect alone.

Steroids have been extensively used in investigations of the relationship between reactivity and the variation of structural features remote from the site of the reaction. The results have been interpreted in terms of conformational transmission,[24] inductive effects, [1b,25] and electrostatic field effects.[22,26] If a substituent is close to a reaction centre it may stabilize a transition state or intermediate. This effect, called neighbouring-group participation, intramolecular catalysis, or anchimeric assistance,[27] is usually accompanied by an increased reaction rate. The effect of a β-carbonyl group upon

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[20] E. Glotter, I. Kirson, A. Abraham, and D. Lavie, *Tetrahedron*, 1973, **29**, 1353.
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[26] (*a*) H. P. Henbest and J. J. McCullough, *Proc. Chem. Soc.*, 1962, 74; (*b*) H. B. Henbest, *ibid.*, 1963, 159; (*c*) N. Bodor, *Rev. Roumaine Chim.*, 1968, **13**, 555; (*d*) N. Bodor and O. Mantsch, *ibid.*, p. 1153.
[27] B. Capon, *Quart. Rev.*, 1964, **18**, 45.

epoxidation of olefins, and possibly on other reactions of electrophilic character, cannot be discussed either in terms of long-range effects (both functionalities are located in proximity to each other) or in terms of neighbouring-group participation (because of the remarkable decrease of the reaction rate). Therefore the term ' intramolecular inhibition ' appears to be pertinent to the effect under discussion.

There seem to be two explanations for the course of the epoxidation of the oxo-olefin (1) as well as other β-oxo-olefins.

(i) *Simultaneous interactions.* In view of the proximity of the carbonyl group and the double bond it may be envisaged that these functions interact simultaneously with peracid molecule or compete for it (Figure 4); a form of co-ordination, which resembles the early, reversible stage in Baeyer–Villiger oxidation, is then possible (Figure 4b). If peracid approaches from the ' *trans* ' direction the carbonyl group is shielded by α- and α'-axial substituents. In the course of the ' *cis* ' approach of the reagent to the double bond the carbonyl group may compete more effectively for the peracid molecule. As a result the rate of ' *trans* ' epoxidation increases at the expense of ' *cis* ' epoxidation. Hydrogen bonding between a carbonyl group and peracid may also slow down the reaction resulting from ' *cis* ' attack.

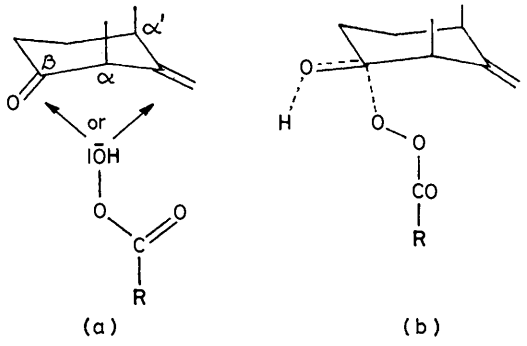

FIGURE 4 (*a*) Simultaneous interaction of the peracid molecule with the carbonyl group and the double bond; (b) co-ordination of the peracid with the carbonyl group

(ii) *Electrostatic field effect.* This may be considered in terms of the interaction of a carbonyl dipole with the transition state of epoxidation which at a certain stage of the transition state development may have slight polar character. This would lead to a situation where charge separation at this stage is greater in the case of peracid attack from the ' *trans* ' direction (Figure 5a) as compared with ' *cis* ' attack (Figure 5b). Consequently, possible like-charge repulsion in the ' *cis* ' transition state should be greater. Therefore, the ' *trans* ' mode of the reaction should be preferred as a consequence of the reduced unfavourable electrostatic interactions in the transition state. This explanation is strongly supported by the fact that the reaction is dependent on the polarity of the solvent. The remarkable increase of ' *cis* ' attack was observed in the epoxidations carried out in aprotic solvents of high dielectric constant, *e.g.* nitromethane, acetonitrile, or nitrobenzene. A similar interpretation of the influence of the cyano-group [26b] upon the stereochemistry of epoxidation was proposed by Henbest. It is reasonable to assume that the above mentioned

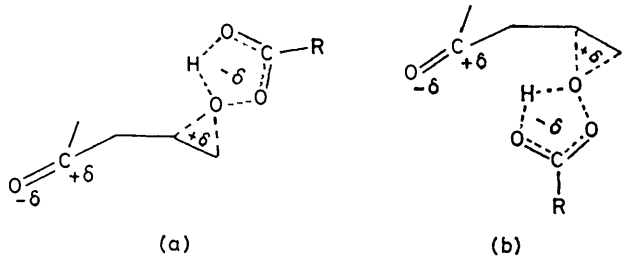

FIGURE 5 Charge separation in the course of *trans* (a) and *cis* (b) epoxidation of an β-oxo-olefin

effects operate simultaneously; however, the main factor is polar in origin.

