QUARTERLY REVIEWS

THE CHEMISTRY OF NATURALLY OCCURRING 1,2-EPOXIDES

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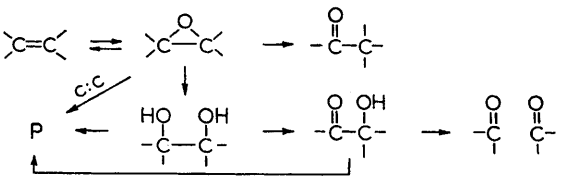
INCREASING attention has been paid to the chemistry of epoxides[1] during the past two decades, much of the stimulus being derived from their importance as synthetic intermediates. Several recent reviews have dealt with sugar epoxides[2] and with mechanisms of epoxide reactions.[3] A later development has been the recognition of the epoxide group in a number of natural products.[4] Elucidation of their structures, which vary greatly in complexity, has frequently been complicated by intramolecular nucleophilic attack upon the reactive epoxide with novel skeletal rearrangements. Interpretations of these reactions have often involved subtle application of mechanistic and stereochemical principles. Indeed, solutions of the structural problems presented by limonin and picrotoxinin must surely rank among the finest achievements of organic chemists. Physical methods have found extensive application, and nuclear magnetic resonance spectroscopy is likely to prove especially useful for the detection and study of the epoxide group.

It is the purpose of this Review to survey the chemistry of naturally occurring epoxides with special reference to interesting reactions of the epoxide group. No significance attaches to the order of presentation since no general classification is possible, though many compounds do fall into the terpene class. Biogenetic relationships with other natural products are considered and the rôle of epoxides as biogenetic precursors is commented upon. An outline of possible biogenetic pathways is annexed.

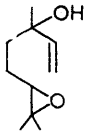


P = Cyclisation products, e.g., furanoid and pyranoid rings.

[1] Throughout this Review the term epoxide refers to the 1,2-epoxide (oxiran) group.
[2] Newth, *Quart. Rev.*, 1959, **13**, 30.
[3] Parker and Isaacs, *Chem. Reviews*, 1959, **58**, 737.
[4] As late as July, 1956, Conroy[5], when proposing his structure for picrotoxinin, wrote "The oxiran group occurs in natural products so exceedingly rarely that its proposal merits exceptional concern."
[5] Conroy, *J. Amer. Chem. Soc.*, 1957, **79**, 1726.

Generally, sources of the various natural products are not enumerated since comprehensive lists of references are cited in footnotes.

Monoterpene Epoxides.—Linaloöl epoxide (I) was identified by Naves and Bachmann,[6] and may be formed by aerial oxidation of linaloöl within the tree.[7] Penfold and Simonsen[8] considered a constituent of the essential oil of *Zieria Smithii* to be "car-3-ene 5,6-epoxide" (II). However,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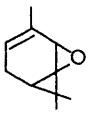
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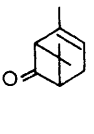
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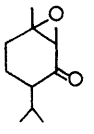
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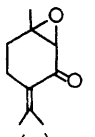
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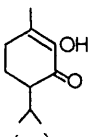
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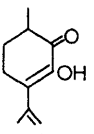
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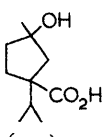

(VIII)

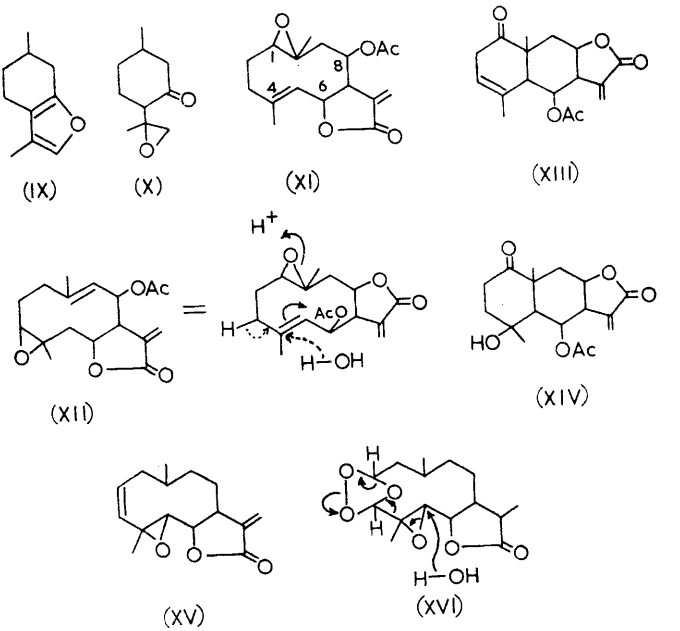
their findings have been re-interpreted by Blanchard,[9] who, after further experiment, concluded that the substance is chrysanthenone[10] (III).

Piperitone oxide (IV) and piperitenone oxide (lippione) (V) occur in several *Mentha* species together with biogenetically related alcohols, ketones, olefins, and the respective diosphenols[11] (VI and VII); the diosphenols are readily obtained by acid treatment of the epoxides. Rotundifolone has been identified with piperitone oxide[12] (IV), and alkaline rearrangement of this epoxide to the cyclopentane acid (VIII) has been rationalised as an intramolecular displacement, through rear attack by the enolate anion upon the epoxide followed by cyclopropanone ring fission.[13] Menthofuran (IX) is also isolable from *Mentha* extracts: its formation from the olefinic ketone, isopulegone, by biochemical or acid-catalysed rearrangement of the intermediate epoxide[14] (X) is considered to duplicate a biosynthetic pathway. Levisalles has briefly discussed this mode of furan biogenesis.[15]

Sesquiterpene Epoxides.—Pyrethrosin was shown to be a 10-membered ring sesquiterpenoid lactone in which the epoxide is singularly susceptible

[6] Naves and Bachmann, *Helv. Chim. Acta*, 1945, **28**, 1227, 1231.
[7] Simonsen and Owen, "The Terpenes", University Press, Cambridge, 1947, Vol. I, 2nd Edn., p. 66.
[8] Penfold and Simonsen, *J.*, 1939, 1496.
[9] Blanchard, jun., *Chem. and Ind.*, 1958, 293.
[10] Cf. Kotake and Nonaka, *Annalen*, 1957, **607**, 153.
[11] Reitsema, *J. Amer. Pharm. Assoc.*, 1958, **47**, 265.
[12] Shimizu, *Bull. Agric. Chem. Soc. Japan*, 1957, **21**, 107.
[13] Nelson and Mortimer, *J. Org. Chem.*, 1957, **22**, 1149.
[14] Fritel and Fetizon, *J. Org. Chem.*, 1958, **23**, 481.
[15] Levisalles, *Perfumery Essent. Oil Record*, 1958, **49**, 627.

to transannular nucleophilic attack.[16] The earlier structure[16] (XI) has been revised[17] to a lactone (XII) with the ring closed at the 8- rather than the 6-position. This change does not affect the original interpretation of the cyclisation mechanism, as for example with chromic acid (XII→XIII + XIV).

