492. *The Lactonisation of Olefinic Acids: the Use of Sulphuric and Trifluoroacetic Acids.*

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The lactonisation of a variety of pentenoic, hexenoic, heptenoic, and octenoic acids by sulphuric and trifluoroacetic acid has been studied. Boiling 50% v/v sulphuric acid gives γ-lactones and small amounts of δ-lactones and cyclic ketones; under these conditions δ- is partly isomerised to γ-hexanolactone. Cold concentrated sulphuric and hot (150°) trifluoroacetic acid give mixtures of γ- and δ-lactones, the proportions of which vary with the position of the ethylenic linkage; with the latter reagent, migration of this linkage is slow.

Fittig[1] observed that hot aqueous sulphuric acid converted straight-chain alk-3- and -4-enoic acids into the corresponding γ-lactones; these observations were confirmed and extended by Linstead *et al.*[2-5] who showed that δ-lactones may be formed in certain reactions, particularly from 5,5-dialkylalk-4-enoic acids; further, contrary to earlier observations, alk-2-enoic acids are also lactonised[2] under these conditions, but more slowly. The relative rates of lactonisation of the various alk-*x*-enoic acids were explained[2] qualitatively in terms of prototropic shifts to give alk-3- or -4-enoic acids (slow reactions), followed by a relatively fast lactonisation.

Thus hex-2- and -3-enoic acids were reported[2] to give pure γ-hexanolactone, and hex-5-enoic acid gave impure δ-hexanolactone,[5] although, with the latter acid, cold aqueous sulphuric acid gave a high proportion of unidentified material of a very soluble or volatile nature. It has since been shown[6] that in similar reactions with polyphosphoric acid cyclic ketones and γ- and δ-lactones are formed, although the proportion of δ-lactone decreases markedly as the reaction temperature is increased.

We have reinvestigated many of the reactions described above, in order to determine more precisely the nature of the lactonic product and to determine the extent of formation of cyclic ketones. A variety of pentenoic, hexenoic, heptenoic, and octenoic acids have been used with sulphuric and trifluoroacetic acid as catalysts; the products obtained, as identified by gas chromatography and infrared spectroscopy, are shown in Tables 1—3.

Reactions of alkenoic acids under these conditions[2-5] gave as the predominant lactonic product the corresponding γ-lactone. The formation of substantial quantities of δ-lactones from olefinic acids of these types, under these conditions, is unlikely since similar treatment of δ-hexanolactone gave only a 41% recovery of lactonic material containing 97% of γ-lactone and 3% of δ-lactone (the implications arising from this isomerisation are discussed later). The observation[5] that hex-5-enoic acid yields mainly δ-hexanolactone under these conditions is therefore incorrect.

Comparison of the reactions of the alkenoic acids in trifluoroacetic acid with those in aqueous sulphuric acid at approximately the same temperature shows that a distinguishing characteristic of the former is the low yield of lactone (and ketone), except from alk-4-enoic acids. Under these conditions δ-hexanolactone is stable, thus explaining the dependence of the ratio of γ- to δ-lactone produced on the initial position of the ethylenic linkage. However, prolonged treatment of the δ-lactones at this temperature may lead to isomerisation, since hept-6-enoic acid in refluxing trifluoroacetic acid (internal temperature 80°) for 11 hours gave approximately equal amounts of γ- and δ-lactone, whereas hept-2-enoic

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[1] Fittig, *Ber.*, 1883, **16**, 373; *Ber.*, 1893, **26**, 40; *Annalen*, 1894, **283**, 47.

[2] Linstead, *J.*, 1932, 115.

[3] Linstead and Rydon, *J.*, 1933, 580.

[4] Boorman and Linstead, *J.*, 1933, 577.

[5] Linstead and Rydon, *J.*, 1934, 1995.

[6] Ansell and Coombs; Ansell, and Emmett, unpublished results.

and hex-5-enoic acids after 2 hours under these conditions gave δ- to γ-lactone ratios of 15 : 85 and 70 : 30, respectively, comparable with the results obtained at 150°.

For each olefinic acid the ratio of δ- to γ-lactone in the product is lower in reactions with concentrated sulphuric acid than with trifluoroacetic acid. Some of this difference probably results from preferential decomposition of the δ-lactone during the isolation (neutralisation) procedure. It was found, however, that δ-hexanolactone is converted into the γ-isomer under these conditions (Table 4), being about 25% isomerised during the reaction period used with these olefinic acids.

TABLE 1.

Cyclisation of alkenoic acids by refluxing 50% v/v sulphuric acid.