Conformational transmission seems not to be involved since it is unlikely that any effect arising from the small change in torsion angles, between an olefin and a β-oxo-olefin, would influence selectively the rates of ' *cis* ' and ' *trans* ' epoxidation of an oxo-olefin and be preserved in the epoxidations of numerous oxo-olefins regardless of the different environment of the double bond.

Finally, the quantitative estimation of the carbonyl group ' directive effect ' is difficult, since the stereochemistry of epoxidation depends strongly on steric factors as well. In particular, the environment of a double bond is critical. It appears that the more hindered the double bond, the more pronounced is the ' directive effect ' of the β-carbonyl group.

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. I.r. spectra were determined with a Unicam SP 200G spectrophotometer for solutions in chloroform. U.v. spectra were determined with a Unicam SP 700A spectrophotometer for solutions in ethanol. N.m.r. spectra were recorded with a Varian EM-360 60 MHz spectrometer for solutions in deuteriochloroform with $SiMe_4$ as internal standard. Mass spectra were recorded with a JEOL JMS-D100 mass spectrometer using direct insertion technique. C.d. spectra were recorded with a Dichrograph Mark III Jobin-Yvon for solutions in dioxan. The product of a particular reaction (if details of isolation are not given) was isolated by extraction with benzene, washing of the organic layer with 5% hydrochloric acid and/or with 5% sodium hydrogen carbonate and finally with water. The acid- and base-free organic layer was dried over magnesium sulphate, filtered, and evaporated to dryness to give a crude product.

Kinetic Measurements.—Epoxidations were carried out in deuteriobenzene or deuteriochloroform in n.m.r. tubes at 20 ± 0.3 °C. In all cases the initial concentration of the solution was $a = 0.2$M of an olefin and $b = 0.3$M of *m*-chloroperbenzoic acid. The progress of a particular reaction (x) was followed by integration of the signal

corresponding to the 11-proton in the olefin (*ca.* 5 p.p.m.) and of the signal corresponding to the 11-proton in the epoxide (*ca.* 3.1—3.6 p.p.m.). The second-order rate constants given in Table 3 are the average values of at

TABLE 3

Rates of epoxidation of 9(11)-olefins with *m*-chloroperbenzoic acid at room temperature

Compound	Rate	Solvent
(1)	$k_\alpha = 4.28 \times 10^{-5}$	$CDCl_3$
	$k_\beta = 1.59 \times 10^{-4}$	
	$k_\alpha = 4.29 \times 10^{-5}$	C_6D_6
	$k_\beta = 1.04 \times 10^{-4}$	
(2)	$k = 1.25 \times 10^{-2}$	$CDCl_3$
(3)	$k = 1.16 \times 10^{-3}$	$CDCl_3$

least eight experimental k values calculated from the expression

$$k = \frac{2.303}{t(a-b)} \log \frac{a(b-x)}{b(a-x)}$$

Epoxidation of Compound (1).—To the solution of the olefin (1) (3.645 g) in chloroform (25 ml) *m*-chloroperbenzoic acid (2.60 g) was added and the reaction mixture was kept at room temperature for 48 h. Chloroform was partially evaporated off and benzene–ether (1 : 1) was added; the resulting solution was washed successively with 10% sodium bisulphite, 5% sodium hydroxide, and finally with water. The organic layer was dried over sodium sulphate and the solvent evaporated off. The residue was crystallized from ethanol and from methanol–acetone to give the epoxide (6) (1.89 g), m.p. 216—218 °C, δ 4.55 (t, *J* 8 Hz, 3α-H), 3.60 (slightly broadened s, 11α-H), 2.82 (s, 8β-H), and 2.06 (s, OAc); $\nu_{max.}$ 1 735, 1 705, 1 260, and 1 035 cm^{-1}, M^+ 500 (Found: C, 76.95; H, 10.45. $C_{32}H_{52}O_4$ requires C, 76.75; H, 10.45%). The mother liquors were combined and chromatographed on an alumina column which was eluted with benzene. Combined fractions afforded an additional crop of the epoxides (6) (0.96 g) and (4) (0.78 g), m.p. 173—175 °C (from methanol), δ 4.48 (t, *J* 8 Hz, 3α-H), 3.16 (d, *J* 5 Hz, 11β-H), 2.82 (s, 8β-H), and 2.02 (s, OAc); $\nu_{max.}$ 1 730, 1 715, 1 260, 1 230, and 1 030 cm^{-1}; M^+ 500 (Found: C, 76.45; H, 10.35%).

