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EDWARD JAMES BOORMAN.

Royal College of Science.

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ABSTRACT OF THESIS.

"The formation of γ-lactones from αβ- and βγ-unsaturated acids; and associated reactions."

by E. J. Boorman.

No systematic work on the lactonisation of olefinic acids has been done since that of Fittig and his school, until the recent discoveries of Linstead on the various factors influencing the formation of the γ-lactone ring.

In the present work, this reaction has been studied for αβ - and βγ-butenoic, pentenoic, cyclohexene carboxylic acid and 3-methyl-cyclohexene carboxylic acids under standard conditions. This has shown the existance of a type of ring-chain tautomerism, named lacto-enoic tautomerism, not previously noted in βγ-acid -γlactone systems. The writer has also studied the addition of hydrobromic acid to the above acids and also to αβ- and βγ-isohexenoic acids, in various types of solvent; also in one case the mode of addition to the corresponding ester has been investigated. The γ-lactones obtained have been studied with respect to their equilibria with the corresponding hydroxy-acids. Parachor measurements have been made on the γ-lactone ring.

The work has necessitated the preparation of the pairs of acids studied in a pure state, and also of the various reference substances required. The existing methods have been used and improved and new methods devised.

The formation of γ-lactones from unsaturated acids appears to depend chiefly on the nature of the double bond as affected by substitution, and, to a less extent, on steric factors, the bending of the chain, and valency deflection. The addition of hydrogen bromide seems to depend solely on the nature of the unsaturated linkage and the type of solvent used, whether polar or non-polar.

The bearing of these results on the nature of the olefinic linkage is discussed.

"The formation of γ -Lactones from $\alpha\beta$ - and $\beta\gamma$ -

Unsaturated Acids; and associated reactions."

The experiments described in this thesis were carried out under the supervision of Dr. R. P. Linstead, in the laboratories of the Imperial College of Science and Technology, South Kensington, London, S. W. 7.

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SECTION 1.

INTRODUCTION.

The investigations that form the subject of this thesis have been undertaken in an attempt to throw some light upon the nature of the double bond. This has been essayed by a study of various addition reactions, and the olefinic acids constitute a particularly suitable field for this work. The chief practical advantages of the acids over other olefines as working materials lie: firstly, in the great accessibility of a wide range of homogeneous unsaturated compounds with varied types of alkyl substitution and known positions of the double bond; secondly, in the fact that both the acids, and nearly all the products obtained from them by the reactions studied, can be obtained as crystalline solids of definite purity, the latter also by independent syntheses; and thirdly, in the great ease of analysis and identification of the substances obtained from the experiments.

The reactions chosen for investigation were (i) the self addition reaction, resulting in the formation of lactone from the isomeric unsaturated acid by intra-molecular addition, and (ii), the heterogeneous addition reaction as typified by the addition of hydrogen bromide to the olefinic acids. Both these have been successfully used, while several other associated reactions have also received attention with a view to aiding the main study. These were, for the great part, concerned with the γ-lactone ring.

The following pages contain an account of the investigations into the reactivity of the olefinic linkage with particular attention to the two reactions (i) and (ii).

The investigations described in this thesis can be subdivided into three broad classes. They are:-

(i) The lactonisation of olefinic acids;

(ii) The addition of hydrobromic acid to the above acids in various solvents; and

(iii) A study of various properties of γ-lactones.

Since the time of Fittig and his school (1880-1894) no systematic work has been done on the formation of lactones from unsaturated acids, until the recent work of Linstead[1] concerning this reaction. The general relationships between $\beta\gamma$-acids and γ-lactones were mainly established by Fittig during the above period. In 1883[2] he showed that certain unsaturated acids could be lactonised by boiling with 50% (by volume) sulphuric acid, and later he emphasised[3,4] the fact that this reaction was confined to $\beta\gamma$-acids (and the one $\gamma\delta$-acid then known, allylacetic acid) but that $\alpha\beta$-acids were completely unaffected by the above treatment. Fittig strongly maintained this point in a communication to the "Annalen"[5] but adduced little actual experimental evidence to uphold his assertions. Indeed, he used this difference in reactivity as a method of analysis of mixed $\alpha\beta$-and $\beta\gamma$- acids. Subsequent work on systems containing a chain branched at the β-carbon atom has indicated that such $\alpha\beta$-acids readily yield lactones with hot 50% sulphuric acid. Instances of this latter fact are noted by Fichter[6] (and collaborators) working on β-methyl-$\alpha\beta$-pentenoic acid; Blaise and Luttringer[7] on various substituted acrylic acids; and more recently, Kon and Linstead[8] on β-ethyl-$\alpha\beta$-

pentenoic acid. It was concluded, however, that these reactions were all exceptions to the general rule.

In 1932, Linstead[1] proved that both $\alpha\beta$-n- and $\alpha\beta$-iso-hexenoic acids yielded large quantities of the corresponding γ-lactones if subjected to the above treatment, and the following pages contain several other examples of this reaction, effectively proving that Fittig was mistaken in his assumption.

The mode of addition of hydrogen bromide to olefinic acids has received attention in many isolated cases, as well as by Fittig during his very extensive researches on the unsaturated acids. He, however, used methods that have since been shown to yield unsatisfactory results, due chiefly to the fact that his usual method was to use a saturated aqueous solution of hydrobromic acid, and to isolate the bromo-acids so obtained, or to distil the addenda in steam and identify the products. It is interesting to note that this last method led to the discovery of γ-lactones as a class, as Fittig and Geisler[9] distilled in steam the addition product of hydrobromic acid and pyro-terebic ($\beta\gamma$-iso-hexenoic)acid and from the distillate isolated γ-iso-caprolactone, the first lactone to be recognised as such.

In 1880, Erlenmeyer senr.[10], and subsequently Fittig[11], discovered that $\alpha\beta$-acids added hydrogen bromide so the the bromine atom went exclusively to the β-carbon atom. Further extensive work by Fittig and his collaborators[12,13,14,15] confirmed this generalisation. Also it was discovered that, if $\beta\gamma$-acids

were allowed to react with hydrobromic acid, steam distillation of the product produced γ-lactones, and that the rate of addition varied with, and was increased by, alkyl substitution. Their bromo-acids could not be obtained solid, and Fittig recognised that the addition may not yield pure γ-bromo-acids, but mixtures of the β- and γ- isomerides, and stated this fact in the 1894[15] paper. A second reason for his failure to obtain even the pure bromo-acids solid is the fact that, in the presence of water, decomposition is facilitated, particularly in the sense γ-bromo-acid → γ-lactone.

The only other noteworthy work along these lines is that of Walker and Lumsden,[16] who found that undecylenic acid, (CH_2=CH(CH_2)$_8$.CO_2H) if dissolved in toluene, added hydrobromic acid to give the terminal bromo-acid [CH_2Br.CH_2(CH_2)$_8$.CO_2H], while in ethereal solution the preponderating reaction is that yielding the non-terminal acid, CH_3.CH(Br).(CH_2)$_8$.CO_2H. These results have since been confirmed by Chuit[17,18] and coworkers. Since this discovery, no other work bearing on the present investigation has been done.

Concerning the properties of lactones, very little earlier work appears to have been done. Hjelt[19,20] has carried out experiments in determining the speed of formation of γ-lactones from the corresponding γ-hydroxyacids in water under standard conditions, and has stated that γ-alkyl substitution increases the velocity of the change, which is a mono-molecular one. The conditions of Hjelt have been used as a basis for the present work, and have given results in fair agreement with

with those of the earlier worker.

Concerning the position of the equilibrium between the γ-lactones and the corresponding γ-hydroxyacids in aqueous solution, the work of Fittig[21] may be mentioned. He showed that γ-lactones (and δ-lactones) on heating with water, were converted into the corresponding hydroxyacids, and that these latter passed back into the lactones under the same conditions. He, however, made no accurate estimate of the position of the equilibrium. Henry[95] determined the position of the equilibrium for γ-butyrolactone in the cold in the presence of hydrochloric acid, and obtained a similar figure to that obtained from the present work.

Measurements have been made on parachor values for the lactones studied in order to ascertain whether the γ-lactone ring possessed a structural parachor, no similar measurements having been made previously.

The study of the above reactions and properties forms the subject of the present thesis, and the acids examined from this standpoint are: αβ- and βγ- Butenoic, pentenoic, iso-hexenoic, cyclo-hexene carboxylic, and γ-methyl cyclo-hexene carboxylic acids. The lactones corresponding to these acids have also been investigated, and are: γ-butyro-lactone, γ-valerolactone, γ-iso-hexolactone, cyclo-hexanolide 1:3 and 1-methyl cyclo-hexanolide 1:3.

SECTION 2.

THEORETICAL.

PREPARATIVE METHODS.

(a) ACIDS.

In the case of the aliphatic $\alpha\beta$ - and $\beta\gamma$ - acids the preparative methods used were those already perfected by workers in the field of three-carbon tautomerism, and which have been proved to yield pure products. The cyclic acids, however, were found to need further investigation.

The three $\alpha\beta$ -aliphatic olefinic acids were all obtained by the general method introduced by Doebner,[25] and Verley,[24] and developed by v. Auwers,[26] Goldberg and Linstead,[27] Boxer and Linstead[22] and others. Briefly, this is the condensation of the appropriate aldehyde with malonic acid under the catalytic influence of pyridine:-

$$R.CHO + CH_2(CO_2H)_2 \longrightarrow R.CH=CH.CO_2H$$

and has been shown in all cases to yield the $\alpha\beta$-unsaturated acid in a high state of purity.

