THE CYCLISATION OF OLEFINIC ACIDS TO KETONES AND LACTONES

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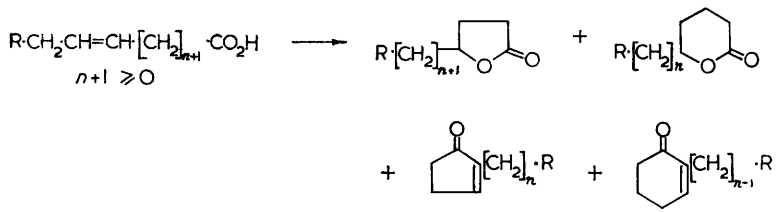
STRONG acids such as polyphosphoric acid or sulphuric acid will,[1] under suitable conditions, convert an olefinic acid into the isomeric γ- and/or δ-lactone together with a mixture of a 2-substituted cyclopent-2-enone and a 2-substituted cyclohex-2-enone as illustrated schematically below.



Such reactions occur irrespective of the relative positions of the double bond and carboxyl group, provided that the double bond is free to migrate (even if in some cases with concommitant skeletal change) to the corresponding alk-4-enoic acid. Related to these reactions are the lactonisation of non-olefinic acids, *via* carbonium-ion intermediates, and of alka-di- and tri-enoic acids, which are considered later. The closely related cyclisations of arylalkanoic acids to benzocycloalkanones are not included since such reactions have been reviewed elsewhere.[2]

The relative proportions of lactones and ketones formed on cyclisation of an olefinic acid are dependent on both the cyclising agent and the reaction temperature. Strong protonating agents such as sulphuric acid,[3] toluene-p-sulphonic acid,[4] formic acid,[5] oxalic acid,[6] trifluoroacetic acid,[1d] hydrogen fluoride,[7] and hydrogen halides in acetic acid[7,8] yield mainly

[1] (*a*) Ansell and Brown, *J.*, 1958, 2955; (*b*) Ansell and Coombs, unpublished results; (*c*) Ansell and Emmett, unpublished results; (*d*) Ansell and Palmer, *J.*, 1963, 2640.

[2] Johnson, *Org. Reactions*, 1944, II, 114.

[3] (*a*) Linstead, *J.*, 1932, 115; (*b*) Linstead and Rydon, *J.*, 1933, 580; (*c*) 1934, 1995.

[4] Plattner and St. Pfau, *Helv. Chim. Acta*, 1937, **20**, 1474.

[5] (*a*) Collin-Asselineau, *Compt. rend.*, 1952, **235**, 634; 1953, **237**, 1535; (*b*) Dietrich and Lederer, *Helv. Chim. Acta*, 1952, **35**, 1148; (*c*) Buchi, Saar, and Eschenmoser, *Experientia*, 1956, **12**, 136; (*d*) Davy, Halsall, and Jones, *J.*, 1951, 2696; (*e*) Robertson, Soliman, and Owen, *J.*, 1939, 2696; Schenk, Gutman, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1952, **35**, 817.

[6] (*a*) Elliot and Linstead, *J.*, 1938, 660; (*b*) Burnop, Elliott, and Linstead, *J.*, 1940, 727; (*c*) Mathieson, *J.*, 1951, 177.

[7] (*a*) Johnson, Johnson, and Peterson, *J. Amer. Chem. Soc.*, 1945, **67**, 1360, 1366; (*b*) Johnson, Stromberg, and Peterson, *ibid.*, 1949, **71**, 1384.

[8] El-Abbady, *J. Amer. Chem. Soc*, 1957, **79**, 1757; Johnson, Davis, Hunt, and Stork, *ibid.*, 1948, **70**, 3021; Reigel, Siegel, and Kritchevsky, *ibid.*, 1948, **70**, 2950.

lactones, whereas hot polyphosphoric acid,[1,9] phosphorus pentoxide,[6b,10] zinc chloride in acetic acid, acetic anhydride,[6c,7,8] stannic chloride,[11] and trifluoroacetic anhydride[12] yield mainly ketones. It seems probable that the first group of reagents preferentially protonate the ethylene linkage whereas the latter group preferentially attack the carbonyl group producing either acylium ions or highly polarised donor-acceptor co-ordination complexes,[13] these mechanistic differences leading to different products. Thus little double-bond migration occurs in reactions with phosphorus pentoxide[9b,10] or trifluoroacetic anhydride[1b,c] and cyclisation occurs only with Δ^4, Δ^5, or Δ^6 alkenoic acids.

Lactonisation of suitably substituted alk-3 and 4-enoic acids may be induced by electrophiles other than protons. Thus halogens[14] or cyanogen iodide[15] yield halogeno-lactones, peracids[16] yield hydroxy-lactones, tellurium halides[17] and aryltellurium halides[17] yield trichloro tellurium and aryldichloro tellurium lactones, sulphenyl halides[18] yield alkylthio-lactones, and in suitable cases mercuric acetate and sodium chloride yield chloromercuri-lactones.[19]

The formation of halogeno-lactones can occur under mild conditions and has been used to determine the positions of ethylene linkages relative to carboxyl groups, particularly among the triterpenoids.[14b]

Lactonisation of Olefinic Acids.—*Mechanism and stereochemistry.* The stereospecific nature of many lactonisations of olefinic acids both in proton and general acid (electrophile) catalysed reactions has led to a modification of Robinson's original mechanism,[20] which postulated addition of the electrophile to the double bond followed by attack of the resulting carbonium ion on the carboxyl group. Furthermore some reagents (e.g. ICN) show little tendency[15] to add to an ethylene linkage in the absence of a neighbouring carboxyl group, or one of its derivatives. In general, lactonisation of *cis*- and *trans*-isomers of an alkenoic acid leads to diastereoisomeric lactones, irrespective of the lactonising agent.[14a] It has been shown,[14a,21] that *trans*-addition to the double bond is usual in these reactions, but that the product isolated may (especially if a strong acid catalyst is used) be

[9] (*a*) Jacobs and Dev, *Chem. and Ind.*, 1956, 576; *J. Indian Chem. Soc.*, 1959, **36**, 429; (*b*) Rai and Dev, *ibid.*, 1957, **34**, 178; *Experientia*, 1955, **11**, 114; (*c*) Riobe, *Compt. rend.* 1958, **247**, 1016.