Epoxidation of Compound (2).—The olefin (2) [28] was epoxidized as above to give the epoxide (5), m.p. 187—189 °C, δ 4.45 (3α-H), 3.10 (d, *J* 4 Hz, 11β-H), and 2.03 (s, OAc) [lit.,[4a] m.p. 188—189 °C; τ (for solution in CCl_4) 5.65 and 7.04]. Examination of the mother liquor indicates the absence of epimeric epoxide.

Epoxidation of Compound (3).—The olefin (3) [6,13] (160 mg) was epoxidized as above. The crude product (171 mg) was crystallized from ethanol to give the epoxide (14) (145 mg), m.p. 195—198 °C, δ 5.03 (br s, 7α-H), 4.46 (t, *J* 7 Hz, 3α-H), 3.11 (dd, *J* 6 Hz, *J* 2 Hz, 11β-H), 2.39 (d, *J* 12 Hz, 8β-H), and 2.04 (s, 2 OAc); $\nu_{max.}$ 1 730, 1 260, 1 030, and 975 cm^{-1} (Found: C, 74.75; H, 10.5. $C_{34}H_{56}O_5$ requires C, 74.95; H, 10.35%). T.l.c. and n.m.r. spectrum of the combined mother liquors from crystallization of (14) indicated the absence of the isomeric 9β,11β-epoxide.

Rearrangement of Compound (6).—To a solution of the epoxide (6) (101 mg) in benzene (2 ml) boron trifluoride–diethyl ether (0.1 ml) was added. The reaction mixture was kept at room temperature for 20 min. After work-up the crude product (101 mg) was purified by t.l.c. (silica gel, methylene chloride) to give compound (7) (64 mg), m.p. 221—224 °C (from methanol–chloroform), mixed m.p. 220—223 °C, δ 4.52 (t, *J* 8 Hz, 3α-H), 2.04 (s, OAc), 1.29, 1.20, 0.90, 0.82, and 0.70 (methyl groups) (the spectrum was identical with that of an authentic sample) (lit.,[8a] m.p. 222—224 °C).

Rearrangement of Compound (4).—A solution of the epoxide (4) (107 mg) in benzene (2 ml) was treated with boron trifluoride–diethyl ether (0.05 ml) at room temperature for 16 h. Work-up gave, on crystallization from methanol, the starting epoxide (4) (93 mg) proved by m.p. and n.m.r. spectrum. The crystals were combined with the mother liquor, evaporated to dryness, and dissolved in benzene (2 ml) and treated with boron trifluoride–diethyl ether (0.1 ml) at room temperature for 4.5 days (t.l.c. control). Work-up gave the crude product (107 mg) which was separated by t.l.c. (silica gel, methylene chloride) to give the diketone (7) (21 mg, 20%), m.p. 222—224 °C, and diketone (8) (71 mg, 66%), m.p. 206—210 °C (from ethanol, pure on t.l.c.), δ 4.79 (t, *J* 8 Hz, 3α-H), 2.06 (s, OAc), 1.16, 0.88, 0.81, and 0.72 (methyl groups); $\nu_{max.}$ 1 732, 1 705, and 1 265 cm^{-1}; $\Delta\varepsilon$ +3.32 at 298 nm; M^+ 500 (Found: C, 76.5; H, 10.5. $C_{32}H_{52}O_4$ requires C, 76.75; H, 10.45%). Compound (8) on treatment with boron trifluoride–diethyl ether in benzene for several days at room temperature afforded a 1 : 5 mixture of compounds (8) and (7) respectively.