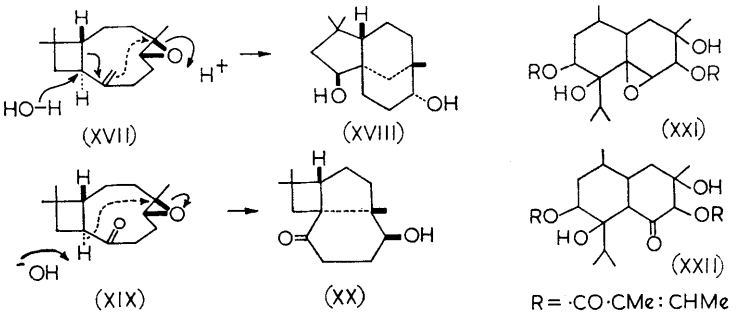


Parthenolide (XV), like pyrethrosin, is found in the *Chrysanthemum* genus.[18] Ozonolysis of dihydroparthenolide gave formic acid and a methyl ketone aldehyde by rearrangement of the $\alpha\beta$-epoxy-ozonide (XVI), probably as outlined.[18] Caryophyllene, a 9-membered ring sesquiterpene of novel structure, also occurs as its epoxide[19] (XVII), the chemistry of which has been reviewed.[16] Features of interest are the acid- and base-catalysed transannular reaction products (XVIII and XX) of caryophyllene oxide (XVII) and a ketonic oxidation product (XIX) respectively. Daucol, the per-acid oxidation product of carotol,[20] is a 1,5-epoxide not a 1,2-epoxide.[21] The Prague group have reported the isolation of isolaserpitin[22] (XXI), also synthesised[23] from its known natural olefinic precursor deoxodehydro-laserpitin[22] by the action of per-acid. Both the epoxide and the olefin may

[16] Barton and de Mayo, *J.*, 1957, 150; *Quart. Rev.*, 1957, **11**, 189.
[17] Barton, Böckman, and de Mayo, *J.*, 1960, 2263.
[18] Herout, Souček, and Šorm, *Chem. and Ind.*, 1959, 1069.
[19] Treibs, *Chem. Ber.*, 1947, **80**, 56.
[20] Asahina and Tsukamoto, *J. Pharm. Soc. Japan.*, 1925, **525**, 961.
[21] Sýkora, Novotný, and Šorm, *Tetrahedron Letters*, 1959, No. 14, 24.
[22] Holub, Herout, and Šorm, *Coll. Czech. Chem. Comm.*, 1959, **24**, 3926.

be regarded as intermediates in the biosynthesis of laserpitin[23] (XXII).

Picrotoxinin and picrotin are the two components of the bitter principle "picrotoxin". The constitution of picrotoxinin (XXIII) was brilliantly deduced by Conroy[24] who interpreted and augmented previous extensive



investigations.[25] No simple proof of the presence of an epoxide in picrotoxinin has been adduced, and its existence is accepted primarily because the structure (XXIII) accounts rationally for the many reactions of this remarkable compound.[4] β-Bromopicrotoxinin (XXIV) is converted by alkali into β-bromopicrotoxinic acid (XXV), which yields α-picrotoxininic acid (XXVII) on zinc debromination.

Reactions involving the epoxide of picrotoxinin demonstrate the supreme importance of three-dimensional geometry in the chemistry of rigid cage systems. Neither picrotoxinin nor its derivatives containing the intact epoxide ring are attacked by hot dilute acid: in no case is the related 1,2-glycol obtainable directly. Consideration of the structures (XXIII—XXV) reveals that the epoxide is strongly shielded by a lactone ring against nucleophilic attack from the rear by external anions. Indeed, the epoxide is only opened when an anion is generated internally from either the shielding lactone or another oxygen atom. Interesting illustrations are the reduction of β-bromopicrotoxininic acid (XXV) by borohydride with an internal nucleophilic displacement as indicated (XXV→XXVI), and of β-bromopicrotoxinin (XXIV) by lithium aluminium hydride to the triol[24] (XXVIII). A similar explanation has been offered for the reduction of picrotoxinin.[24,28]

[23] Šorm, personal communication.

[24] Conroy, *J. Amer. Chem. Soc.*, 1951, **73**, 1889; 1957, **79**, 1726, 5550; *Chem. and Ind.*, 1957, 604.

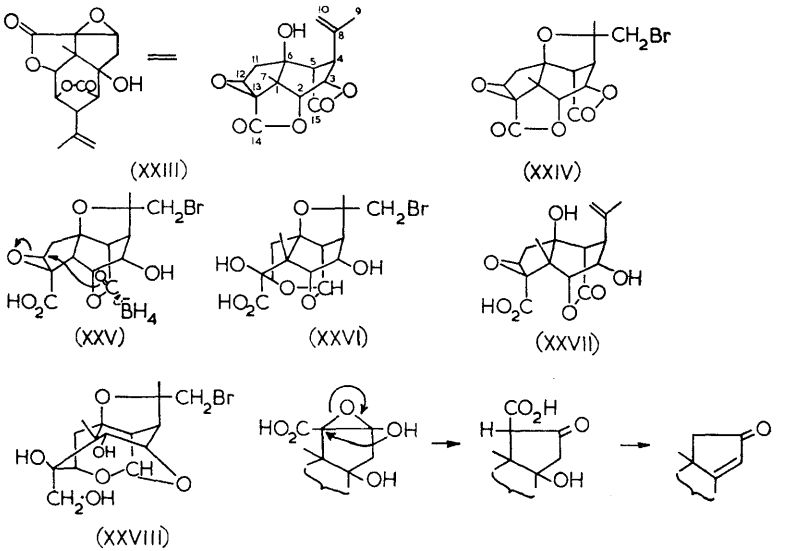
[25] The early literature (to mid-1949) has been collected,[26] and more recently reviewed together with the later publications (to mid-1957) which led to the structure [27](XXIII). For this Review, primarily concerned with the epoxide chemistry, the post-1956 publications are particularly relevant.

[26] Sutter and Schlittler, *Helv. Chim. Acta*, 1949, **32**, 1855.

[27] F. Korte, Barkemeyer, and I. Korte, *Fortschr. Chem. org. Naturstoffe*, 1959, **17**, 155.

[28] J. S. E. Holker, K. U. Holker, McGookin, Robertson, Sargeant, and Hathway, *J.*, 1957, 3746.

Thermal decarboxylation of dihydro-α-picrotoxininic acid (XXVII, isopropenyl reduced) furnishes picrotoxinide, an αβ-unsaturated cyclopentenone. Though glycidic acids are usually decarboxylated to the α-ketone, abnormal opening with hydride-ion migration is postulated by Conroy for this reaction, as outlined.[24] Alkali attacks β-bromopicrotoxininic acid (XXV) at the δ-lactone carbonyl to give an oxanion (cf. action of BH_4^-) which displaces the epoxide to yield an ortho-acid, itself susceptible to attack by base. Formation of picrotoxic acid (XXIX) involves internal nucleophilic attack on the epoxide by the $C_{(3)}$ hydroxyl liberated on opening of the lactone ring in picrotoxinin by base.[24,29,30]



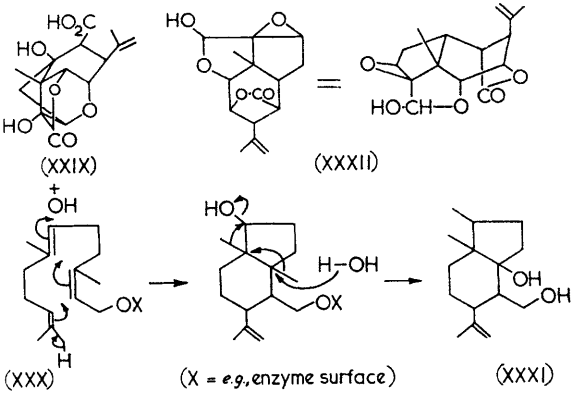
In these, and other,[31] intramolecular rearrangements conformational changes to less strained structures are apparent and probably provide a driving force for many of the reactions. Conformational factors dictate which oxygen atom attains the sterically favourable position for epoxide displacement.