[10] Frank and Pierle, *J. Amer. Chem. Soc.*, 1951, **73**, 724, and references there cited.

[11] Mathieson, *J.*, 1953, 3251.

[12] Ferrier and Tedder, *J.*, 1957, 1439.

[13] Palmer, *Chem. and Ind.*, 1963, 589.

[14] (*a*) Berti, *Tetrahedron*, 1958, **4**, 393; (*b*) Simonsen and Ross, "The Terpenes", Vol. 5, Cambridge Univ. Press, 1957.

[15] Arnold and Lindsay, *J. Amer. Chem. Soc.*, 1953, **75**, 1048.

[16] Berti, Bottari, and Macchia, *Gazetta*, 1960, **90**, 1763.

[17] de Moura Campos, *Tetrahedron*, 1962, **18**, 521.

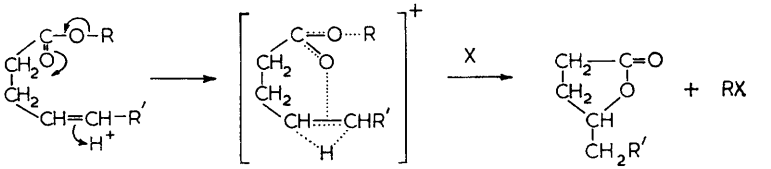
[18] de Moura Campos, *J. Amer. Chem. Soc.*, 1954, **76**, 4480.

[19] Malaiyandi and Wright, *Canad. J. Chem.*, 1963, **41**, 1493; Arakelyn, Dangyan, and Avetisyan, *Izvestea Akad. Nauk Arm. S.S.R.; Khim. Nauk*, 1962, **15**, 438.

[20] cf. Linstead and May. *J.*, 1927, 2565.

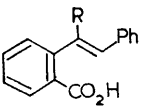
[21] Klein, *J. Amer. Chem. Soc.*, 1959, **81**, 3611.

that expected from a *cis*-addition. This is explicable on the basis of an acid-catalysed epimerisation (see p. 214). The steric course of the lactonisations is consistent with a concerted or near-concerted mechanism,[22] which is also consistent with the fact that lactonisation of esters of alkenoic acids leads[23] to an inversion of the configuration of the expelled alkyl group. Thus the following mechanism, exemplified by the formation of a γ-lactone seems probable.



R = H, or alkyl X = Cl^-, H_2O, etc.

Whether a γ- or δ-lactone is formed in a particular reaction depends mainly on the stability of the lactone under the reaction conditions (thermodynamic control). In cases where kinetic control is dominant, *e.g.*, in many halogeno-lactonisations, the carbonyl group (nucleophile) attacks the more stable carbonium ion. That is, in reactions where steric factors are relatively unimportant, the order of preference is tertiary > secondary > primary carbonium ion.[24] Steric factors are important by virtue of the fact that the two reactive centres must approach sufficiently closely for bond formation to occur. Lactonisation of alk-4-enoic acids by trifluoroacetic acid,[1d] that is under conditions where both γ- and δ-lactones are stable, yield mainly the γ-lactone. Molecular models of the suggested transition state (see above) show a greater overlap between the 2*p* orbitals of the carbonyl oxygen and the vacant orbital of the γ-carbonium ion, than with that of the δ-carbonium ion. Other examples of the influence of steric factors are the lactonisation[25] of the substituted stilbenecarboxylic acids (1) which yield more of the γ-lactone as the size of the group R increases.

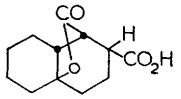


(1)

The lactonisation of Δ^4-octalin-1,2-dicarboxylic acids[26] and related compounds,[27] has been studied; the *syn-cis* (1-CO_2H,*ax*; 2-CO_2H,*eq*) and

[22] Stork and Burgstahler, *J. Amer. Chem. Soc.*, 1955, **79**, 5068.
[23] Arnold, de Moura Campos, and Lindsay, *J. Amer. Chem. Soc.*, 1953, **75**, 1044.
[24] Linstead, *J.*, 1932, 115.
[25] Dr. G. Berti, personal communication.
[26] Nazarov, Kucherov, and Andreev, *Izvest. Akad. Nauk S.S.S.R., Otdel khim. Nauk.*, 1955, **89**, 289; *ibid.*, 1956, 951.
[27] Nazarov, Kucherov, and Segal, *ibid.*, 1956, 559; Kucherov, Andreev, and Grigoreva, *Bull. Soc. chim. France*. 1960, 1406, and later papers.

syn-trans (1-CO_2H,*eq*; 2-CO_2H,*eq*) isomers readily from the γ-lactones (2), in the latter case presumably *via* a *syn-trans* (*eq*,*eq*) ⇌ *syn-trans* (*ax*,*ax*) ⇌ lactone (2) equilibrium. Hydrogen halide addition (3), *via* a migration, competes with formation of δ-lactone (4) from the *anti-cis*-isomer (1-CO_2H,*eq*; 2-CO_2H,*ax*), and the *anti-trans*-isomer (5) (1-CO_2H,*eq*; 2-CO_2H,*eq*) is unreactive, the change to *anti-trans* (5) (1-CO_2H,*ax*; 2-CO_2H,*ax*) being inhibited by C_{8a}–H, C_1–CO_2H interaction.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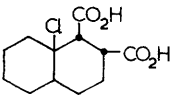
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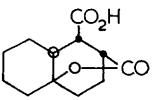
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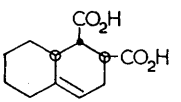
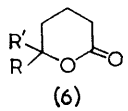

(5)