The $\beta\gamma$-isomerides of the above acids were obtained by a variety of methods. $\beta\gamma$-Pentenoic acid was obtained by the condensation of propionaldehyde and malonic acid using as a catalyst, instead of pyridine, triethanolamine, tris(β-hydroxy ethyl)-amine, following the discovery of Boxer and Linstead,[22] the method having been further improved by Linstead and Noble.[23]

From the high fraction from the first distillation of this acid was obtained an oil which deposited white needles on long standing. This solid was purified and shown to be β-ethyl glutaric acid. This would appear to be formed either from some $\alpha\beta$-unsaturated compound by condensation with a further molecule

of malonic acid, or by simultaneous combination of two molecules of this acid with one of the aldehyde, subsequent decarboxylation yielding the substituted glutaric acid. This is formed in considerable quantity (c. 30% of the total), and accounts for the bad yield of pentenoic acid. Similar results for analagous condensations have since been obtained by Linstead and Noble[23] from the high residues from the preparation of βγ-butenoic and βγ-n-hexenoic acids.

βγ-Butenoic acid was obtained by the procedure of Linstead and Noble,[23] which is a considerably modified method of Bruylants and his coworkers,[30,31] and appears substantially better than the original method from the point of view of the purity of the product.

βγ-iso-Hexenoic acid was prepared from the αβ-isomer by boiling this acid with a large excess (9 mols.) of concentrated caustic potash solution until the equilibrium αβ-acid $\rightleftharpoons$ βγ-acid had been established, and subsequently obtaining the pure βγ-acid by partially esterifying the recovered and distilled acid to obtain pure βγ-iso-hexenoic ester. Hydrolysis of this in the cold by alkali yielded the pure βγ-acid.

All the acids resulting from the above preparations were obtainable as crystalline solids, and their general physical properties agreed very closely with those of the corresponding acids of the workers mentioned.

The preparation of the two pairs of homocyclic acids was found to need investigation before the acids could be

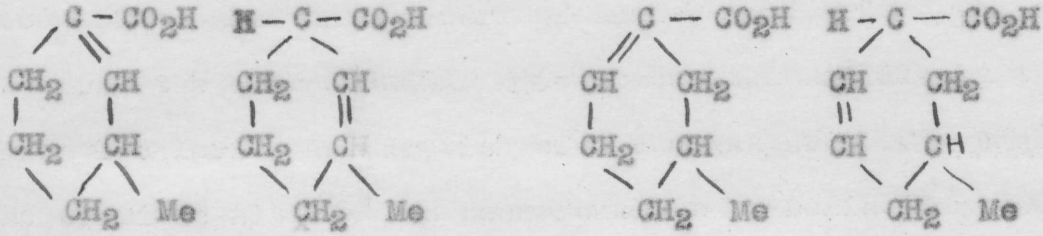
obtained pure.

Δ-1 cyclo-hexene carboxylic acid, (tetrahydrobenzoic acid), was originally obtained by Aschan[32] by the action of cold alcoholic potassium hydroxide solution on α-bromocyclo-hexane carboxylic acid, and later, by the equilibration of the βγ-isomeride by the action of caustic alkali. The equilibrium, he considered, was 100% αβ acid; actually it has been now shown to be 95.5% αβ acid. Aschan never obtained his acid as a solid due, probably, to contamination with the βγ-isomer. Einhorn,[33] by the reduction of dihydrobenzoic acid by sodium amalgam, obtained the acid in a slightly purer form melting at 29°.

None of these methods was adopted, the one finally used being based on the work of Ruzicka and Brügger,[34] who prepared the corresponding αβ-unsaturated nitrile by the thionyl chloride dehydration of the cyanhydrin of cyclohexanone. The olefinic nitrile has been found to hydrolise in good yield to the equilibrium mixture of αβ -and βγ-cyclohexene carboxylic acids, these being separable by partial esterification. By this process the αβ-acid was obtained in large white overlapping plates, melting at 38°. The βγ-isomer had also been investigated by Aschan,[35,36] who obtained it by the reduction of benzoic acid in hot alkaline solution by sodium amalgam in a current of carbon dioxide. This was repeatedly tried under Aschan's conditions, but only very poor yields of βγ-acid were obtained, much tautomeric change to the αβ-acid having occurred. Various modifications were also attempted, but these also failed.

Attention was then directed to a possible electrolytic reduction of sodium benzoate at a mercury kathode. Various conditions of current density, temperature, etc. were tried but all gave negative results. Eventually a considerably modified method of reduction by sodium amalgam, based on Asahan's original method, was found to be satisfactory, the final purification being achieved by the removal, by zinc dust in alcohol, of two atoms of bromine from the recrystallised $\beta\gamma$-dibromide prepared by addition of bromine to the crude reduction product. The pure acid had m.p. 7.0°.

The homologous m-methyl acids may exist in four isomeric forms differing in position of the double bond: viz.



Δ-1- Δ-2- Δ-6- Δ-5-

the acids required being Δ-1- and Δ-2-. All four acids have been prepared by Perkin[37,38] and his coworkers in the course of the synthesis of sylvestrene. The Δ-1- acid was prepared, mixed with the Δ-6-acid, by the dehydrobromination of the α-bromo-saturated acid, and their separation accomplished by fractional crystallisation of their calcium salts. Perkin did not obtain the acid quite pure. The method used in the following work was analagous to the preparation of the previous $\alpha\beta$-acid, i.e., by the hydrolysis of the unsaturated nitrile obtained by the dehydration of the cyanhydrin of mmethyl cyclohexanone. It was found that the ratio of the Δ-1-acid to the Δ-6-acid was

greatly in favour of the Δ-1-form, and so the method was adopted, final purification of the acid being effected by recrystallisation of the calcium salt[37], or by removal of 2Br from the 1:2 dibromo-acid, prepared from the impure acid and recrystallised. The acid is a solid forming large overlapping plates, m.p. 25-6°: also from a study of the three carbon systems of the acids, the ratio between the second αβ-form (Δ-6) and the corresponding βγ-form (Δ-5) will probably be of very much the same order as that in the case of αβ - and βγ-cyclo-hexene carboxylic acids, as the two systems are, for practical purposes, identical. In the case of the two acids required, Δ-1-and Δ-2-, the introduction of a γ-methyl substituent on the double bond will doubtless increase the amount of the Δ-2-acid present at equilibrium. Thus the βγ-acid formed from the alkaline hydrolysis will probably be almost entirely the Δ-2-form, the one required. There may, or may not, be an equilibrium between all four forms, but if there is the acid Δ-2 will act as a sink and cause a preponderance of the Δ-1-and Δ-2-acids in the mixture obtained. Actually the amounts of Δ-1-and Δ-2-are found to be the great portion of the mixture, so that the amount of the Δ-5-acid formed is probably negligeable.

The βγ-acid, Δ-2 was obtained by alkali equilibration of the acid(Δ-1), and purified by partial esterification. Unfortunately, this acid could not be finally purified in the usual way via the dibromide, as any attempt to prepare the latter involves a great loss of bromine as hydrobromic acid from the substance, and leaves an oil which is probably the β-bromo-γ-lactone. Other methods of purification, e.g. through the

p-toluidide, were not attempted as the acid was only available in very limited amount. However, the acid obtained contained, as a minimum, 95% of the 3-methyl-Δ-2-cyclohexene carboxylic acid, and was used as such.

(b) REFERENCE SUBSTANCES.

These substances were used in various ways, chiefly for the identification of products of reaction, and as a means checking analytical methods and results. They fall naturally into two classes: (i) Lactones; (ii) Bromo-acids and associated compounds.

(i) LACTONES.

The usual mode of preparation was from the γ-hydroxy-acids, whose constitutions have been proved beyond all doubt. Dehydration of these acids yields the corresponding γ-lactone:-

$$R.CH(OH).CH_2.CH_2.CO.OH \longrightarrow R.\underset{\displaystyle O}{\underset{|}{CH}}.CH_2.\underset{\displaystyle OC}{\underset{|}{CH_2}}$$

This method was used in all cases except that of γ-iso-hexo-lactone (see later). The methods of obtaining the hydroxyacid varied with the compound. Existing methods have been used, modified in some cases to improve the yield and purity of the final product.

γ-Valerolactone has been prepared by several workers, chief among whom can be cited Neugebauer[39] and Wolff.[40] Both these authors used as the basis of their preparation the formation of laevulic acid (γ-keto-valeric acid) by the action of hot hydrochloric acid on a carbohydrate, subsequent reduction of the keto acid to the γ-hydroxyacid by sodium amalgam, and ring-

closure in the way indicated above yielding γ-valerolactone. Vanino[41] advocates the use of starch to obtain laevulic acid, but this was found to lead to extensive charring, sucrose being a more generally satisfactory starting material. The elimination of water from the γ-hydroxyacid is usually very easy, indeed, so much so that it occurs spontaneously in some cases.