A biogenetic relation between picrotoxinin and steroids has been suggested,[32] but it appears more attractive to consider picrotoxinin as a sesquiterpenoid whose carbon skeleton is arrived at by cyclisation of a farnesyl chain followed by two 1,2 *C*-methyl migrations (XXX→XXXI) with subsequent oxidation and lactonisation.

Tutin and coriamyrtione occur in several *Coriaria* species. Both show an extraordinarily similar physiological activity to picrotoxinin and,

[29] Burkhill, J. S. E. Holker, Robertson, and Taylor, *J.*, 1957, 4945.
[30] Hathway, *J.*, 1957, 4953.
[31] J. S. E. Holker, Robertson, Taylor, K. U. Holker, and Williamson, *J.*, 1958, 2987; Carman, Hassan, and Johns, *J.*, 1959, 130.
[32] Conroy, *J. Amer. Chem. Soc.*, 1952, **74**, 3046.

mainly on the basis of analogous chemical reactions, Kariyone and Okuda advanced constitution (XXXII) for coriamyrtione.[33]

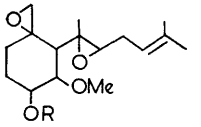


Fumagillin is a potent antibiotic isolable from the mould *Aspergillus fumigatus*. Early reports established fumagillin as the hemiester of deca-2,4,6,8-tetraene-1,10-dicarboxylic acid and alcohol-I, the monomethyl ether of a sesquiterpenoid diol.[34] First results underlined the complexity and practical difficulties of the problem, and confirmed the presence of one methoxyl, a secondary hydroxyl, and a 4-methylpent-3-enyl side chain oxygenated in the 1-position. After the existence of an epoxide ring in alcohol-I was proved,[35,36] a range of reduction products was prepared which required that alcohol-I contain a second reducible ether ring and only one carbocycle.[36] Tarbell and his collaborators thereafter solved the structural problem, finally assigning non-isoprenoid structures to fumagillin (XXXIII) and alcohol-I[37] (XXXIV). Nuclear magnetic resonance spectral data provided valuable confirmatory evidence in the later work.

The two epoxides dominate the chemistry of alcohol-I and are responsible for the profusion of acid-[38] and base-catalysed[39] isomerisation and hydration products. Much interest remains in the stereochemistry and mode of formation of these derivatives. Of the two epoxides, that on the side chain is less reactive than the spiro-epoxide. Elimination of the tertiary hydroxyl from tetrahydro-alcohol-Iab monoacetate† (XXXV; R = OH, R′ = OAc) took place without skeletal rearrangement to give a mixture of olefins, and epoxidation of the exomethylene isomer afforded

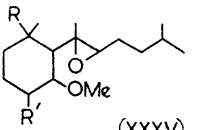
[33] Kariyone and Okuda, *Bull. Inst. Chem. Res., Kyoto Univ.*, 1953, **31**, 387; cf. *Chem. Abs.*, 1954, **48**, 9971.
[34] Schenk, Hargie, Tarbell, and Hoffman, *J. Amer. Chem. Soc.*, 1953, **75**, 2274; Brown and Landquist, *Chem. and Ind.*, 1953, 973.
[35] Landquist, *J.*, 1956, 4237.
[36] Ross, Tarbell, Lovett and Cross, *J. Amer. Chem. Soc.*, 1956, **78**, 4675.
[37] Tarbell, Carman, Chapman, Huffman, and McCorkindale, *J. Amer. Chem. Soc.* 1960, **82**, 1005.
[38] Cross and Tarbell, *J. Amer. Chem. Soc.*, 1958, **80**, 3682.
[39] Chapman and Tarbell, *J. Amer. Chem. Soc.*, 1958, **80**, 3679.
† Nomenclature for the reduction products is given in ref. 36.

dihydro-alcohol-Ia acetate (XXXIV; R = Ac, side chain reduced). The isomeric cyclic olefin gave isohexanaldehyde on treatment with periodate. Before the existence of a second epoxide ring was established this last result had been interpreted by assigning the terminal methylene epoxide function to the side chain α-position.[40]

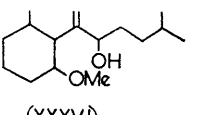


(XXXIII; R = CO·[CH:CH]$_4$·CO$_2$H)

(XXXIV; R = H)

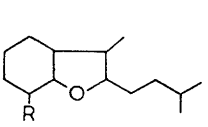


(XXXV)

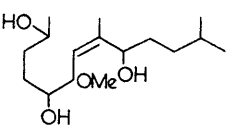


(XXXVI)

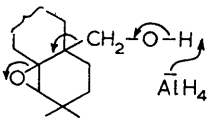
Hydrogenation of the olefin mixture and reduction of the derived tosylate (XXXV; R = H, R′ = OTos) led to a dideoxy-derivative (XXXV; R = R′ = H), the epoxide of which is isomerised by acid to furnish an allylic alcohol (XXXVI). Attempted tosylation of the deoxy-disecondary alcohol (XXXV; R = H, R′ = OH, epoxide reduced) gave the perhydrobenzofuran (XXXVII; R = OTos) by cyclisation with loss of methanol: analogous cyclisations are known.[42] Dehydrogenation of the perhydrobenzofuran (XXXVII; R = H) furnished the corresponding benzofuran, identical with a synthetic specimen, and 6-methyl-2-*o*-tolylheptane.[42]



(XXXVII)



(XXXVIII)



(XXXIX)

When the β-hydroxy-epoxide (XXXV; R = R′ = OH) was treated with lithium aluminium hydride, simple reduction of the epoxide occurred, and also a base-catalysed isomerisation, followed by reduction, to the allylic alcohol (XXXVIII), presumably by the mechanism which operates when moradiol diacetate oxide (XXXIX) is treated with this reagent.[41] Olefin formation from a β-hydroxy-epoxide may be considered[41a] a further example of 'fragmentation'.[41b]

Steroid and Triterpene Epoxides: Microbiological Epoxidation.—Apart from a small group of toad venoms, and limonin and its congeners, epoxides are rare among steroids and triterpenes. This is surprising since

[40] Carman, Chapman, McCorkindale, Tarbell, Varino, West, and Wilson, *J. Amer. Chem. Soc.*, 1959, **81**, 3151.