Stability of lactones in acid solution. The nature of the lactonic product from reactions catalysed by strong acids depends on the stability of the lactone in the reaction media. For simple lactones such as hexano-, heptano-, and octano-lactone the δ-lactone (6; R=H, R′=n-alkyl) is converted into the isomeric γ-lactone by hot 50% sulphuric acid.[1d] However, the δ-lactone (7; R=R′=Me), which is stable to cold concentrated sulphuric acid, undergoes a skeletal rearrangement (see below) in hot 50% sulphuric acid, but γ-lactones of the type (7; R=Me; R′=Et) are not isomerised by hot 50% sulphuric acid.[1c] In cyclic systems, examples are known of the conversion of γ- into δ-lactones *e.g.* (8)→(9)[26] and (10)→(11)[28].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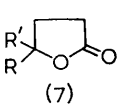
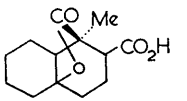

(7)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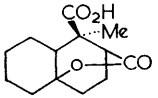
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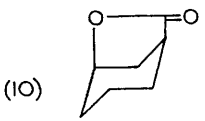
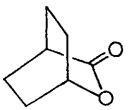
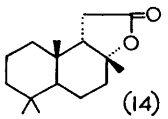

(10)


(11)

Acid catalysis will sometimes, as often noted in the diterpene field, effect epimerisation of lactones. Thus norambreinolide (12) is, according to the reaction conditions, converted into either the lactone (13) or the lactone (14).[29]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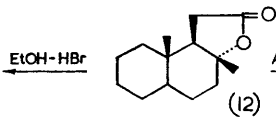

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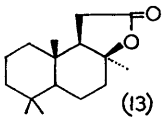
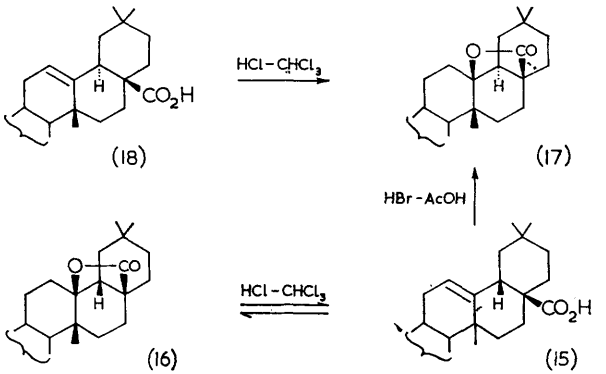

(13)

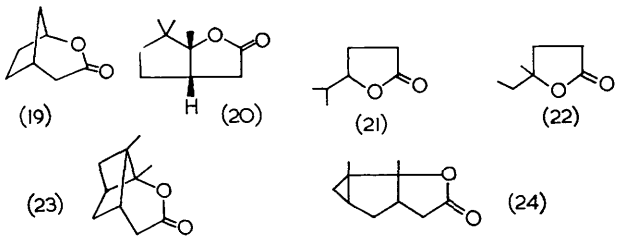
[28] Noyce, Weingarten, and Dolby, *J. Org. Chem.*, 1961, **26**, 2101.
[29] (*a*) Lucius, *Chem. Ber.*, 1960, **93**, 2663; (*b*) Corey and Sauers, *J. Amer. Chem. Soc.*, 1959, **81**, 1739.

Analogous reactions have been observed in the santonin series.[30] Such epimerisations presumably lead to the release of steric strain in the lactone ring, formed by methods other than lactonisation of the related unsaturated acid, and appear to occur *via* alkyl–oxygen bond fission of the lactone ring followed by re-lactonisation either directly or *via* the related unsaturated acid. The latter route may occur particularly in examples involving δ-lactones which are known[3] to exhibit ring–chain tautomerism. Recently it has been shown[31] that some γγ-dialkyl-γ-lactones (*e.g.* γ-methyl-γ-caprolactone) are hydrolysed in aqueous ethanolic acid *via* acyl–oxygen bond fission. Should this be a general mode of cleavage of lactones, and applicable to reactions in stronger-acid media, then the role of the tertiary alcohol in epimerisation reactions must be considered.

The configuration of the lactone derived from an olefinic acid may depend on the nature of the acid catalyst used, as is shown by the conversion[32] of oleanolic acid (15) into either oleanolic lactone (16) or 18-iso-oleanolic lactone (17) which is obtainable directly from iso-oleanolic acid (18).



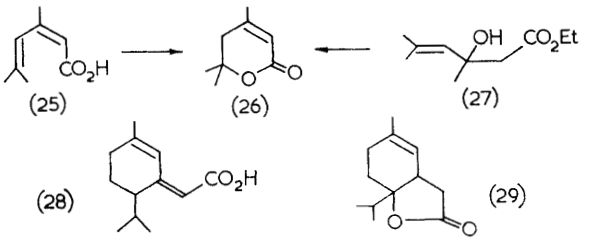
Examples of structural changes occurring when lactones are treated with strong acid have been observed. For example,[33] the conversion of the lactone (19) into dihydro-β-camphenolactone (20) and the conversion[1c] of γ-isopropyl-γ-butyrolactone (21) into γ-ethyl-γ-methylbutyrolactone (22).



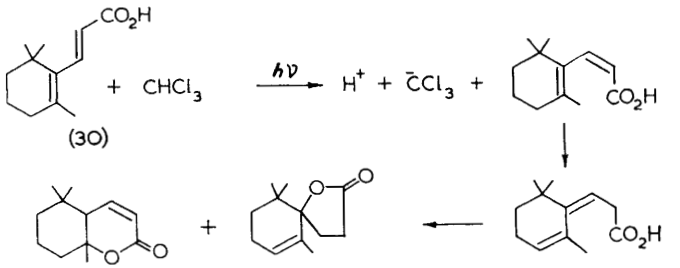
[30] Barton, *J. Org. Chem.*, 1950, **15**, 466; Huang-Minlon, *J. Amer. Chem. Soc.*, 1948, **70**, 611.
[31] Sandberg, *Acta Chem. Scand.*, 1962, **16**, 1124.
[32] Barton and Holness, *J.*, 1952, 86.
[33] Sauers, *J. Amer. Chem. Soc.*, 1959, **81**, 925.

The rearrangement[34] of lactone (23) into lactone (24) on silica-gel chromatography shows the danger of even attempting to separate some compounds by this technique.