Acid	γ-Lactone (%)	δ-Lactone (%)	Total yield (%) of lactone *
Pent-4-enoic	100	0	49 †
trans-Pent-3-enoic	100	0	41 †
trans-Pent-2-enoic	100	0	17 †
Hex-5-enoic	98·4	1·6	50 ‡
trans-Hex-4-enoic	97·7	2·3	60 ‡
trans-Hex-3-enoic	97·9	2·1	65 ‡
trans-Hex-2-enoic	97·6	2·4	49 ‡
Hept-6-enoic	97·2	2·8	30 §
trans-Hept-5-enoic	96·0	4·0	44 §
trans-Hept-4-enoic	92·7	7·3	38 §
trans-Hept-2-enoic	93·0	7·0	28 §
trans-Oct-6-enoic	97·1	2·9	69 ¶
trans-Oct-5-enoic	96·3	3·7	50 ¶
trans-Oct-4-enoic	97	3	22 ¶
trans-Oct-2-enoic	>99	<1	23 **

* In the following footnotes, I is 2-methylcyclohex-2-enone, II is 2-ethylcyclopent-2-enone, III is 2-ethylidenecyclopentanone, IV is 2-ethylcyclohex-2-enone, V is 2-propylcyclopent-2-enone, VI is 2-propylidenecyclopentanone, and VII is 2-ethylidenecyclohexanone. † No ketones formed. ‡ Trace of cyclohex-2-enone formed. § 3—6% of I and/or II, and a trace of III formed. ¶ Traces of IV and V, 3—8% of VI, and 3—8% of VII formed. ** Traces of VI and VII formed.

TABLE 2.

Cyclisation of alkenoic acids by trifluoroacetic acid at 150°.†

Acid	Lactones γ- (%)	δ- (%)	Total (%) *
Hex-5-enoic	16·3 (18)	83·7 (82)	28 (28) ‡
trans-Hex-4-enoic	64·3 (83·9)	35·7 (16)	95 (34)
trans-Hex-3-enoic	ca. 95	ca. 5	3 §
trans-Hex-2-enoic	0	0	0
Hept-6-enoic	12 (17)	88 (82)	11 (5) ¶
trans-Hept-5-enoic	4·5	95·5	32 ¶
trans-Hept-4-enoic	56·7 (73)	43·3 (27)	77 (81) **
cis-Hept-4-enoic	77 (75)	23 (25)	56 **
trans-Oct-6-enoic	24·8	75·2	4 ††
trans-Oct-5-enoic	6 (17)	94 (83)	42 (27) ‡‡
trans-Oct-4-enoic	62 (69)	38 (31)	71 (61) §§
cis-Oct-4-enoic	78·9 (76)	21·1 (24)	72[8]

* For I—VII below, see Table 1. † The main figures refer to the gas-chromatographic analysis of the reaction product after removal of trifluoroacetic acid by distillation. Figures in parentheses refer to material obtained after removal of trifluoroacetic acid by neutralisation with sodium hydrogen carbonate. ‡ Cyclohex-2-enone (3%) formed. § Cyclohex-2-enone (1%) formed. ¶ I, II, and III (total 2%) formed. ** I, II, and III (total 1%) formed. †† VII (4%), VI, and/or V (2%) formed. ‡‡ VII (4%) ,VI, and/or V (2%) formed. §§ VII (3%), VI, and/or V (1%) formed.

Intramolecular Acylation.—The formation of cyclic ketones, in small proportion, occurs with each cyclising agent (Tables 1—3). At similar temperatures polyphosphoric acid-catalysed cyclisations lead[6] to a far higher ketone : lactone ratio; it is probable that acylium ions which are precursors to ketone formation, are largely destroyed in sulphuric acid as a result of self-ionisation of the solvent:[7]

$$2H_2SO_4 \rightleftharpoons H_3O^+ + HS_2O_7^-;\ RCO^+ + H_3O^+ \longrightarrow R{\cdot}CO_2H_2^+ + H^+$$

Lactonisation.—Cyclisation of alk-4-enoic acids may lead to γ- or δ-lactones without migration of the ethylenic linkage or rearrangement of the derived carbonium ion. In experiments with these acids under conditions where the δ-lactone is sufficiently stable to be formed in the final product in reasonable amounts, the γ-lactone is the preferred product, irrespective of the length of the carbon chain or the cyclising reagent (cold concentrated sulphuric acid or hot trifluoroacetic acid). It is improbable that the marked preference for the formation of the 5-membered ring arises either from the greater instability of δ- than of γ-lactones, or from the differential inductive effects of the substituents (methyl, ethyl, or n-propyl compared with 2-carboxyethyl), although such factors must have some effect, the former being slightly offset by the latter. An alternative explanation, based on the geometry of the transition state of the lactonisation, seems probable; consideration of the probable reaction mechanism provides such an explanation.

TABLE 3.

Cyclisation of alkenoic acids by concentrated sulphuric acid at 20°.