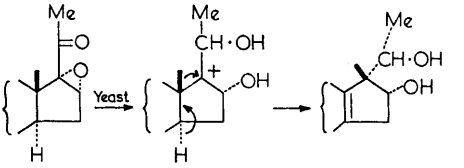
[41] Barton and Brooks, *J.*, 1951, 257.

[41a] Tarbell, personal communication

[41b] Grob, *Experientia*, 1957, **13**, 126.

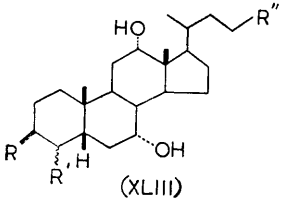
[42] Chapman, Cremer, Carman, Kunstmann, McNally, Rosowsky, and Tarbell, *J. Amer. Chem. Soc.*, 1960, **82**, 1009.

Bloom and Shull have established that several micro-organisms capable of introducing an axial hydroxyl at C_n of a saturated steroid can also introduce an epoxide group "axial" at C_n in the corresponding unsaturated compound.[43] Moulds which cause equatorial hydroxylation do not effect epoxidation.[43] Hydroxylation and epoxidation may represent two aspects of the same or similar mechanisms involving initial attack by peroxy-radical (or the equivalent in the enzymatic system) followed by loss of hydroxyl.[44] By these means Bloom and Shull prepared 9β,11β- and 14α,15α-epoxides. Examples of hydroxylated steroids are legion: the corresponding epoxides do not therefore appear to be intermediates in sterol formation *in vivo*, except possibly where 1,2-glycol systems result. Microbiological transformation of epoxides are known, as exemplified by the conversion of the pregnanone (XL) by fermenting yeast into the diol (XLII),[45] a *C*-methyl migrating in the initially-formed carbonium ion (XLI).



(XL) (XLI) (XLII)

Tschesche's structure (XLIII*a*) for scymnol,[46] a constituent of shark oil, was altered to (XLIII*b*) by Asikari[47] on the strength of its conversion into a known cholic acid. Fieser and Fieser[48] noted that warm chromic acid would attack such an epoxide and proposed a trimethylene oxide ring (XLIII*c*) as a likely alternative. Glycol-cleavage experiments on products obtainable from opening of the oxide ring by reduction or hydration, and nuclear magnetic resonance spectral studies, should permit a more definite assignment of structure.



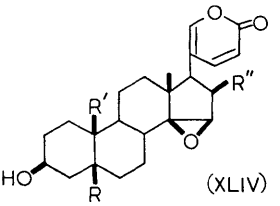
(XLIII)

	R	R′	R″
a	H	OH	-CH(O)-C(O,Me)-CH$_2$OH
b	OH	H	
c	α-OH	H	-CH(O-CH$_2$)-CH·CH$_2$·OH

From their investigations of the toad poisons, Meyer and his collabora-

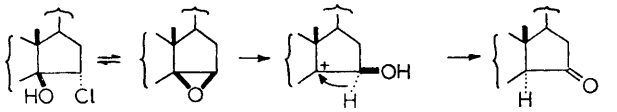
[43] Bloom and Shull, *ibid.*, 1955, **77**, 5767; U.S. Patent, 2,830,935; cf. *Chem. Abs.*, 1958, **52**, 14723*h*
[44] Bloom, Hayano, Saito, Stone, and Dorfman, *Federation Proc.*, 1956, **15**, 222.
[45] Camerino and Vercellone, *Gazzetta*, 1956, **86**, 260.
[46] Tschesche, *Z. physiol. Chem.*, 1931, **203**, 263.
[47] Asikari, *J. Biochem., Japan*, 1939, **29**, 319.
[48] Fieser and Fieser, "Steroids", Chapman and Hall, London, 1959, p. 432.

tors[49,50] arrived at structures for marinobufagin (XLIV*a*) and resibufogenin (XLIV*b*). The 14β,15β-epoxide group, a possibility also envisaged by Thiessen,[51] is demonstrated by the reactions with anhydrous and with aqueous acid, as depicted. Meyer's group[52] also developed structures for the closely related compounds cinobufagin (XLIV*c*), and cinobufotalinin, probably (XLIV*d*),[53] while jamaicobufagin appears to contain an epoxide[54] (infrared absorption data), presumably 14β,15β by analogy. Bufotalinin has the constitution (XLIV*e*).[55] All five compounds (XLIV, *a*—*e*) have been inter-related or converted into other toad poisons of established structure.



(XLIV)

	R	R′	R″
a	OH	Me	H
b	H	Me	H
c	H	Me	OAc
d	OH	Me	OAc
e	OH	CHO	H

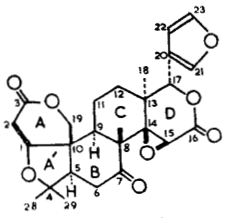


In view of Bloom and Shull's observations[43] (see above) it is of interest that all toad poisons of known constitution contain a 14β-hydroxyl[56] or a 14β,15β-epoxide with a *cis*-fused C/D ring junction in which the 14β-O bond has an equatorial (with respect to ring C) orientation. Formation of both α- and β-epoxides in the cholestane series suggests that enzymatic oxidation is not seriously subject to steric hindrance. Nevertheless, it would be of interest to know whether enzymes capable of oxidation at the α-face in the cholestane series can also effect oxidation of the same carbon atom from the β-face in the coprostane series. Derivation of the 14β,15β-epoxide in the toad venoms by direct enzymatic oxidation as proposed here differs from the mode of formation suggested by Thiessen.[49]

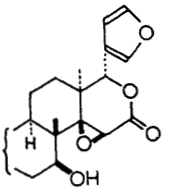
The structure[57,58] and stereochemistry[58] of limonin (XLV), the bitter principle of citrus fruits, have been elucidated more than 100 years after

[49] Linde and Meyer, *Helv. Chim. Acta*, 1959, **42**, 807.
[50] Schröter, Rees, and Meyer, *Helv. Chim. Acta*, 1959, **42**, 1385.
[51] Thiessen, *Chem. and Ind.*, 1958, 440.
[52] Hofer, Linde, and Meyer, *Experientia*, 1959, **15**, 297.
[53] Prof. Meyer, personal communication.
[54] Barbier, Schröter, Meyer, Schindler, and Reichstein, *Helv. Chim. Acta*, 1959, **42**, 2486.
[55] Schröter, Tamm, and Reichstein, *Helv. Chim. Acta*, 1958, **41**, 720.
[56] Tamm, *Fortschr. Chem. org. Naturstoffe*, 1956, **13**, 188.
[57] Arigoni, Barton, Corey, and Jeger, in collaboration with Cagliotti, Dev, Ferini, Glazier, Melera, Pradhan, Schaffner, Sternhell, Templeton, and Tobinaga, *Experientia*, 1960, **16**, 41.
[58] Arnott, Davie, Robertson, Sim, and Watson, *Experientia*, 1960, **16**, 49.

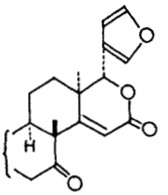
its isolation was announced.[59] Three teams led by Arigoni and Jeger, Barton, and Corey deduced two alternative structures, one (XLV), being independently arrived at through *X*-ray crystallographic study by Monteath Robertson and his co-workers.[58] The *X*-ray group examined the iodoacetate of epilimonol (XLVI), the borohydride reduction product of limonin, and were solely responsible for the determination of the stereochemistry.