Lactonisation of Diolefinic Acids.—Alka-2,4-dienoic acids (*e.g.* 25) lactonise[35] in strong acids to the isomeric $\alpha\beta$-unsaturated δ-lactones (*e.g.* 26); conversion of the usually all-*trans*-acid to the all-*cis*-acid is apparently a necessary prerequisite since *cis,trans*-hexa-2,4-dienoic acid[35b] is only slowly lactonised. Analogous lactonisations have been carried out with 3-hydroxyalk-4-enoic acids (27) and thionyl chloride[36a] and potassium bisulphate.[36b] Halogeno-lactonisation of such acids under the usual conditions is unsuccessful,[37] probably because of failure of the reagent to isomerise the all-*trans*- to the all-*cis*-acid. Lactonisation of piperitylideneacetic acid (28) yields[38] the lactone (29) and not an $\alpha\beta$-unsaturated lactone, as formation of the latter is not sterically possible from the intermediate transoid diene.

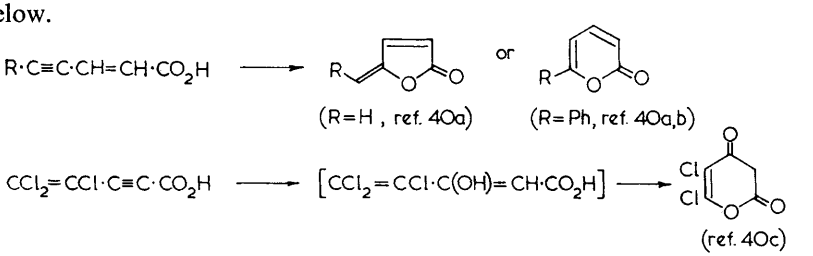


An interesting photochemical lactonisation of the *trans, trans*-dienoic acid (30) has been reported[39] and the following mechanism suggested:

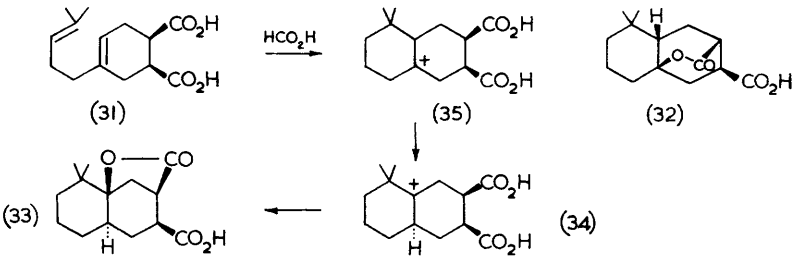


[34] Buchi and Goldman, *J. Amer. Chem. Soc.*, 1957, **79**, 4741.
[35] (*a*) Korte and Machleidt, *Chem. Ber.*, 1955, **88**, 136; (*b*) Eisner, Elvidge, and Linstead, *J.*, 1953, 1372.
[36] (*a*) Korte and Scharf, *Chem. Ber.*, 1962, **95**, 443; (*b*) Mousseron and Neyrolles, *Bull. Soc. chim. France*, 1960, 598.
[37] Bougault, *Compt. rend.*, 1906, **143**, 398.
[38] Tribolet, Gamboni, and Schinz, *Helv. Chim. Acta*, 1958, **41**, 1587.
[39] Mousseron-Canet, Mousseron, and Legendre, *Compt. rend.*, 1961, **252**, 3928.

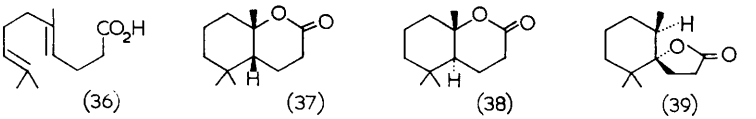
The acid-catalysed conversions of conjugated alkenynoic acids into unsaturated lactones has been reported recently,[40] and are illustrated below.



The lactonisation of many monocyclic and acyclic nonconjugated diolefinic acids has been recorded,[41] in which lactonisation is accompanied by intramolecular alkylation. The order in which the cyclisation steps occur can often be inferred from the stereochemistry and structure of the product. Thus, the acid (31) could yield the lactone (32) by either a concerted or non-concerted alkylation–lactonisation process, whereas the actual product (33) cannot be formed by a concerted process but must arise *via* the carbonium ion (34), formed from the ion (35) either by a 1,2-hydride ion shift or *via* the $\Delta^{1,8a}$ or $\Delta^{8a,9a}$ olefin.



Cyclisation[42] of geranylacetic acid (36) with phosphoric acid at 25° gives a separable mixture of the epimeric lactones (37 and 38) with the *cis*-isomer (37) predominating, indicating that the reaction is essentially non-concerted, but that steric factors are important. However, it is possible that the reaction is concerted and that the *trans*-product is then mainly



[40] (*a*) Schutte and Basanowsky, *Pharm. Zentralhalle*, 1959, **98**, 403; (*b*) Jacobs, Danker, and Danker, *J. Amer. Chem. Soc.*, 1958, **80**, 864; (*c*) Roedig, Kleppe, and Markl, *Chem. Ber.*, 1962, **95**, 1245.

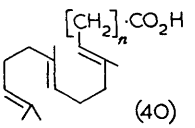
[41] Mousseron-Canet and Mousseron, *Compt. rend. congr. internat. chim. et. ind.*, 31e Liège (published as *Ind. chim. belge*, (suppl. 1952, **2**, 625) cf. *Chem. Abs.*, 1960, **54**, 10966.

[42] Mondon and Teege, *Chem. Ber.*, 1958, **91**, 1020; Mondon and Erdman, *Angew. Chem.*, 1958, **70**, 399.

epimerised to the *cis*-product. The same acid (36) with sulphuric acid at 60° yields the isomeric γ-lactones, with epimer (39) predominating.

Lactonisation of Triolefinic Acids.—Many of the early studies of the cyclisation of triolefinic acids were made under conditions where either kinetic or thermodynamic control of the reaction may have been operating, and interpretation of the origin of the mixed isomers is not always possible. Furthermore, many of the acids were obtained by dehydration of β-hydroxy-esters,[5a,43] thus leading to uncertainty as to the position of the ethylene linkage.