Hydrolysis of the Epoxide (4).—A solution of the epoxide (4) (52 mg) in ethanol (4 ml) and benzene (1 ml) was treated with a solution of potassium hydroxide (164 mg) in ethanol (2 ml) for 18 h at room temperature. Work-up gave the crude product (11) (50 mg) [δ 4.49 (m, $w_{1/2}$ 18 Hz, 11β-H) and 3.31 (t, *J* 8 Hz, 3α-H); $\lambda_{max.}$ 253 nm (ε 9 600)] which was acetylated with pyridine–acetic anhydride to afford the diacetoxy-derivative (12), m.p. 133—135 °C (from methanol), $\nu_{max.}$ 1 735, 1 675, 1 595, and 1 260 cm^{-1} (the spetrum was in accord with that recorded [12]); δ 5.52 (dd, *J* 9 Hz, *J* 5 Hz, 11β-H), 4.57br (m, 3α-H), 2.06 (s, 2 OAc), 1.24, 1.11, 0.94, 0.90, 0.81, and 0.67 (methyl groups), [lit.,[12] m.p. 131—132 °C, $\lambda_{max.}$ 252 nm (log ε 4.00)].

The epoxide (4) failed to react with ethylamine in ethanol (1 : 1) both at room temperature and when refluxed. Potassium carbonate in methanol at room temperature gave compound (11) (as proved by t.l.c.).

Hydrolysis of the Epoxide (6).—A solution of the epoxide (6) (53 mg) in ethanol (4 ml) and benzene (1 ml) was treated with a solution of potassium hydroxide (164 mg) in ethanol (2 ml) for 18 h at room temperature. Work-up gave the residue (50 mg), which was shown on t.l.c. to be a mixture of two components. Preparative t.l.c. [silica gel, benzene–ethyl acetate (1 : 1)] afforded 3β-hydroxy-5α-lanost-8-ene-7,11-dione (12 mg), m.p. 146—148 °C (from methanol), $\nu_{max.}$ 3 620, 3 490, 1 680, and 1 020 cm^{-1}; $\lambda_{max.}$ 273 nm (ε 7 300), M^+ 456 (mass and i.r. spectra were identical with those of an authentic sample [8a]) and compound (13) (37 mg), m.p. 206—210 °C, δ 4.52 (d, *J* 6 Hz, $w_{1/2}$ 10 Hz, 11α-H) and 3.29 (t, *J* 6 Hz, 3α-H); $\nu_{max.}$ 3 630, 3 490, 1 670, 1 020, and 990 cm^{-1}; $\lambda_{max.}$ 256 nm (ε 13 850); M^+ 458 (Found: C, 78.5; H, 10.9. $C_{30}H_{50}O_3$ requires C, 78.55; H, 11.0%).

The epoxide (6) failed to react with ethylamine in ethanol (1 : 1). Potassium carbonate in methanol cleaved the epoxide ring and compound (13) was the major product (as proved by t.l.c.).

[28] J. Fried, J. W. Brown, and M. Applebaum, *Tetrahedron Letters*, 1965, 849.

Manganese Dioxide Oxidation of Compound (13).—To a solution of 3,11-dihydroxylanost-8-en-7-one (13) (26 mg) in chloroform (5 ml) manganese dioxide (290 mg) was added and the suspension was stirred at room temperature for 12 h. The solution was filtered through a short alumina column and the solvent evaporated to give 3β-hydroxylanost-8-ene-7,11-dione (14 mg), m.p. 143—145 °C, mixed m.p. 140—142 °C, δ 3.23br (t, 3α-H), 1.29, 1.15, 1.02, 0.89, 0.86, and 0.80 (methyl groups); $\nu_{max.}$ 3 620, 3 490, 1 680, and 1 020 cm^{-1}; $\lambda_{max.}$ 272 nm (ε 8 450) (n.m.r. and i.r. spectra were identical with the spectra of the original sample prepared by a literature method [8a]).

Hydrolysis of the Diacetoxy-epoxide (14).—A solution of the diacetoxy-epoxide (14) (161 mg) in 0.3N-ethanolic potassium hydroxide (15 ml) and benzene (5 ml) was kept for 10 days at room temperature. Work-up yielded the dihydroxy-epoxide (15), m.p. 197—199 °C (from methanol–water), δ 3.90 (sextet, 7α-H), 3.21br (t, *J* 6 Hz, 3α-H), 3.07br (s, 11β-H), and 2.06 (d, *J* 12 Hz, 8β-H); $\nu_{max.}$ 3 630, 3 460, 1 090, 1 050, 1 030, and 1 020 cm^{-1}; *m/e* 460 (M^+), 445, 427, 319, and 305 (Found: C, 78.0; H, 11.3. $C_{30}H_{52}O_3$ requires C, 78.2; H, 11.35%).