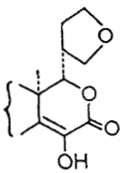
(XLV)



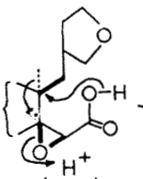
(XLVI)



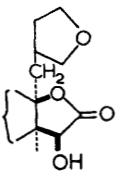
(XLVII)



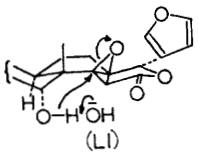
(XLVIII)



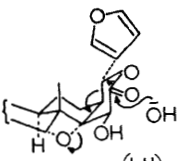
(XLIX)



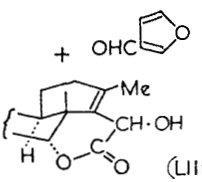
(L)



(LI)



(LII)



(LIII)

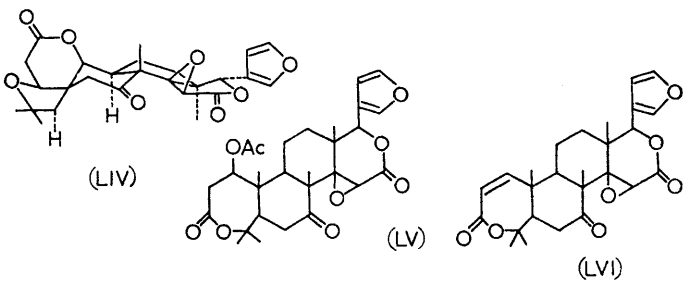
Evidence for the $\alpha\beta$-epoxy-δ-lactone came from the conversion of limonin into desoxylimonin[60] (XLVII) by hydriodic acid or chromous chloride. Tetrahydrolimonin (XLV; furan ring reduced) was transformed by acid, with epoxide ring opening and a *cis*-hydrogen shift, into a keto-lactone isolated as the enolic form (XLVIII) and which, on ozonolysis, followed by hydrolysis, furnished oxalic acid: similar acid treatment of deoxytetrahydrolimonin caused no reaction, as expected. A novel rearrangement of the glycidic acid moiety of hexahydrolimoninic acid (XLIX) with acid led to a neutral γ-lactone (L). Oxidation of the latter gave a non-enolisable α-keto-γ-lactone. Another noteworthy reaction involving the epoxide was the treatment of limonol (LI) with base, leading

[59] Bernays, *Annalen*, 1841, **40**, 317.

to merolimonol (LIII) and furan-3-aldehyde,[60] apparently *via* the intermediate trimethylene oxide (LII), since neither epilimonol (equatorial 7β-hydroxyl) nor limonin gives the same reaction.

Limonin* (XLV) may be considered a degraded tetracyclic triterpenoid of the euphol type: a biogenetic scheme has been outlined involving cleavage and rearrangement reactions of established precedent.[57] Ring D is postulated to arise by epoxidation of a cyclopentenone followed by a Baeyer–Villiger ring expansion to the αβ-epoxy-δ-lactone. This necessitates epoxidation from the hindered side of the molecule (cf. the toad venoms, p. 325), as a consideration of limonin (LIV) and molecular models of 13α-methyl-7-oxo-14,15-unsaturated triterpenoids illustrates. β-Epoxidation locks ring C in its boat conformation.

Plausible structural formulæ have been suggested[57] for nomilin[61,62] and obacunone (casimirolide),[61–63] (LV) and (LVI) respectively. No stereo-



(LIV) (LV) (LVI)

chemical correlations have, as yet been established, though recent experimental work supports these structures and C/D *trans*-ring fusion.[64] By analogy with limonin the epoxide is expected to be 14β,15β.

Carotenoid Epoxides.—A neat picture of biogenetic relations within a class of natural products is presented by the carotenoids, with epoxides as intermediates in the formation of furanoid oxides from olefins (*e.g.*, LVII→LIX). Epoxides of one or both terminal cyclic ethylenic bonds of the polyene chromophore (LVII or LXII) are found, and the isomerisation (enzymatic or acid-catalysed) to 2,5-dihydrofurans (furanoid oxides) is of diagnostic value since it results in a characteristic change of the visible spectrum. The known natural epoxides, all C_{40} compounds (LX; R and R′ = C_{11} units), are listed in Table 1. Discovery of more epoxides is to be expected, and an early review by Karrer[65] already requires revision.

* Numbering and lettering in limonin (XLV) follow biogenesis from a euphol skeleton.

[60] Melera, Schaffner, Arigoni, and Jeger, *Helv. Chim. Acta*, 1957, **40**, 1420, and the earlier literature summarised therein.

[61] Emerson, *J. Amer. Chem. Soc.*, 1948, **70**, 545; 1951, **73**, 2621.

[62] Dean and Geissman, *J. Org. Chem.*, 1958, **23**, 596.

[63] Sondheimer, Meisels, and Kincl, *J. Org. Chem.*, 1959, **24**, 870.

[64] Barton, Sternhell, and Templeton, personal communication.

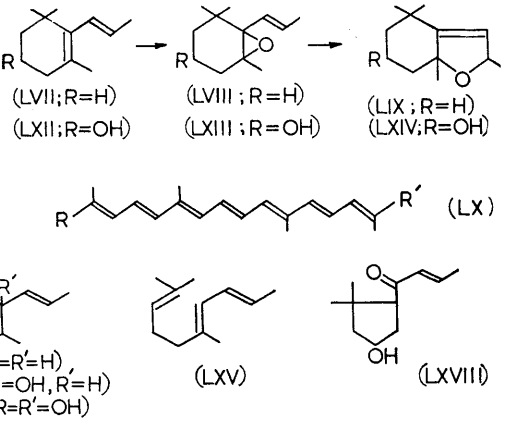
[65] Karrer, *Fortschr. Chem. org. Naturstoffe*, 1948, **5**, 1.

TABLE 1. *Related C_{40} carotenoid olefins, epoxides, and furanoid oxides*** (LX)

Ethylenic precursor	Mono-epoxide	†	‡	Mono-furanoid oxide	Di-epoxide	†	‡	Di-furanoid oxide
α-Carotene	α-Carotene epoxide			Flavochrome	*			*
R = LVII	R = LVIII	*66a*	*66b*	R = LIX				
R′ = LXI	R′ = LXI			R′ = LXI				
β-Carotene	β-Carotene monoapoxide			Citroxanthin (mutatochrome)	*β-Carotene di-epoxide*	—	69	*Aurochrome*
R = R′ = LVII	R = LVIII R′ = LVII	67	*66c*	R = LIX R′ = LVII	R = R′ = LVIII			R = R′ = LIX
Rubixanthin	*Rubixanthin epoxide*			Rubichrome	*			*
R = LXII	R = LXIII	—	*66d*	R = LXIV				
R′ = LXV	R′ = LXV			R′ = LXV				
Zeaxanthin	Antheraxanthin			*Mutatoxanthin*	Violaxanthin			Auroxanthin
R = R′ = LXII	R = LXIII R′ = LXII	*66e*	*66e*	R = LXIV R′ = LXII	R = R′ = LXIII	*66e*	*66e*	R = R′ = LXIV
Xanthophyll	Eloxanthin	*66ef*	*66e*	Flavoxanthin (chrysanthemaxanthin)	*			*
R = LXII	R = LXIII			R = LXIV				
R′ = LXVI	R′ = LXVI			R′ = LXVI				
Unknown	Trollixanthin			*Trollichrome*	*			*
R = LXII ?	R = LXIII ?	*66g*	—	R = LXIV ?				
R′ = LXVII	R′ = LXVII			R′ = LXVII				
Cryptoxanthin	*Cryptoxanthin monoepoxide*			*Cryptoflavin*	*Cryptoxanthin diepoxide*			*Cryptochrome*
R = LVII	R = LVIII	—	*66h*	R = LIX	R = LVIII	—	*66h*	R = LIX
R′ = LXII	R′ = LXII			R′ = LXII	R′ = LXIII			R′ = LXIV