Cyclisation of farnesylacetic acid (40; $n=2$)[22,44] and homofarnesylic acid (40; $n=1$)[29a] in the presence of formic and sulphuric acid leads mainly to the products (41; $n=2$) and (41; $n=1$), respectively, derived from a nearly concerted series of additions to the ethylene linkages, although in the latter other stereoisomers were also isolated when sulphuric acid was present.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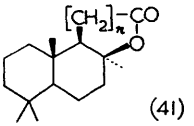
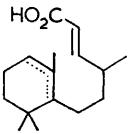
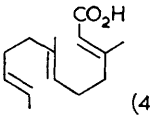
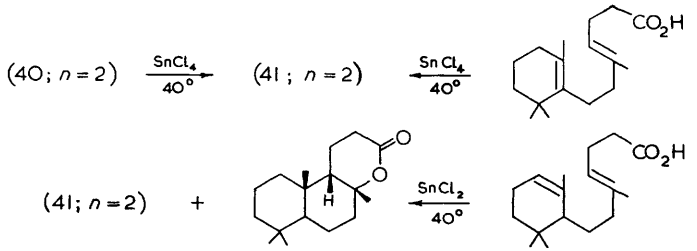

(41)

The failure[29b] of the αβ-conjugated isomers of "α"- and "β"-monocyclohomofarnesylic acid (42) to cyclise under the conditions where the β-non-conjugated isomer and farnesic acid (43) react is due to steric and electronic factors being unfavourable for a concerted or near-concerted reaction.


(42)


(43)

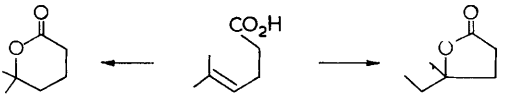
Lewis-acid catalysis has been little used in lactonisations but is important since in some cases[22] it is possible by choice of reaction conditions to arrest the cyclisations at different stages and thus identify possible intermediates.



Skeletal Rearrangements during Lactonisation of Olefinic Acids.—Although the occurrence of skeletal rearrangement during lactonisation in

[43] Trebolet, Gamboni, and Schinz, *Helv. Chim. Acta*, 1958, **41**, 1589; 1962, **45**, 1036.
[44] Dietrich and Lederer, *Helv. Chim. Acta*, 1952, **35**, 1148.

complex systems has been known for some time (see below) it has recently been observed in simple systems. Thus, although 5-methylhex-4-enoic acid (45) with cold concentrated sulphuric acid yields[1c,3b] the expected δ-methyl-δ-hexanolactone (44), treatment with boiling 50% sulphuric acid yields[1c] γ-methyl-γ-hexanolactone (46) as the main lactonic product.



(44) (45) (46)

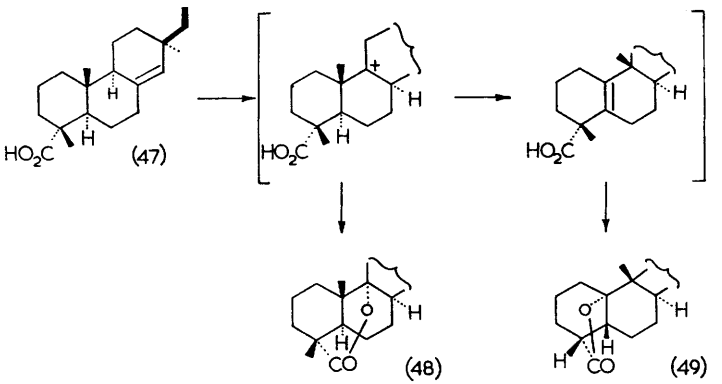
This rearrangement can be rationalised by the following reaction sequence, which involves the rearrangement of a tertiary carbonium ion to a secondary carbonium ion and the subsequent migration of a methyl group. A similar mechanism has been suggested[45] for the aluminium chloride catalysed rearrangement of 2-chloro-2-methyl[2-C^{14}]butane to 2-chloro-2-methyl[3-C^{14}]butane.

$$(CH_3)_2C{=}CH{\cdot}[CH_2]_2{\cdot}CO_2H \overset{H^+}{\rightleftharpoons} (CH_3)_2\overset{+}{C}{\cdot}CH_2{\cdot}[CH_2]_2{\cdot}CO_2H \overset{H\curvearrowright}{\rightleftharpoons}$$

$$(CH_3)_2\overset{+}{C}H{\cdot}CH{\cdot}[CH_2]_2{\cdot}CO_2H \overset{CH_3\curvearrowright}{\rightleftharpoons} CH_3{\cdot}\overset{+}{C}H{\cdot}\overset{CH_3}{\overset{|}{C}}H{\cdot}[CH_2]_2{\cdot}CO_2H \overset{H\curvearrowright}{\rightleftharpoons}$$

$$CH_3{\cdot}CH_2{\cdot}\overset{CH_3}{\overset{|}{\overset{+}{C}}}{\cdot}[CH_2]_2{\cdot}CO_2H \rightleftharpoons (46).$$

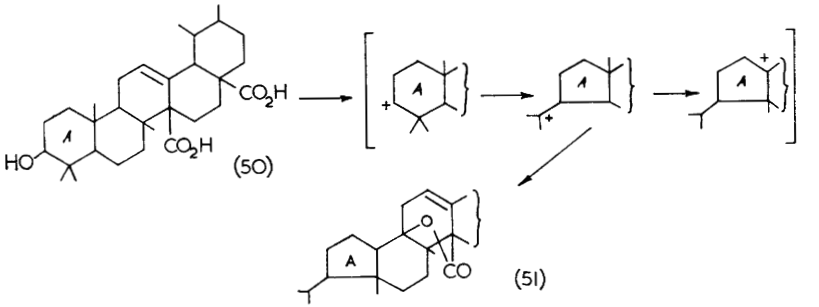
Examples of rearrangements in more complex systems are observed in the lactonisation of dihydroabietic acid[46] and of dihydro- and iso-pimaric acid.[47] In these cases the initial protonation is followed by a methyl shift (12→13), as is illustrated below for dihydropimaric acid (47→48 + 49).