(11) γ-Butyrolactone was more difficult to obtain. The method of preparation of Fittig and Ström,[42] involving the alkaline hydrolysis of the product of condensation of ethylene chlor--hydrin and sodio-acetoacetic ester, as also described by Vanino[43] was found to give only a very poor yield of impure lactone. A somewhat similar method has been used by Johansson and Sebelius[96] and Traube and Lehrmann.[97] The method eventually adopted was based on the work of Frühling,[44] and is shown below:

$$OH(CH_2)_3OH \xrightarrow{HCl} OH.(CH_2)_3Cl \xrightarrow{KCN} OH.(CH_2)_3CN \xrightarrow{H_2O} OH.(CH_2)_3CO_2H$$

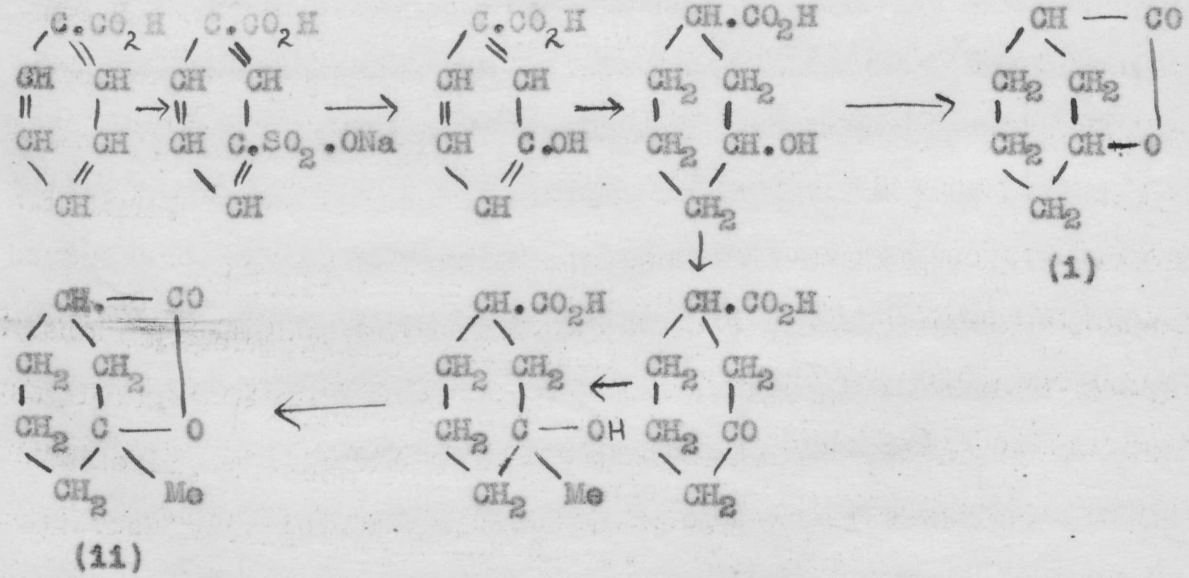
$$CH_2.CH_2.CH_2 \xrightarrow{-H_2O} O\text{—}CO \quad (11)$$

Various slight modifications were introduced; for instance, the chlorhydrin of the glycol, made by the method of Marvel and Calvery,[45] was used instead of the bromhydrin as recommended by Frühling.

γ-iso-Hexolactone was not prepared by the method of Bredt[98] (by permanganate oxidation of iso-hexoic acid) but very simply from βγ-iso-hexenoic acid by heating it to boiling for five hours, the conversion to lactone being practically complete in this time (Linstead[1]). The residual acid was removed by potassium carbonate and the pure lactone distilled.

For the dicyclic lactones, the methods of Perkin and

Tattersall[37,38] were used. The non-methylated lactone (i) was obtained in good yield from cis- 3-hydroxycyclohexane carboxylic acid by dry distillation (to eliminate water and cause ring-closure) the solid lactone being finally recrystallised. The saturated γ-hydroxyacid was made by reduction, by sodium in boiling alcohol, of m-hydroxybenzoic acid, itself obtained by the fusion of the m-sulphonic acid of benzoic acid with caustic alkali, using the modifications of Offerman.[46] The homologous lactone (ii), 1-methyl-cyclohexanolide 1:3, was also prepared from the cis-3-hydroxycyclohexane carboxylic acid by careful oxidation to the corresponding keto-acid, this esterified, and the pure 3-ketoester submitted to the Grignard reaction with methyl iodide. The product, 3-methyl-3-hydroxy-cyclohexane carboxylic acid, on dry distillation, yielded the lactone in the usual way. This was obtained as a crystalline solid, m.p. 45°, previous workers having obtained an oil. These methods are represented below:-



(ii) BROMO-ACIDS AND ASSOCIATED COMPOUNDS.

The reference compounds needed in this section were

β- and γ-bromoacids, which are the only possible products of direct addition of hydrobromic acid to olefinic acids.

In all cases the β-bromoacids were obtained in a pure state by the addition of hydrobromic acid gas to the pure αβ-olefinic acids, and were all obtained as solids. Similarly all the γ-bromoacids needed were prepared from the corresponding γ-lactones, the lactone ring being opened by means of hydrobromic acid. The two bromoesters required were prepared by esterification of the corresponding bromoacids by Wohlgemuth's[47] method, modifications being introduced as occasion arose.

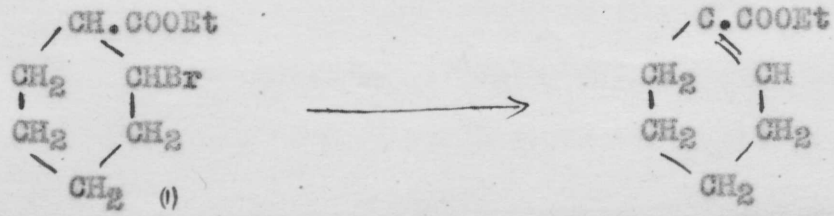
METHODS OF ANALYSIS AND IDENTIFICATION

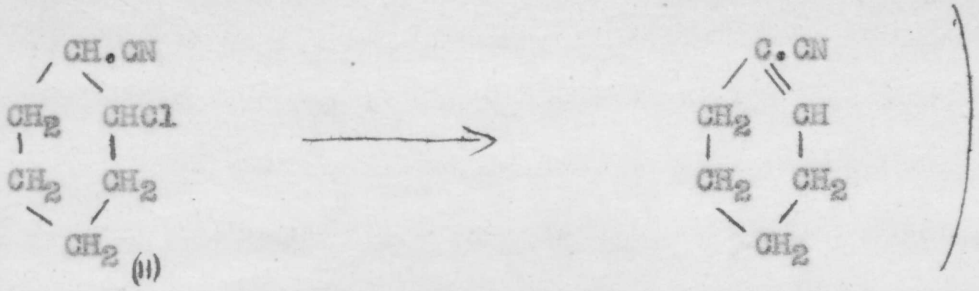
Mixtures of acid and lactone were estimated by the barium hydroxide method described by Linstead,[1] which was found to give very good results in all cases. The mixtures of isomeric acids were analysed as to their αβ- and βγ-acid components by either the iodimetric method of Linstead and May,[50] or by the modified bromometric method of Linstead and Noble.[23]

The analyses of mixtures of bromoacids varied with the acids used, but were based on the following principle: that heating an aqueous solution of the sodium or barium salt of a γ-bromoacid causes rapid, quantitative conversion to the γ-lactone, which can be estimated as such; while similar treatment of the salts of a β-bromoacid produces, (besides a certain small amount of unsaturated hydrocarbon) the β-hydroxy acid, probably via the β-lactone. The conditions were standardised. Attempts were made to estimate the amount of unsaturated

hydrocarbon evolved by collecting in chloroform and titrating with bromine solution, but with no success. The lactone formed from any γ-bromoacid present was also isolated semi-quantitatively, as a check on the titration method, and identified. In all cases the methods of analysis were controlled by reference to the pure bromoacids, obtained by independent syntheses.

In the case of the additions to the βγ-butenoic ester, the analyses were performed by semi-quantitative condensation of the bromoester with ethyl sodio-malonate by a new method, based on a reaction of Gabriel and Colman.[51] In several cases, an 85% yield of the pure dicarboxylic acid from the bromoester was obtained (cf. Montemartini[99]). This method was used in support of the evidence of the physical properties. A similar method was used to check the titration results in the case of the products of addition of hydrogen bromide to Δ-2-cyclohexene carboxylic acid. The addition product was esterified in the usual way, and the ester subjected to the above treatment. The β-bromoester[(i)] has been shown to lose hydrogen bromide quantitatively to yield the pure αβ unsturated ester (compare Cocker, Lapworth and Peters,[52] who have shown the great ease with which halogenated esters of this type lose hydrobromic acids in the above sense, and also the ease of removal of hydrogen chloride from 2-chloro-1-cyano-cyclohexane,[(ii)] which is seen to be an analagous reaction





(II)

The two (cis- and trans-) γ-bromoesters are quite unaffected by this treatment, and are recovered unchanged. Unfortunately, no method of analysis to determine the relative amounts of cis- and trans- acids present has yet been found.

The products obtained from the various reactions studied were all isolated in a pure state and identified. In the lactonisation experiments, The final mixtures of acid and lactone were separated through sodium bicarbonate and the recovered acid identified by physical property evidence, equivalent, halogen addition, and melting points. In the case of γ-valerolactone the technique of low temperature melting points had not at that time been perfected , and consequently a solid derivative was made from each sample of lactone. This was the amide of the γ-hydroxyacid which is formed by the opening of the lactone ring with ammonia. In all subsequent lactone work, the melting point, and melting point mixed with the pure reference lactone were used instead of the preparation of a solid derivative.

LACTONISATION EXPERIMENTS PERFORMED.

The acids mentioned in a previous section have been examined with respect to their tendency to form lactones under certain standard conditions. The conditions chosen were:

(1) Boiling the acid with five volumes of sulphuric acid

50% by volume, for a certain known period;

(ii) Allowing the acid to stand with five volumes of sulphuric acid, 60% by volume for a known time at about 20°;

(iii) Heating the acid, either alone or in an inert solvent.

At the end of an experiment the products of the reaction were isolated and investigated from the point of view of amount of lactone formed. The acid portion was also analysed for mixtures of $\alpha\beta$-and $\beta\gamma$-acids

The γ-lactones were also treated under the above conditions to ascertain whether reversal of lactonisation occurs or not.

From the work of Linstead it can be seen that two main factors appear to affect the tendency of an olefinic acid to lactonise: the polarisation of the double bond, and the "approach factor". In the present work some attempt has been made to separate these two effects by consideration of two pairs of acids (the cyclic acids) that contain a rigid framework, and in which the approach factor is probably considerably modified. Further consideration of the mechanism of the reaction has been deferred to the next section.