† Reference to elucidation of structure of epoxide.
‡ Reference to synthesis of epoxide.
* Epoxides of unconjugated or acyclic terminal olefin groups are not found.
** Italics denote synthetic only.

Structures[66g] for trollixanthin and trollichrome (see Table) may require revision, since the allylic tertiary alcohol functions proposed should prove highly labile, especially in acid, leading to rearrangements. Taraxanthin and tarachrome appear to be stereoisomers of trollixanthin and trollichrome.[66i] Revised structures for capsanthin (LX; R = LXII, R′ = LXVIII) and capsorubin (LX; R = R′ = LXVIII) are consistent with



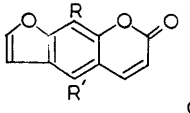
biosynthesis from antheraxanthin and violaxanthin respectively by pinacolic rearrangement of the epoxides or related oxygenated intermediates.[68] Nuclear magnetic resonance spectral studies of carotenoids indicate that this technique may aid detection of the epoxide group through proton signals of the methyl attached to epoxidic carbon.[69]

Carotenoid epoxides seem to fulfil an important rôle in Nature as oxygen donors.[70] Both α- and β-carotene epoxides display provitamin A effects in mammals,[66j] but the epoxide group is not the cause of the physiological activity.

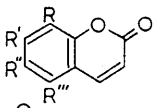
Epoxides of Coumarins, etc.—A number of oxygen heterocycles is known in which an isoprenoid side chain exhibits the sequence olefin→epoxide →glycol→cyclisation products, the related compounds sometimes occurring in a single plant. Cyclisation products may conceivably arise from one of several oxidation states of the side chain. Seshadri and his colleagues[71] have reviewed such compounds and, since the epoxide chemistry is unexceptional, only brief mention is made here.

[66] Karrer *et al.*, (*a*) *Helv. Chim. Acta*, 1945, **28**, 1146; (*b*) *ibid.*, p. 471; (*c*) *ibid.*, p. 427; (*d*) *ibid.*, 1947, **30**, 531; (*e*) *ibid.*, 1945, **28**, 300; (*f*) *ibid.*, p. 1526; (*g*) *ibid.*, 1955, **38**, 638; (*h*) *ibid.*, 1946, **29**, 229; (*i*) *ibid.*, 1957, **40**, 69; (*j*) *ibid.*, 1950, **33**, 1481.
[67] Savinov and Protsenko, *Ukrain. khim. Zhur.*, 1954, **20**, 399.
[68] Barber, Jackman, Warren, and Weedon, *Proc. Chem. Soc.*, 1960, 19.
[69] Barber, Davis, Jackman, and Weedon, *J.*, 1960, 2870.
[70] Cholnoky, Györgyfy, Nagy, and Pánczel, *Nature*, 1956, **178**, 410.
[71] Aneja, Mukerjee, and Seshadri, *Tetrahedron*, 1958, **4**, 256.

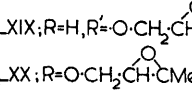
Oxypeucedanin[72] (LXIX), isoimperatorin, the corresponding olefin, and ostruthol, a monoester of the related 1,2-glycol, are all found in *Imperatoria ostruthium*. Phellopterin and byakangelicin are the biogenetically related olefin and glycol respectively of byakangelicol[73] (LXX). Auropten[74] (maranzin) (LXXI) is the epoxide of osthol, and aculeatin[75] (LXXII) is related to the glycol toddalolactone. Fukugetin (garcinin) is an epoxide[76] (LXXIII).



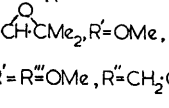
(LXIX; R=H, R'=O·CH$_2$·CH(O)·CMe$_2$)



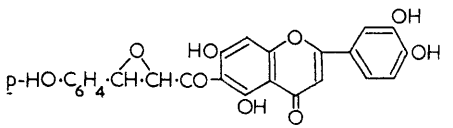
(LXXI; R=CH$_2$·CH(O)·CMe$_2$, R'=OMe, R''=R'''=H)



(LXX; R=O·CH$_2$·CH(O)·CMe$_2$, R'=OMe)

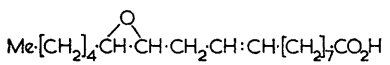


(LXXII; R=H, R'=R'''=OMe, R''=CH$_2$·CH(O)·CMe$_2$)

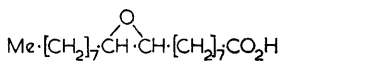


(LXXIII)

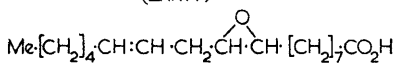
Fatty Acid Epoxides.—Since Gunstone[77] showed vernolic acid to be *cis*-12,13-epoxyoctadec-9-enoic acid (LXXIV), not 11-hydroxyoctadec-9-enoic acid as suggested earlier,[78] three more *cis*-epoxy-acids have been discovered and their structures determined: all are C_{18} compounds.



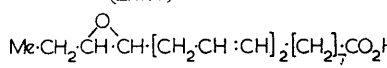
(LXXIV)



(LXXV)



(LXXVI)



(LXXVII)

15,16-Epoxylinoleic acid (LXXVII) is a constituent of cameline oil,[79] and coronaric acid is, very probably, *cis*-9,10,epoxyoctadec-12-enoic acid (LXXVI).[80] Very recently *cis*-9,10-epoxystearic acid (LXXV) was isolated from tragopogon oil,[81] and from the spores of numerous parasitic fungi.[82]

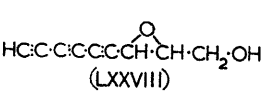
[72] Späth and Klager, *Ber.*, 1933, **66**, 914.
[73] Noguchi and Kawanami, *Ber.*, 1939, **72**, 483.
[74] Böhme and Schneider, *Ber.*, 1939, **72**, 780.
[75] Dutta, *J. Indian Chem. Soc.*, 1942, **19**, 425.
[76] Murakimi and Irie, *Proc. Imp. Acad. Tokyo*, 1934, **10**, 568.
[77] Gunstone, *J.*, 1954, 1611.
[78] Vidgarthi, *Patna Univ. J.*, 1945, **1**, 51.
[79] Gunstone and Morris, *J.*, 1959, 2127.
[79a] Osbond, *Proc. Chem. Soc.*, 1960, 221.
[80] Smith, jun., Koch, and Wolff, *Chem. and Ind.*, 1959, 259.
[81] Chisholm and Hopkins, *Chem. and Ind.*, 1959 p. 1154.
[82] Tulloch, Craig, and Ledingham, *Canad. J. Microbiol.*, 1959, **5**, 485; Tulloch, personal communication, and *Canad. J. Chem.*, 1960, **38**, 204.