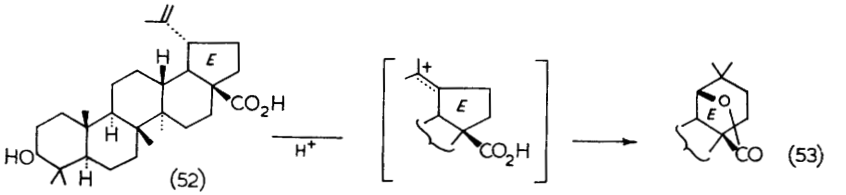
(47) (48) (49)

[45] Roberts, McMahon, and Hine, *J. Amer. Chem. Soc.*, 1950, **72**, 4237.
[46] Subluskey and Sanderson, *J. Amer. Chem. Soc.*, 1954, **76**, 3512.
[47] Wenkert, *Chem. and Ind.*, 1955, 282; *J. Amer. Chem. Soc.*, 1958, **80**, 2912.

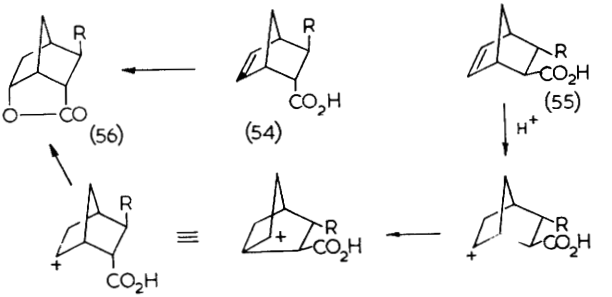
More extensive rearrangements have been observed in the triterpene series; thus[48] quinovic acid (50) on treatment with either concentrated sulphuric acid or zinc chloride in acetic acid yields novic acid (51), probably *via* the route indicated.



Another example is the action of acid on betulic acid (52) in which[49] lactonisation is accompanied by expansion of ring E, resulting in the formation of lactone (53).



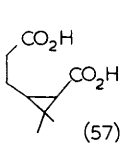
Owing to the possibility of rearrangement occurring, lactonisation is not always applicable to the determination of the *exo-* or *endo*-nature of substituents in various bridged ring compounds. Thus, the Diels–Alder adducts from cyclopentadiene and alk-2-enoic acids might be expected to lactonise only if the carboxyl group occupies the *endo* (axial) position. However, both the *endo-* (54) and the *exo-* (55) isomer yield the same lactone (56), because of rearrangement both in acid-catalysed reaction[50]



[48] Barton and de Mayo, *J.*, 1953, 3111.
[49] Davy, Halsall, and Jones, (*a*) *Chem. and Ind.*, 1951, 233; (*b*) *J.*, 1951, 2696.
[50] Beckmann, Schaber, and Bamberger, *Chem. Ber.*, 1954, **87**, 997; McBee, Hsu, and Roberts, *J. Amer. Chem. Soc.*, 1956, **78**, 3389.

and on bromo-lactonisation;[51] but iodo-lactonisation[51] succeeds only with the *endo*-isomer.

Lactonisation During Carbonium-ion Rearrangements.—From the preceding discussion it is apparent that protonation of olefinic acids leads to a carbonium ion which may yield a lactone directly or after an initial rearrangement. It follows, therefore, that lactonisation should occur however the carbonium ion arises, provided that a carboxyl group is suitably situated within the molecule. Thus the acid-catalysed ring opening of the cyclopropane-[52] and cyclobutane-carboxylic acids[53] (57 and 58) leads to the lactones (59) and (60), respectively. Other examples are found[54] among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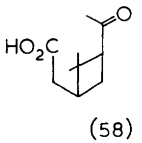
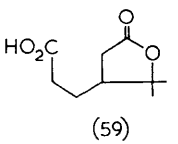
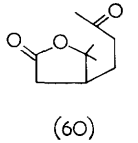
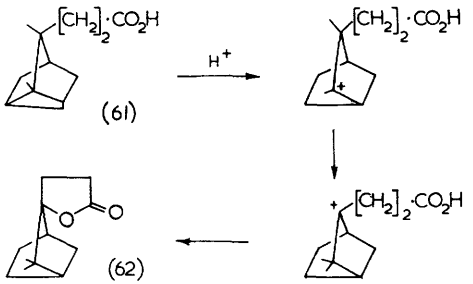

(58)

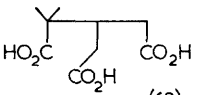

(59)

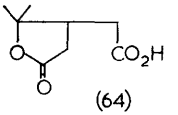

(60)

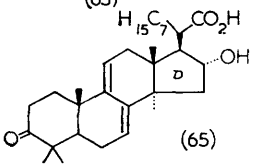
the bridged-ring terpenes. Thus the acid (61) in the presence of formic acid and sulphuric acid yields the lactone (62).

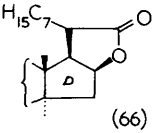

(61) (62)

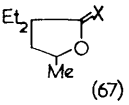
The nitrous acid deamination of (+)-γ-aminovaleric acid[55] yields (−)-γ-valerolactone *via* the γ-carbonium ion rather than by way of the γ-hydroxy-


(63)


(64)


(65)


(66)


(67)

[51] Ver Nooy and Rondestvedt, *J. Amer. Chem. Soc.*, 1955, **77**, 3583, 4878; Braendlin, Zielinski, and McBee, *ibid.*, 1962, **84**, 2109.

[52] Sandberg, *Arkiv. Kemi*, 1960, **16**, 255; Simonsen, *J.*, 1922, 2298; 1929, 305; Baeyer and Gratieff, *Ber.*, 1896, **29**, 2796.

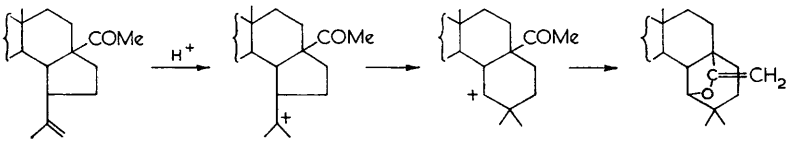
[53] Baeyer, *Ber.*, 1896, **29**, 32, 1907.