The next section (3) is devoted to a discussion of the results obtained and which are given at length in section 4. For the sake of convenience, a tabularised summary of the salient results obtained by treatment of the olefinic acids under the above lactonising conditions will inserted here.

Summary of lactonisation results.

Note: "Hot 50%" = Treatment with boiling sulphuric acid 50% by vol

"Cold 60%" = Treatment with cold sulphuric acid 60% by volume

F. = Conditions used by Fittig; m. = minutes; h. = hours;

d. = days; The recoveries quoted are of "pure" mixtures.

Acid. used.	Treatment.	% Recovery.	% Acid.	% Lactone.
αβ-Butenoic	Hot 50 F.	43	99.0	1.0
	" 60 m.	54	97.5	1.5
	Cold 60 7d.	94	99.0	0.5
βγ-Butenoic	Hot 50 F.	51	98.0	1.5
	60 m.	51	97.0	2.0
	Cold 60 4h.	90	98.0	2.0
	2 d.	71	98.0	2.0
	7d.	51	98.0	1.5
	Boiled in dekalin 24h.	91	99.5	0.5
αβ-Pentenoic	Hot 50 F.	73	63.5	35.0
	30 m.	60	6.5	93.0
	60 m.	58	1.5	97.0
	Cold 60 2 d.	91	95.0	3.0
	7 d.	-	97.0	2.5
βγ-Pentenoic	Hot 50 F.	55	4.5	94.5
	Cold 60 1 h.	79	84.5	15.0
	5 h.	77	41.0	57.5
	8 h.	58	19.5	79.5
	48 h.	-	5.5	95.0

Acid used.	Treatment.	% Recovery.	% Acid.	% Lactone.
Δ-1-cyclohexene	Hot 50 F.	92	97.5	1.5
carboxylic acid.	30 m.	46	90.0	8.5
	Cold 60 7 d.	59	97.5	2.0
Δ-2-cyclohexene	Hot 50 F.	73	35.0	63.0
carboxylic acid.	Cold 60 45 m.	46	89.5	10.0
	2 h.	33	73.5	26.0
	4 h.	25	11.0	88.5
	Boiled 60 m.		99.0	0.5
3-methyl-Δ1cyclo-	Hot 50 F.	81	98.0	2.5
hexene carboxylic	15 m.	71	96.5	2.0
acid	Cold 60 2 d.	100	99.0	0.0
	7 d.	85	99.5	1.0
3-methyl-Δ2cyclo-	Hot 50 1 m.	The acid was destroyed.		
hexene carboxylic	Cold 60 5 m.	88	15.5	86.0
acid	15 m.	85	12.5	88.5
	60 m.	83	8.5	92.5
	Boiled 30 m.	-	74.0	26.0
	90 m.	-	68.0	31.5
	300 m.	-	65.0	30.5

Summary of the effect of the above conditions on the γ-lactones.

Lactone used.	Treatment.	% Recovery.	% acid.	% Lactone.
γ-Butyrolactone.	Hot 50 3 h.	67	1.5	98.5
	Cold 60 7 d.	-	1.5	95.5
γ-Valerolactone.	Hot 50 1.h.	-	1.0	99.0
	Cold 60 7 d.	-	0.5	99.5

Lactone used.	Treatment.	% Recovery.	% Acid.	% Lactone.
Cyclohexanolide	Hot 50 30 m.	The lactone was destroyed.		
1:3	Cold 60 7 d.	60	2.0	97.0
1-methyl-cyclo-	Hot 50 5 m.	The lactone was destroyed.		
hexanolide 1:3.	Cold 60 2 d.	85	0.5	101
	Boiled 15 m.	-	13.0	94.0
	74 m.	-	42.5	58.0
	255 m.	-	61.5	36.5
	375 m.	-	57.5	36.5

EXPERIMENTS PERFORMED ON THE ADDITION OF HYDROGEN BROMIDE.

Additions of hydrogen bromide were also carried out under standardised conditions. Pure dry hydrobromic acid gas, generated in an apparatus connected by ground glass joints to avoid contamination of the gas by contact with rubber, was passed into the olefinic acid, usually cooled in ice, in a glass stoppered U-tube. The additions were performed under a variety of conditions, the bromoacids so formed being finally isolated and analysed. Similar experiments were also carried out on $\beta\gamma$-butenoic ester. The actual experiments are fully described in section 4, but a summary is given here of the results obtained.

The two common conditions used were: addition to the dry acid; and to the acid containing ½% water. This small amount of water does not lead to the decompositions occasioned by the use of larger amounts. In the case of the butenoic acid, several other solvents were used as will be seen in the table.

Summary of hydrogen bromide addition results.

Acid used.	Solvent and conc^{n}.	%β-	%γ-Bromo-acid.
αβ-Butenoic.	None. (fused).	100	0
βγ-Butenoic.	None.	100	0
	Water.	100	0
	Ether. (50%).	100	0
	Acetic acid. (50%).	100	0
	Toluene. (50% and 20%).	0	100
	Petroleum. (20%).	0	100
αβ-Pentenoic.	None	100	0
βγ-Pentenoic.	None.	8	92
	Water.	8	92
αβ-iso-Hexenoic.	None	100	0
βγ-iso-Hexenoic.	None.	0	100
	Water.	0	100
Δ-1-cyclohexene carboxylic acid.	None.	100	0
	Toluene. (50%).	100	0
	Acetic acid. (50%).	100	0
Δ-2-cyclohexene carboxylic acid.	None.	18	82
	Water.	18	82
βγ-Butenoic Ester.	None.	0	100

PROPERTIES OF LACTONES.

The γ-lactones themselves have also been studied from several different points of view. These compounds, on heating with water, are found to proceed to an equilibrium between the γ-lactone and the corresponding γ-hydroxyacid.

The positions of these equilibria at a uniform concentration of (lactone + acid) of M/25 have been studied for a series of lactones.

Somewhat similar measurements, in the form of velocity determinations, have been made on the reverse of the above reaction, i.e. the formation of the γ-lactones from the γ-hydroxyacids in aqueous solution under standardised conditions.[19,20]

The third measurement done on the lactones, that of parachor values, was performed by the method of Sugden,[54] in an attempt to find the parachor constant of the γ-lactone ring.

Summary of the properties of the lactones.

(i) Water equilibration figures: at equilibrium.

Lactone used.	% Acid.	% Lactone.	Ratio Lactone / acid.
γ-Butyrolactone.	25.2	74.8	2.97
γ-Valerolactone.	7.1	92.9	13.1
γ-n-Hexolactone.	6.6	93.4	13.9
γ-iso-Hexolactone.	3.5	96.5	27.6
Cyclohexanolide 1:3.	88.0	12.0	0.136
1-methyl " " "	28.0	72.0	2.51

(ii) Values of time of half-change of ring-closure.

γ-Hydroxybutyric acid → γ-butyrolactone. 135 minutes.

γ-Hydroxyvaleric acid → γ-valerolactone. 64 minutes

cis-3-hydroxy-3-methyl cyclohexane carboxylic acid } → 1-methyl-cyclohexanolide 1:3. 198 m.

(iii) Parachor values.

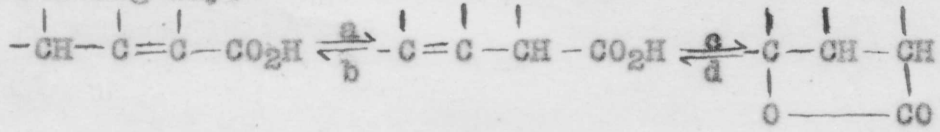
	Found. Low temperature.	Found. High temp.	Calculated on: Sugden.	Calculated on: M.&P.
γ-Butyrolactone	196.3	198.4	190.3	194.2
γ-Valerolactone	235.1	237.6	229.3	234.2

Note: M.&.P. represents Mumford and Phillips values.

SECTION 3.

DISCUSSION OF RESULTS.

The work of Linstead[1] has conclusively shown that the lactonisation of αβ-acids depends on their tautomeric change to the βγ-isomerides, and subsequent lactonisation of the latter. The system studied can be symbolised in the following way:



αβ-acid. βγ-acid. γ-lactone.

The change d, from lactone to acid, has not yet been found to occur during treatment with either cold sulphuric acid (60% by volume), or hot sulphuric acid (50% by volume), and under these conditions the variations between the different systems depends on the ratio of the velocity of the changes a,b, to the velocity of the change c. The acids can thus be classified under four headings:-

(a). Systems in which changes a,b, and c are all slow, but lactonisation c, is the fastest. Examples of this have been found in the pentenoic and cyclohexene carboxylic acids, those with one γ- and no β-alkyl substituent.

(b). Those in which the tautomeric changes a and b are fast, while the change c is slow. An instance of this type is found in the β-methyl pentenoic acids of Linstead and Wright,[103] i.e. the acids containing one β - and one γ -alkyl substituent.

(c). Those acids in which tautomeric change is slow and lactonisation is fast,,as shown by the 3-methyl cyclohexene carboxylic acids studied, and also the iso-hexenoic acids of Linstead.[1] These acids also appear to possess the property of forming lactones on heating alone, and are those with two

γ-alkyl substituents and no β-alkyl substituents.

(d). The fourth class tentatively proposed by Linstead; that in which the tautomeric change is fast and irreversible in the direction βγ-acid → αβ-acid, as in acids with neither β-nor γ-alkyl substituent. This has been shown to be the case with the butenoic acids.