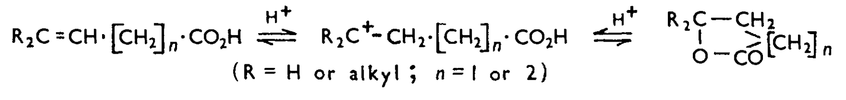
Acid	Lactones γ- (%)	δ- (%)	Total yield (%)
Hex-5-enoic	31	69	33 *
trans-Hex-2-enoic	0	0	Negligible
Hept-6-enoic	32	68	43 †
trans-Hept-5-enoic	41	59	—†‡
trans-Hept-2-enoic	~99	*ca.* 1	—†‡
Oct-7-enoic	33	67	43§
trans-Oct-6-enoic	44	56	30§
trans-Oct-5-enoic	44	56	12§
trans-Oct-4-enoic	62	38	19§

* Cyclohex-2-enoic (7%) formed. † Traces of unidentified ketones formed. ‡ Yield not determined. § Traces of 2-ethylcyclohex-2-enone, 2-propylcyclopent-2-enone, 2-propylidenecyclopentanone, and 2-ethylidenecyclohexanone were formed.

TABLE 4.

Equilibration of γ- and δ-hexanolactones in concentrated sulphuric acid.

Reaction period (hr.)	Neutral fraction Recovery (%)	Neutral fraction δ : γ-Lactone ratio	Acid fraction δ : γ-Lactone ratio
2	21	72/28	—
18	23	40/60	88/12
24	21	31·6/68·4	89/11
96	27	33·1/66·9	93/7



$$R_2C{=}CH{\cdot}[CH_2]_n{\cdot}CO_2H \overset{H^+}{\rightleftharpoons} R_2\overset{+}{C}{-}CH_2{\cdot}[CH_2]_n{\cdot}CO_2H \overset{H^+}{\rightleftharpoons} R_2C{-}CH_2{\cdot}[CH_2]_n{\cdot}CO{-}O\ (\text{ring})$$

(R = H or alkyl; *n* = 1 or 2)

During lactonisation of olefinic acids, where bond migration is a prerequisite, the transient formation of carbonium ions is reasonable. The high dependence of γ : δ-lactone ratio on the initial position of the ethylenic linkage (Table 2) indicates rapid cyclisation of the ion to the lactone. It is probable that the rate-determining step in the overall process olefinic acid ⟶ lactones is the localisation of positive charge at positions where lactonisation can occur (cf. ref. 2). For the alk-4-enoic acids, inspection of molecular models of the proposed transition state (see below),* leading to γ- and δ-lactones, shows

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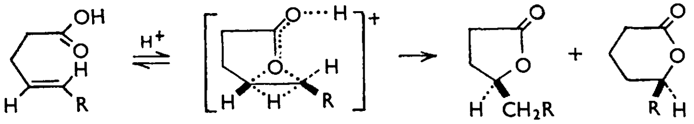
* A transition state similar to that proposed here has been suggested (Arnold, Campos, and Lindsey, *J. Amer. Chem. Soc.*, 1953, **75**, 1044) for the related halogeno-lactonisation.

[7] Leisten, *J.*, 1955, 298.

greater overlap between the $2p$ orbital of the carbonyl-oxygen atom and the vacant orbital of the γ-carbonium ion than with that of the δ-carbonium ion. In models of this type the carboxyl group is considered planar, bisecting the angle between the α-hydrogen atoms. Similar considerations explain the failure to obtain ε- and higher lactones from the octenoic and other acids. The possibility that similar reactions with suitable longer-chain olefinic acids may lead to the formation of large-ring lactones cannot, however, be excluded. Lactonisation of two alk-6-enoic acids with trifluoroacetic acid yields a lower proportion of δ-lactone in the resulting mixture than in comparable experiments with alk-5-enoic acids. These observations suggest that the double bond may migrate both by 1,3- and by 1,2-hydride-ion shifts.



EXPERIMENTAL

Materials.—*trans*-Pent-2-enoic and -hex-2-enoic acid were prepared by the Knoevenagel reaction,[8, 9] with pyridine as catalyst; similar reactions with triethanolamine as catalyst gave *trans*-pent-3-enoic and hex-3-enoic acid. In these products the absence of significant quantities of the *cis*-isomer or position isomers was apparent from their infrared spectra (cf. ref. 10). *trans*-Hex-4-enoic acid was prepared through pent-3-yn-1-ol,[11] 1-cyanopent-3-yne, and hex-4-ynoic acid; *trans*-hex-5-enoic acid was prepared from 5-chloropent-2-ene.[12] Oct-5- and -4-ynoic acids were prepared from hex-3-yn-1-ol [10, 13] and hept-3-yn-1-ol (cf. ref. 13), respectively, through their toluene-*p*-sulphonates by reaction with the sodium derivative of diethyl malonate and potassium cyanide. Reduction of these acids with sodium and liquid ammonia [10] (cf. ref. 14) and Lindlar catalyst [10] and hydrogen gave *trans*- and *cis*-oct-4- and -5-enoic acid, respectively.