[54] Battacharyya, *Science and Culture*, 1947, **13**, 158; de Mayo "Mono- and Sesquiterpenoids", Interscience, New York, 1959.

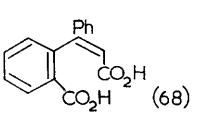
[55] Austin and Howard, *Chem. and Ind.*, 1960, 625; 1959, 1413.

acid. Also formation[56] of the lactone (64) on decarboxylation of the acid (63) may provide a further example as does the lactonisation with epimerisation at C-16 of 16α-hydroxy-3-oxo-20-isoeburico-7,9(11)dien-21-oic acid (65→66) in the presence of thionyl chloride.[57]

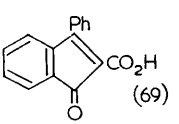
Cognate Cyclisations.—As might be expected from the mechanism of lactonisation of unsaturated acids and esters a variety of analogous cyclisations occur. Thus, unsaturated amides with bromine yield cyclic quaternary immonium salts;[58] unsaturated nitriles or amides[59] (*e.g.* 2,2-diethylpent-4-enonitrile and the corresponding amide) with sulphuric acid yield the imine (*e.g.* 67; X=NH) which can be hydrolysed to the lactone (67; X=O). Suitable unsaturated ketones[49] under acid conditions yield cyclic vinyl ethers as illustrated by the partial formulae below.



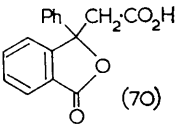
Cycloalkenone Formation.—Whereas lactonisation of an olefinic acid is an isomerisation, the formation of a cycloalkenone from an olefinic acid (see p. 211) is an overall cyclodehydration reaction. As expected, the more vigorous dehydrating agents or conditions lead to a higher proportion of ketone, the reaction apparently being irreversible. As mentioned earlier, sulphuric acid, the most frequently used lactonising agent, generally promotes ketone formation from alkenoic acid to only a small extent although under comparable conditions the intramolecular acylation of β- and γ-arylalkanoic acids[2] often proceeds in good yield. Intermediate between these two extremes is the action[60] of sulphuric acid on β-*o*-carboxyphenylcinnamic acid (68) which yields approximately equal amounts of ketone (69) and lactone (70).



(68)



(69)

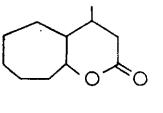


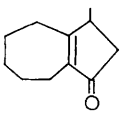
(70)

Johnson and his co-workers[7] have given many examples of the conversion of olefinic acids into lactones by the action of hydrogen chloride in acetic acid, whereas cycloalkenones may be obtained either from the lactones, or directly from the acids, by the action of zinc chloride in acetic acid–acetic anhydride, presumably as a result of the greater de-

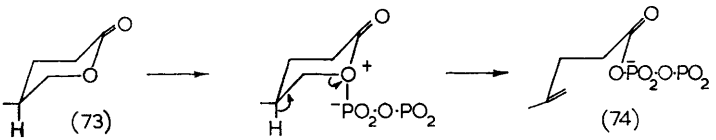
[56] Tiemann, *Ber.*, 1896, **29**, 2612.
[57] Bowers, Halsall, and Sayer, *J.*, 1954, 3070.
[58] Craig, *J. Amer. Chem. Soc.*, 1952, **74**, 129.
[59] Raffauf, *J. Amer. Chem. Soc.*, 1952, **74**, 4460.
[60] Marsili, *Ann. Chim. (France)*, 1961, **51**, 237.

hydrating power of the latter reagent. A given reagent generally leads to a higher yield of ketone as the reaction temperature is increased. Thus,[1c] whereas oct-4-enoic acid with polyphosphoric acid at 50° yields mainly the γ- and δ-lactones, as the temperature is raised to 100° the yield of cycloalkenone increases at the expense of the δ-lactone. The action of hot acids, especially polyphosphoric acid,[9] on δ-lactones (*e.g.* 71) has been used in the preparation of cycloalkenones (*e.g.* 72). γ-Lactones behave similarly when heated with polyphosphoric acid or phosphorus pentoxide.[61]

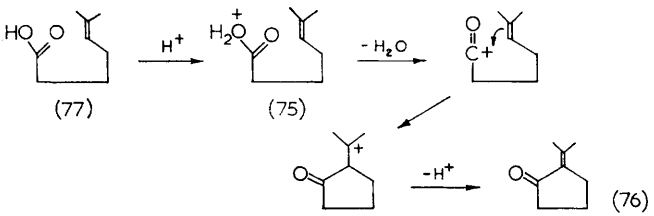

(71)


(72)

Lactonisation has been postulated[9c] as an intermediate step in the formation of cycloalkenones from olefinic acid since lactonisation occurs more easily (*i.e.* at a lower temperature) than ketone formation. This, however, seems unlikely as several examples are known[7a] of higher yields of ketones being obtained from the olefinic acid than from the corresponding lactone, suggesting in fact that conversion of lactones into ketones proceeds *via* the unsaturated acid. A mechanism for this step (73→74) has been suggested[9a,b] but various other mechanisms involving carbonyl co-ordinated species[13] are possible.


(73) (74)

It has been suggested[1a,61] that cycloalkenone formation occurs *via* an acylium ion, presumably formed, since[13] protonation of carboxylic acid derivatives normally occurs at the carbonyl oxygen atom *via* the less favoured species (75),[62] as is illustrated below for the formation[1a] of 2-isopropylidenecyclopentanone (76) from 6-methylhept-5-enoic acid (77).[1a] Thus in strong acid, such as polyphosphoric acid, the reactions of olefinic acids and the corresponding lactones are qualitatively the same.