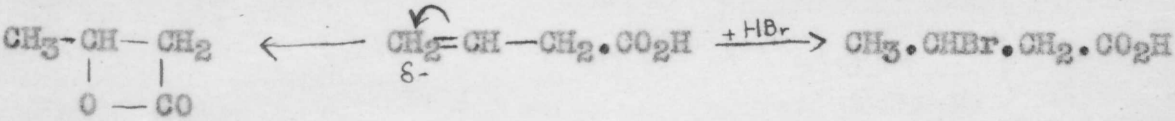
During the discussion of the lactonisation results it has been found necessary to make reference to the results obtained by the addition of hydrobromic acid to the acids. A more complete consideration of these latter results will be given after the lactone portion of the discussion.

The results obtained in the present work can be made more complete from the comparative standpoint by the inclusion of figures obtained by Linstead[1] for n- and iso-hexenoic acids, and reference will be made to these.

In the series of aliphatic olefinic acids the general formula $\begin{matrix} R' \\ \diagdown \\ R'' \end{matrix}\!\!>C=CH-CH_2.CO_2H.$ represents the βγ-acids studied. In βγ-butenoic acid, $R' = R'' = H$. This acid was found to yield no lactone whatever under any of the conditions used, even in boiling dekalin solution. In this last-named attempt, consideration of the fact that βγ-butenoic acid in hydrocarbon solvents adds hydrogen bromide to yield exclusively γ-bromobutyric acid suugests that it is under these conditions that formation of lactone is most probable. No lactone, however, was detected at all. This was not due to the acid tautomerising to the αβ-isomeride, as the recovered acid was a mobile liquid closely resembling the starting

material, but simply to the inertia of the system. The fact that no lactone can be obtained from the βγ-acid is supported by the work of Fichter and Sonneborn[80], who also endeavoured to lactonise it; and by the non-formation of any lactone during the preparation of the acid from the nitrile under conditions normally favourable to lactonisation.[28,31,30]

The fact that addition of hydrogen bromide to βγ-butenoic acid in active solvents yields pure β-bromobutyric acid, suggests that the lactone that should be formed is the β-lactone and that the formation of γ-lactone is opposed due to the polarisation:



β-lactone. β-bromobutyric acid.

If, however, the carbon chain in the phase most favourable for ring-closure, is coiled with tetrahedral angles at all corners, it will be seen that the oxygen of the carbonyl group does not approach the β-carbon atom as close as is necessary for the formation of β-butyrolactone. Also the β-lactone ring would be very highly strained if formed and would not be stable under the conditions of reaction employed. Theory thus suggests that lactonisation of βγ-butenoic acid in either sense is inhibited, and that the principal reaction, if any, will be the tautomeric change to the stable αβ-acid. This was found to be so, the experiments conducted by boiling βγ-butenoic acid with sulphuric acid, 50% by volume, yielded in all cases, practically pure αβ-butenoic acid (<u>trans</u>-crotonic acid). The nonformation of lactone, however, cannot be

entirely due to the tautomeric activity,,as treatment of the βγ-acid with sulphuric acid, 60% by volume, in the cold yielded no lactone at all but the tautomeric change was only detected to a very small extent. The αβ-butenoic acid, in accordance with the above theory, yielded no lactone under any conditions, while γ-butyrolactone was stable to the agents used for lactonisation. In its inertia to the reagents used, βγ-butenoic acid is unique among βγ-acids so far studied.

In the case of the pentenoic acids (R' = H; R'' = Me) the salient structural difference between these and the butenoic acids is the existence of one γ-methyl substituent. This has caused the acids t differ sharply from the butenoic acids in practically all the chemical properties studied. βγ-Pentenoic acid gives γ-valerolactone rapidly on boiling with sulphuric acid (50% by volume); fairly slowly with cold, 60% by volume sulphuric acid; and not at all on boiling alone. αβ-Pentenoic acid yields γ-valerolactone, obviously by preliminary tautomeric change to the βγ-isomer, if boiled with sulphuric acid, 50% by volume, but is quite unaffected in the cold, even by long standing with sulphuric acid, 60% by volume. This is again in agreement with the hypothesis that αβ-acids form lactones via tautomeric change to βγ-acids; the speed of lactonisation thus depending on the velocity of this latter change, which explains the non-formation of lactone from αβ-pentenoic acid during the cold treatment described. γ-Valerolactone was recovered unchanged from all attempts to reverse the ring-closure.

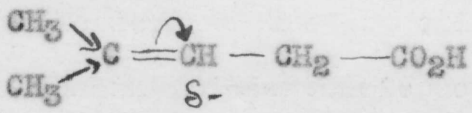
The speed of formation of lactone is slightly slower in the case of αβ-pentenoic acid than in the case of αβ-n-hexenoic acid, but the two βγ-acids lactonise at about the same speed. From this it appears that the reactivity of the double bond has been greatly increased by the introduction of one γ-alkyl substituent, but that the nature of the substituent is only of secondary importance. The addition of hydrogen bromide to βγ-pentenoic acid indicates the profound polar change caused in the double bond by introduction of this one γ-alkyl group, inasmuch as the addition proceeded to give 92% of γ-bromovaleric acid and 8% of the β-bromoacid. This is almost complete reversal of the mode of addition to the non-substituted analogue, and the deduction may be drawn that now, the polarisation in βγ-pentenoic acid is as shown :

$$CH_3 \rightarrow CH = \overset{\delta}{CH} - CH_2 - CO_2H \ .$$

This type of activation, it will be seen, will be in favour of the addition of the carboxyl group, as its constituent parts $-C\overset{-}{O}.O$ and $\overset{+}{H}$, to the unsaturated centre to yield γ-valerolactone. A further fact in favour of ring closure is, that, in a five-membered ring so formed, the angle at each corner is very nearly equal to the tetrahedral angle so that, if the carbon chain be assumed to be coiled with tetrahedral angles at all corners as before, the formation of the ring does not impose undue strain on the molecule and yields a stable configuration. Further evidence for this will be discussed later (p. 36).

Consideration of the iso-hexenoic acids ($R' = R'' = Me$) shows that, while substitution of γ-ethyl for γ-methyl in pentenoic acid (to obtain n-hexenoic acids) causes very little

change in the reaction under consideration, the introduction of a second γ-methyl group into pentenoic acid to yield iso-hexenoic acid has a marked effect in increasing the ease of lactonisation of the βγ-acid, and enables the acid to form lactone by heating alone; while the speed of lactonisation of the αβ-acid, being dependent on that of the tautomeric change αβ-acid ⟶ βγ-acid, is not greatly affected. Addition of hydrobromic acid to βγ-iso-hexenoic acid produces pure γ-bromo-iso-hexoic acid, no trace of the β-isomeride being formed. This indicates an even stronger polarisation as shown below, which can be correlated with the ease of formation of γ-lactone from βγ-acid.

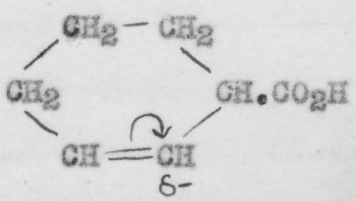


From these results the conclusion may be drawn that the reactivity and direction of polarisation of the double bond are dependent on the order, but only to a much smaller extent on the nature, of the γ-alkyl substitution.

The study of the cyclic acids was to a certain extent marred by the ready decomposition of some of the acids under the lactonising conditions used, both acids and lactones being rapidly attacked by boiling sulphuric acid, 50% by volume. The approximate positions of equilibrium in the three carbon system have been determined, and these, it appears, are not affected so considerably by γ-alkyl substitution as in the case of the aliphatic acids, while the mobility of the change appears to be abnormally low in, at least, the second case studied, the 3-methyl cyclohexene carboxylic acids

This of course has its effect on the formation of lactones from the $\alpha\beta$-acids. Δ-2-cyclohexene carboxylic acid lactonised by treatment with sulphuric acid, 60% by volume, in the cold at almost the same speed as $\beta\gamma$-pentenoic acid, although experimental figures may be rather high in lactone content from the comparative point of view, as the $\beta\gamma$-acid was also removed from the seat of reaction by some side reaction as well as by that being investigated. The experiments carried out in hot 50%(by volume)sulphuric acid led to the formation of lactone in considerable amount, although it was not possible to use conditions more drastic than those used by Fittig. The $\alpha\beta$-acid, as usual, formed no lactone in the cold on standing with sulphuric acid, 60% by volume, but on boiling with the more dilute sulphuric acid, slow formation of lactone was noticed. The γ-lactone could not be converted into the unsaturated acid under the above conditions. The $\beta\gamma$-acid would not form lactone on boiling alone in an inert atmosphere for some time, showing that the inertia of the system is too great for any reaction to occur without other agency.

The addition of hydrogen bromide to the $\beta\gamma$-acid both in the presence and absence of water led to the formation of 18% of β-bromoacid and 82% of mixed cis and trans-γ-bromo-acids. This result leads to the assumption that the double bond is polarised in the sense shown here :



which, as previously noted, would also be that favourable to

γ-lactonisation. The amount of β-bromoacid formed being somewhat greater than the amount formed in the case of addition to βγ-pentenoic acid, it may be, with reason, concluded that, either the γ-alkyl substituent in this case does not exert so large an effect, or that the ring can be considered as substituting itself in the α-position, thereby tending to oppose the γ-alkyl effect and the polarisation in the direction shown is thus decreased. Unfortunately, insufficient evidence from other sources (e.g. α-substituted aliphatic acids) is not yet available, and so no safe deductions can be drawn .