Thus the series 9,10-epoxy-stearic, oleic, and linoleic acid exists, as predicted by Gunstone and Morris.[79] (±)-Vernolic acid has been synthesised.[79a]

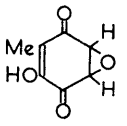
Fatty acid epoxides undergo standard epoxide addition, hydrogenation, and olefin and 1,2-glycol oxidative cleavage reactions. Hopkins and Bernstein[83] have described a nuclear magnetic resonance spectroscopic method for detection of epoxides in natural oils where the amount exceeds 5%. In support of the biosynthetic scheme the corresponding 1,2-dihydroxy- and keto-acids occur naturally.

Mould Metabolite Epoxides.—Moulds are the source of a rich variety of chemical structures. Among the simpler products is ethylene oxide-*trans*-1,2-dicarboxylic acid,[84] another metabolite of *Aspergillus fumigatus* (see p. 322). Three of the seven metabolites isolated from *Coprinus quadrifidus* are believed to constitute the sequence olefin→epoxide (LXXVIII)→1,2-glycol.[85] A provisional structure, incorporating an epoxide ring, for sclerotiorin[86a] has been abandoned by the same authors.[86b]

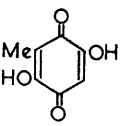
Alkali isomerisation of the epoxide in terreic acid (LXXIX)[87] led to a mixture in which the presence of 3,6-dihydroxytoluquinone (LXXX) was verified by reductive acetylation to the tetra-acetoxytoluene (LXXXI; R = H). Opening of the epoxide by treatment with boron trifluoride–acetic anhydride furnished the penta-acetate (LXXXI; R = OAc). Proton resonance absorption for the epoxidic protons of terreic acid occurs at the same field strength as those in 2,3-epoxynaphthaquinone.



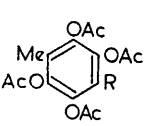
(LXXVIII)



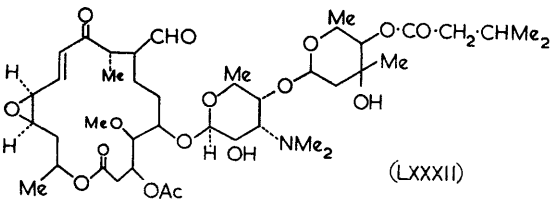
(LXXIX)



(LXXX)



(LXXXI)

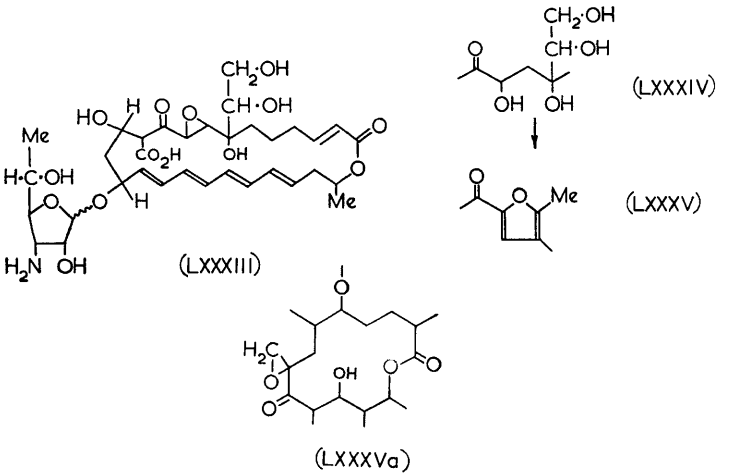


(LXXXII)

Magnamycin[88] (LXXXII), the first of the macrolide epoxides to yield to structural investigation, has been amply reviewed.[89] Another macrolide

[83] Hopkins and Bernstein, *Canad. J. Chem.*, 1959, **37**, 775.
[84] Birkinshaw, Bracken, and Raistrick, *Biochem. J.*, 1945, **39**, 70.
[85] Jones and Stephenson, *J.*, 1959, 2197.
[86] (*a*) Robertson, Whalley, *et. al.*, *Chem. Soc. Special Publ.*, 1956, No. 5, p. 27; (*b*) *idem*, *J.*, 1958, 1814.
[87] Sheehan, Lawson, and Gaul, *J. Amer. Chem. Soc.*, 1958, **80**, 5536.
[88] Woodward, *Angew. Chem.*, 1957, **69**, 50; "Festschrift Arthur Stoll", Birkhäuser, Basel, 1957, p. 524.
[89] van Tamelan, *Fortschr. Chem. org. Naturstoffe*, 1958, **16**, 90; Brink and Harman *Quart. Reviews*, 1958, **12**, 93.

antibiotic, pimaricin[90] (LXXXIII), contains an $\alpha\beta$-epoxy-carbonyl function manifest from the liberation of iodine on addition of iodide ion. Hydrogenation saturated the tetraene chain, and reduced the epoxide to an acetylatable hydroxyl. Cyclodehydration of *N*-acetyldodecahydropimaricin took place in acidic media with the formation of a furyl ketone (LXXXIV→LXXXV).



Oleandomycin, a third macrolide, readily forms a chlorohydrin from which the antibiotic is re-formed by treatment with base, properties indicative of an epoxide.[91] The complete structure of oleandomycin (LXXXVa) is now known.[91a]

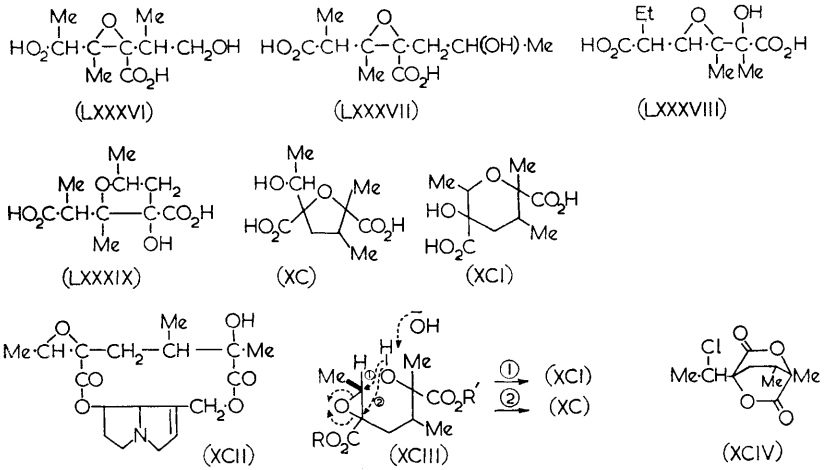
Alkaloid Epoxides.—A few Senecio alkaloids, some tropane alkaloids, undulatine, and annotinine contain an epoxide group. An early structure for quinamine was based on its conversion into cinchonamine by lithium aluminium hydride.[92] Witkop rejected an epoxidic structure after effecting this transformation in reverse, using peracetic acid which does not oxidise indoles to their 2,3-epoxy-derivatives.[93]