(77) (75) (76)

Effect of Reagent and Reaction Conditions.—The intramolecular acylation of olefinic acids by polyphosphoric acid or sulphuric acid yields only five-

[61] La Forge and Barthel, *J. Org. Chem.*, 1945, **10**, 222; Gupta and Deshapande, *J. Indian Chem. Soc.*, 1953, **30**, 23; Achmad and Cavill, *Proc. Chem. Soc.*, 1963, 166.
[62] Halsall, Meakins, and Swayne, *J.*, 1953, 4139.

and six-membered cyclic ketones irrespective of the relative positions of the carboxyl group and the double bond, indicating that the double bond migrates freely both towards and away from the carboxyl group.[1a,b,c] Reactions at low temperatures (*ca.* 50°) indicate the preferential formation of exocyclic unsaturated ketones.[1b,c] It has been shown that isomerisation of the latter class of compounds to endocyclic unsaturated ketones occurs in acid solution at higher temperatures.[63] At room temperature the ultraviolet spectra of exo- and endo-cyclic unsaturated ketones are markedly different[64] and very little if any interconversion occurs. At higher temperatures (*ca.* 100°) in polyphosphoric acid formation of cycloalkenone is virtually irreversible and very little interconversion between rings of different size is apparent.[1b]

Trifluoroacetic anhydride effects the intramolecular acylation of certain olefinic acids,[12] probably *via* a mixed anhydride which breaks down to give the acylium ion of the olefinic acid:

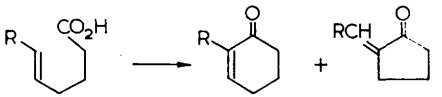
$$R{\cdot}CO_2H + (CF_3{\cdot}CO)_2O \rightarrow R{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CF_3 + CH_3{\cdot}CO_2H$$

$$\downarrow$$

$$RCO^+ + {}^-O{\cdot}CO{\cdot}CF_3.$$

No decision can at present be made as to the mechanism of the reaction, but the presence of non-fluorinated anhydrides has been established.[1b,c]

The reaction conditions are such that double-bond migration does not occur (trifluoroacetic acid, a by-product of the reaction only promotes double-bond migration slowly and at elevated temperatures[1d,65]) and cyclisations have, with one exception, only been effected with alk-5-enoic acids (78), which when R=Me or Et yield mixtures of the corresponding 2-alkylcyclohex-2-enone (79) and 2-alkylidenecyclopentanone (80). With hex-5-enoic acid (78; R=H) only cyclohex-2-enone (79; R=H) is iso-



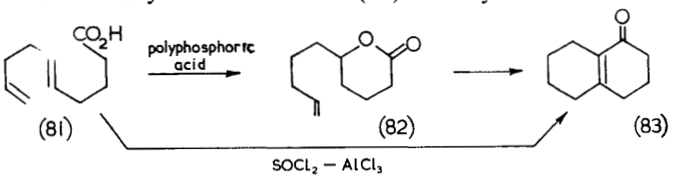
(78) (79) (80)

lated,[12,1b] probably due to the instability of 2-methylenecyclopentanone.[66] The cyclisation of hept-6-enoic acid[1b] with trifluoracetic anhydride yielded cyclohept-2-enone (10%). The unstable[66] isomeric 2-methylenecyclohexanone was not detected. This is the first example of the formation of a seven-membered ring by the intramolecular acylation of an alkenoic acid.

Ketones from Diolefinic Acids.—The direct conversion of a diolefinic acid (81) into a bicyclic ketone (83) has not been observed,[67] only the lactone (82) being isolated, which could in turn be converted into the

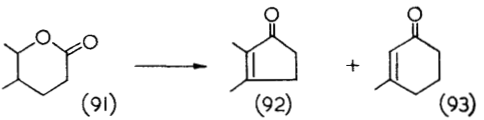
[63] Brown, Brewster, and Schecter, *J. Amer. Chem. Soc.*, 1954 **76**, 467.
[64] Palmer and Urch, *J.*, 1963, 174.
[65] Peterson and Allen, *J. Org. Chem.*, 1962, **27**, 1505.
[66] Erskine and Waight, *J.*, 1960, 3425.
[67] Ansell and Ducker, *J.*, 1960, 5219.

octalone (83). However, the corresponding acid chloride on treatment with aluminium chloride yields the octalone (83) in low yield.[67]

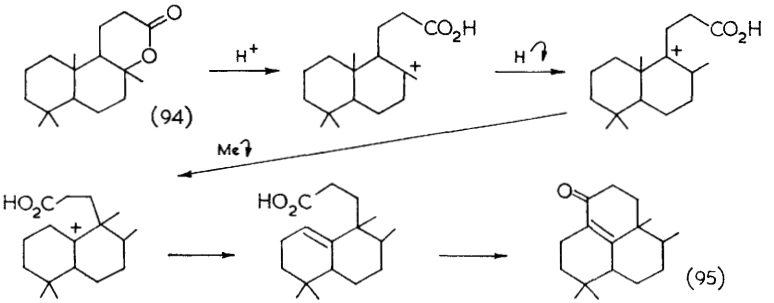


Recently,[68] the action of acetic anhydride containing small amounts of acidic compounds such as zinc chloride, aluminium chloride, stannic chloride, or sulphuric acid has been shown to convert alka-2,4-dienoic acids (89) into phenols (90). This reaction can clearly be considered as the formation of a cyclohexadienone followed by enolisation.

Rearrangements during Ketone Formation.—Just as carbonium-ion rearrangements occur in the lactonisation of olefinic acids, they can also be observed in the formation of ketones from olefinic acids or the related lactones. Thus the action[1c] of hot 50% sulphuric acid on γ-methyl-δ-hexanolactone (91) yields besides the expected 2,3-dimethylcyclopent-2-enone (92) appreciable quantities of 3-methylcyclohex-2-enone (93). The formation of the latter clearly involves the migration of a methyl group, and is related to the rearrangements associated with 5-methylhex-4-enoic acid discussed on p. 219.



Ambreinolide (94) in the presence of hot 80% sulphuric acid yields[69] the perinaphthene derivative (95). This reaction can be interpreted as illustrated below.



[68] Chiusoli and Agnes, *Proc. Chem. Soc.*, 1963, 310.
[69] Buchi, Saar and Eschenmoser, *Experientia*, 1956, **12**, 136.