On substituting a γ-methyl group into the ring as in 3-methyl Δ-1-cyclohexene carboxylic acid, the position of the three carbon equilibrium is shifted more to the βγ-side of the equation, (from 95.5% αβ -acid at equilibrium in the cyclohexene carboxylic acids to 74.8% αβ-acid at equilibrium in the 1-methyl cyclohexene carboxylic acids). Lactonisation of the βγ-acid is greatly facilitated, treatment of this acid in the cold with sulphuric acid, 60% by volume, producing formation of lactone at a speed comparable with that in the case of βγ-iso-hexenoic acid under similar conditions. The acid was very rapidly attacked by the boiling sulphuric acid (50% by volume) used, but not before some lactone had been formed. The αβ -acid with cold 60% sulphuric acid yielded, as is usual, no lactone, while boiling the acid with sulphuric acid of the usual strength produced only about 2% of lactonic material. This latter change, of course, is very greatly retarded by the extraordinarily low mobility of the change

$\alpha\beta$-acid $\rightarrow$ $\beta\gamma$-acid, and this militates against any lactone being obtained. The γ-lactone was found to be very stable, no reversal to the unsaturated acids being detected in the treatment of the lactone under the lactonising conditions used.

On boiling the $\beta\gamma$-acid alone, lactone was formed. The reaction from the acid side appeared to reach equilibrium with a content of about 33% lactone. The pure γ-lactone was boiled under the same conditions and was found to revert to the unsaturated acid, and also came to equilibrium with a lactone content of 36,- 37%. Discussion of this phenomenon will be resumed later (p 40).

The fact that $\beta\gamma$-acids can form lactone in the pure, dry state indicates that self addition is a simple process, and makes it unnecessary at the present time, to assume any other mechanism in the reaction in sulphuric acid; as, for instance, the intermediate formation of γ-hydroxy acid, or an ester with the sulphuric acid by addition to the olefinic linkage.

From the evidence set out above, it can be seen that, in the lactonisation of unsaturated acids, by far the most important effect is that of the polarisation of the double bond as affected by alkyl substitution, and that the "approach factor" has only a very minor effect.

Consideration of the results obtained by addition of hydrogen bromide to unsaturated acids.

It is generally accepted that the addition of a hydrogen halide to an olefine is directed, almost exclusively,

by the degree of alkyl substitution around the double bond. This has been long expressed by the empirical rule of Markownikow, which states that the halogen atom adds preferrentially to the carbon atom poorer in hydrogen, i.e. the kationic hydrogen is attracted to that end of the double bond farthest from the preponderating alkyl substitution. The orientation of addition of hydrogen bromide to an olefinic acid would appear, from the results quoted in sections 2 and 4, to depend on two factors :

(a). The greater, the alkyl substitution about the double bond

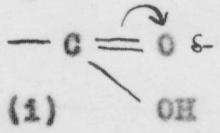
(b). The external conditions,

The mode of addition to an $\alpha\beta$-acid appears to be invariable and to yield in all cases the pure β-bromoacid, the carboxyl group directing the orientation.

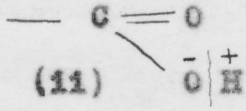
The addition of hydrogen bromide to an unsaturated acid will be considered as an irreversible process under the experimental conditions used, any elimination of hydrogen bromide occurring to yield lactone, and not parent acid, if the loss be spontaneous. As mentioned previously, this type of fission has been found to occur only appreciably in the presence of considerable quantities of water, and can be neglected in consideration of all the additions studied here. The addition being irreversible, the formation of mixed bromo-acids by no means indicates an equilibrium, but rather the product of two competing reactions. The production of an acid that is homogeneous, or nearly so, indicates that the velocity of one of the competitors is considerably greater than that of the other, i.e. one reaction is preferrentially

activated. The influence of both solvents and substituents on the orientation of hydrogen bromide addition to olefinic acids can be interpreted on the electrochemical theory of reaction recently developed by Lapworth, Robinson, and Ingold. This theory affords a simple explanation of the facts and is in excellent agreement with them so that, at the present stage, it will be considered that no other factors influence the reaction. In relation to the present work, the theory is based on the recognition of the anionoid reactivity of the double bond (Lapworth,[100] Robinson[53]), and on the distinction drawn between the operation of the permanent (inductive) polar effects, and those latent polarisations which lead to reaction.[53] Also it is appropriate to mention the work of Lucas[101] who was the first to correlate the directing influence of alkyl groups on the addition of hydrogen halide to olefines with the capacity of these groups for repelling electrons as compared with hydrogen.

The carboxyl group of an acid can polarise in two ways, dependent on its immediate surroundings. In an inert solvent the ionisation of the acid is depressed and the group then polarises as (i).



(i)



(ii)

If however the acid is in an active or ionising solvent the ionisation of the acid will leave a negative charge on the oxygen atom of the carboxyl group as in (ii).

Provided that some mechanism be present, the effect (i) will be transmitted to the double bond and will facilitate polarisation in the manner shown below:-



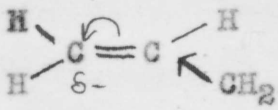
and this will lead to preferential addition of hydrogen ($\delta+$) to the proximate carbon atom, and of bromine ($\delta-$) to the distant one. However, as will be seen from a variety of evidence (e.g. dissociation constants) the effect can only be transmitted with any force through one methylene group, and as the effect has been noticed (see Walker and Lumsden;[16] also Boorman, Linstead and Rydon[104]) in acids with distant double bonds, there must also be an effect operative through space. In the consideration of this latter effect, no appreciable opposition will be expected by the inert solvent or the equally inert methylene chain (provided that the solution of the acid be weak enough) and thus a strong effect will, in any case, reach the β-carbon atom. The portion of the effect, if any, transmitted through the methylene group will not be affected by the configuration of the molecule, while the direct effect might be expected to depend on the degree of coiling of the carbon chain, as this will affect the distance between the active centre and the carbonyl group. A similar effect has been noticed in addenda to undecylenic acid by Robinson,[52] and he suggests that in a polar solvent, such as water, or an acid, the effect of the carbonyl group transmitted through space is interrupted by the ions present. Ingold, however, suggests that the interference is due to the ionised carbonyl groups packing themselves so as to partially neutralise their effect in quadrupoles, or possibly larger rings; very much in the same way as a series of bar magnets in a closed circuit with opposite poles touching has only a small external field.

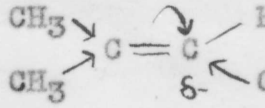
If, then, the effect of the carboxyl group be removed in ionising solvents in some such way, the addition of hydrogen bromide will be largely controlled by the alkyl substitution about the double bond and orientation will occur very much in the manner expected by considering the residue as an olefine.

It may be suggested alternatively, that the distinction between the two different types of solvent is due to the formation of oxonium compounds between the hydrogen bromide and the oxygenated solvents (cf. McIntosh and coworkers[81,82]). This explanation, however, fails to account for the fact that unsaturated esters containing the group $CH_2=CH-$ will undoubtedly tend to form an oxonium compound with the hydrogen bromide (cf. Maass and McIntosh[83] for ethyl acetate); yet they add hydrobromic acid in the absence of solvent in the same direction as the corresponding acids in an inert (hydrocarbon) solvent, in which, consequently, the acid appears to act as a "hydrogen ester". Again, any explanation based on the association of the acid in oxygenated solvents does not appear tenable, as acetic acid is known to associate in benzene, and thus the assumption that association in the homologous toluene occurs is justified.

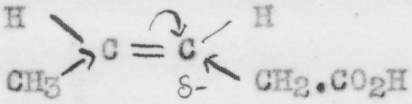
Hence the only tenable hypothesis would appear to be that based on the electrochemical theory. The addition of hydrogen bromide to the acids alone, and also containing ½% of water, (two conditions that always gave the same results) can be studied from this point of view. Under these conditions the field effect of the carboxyl group has been shown to have been eliminated as in additions in acetic acid or

ether, and so it is expected that the direction of addition will be controlled by the alkyl substitution about the double bond. Experiment has shown this to be so. In considering the aliphatic acids, the two extreme cases studied were (i), βγ-butenoic acid, and (ii) βγ-iso-hexenoic acid :-

(i).  leading to $CH_3.CH(Br).CH_2.CO_2H$

(ii).  leading to $(CH_3)_2.C(Br).CH_2.CH_2.CO_2H$

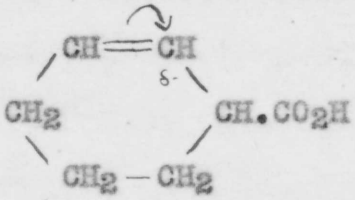
The observed figures for the addenda to βγ-butenoic acid (100% β-; 0% γ- addition of bromine) and to βγ-iso-hexenoic acid (0% β ; 100% γ- addition of bromine) are in complete agreement with this. In the more balanced system, βγ-pentenoic acid, we have polarisation as in (iii) :-

(iii) 

The effect of the one γ-methyl substituent is opposed by the effect exerted by the α-methylene group. This latter, however, is weakened by the attachment of a carboxyl radicle and so the γ-methyl substituent can exert the major influence. Experimental evidence upholds this theoretical deduction, as addition of hydrogen bromide to the acid (iii) results in the formation of 92% of γ-bromoacid, but with simultaneous production of 8% of β-bromo-addition product.

In the case of the cyclic acids, only the unsubstituted series has been yet studied from this point of view. Addition of hydrobromic acid to Δ-2-cyclohexene carboxylic acid has been found to yield 18% of 2-bromo-

Cyclohexane carboxylic acid, and 82% of the 3-bromo-isomers. From a study of the formula it would appear that the tendency to polarise in the following way is the main type, due to substitution on the γ-carbon atom :-



The fact that the α- and γ-carbon atoms are connected by a propane chain appears to reduce the effect of this γ-alkyl group, which results in the increase of the percentage of β-bromo-adduct formed. Lack of further evidence on this point precludes the deduction of more extensive theories.

Properties of Lactones.