Jacobine[94] and tomentosine[95] (otosenine[96]), two Senecio alkaloids, contain the same epoxidic acid moiety. Alkaline hydrolysis of jacobine yields retronicine (an amino-alcohol), jaconecic acid, and isojaconecic acid. Jaconecic acid and an unknown amino-alcohol have been obtained

[90] (*a*) Patrick, Williams, Wolf, and Webb, *J. Amer. Chem. Soc.*, 1958, **80**, 6688; (*b*) Patrick, Williams, and Webb, *J. Amer. Chem. Soc.*, 1958, **80**, 6689.
[91] Els, Celmer, and Murai, *J. Amer. Chem. Soc.*, 1958, **80**, 3777.
[91a] Woodward, personal communication.
[92] Goutarel, Janot, Prelog, and Taylor, *Helv. Chim. Acta*, 1950, **33**, 150.
[93] Witkop, *J. Amer. Chem. Soc.*, 1950, **72**, 2311.
[94] Adams and Gianturco in "Festschrift Arthur Stoll", Birkhäuser, Basel, 1957, p. 72; Bradbury and Culvenor, *Austral. J. Chem.*, 1954, **7**, 378.
[95] Adams, Gianturco, and van Duuren, *J. Amer. Chem. Soc.*, 1956, **78**, 3513.
[96] Santavy, *Planta Med.*, 1958, **6**, 78; *Chem. Abs.*, 1958, **52**, 14,971.

from similar treatment of tomentosine, though isojaconecic acid should also be formed.[97]

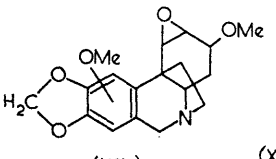
Several structures were advanced for jaconecic acid (LXXXVI,[98] LXXXVII,[99] and LXXXVIII[95]) and isojaconecic acid[98] (LXXXIX), but none accounted satisfactorily for the known facts,[94] since the tacit assumption was made that the epoxide ring present in the alkaloid remained intact during alkaline hydrolysis. Acceptable structures have now been formulated by Geissman[100] and Bradbury and Masamune[97] for jaconecic acid (XC), isojaconecic acid (XCI), and jacobine (XCII). The cyclisation mechanism (XCIII; R and R′ = H or amino-alcohol) could operate before, or after, hydrolysis of one or both of the ester linkages. Related alkaloids, found with jacobine, include jacoline, jaconine, and senecionine, which are respectively the 1,2-glycol,[100] chlorohydrin,[100] and olefin corresponding to the epoxide group in jacobine. Laboratory interconversions have been realised.[100] With hydrochloric acid jacobine is converted into jaconine, and a chloro-dilactone long thought to be a di-γ-lactone ($\nu_{C=O}$ 1781 cm.$^{-1}$), but now assigned[97,100] a δ-lactone structure (XCIV) formed by abnormal epoxide opening, ester hydrolysis, and lactonisation. Infrared and nuclear magnetic resonance spectral studies on analogous compounds supported the new structures.



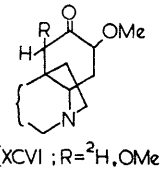
Warnhoff and Wildman[101] have clarified the structure of undulatine (XCV). A useful method of epoxide detection consisted of successive reduction with lithium aluminium deuteride, oxidation, and base equilibration

[97] Bradbury and Masamune, *J. Amer. Chem. Soc.*, 1959, **81**, 5201.
[98] Bradbury and Willis, *Austral. J. Chem.*, 1956, **9**, 258.
[99] Bradbury, *Tetrahedron*, 1958, **2**, 363.
[100] Geissman, *Austral. J. Chem.*, 1959, **12**, 247.
[101] Warnhoff and Wildman, *Chem. and Ind.*, 1958, 1293.

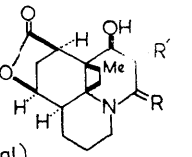
of the resultant monodeuterated ketone (XCVI) to obtain the deuterium-free epimer (XCVII).[101] Reduction leads to hydroxyl and deuterium substituents at the carbon atoms originally attached to the cyclic ethereal oxygen atom, and, since loss of deuterium during base equilibration can occur only if the deuterium is on carbon α with respect to the carbonyl (XCVI), the cyclic ether must be an epoxide.



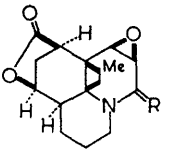
(XCV)



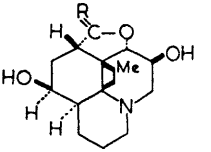
(XCVI ; R=^{2}H,OMe axial)
(XCVII ; R= H,OMe equatorial)



(XCVIII)



(XCIX)



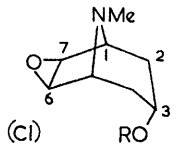
(C)

Conflicting opinion[102,103] on the structure of annotinine, an alkaloidal constituent of the club moss, *Lycopodium annotinum*, has been resolved by *X*-ray crystallography which established the structure of annotinine bromohydrin (XCVIII; R′ = Br, R = H_2),[104] and hence vindicated the structure for annotinine (XCIX; R = H_2) developed by Weisner, Valenta, and their collaborators.[102] Maclean and Prime had earlier demonstrated the presence of an epoxide by conversion of annotinine lactam (XCIX; R = O) into a chlorohydrin (XCVIII; R = O, R′ = Cl).[105] Whereas acid-catalysed hydration of annotinine leads to a 1,2-glycol,[103] alkali yields first an epimeric carboxylic acid which, under more vigorous conditions, gives the diol (C; R = O).[102] Formation of the latter is made possible by α-orientation of the carboxylate anion in the epimerised acid.[102] A similar argument has been advanced for the formation of diphenylannotinine (C; R = Ph_2) from the alkaloid and phenyl-lithium.[106]

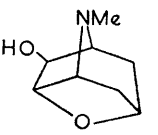
The tropane alkaloid scopolamine (CI; R = ·CO·CHPh·CH_2·OH) on very mild hydrolysis furnishes scopine (CI; R = H). More vigorous treat-

[102] Weisner, Valenta, *et al.*, *Chem. and Ind.*, 1957, 564; *J. Amer. Chem. Soc.*, 1956, **78**, 2867; *Tetrahedron*, 1958, **4**, 87.
[103] Martin-Smith, Greenhalgh, and Marion, *Canad. J. Chem.*, 1957, **35**, 409.
[104] Przybylska and Marion, *Canad. J. Chem.*, 1957, **35**, 1075.
[105] MacLean and Prime, *Canad. J. Chem.*, 1953, **31**, 543.
[106] Perry, MacLean, and Manske, *Canad. J. Chem.*, 1958, **36**, 1146.

ment with base or acid leads to scopoline (CII) by the now familiar rearward displacement of epoxide oxygen. As expected, pseudoscopine (3-epimer of CI) does not undergo this transformation. Fodor and his colleagues[107] have recently achieved a total synthesis of scopolamine.



(CI)



(CII)

[107] Fodor *et al.*, *J.*, 1959, 3461, and references summarised therein.