δ-Hexanolactone was prepared from methyl acrylate [14] through 5-oxohexanoic acid, and γ-hexanolactone from β-methoxycarbonylpropionyl chloride [15] through methyl 4-oxohexanoate.[16]

Analytical Procedure.—The unpurified " neutral " and " acid " fractions (below) were examined by gas chromatography in a Pye argon chromatograph with poly(propylene sebacate) as stationary phase at 150° and 100° and an argon inlet pressure of 6 lb. in.$^{-2}$. In these conditions hydroxy-acids are converted into the corresponding lactones. The yields of lactonic and ketonic products were determined by gas chromatography of weighed samples of γ-pentanolactone as standard, the mean of three injections being taken. Calibration of the apparatus with weighed mixtures of γ- and δ-hexano- and -octano-lactones showed that little correction was necessary. The overall accuracy of these determinations is about $\pm 6\%$, but, in general, duplicate injections of the same mixture or mixtures from different experiments gave reproducibility of about $\pm 3\%$.

Lactonisation of Alkenoic Acids.—(*a*) *By boiling sulphuric acid* (50% v/v). A mixture of the alkenoic acid (2 g.) and sulphuric acid (20 ml.) was boiled for 15 min., cooled, and neutralised with sodium hydrogen carbonate and ice. Neutral materials were obtained by extraction with ether (4 × 100 ml.), and evaporation of the dried (Na_2SO_4) extract. Acidification of the aqueous solution followed by extraction with ether and evaporation of the dried (Na_2SO_4) extract gave the " acid fraction."

(*b*) *By concentrated sulphuric acid.* The alkenoic acid (2 g.) was dissolved in concentrated

[8] Linstead and Boxer, *J.*, 1931, 740.

[9] Linstead, Noble, and Boorman, *J.*, 1933, 557.

[10] Howton and Davis, *J. Org. Chem.*, 1951, **16**, 1405.

[11] Schulte and Reiss, *Chem. Ber.*, 1954, **87**, 964.

[12] Ansell and Brown, *J.*, 1950, 1788.

[13] Sondheimer, *J.*, 1957, 877.

[14] Nazarov and Zav'yalov, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1952, 300.

[15] Cason, *Org. Synth.*, Coll. Vol. III, p. 169.

[16] Cason and Prout, *J. Amer. Chem. Soc.*, 1944, **66**, 47.

sulphuric acid (97% w/v; 20 ml.) with external cooling. After 4 hr. at room temperature (*ca.* 20°) the mixture was separated into " neutral " and " acid " fractions as before.

(*c*) *By trifluoroacetic acid.* A solution of the alkenoic acid (2 g.) in trifluoroacetic acid (20 ml.) in a sealed tube was placed in a Carius furnace at 150° for 30 min. The resulting mixture was divided into equal portions: one portion was evaporated to constant volume at 30°/20 mm.; the other was treated with sodium hydrogen carbonate as above. The results obtained by the latter procedure are given in parentheses in Table 2.

Stability of γ- and δ-Lactones.—The δ-hexano- and γ-octano-lactones were treated with sulphuric or trifluoroacetic acid according to the procedure used with the alkenoic acids. Boiling sulphuric acid (50% v/v) converted δ-hexanolactone (1·55 g.) into a mixture (0·64 g., 41%) of γ- (97·4%) and δ-hexanolactone (2·6%); the equilibration of γ- and δ-hexanolactone with concentrated sulphuric acid is recorded in Table 4. δ-Hexanolactone was recovered unchanged on treatment with trifluoroacetic acid. γ-Octanolactone (2 g.) in concentrated sulphuric acid gave a mixture (1·61 g., 81%) of γ- (96·4%) and δ-octanolactone (3·6%).

The authors are indebted to the following: Dr. R. V. Coombs (for the supply of hept-6-, -5-, and -2-enoic acid and γ- and δ-heptanolactone); Dr. P. R. Huddleston (pent-4-enoic acid); Mr. J. C. Emmett (*cis*- and *trans*-hept-4-enoic, *trans*-oct-6-enoic, and oct-7-enoic acid), and for his assistance in the preparation of *cis*- and *trans*-oct-4- and 5-enoic acid and γ- and δ-octanolactone; the D.S.I.R. for an award (to M. H. P.); and the Royal Society for financial assistance.

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[*Received, October* 19*th*, 1962.]