Determination of the equilibrium reached during the hydrolysis of γ-lactones in water is concerned with the stability of the lactone ring to the above agent. The obvious facts emerging from thefigures obtained in this section of the work are : the great stabilising effect of γ-alkyl substitution into an unsubstituted lactone; the even greater effect of γ-gem-dialkyl substitution; and the slowness of the dicyclic lactones in hydrolysing as compared with the lactones of the aliphatic series.

The great stabilising effect of γ-alkyl groups can be correlated with several facts previously known. The effect of alkyl substitution has been investigated in the extensive researches of Thorpe and his school, and particularly by Deshapande and Thorpe[84]; Singh and Thorpe[85]; Bains and Thorpe[86]; and Lanfear and Thorpe[87]. These authors

have clearly indicated the effect of substitution in bringing the angle between the two emergent valencies of the substituted carbon atom nearer that of the tetrahedron, and thus in stabilising any five-membered ring in which these two valencies participate. γ-Butyrolactone has a ratio L/A (lactone/acid) of 2.97, this ratio being taken as a measure of the stability of the lactone ring. Introduction of one γ-alkyl group immediately renders the lactone more stable, γ-valerolactone having L/A 13.1, and γ-n-hexolactone L/A 13.9, the effect of methyl being only very slightly less than that of ethyl. Introduction of a second γ-methyl substituent as in γ-iso-hexolactone stabilises the ring still more as shown by L/A for this lactone being 27.6, there being only 3.5% of γ-hydroxy-acid present at equilibrium. This evidence is strongly in favour of the angle between the emergent valencies of a dialkylated carbon atom being very nearly that of the tetrahedron and also that of the five-membered ring, (cf. Lanfear and Thorpe[87]).

The evidence adduced by Gane and Ingold[88] from electrometric titrations on disubstituted acids also shows that introduction of alkyl groups onto a methylene chain causes distortion of the "zig-zag" carbon chain tending to form a ring structure. In the lactones formed from the cyclic acids studied there is another factor influencing the stability of the γ-lactone ring. This is the extra strain thrown upon this ring by the "locking" of the three methylene groups in it by their inclusion in a cyclohexane ring, in a position almost certainly not that existant normally in a γ-lactone

ring. The result of this is seen immediately in the case of cyclohexanolide 1:3, which has L/A 0.136, only a small amount of lactone being left at equilibrium. Introduction of a γ-methyl group again renders the ring more stable, the value of L/A for 1-methyl cyclohexanolide 1:3 being 2.51. A second difference between these dicyclic γ-lactones and the γ-lactones of the aliphatic series is noticed on comparing their speeds of hydrolysis. This was found to be considerably slower in the case of the dicyclic compounds. This is prbably due to the fact that the large cyclohexane ring present in these substances exerts a notable steric hindrance effect on the attack of the water molecules, and consequently the velocity of hydrolysis is lowered.

The weakest link in the lactone ring, naturally, is the one which breaks under the above conditions. From the evidence of the action of ammonia on the lactone ring, as in the case of γ-valerolactone, the product is always the amide of the corresponding hydroxyacid, and never the ammonium salt (cf. Fittig[105]). Hence the ring must open by fission of the bond (a), as no other bond could break and form the amide.



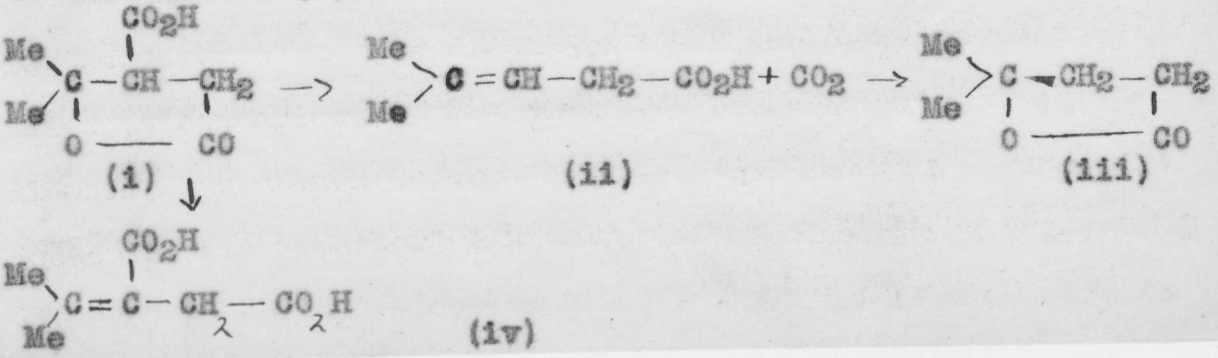
Further proof of this fact has been found by Kenyon and Phillips[106] by a study of the optical properties of the fission products, during which no inversion occurs. This being the bond that breaks, a connection between the opening of a lactone ring by water and the hydrolysis of an ester by the same agent can be

seen. The work of Menschutkin[89] on the equilibrium mixtures of various alcohols and acetic acid, starting with methyl alcohol clearly indicates that, in the limit, the amount of a secondary alcohol present is more than the amount of the corresponding primary, and also that the esters of tertiary alcohols are abnormal and decompose, the tendency for the alcohol to form an ester being negligeable. These facts, however, are in direct opposition to the figures obtained in the above work, and thus the "ester hydrolysis" factor in the hydrolysis of lactones appears to be totally overpowered by the other factors.

For a study of the reverse reaction, the speeds of ring closure of γ-hydroxyacids to the γ-lactones have been determined under standard conditions, and comparison made by the times taken to reach the half-change point. The velocity of this change depends on the readiness of formation of the γ-lactone as governed by its stability, the approach factor, and, possibly, the readiness of the hydroxy group to esterify. Again according to Menschutkin[89], primary alcohols esterify about three times as fast as corresponding secondaries, while the tendency for tertiary alcohols to esterify is very small indeed. This does not accord with figures obtained from velocity measurements on the lactones, as γ-hydroxy-iso-hexoic acid (a tertiary alcohol) forms lactone only very little faster than γ-hydroxy-n-hexoic and γ-hydroxyvaleric acids (secondaries), while γ-hydroxybutyric acid, a primary alcohol, has a much lower speed of lactonisation. Hence the "esterification factor" can only exert a very minor influence.

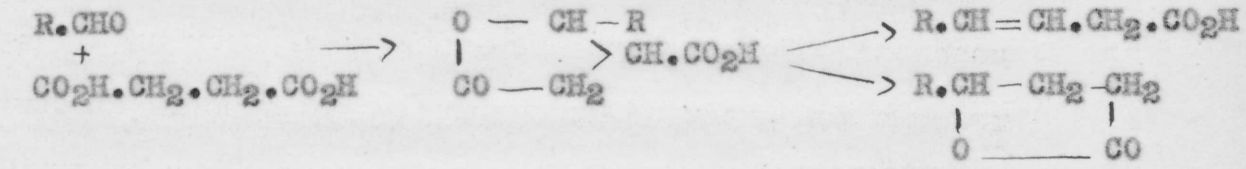
The two remaining factors, ring stability and the approach factor, can be separated by consideration of the results obtained from the hydrolysis experiments just described, and taking these as a measure of the stability of the γ-lactone ring under the conditions used. By comparison of the values of L/A and the half-change times for each lactone, it can be seen that the stability of the lactone ring is the controlling influence in the change, as those hydroxyacids containing a rigid framework in their molecules (the cyclic acids) form lactone at the speed that would be expected from consideration of the values of L/A, the approach factor being negligeable.

The case of ring-chain tautomerism can now be discussed in the light of the evidence obtained from the foregoing experiments. Ingold, Perrin and Thorpe,[91] Lanfear and Thorpe,[92] and Baker, Ingold and Thorpe[93] and others have carried out experiments on the various types of ring-chain tautomerism known at that time. The case under consideration however, appears to be the first case known of a γ-lactone tautomerising to a βγ-acid. Examples of more complex lactones changing have been long described, the best-known case probably being that investigated by Fittig and Geisler,[107] and later by Goldberg and Linstead;[27] the pyrogenic decomposition of terebic acid(i) :



(i) (ii) (iii) (iv)

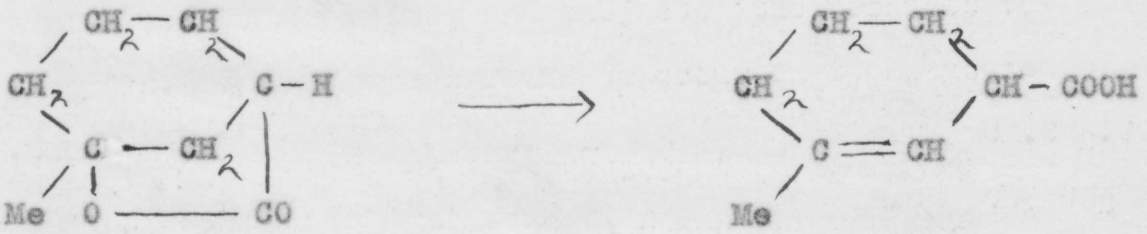
This, a lactonic acid, on heating alone produces $\beta\gamma$-isohexenoic acid (ii) and this on further heating, yields the γ-lactone (iii). A second reaction also occurs; the formation of teraconic acid (iv) directly from the terebic acid by opening of the lactone ring. A further more general example of this type of reaction was discovered by Fittig and coworkers.[108] He condensed aldehydes (e.g. acetaldehyde, propionaldehyde, butyraldehyde etc.) with succinic or homologous dibasic acids, and subjected the products to pyrolysis. Reaction was found to occur in two ways :-



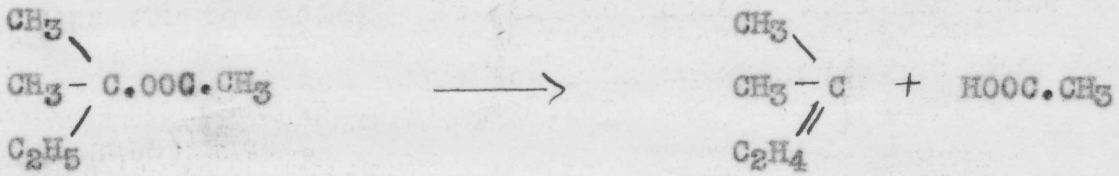
the γ-lactone ring having opened in one case to yield an unsaturated acid. It will be noticed that all these reactions mentioned above occur in substances that are much substituted.