Acetylation of the Dihydroxy-epoxide (15).—A solution of compound (15) (60 mg) in benzene (1 ml) and acetic anhydride (4 ml) was kept at room temperature for eleven days. Work-up afforded an oil (66 mg, two component mixture) which was separated by t.l.c. [silica gel, benzene–ethyl acetate (10 : 1)] to give the diacetoxy-compound (14), m.p. 196—198 °C, and monoacetoxy-compound (16) (26 mg), m.p. 213—216° (from ethanol), δ 4.48 (t, *J* 8 Hz, 3α-H), 3.92 (sextet, 7α-H), 3.06 (dd, 11β-H), 2.06 (d, *J* 12 Hz, 8β-H), and 2.04 (s, OAc); $\nu_{max.}$ 3 620, 3 460, 1 730, 1 265, 1 050, 1 035, and 980 cm^{-1}; *m/e* 502 (M^+), 487, 484, and 442 (Found: C, 76.5; H, 10.8. $C_{32}H_{54}O_4$ requires C, 76.45; H, 10.8%).

Oxidation of the Hydroxy-epoxide (16) *to the Oxo-epoxide* (4).—Compound (16) (24 mg) in acetone (2 ml) was oxidized with Jones reagent. Work-up afforded the oxo-epoxide (4) (19.5 mg), m.p. 171—174 °C, mixed m.p. 170—174 °C. I.r. and n.m.r. spectra were identical with the spectra of an authentic sample.

Oxidation of the Dihydroxy-epoxide (15) *to the Dioxo-epoxide* (17).—Compound (15) (54 mg) in acetone (2 ml) was oxidized with Jones reagent. Work-up afforded the dioxo-epoxide (17), m.p. 190—193 °C (from methanol, 39 mg), δ 3.14 (d, *J* 5 Hz, 11β-H), 2.87 (s, 8 β-H), and 2.7—1.8 (signals of protons α to carbonyl); $\nu_{max.}$ 1 720 cm^{-1}; *m/e* 456 (M^+), 441, 427, 343, 315, and 221; Δε −1.35 (294 nm) (Found: C, 78.8; H, 10.6. $C_{30}H_{48}O_3$ requires C, 78.9; H, 10.6%).

Rearrangement of the Epoxide (14).—A solution of the epoxide (14) (240 mg) in benzene (6 ml) was treated with boron trifluoride–diethyl ether (0.45 ml) at room temperature for 84 h. Work-up gave an oily residue which crystallized from methanol to give a crystalline material (130 mg). This was separated by t.l.c. [silica gel, benzene–ethyl acetate (50 : 1)] to give the fraction of an unseparated mixture of compound (19) and its 9α-isomer and pure 9β-11-ketone (19), m.p. 213—214 °C (54 mg, from methanol); δ 4.91br (7α-H), 4.70 (t, *J* 7 Hz, 3α-H), and 2.01 (s, 2 OAc); $\nu_{max.}$ 1 735, 1 720sh, 1 260, and 1 030 cm^{-1}; Δε +2.49 (297 nm); *m/e* 544 (M^+), 484, 424, 408, 347, 302, and 289 (Found: C, 74.8; H, 10.2. $C_{34}H_{56}O_5$ requires C, 74.95; H, 10.35%).

Isomerization of the 9β-11-*Ketone* (19).—A solution of the ketone (19) (31 mg) in ethanol (4 ml) containing sodium ethoxide (100 mg) was refluxed for 2 h. Work-up followed by filtration through a short silica column in chloroform afforded the 9α-11-ketone (20) (27 mg), m.p. 212—216 °C, mixed m.p. 212—215 °C (from methanol); *m/e* 460, 442, 306, 277, and 209; Δε +0.21 (298.5 nm). The fragmentation pattern of this sample was identical with that of an authentic sample (see below).

3β,7β-*Dihydroxy*-5α-*lanostan*-11-*one* (20).—A solution of 3β,7β-diacetoxy-5α-lanostan-11-one (prepared from 3β-acetoxy-5α-lanostane-7,11-dione by a literature method [29]) in ethanolic potassium hydroxide was left at room temperature for 48 h. Work-up afforded the dihydroxy-derivative (20), m.p. 213—215 °C; δ 3.66br (7α-H), 3.32 (t, *J* 8 Hz, 3α-H), 1.16, 1.09, 0.97, 0.89, 0.80, and 0.70 (signals of methyl groups), Δε +0.22 (298.5 nm); *m/e* 460 (M^+).

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[7/873 *Received*, 18*th May*, 1977]

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