The change described between 3-methylΔ-2-cyclohexene carboxylic acid and 1-methyl-cyclohexanolide 1:3 undoubtedly depends on many factors. From the point of view of the acid, the tendency to form lactone depends in all probability on similar factors to those operating in lactonisation in acid solution, i.e. the polarisation of the double bond practically controls the reaction, while the other factors mentioned before may have some very slight and negligeable effect, although the approach factor may come more into prominence in the thermally activated molecule, but only slightly so. From the side of the lactone, the stability of the lactone ring is

of paramount importance, although the issue is complicated by consideration of the lactone as the internal ester of a tertiary alcohol, as Menschutkin[94] has shown that acetates of tertiary alcohols as typified by tertiary amyl acetate, are decomposed on heating to temperatures over 100°, eventually completely, with the formation of the acid and an unsaturated hydrocarbon. The connection between the two reactions is shown as follows :-



1-methyl-cyclohexanolide 1:3. 3-methyl-Δ-2-cyclohexene carboxylic acid,

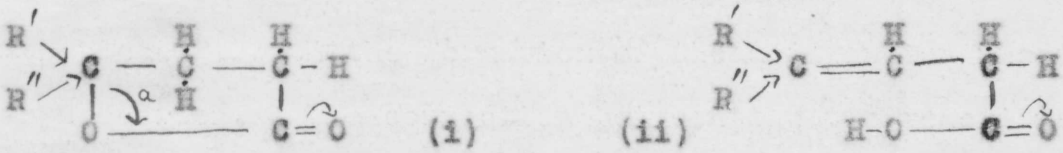


Tertiary amyl acetate. Amylene Acetic acid.

γ-iso-hexolactone, another lactone with a tertiary γ-carbon atom, was found by Linstead to yield no appreciable acid on long boiling. This lactone, however, has been shown above to have a very stable ring, while the cyclic lactone has a comparatively highly strained ring. Hence the opening of the lactone ring on heating alone appears to depend on the existance of a tertiary γ-carbon atom, together with the some factor causing strain in the ring to facilitate the fission.

The following is proposed as a theoretical

explanation of the lacto-enoic tautomeric change. Consideration of the general type of substance undergoing this change, as stated previously, shows that one of the essentials is a tertiary γ-carbon atom. Hence the type is as follows, where R′, R″ are alkyl groups



(i) (ii)

The combined electromeric effects of these two γ-alkyl groups cause the change "a" shown in formula (i) and subsequent fission of the bond(shown in red)in the highly thermally activated liquid; the resulting δ+charge remaining on the γ-carbon atom causes the loosening of one of the protons of the β-methylene group on account of electron drift to the γ-carbon atom, and this is set free with the formation of a βγ-double bond, as in (ii). The whole series of changes probably occurs practically simultaneously, resulting in the formation of an ionised βγ-acid. The acid reverts to the lactone in the manner previously described, i.e. by the attachment of the proton to the β-carbon atom, which carries a δ- charge due to the alkyl groups R′, R″, the residue of the carbonyl group satisfying the valency of the γ-carbon atom. The fact that γ-iso-hexolactone yields no acid on boiling although βγ-iso-hexenoic acid forms lactone with ease under the same conditions can be explained by the great stability of the lactone ring in this case which acts to preserve the closed system. In the case of 1-methyl-cyclo-hexanolide 1:3 the γ-lactone ring is severely strained, and

this facilitates the opening of the ring. This also explains the somewhat similar case discovered by Linstead and Rydon[109] in the case of δ-iso-heptenoic acid and δ-iso-heptolactone.

Very little need be said about the results obtained from parachor measurements on γ-lactones. The experimental values differ considerably from the theoretical values calculated on Sugden's[73,74] atomic and structural parachors, but are in fairly good agreement with theoretical requirements if the values of Mumford and Phillips[75] be used. From these latter figures, it appears that the γ-lactone ring behaves normally and has no specific effect on the parachor.

Summary of results obtained.

(i) αβ- and βγ- unsaturated acids, if they form lactone, always form the γ-lactone, and, as far as has yet been determined, irreversibly in sulphuric acid solution.

(ii) The formation of lactone from βγ-acids is governed almost entirely by the nature of the double bond as affected by the alkyl substitution about it. The effect of the approach factor is very small.

(iii) The formation of lactone from αβ-acids is consequent on their tautomeric change to the βγ-isomerides, and lactonisation of the latter.

(iv) That βγ-olefinic acids with no β- or γ-alkyl substituents do not form lactone at all due to inertia of the system and if any changs occurs at all it is the fast irreversible tautomeric change to the αβ-acid.

(v) That lactonisation occurs reversibly in acid systems containing two alkyl substituents on the γ-carbon atom if the ring of the lactone so formed is strained. This has been named "lacto-enoic" tautomerism, but only occurs in the pure acid or lactone when thermally activated.

(vi) Addition of hydrogen bromide to olefinic acids is independent of the position of the carboxyl group with respect to the double bond except in the case of the $\alpha\beta$-acids when the orientation is governed by the latter and results in the production of pure β-bromo-acids in all cases, This is not affected by solvents.

(vii) Addition of hydrobromic acid to $\beta\gamma$-acids depends on two factors:

(viii) The effect of solvents on the direction of addition. In hydrocarbon solvents the acid behaves as a hydrogen ester; the carboxyl group controls the reaction and the bromine goes to the γ-(i.e. the distant) carbon atom, apparently regardless of alkyl substitution. The direction is the same as that in the addition of hydrogen bromide to the corresponding olefinic ester. In active (ionising)solvents, as in ether, acetic acid, water or alone, the effect of the carboxyl group is eliminated and addition proceeds as to an olefine, i.e. the alkyl substitution controls orientation.

(ix) The effect of alkyl substitution operates in the second of the cases described in (viii), and the effect is that expected by application of the law of Markownikow. It also increases the velocity of the addition reaction

(x) The γ-lactone ring is stabilised by γ-alkyl substitution

due probably to the alteration of the valency angle as described. Inclusion of a rigid molecular framework in the molecule increases the strain on the lactone ring.

(xi) The ease of formation of the lactone ring from the corresponding hydroxy-acid depends chiefly on the stability of the ring as affected by the factors mentioned in (x) other effects being negligeable.

(xii) The γ-lactone ring has no detectable structural parachor.[a]

SECTION 4.

EXPERIMENTAL.

Note Densities (d) and refractive indeces (n) are for d_4^{20} and n_D^{20} throughout unless otherwise stated. Halogen additions (J) were performed at 20°, and melting points at low temperatures are corrected for stem exposure.

PART 1; PREPARATIONS.

(a). Preparation of the acids and associated compounds.

(i) α/β-Pentenoic acid.

This acid was prepared by the usual Doebner condensation (cf. v. Auwers,[26] Goldberg and Linstead,[27] Linstead and Noble[23]) and consistently good yields were obtained by the following process:-

n-Propionaldehyde was redistilled and the fraction of boiling point 48°- 50° was used. 1 mol. of the aldehyde, and pyridine dried over potash (1⅓mol.) were mixed in a flask fitted with good reflux condensers. Malonic acid (1 mol.) was then added, the whole well mixed, and allowed to stand at room temperature for seven days, the top of the condenser being loosely plugged to minimise loss of the volatile aldehyde by draughts. The mixture was finally heated on the steam until all evolution of gas had ceased (about twelve hours). The reaction mixture was cooled and carefully acidified with concentrated hydrochloric acid (excess calculated on the pyridine used) until acid to Congo red. The upper layer of unsaturated acid was separated off, and the residual aqueous layer extracted four times with ether, the extracts being added to the top layer. The whole was washed once with water and the ether distilled off. The residual liquid was then

neutralised by the addition of about 200 cc. of water and a slight excess of crystalline sodium carbonate, with shaking at intervals until the reaction was complete. The alkaline liquid was extracted twice with ether to remove basic and neutral impurities (chiefly aldehyde polymer). The aqueous liquid was then acidified with concentrated hydrochloric acid and the acid obtained from the solution by extraction with ether as before, the combined top layer and ether extracts being washed with water, dried over calcium chloride; the ether distilled off; and the remaining acid fractionally distilled in vacuo, the fraction collected being that boiling at 106/20mms. The acid was further purified by fractional fusion. The distillate was frozen completely solid and the approximate melting point determined. The acid was again frozen and kept in a bath at 1° - 2° above this temperature for about half an hour and any liquid drained off. The process was repeated until a homogeneous acid was obtained. The acid was finally redistilled and had the following physical properties :-

m.p.	9.5°.	n.	1.4513
b.p.	106/20 mms.	d.	0.9903

J. (iodine; 60 mins.) 2.7. whence $[R_L]_D$ 27.22

(calc. $[R_L]_D$ 26.36)

(ii). βγ-Pentenoic acid.

The method of Boxer and Linstead,[22] modified by Linstead and Noble,[23] was used as follows:

Redistilled propionaldehyde (1 mol.) was placed in a dry one litre flask under good reflux and to it added

triethanolamine, tris(β-hydroxyethyl)amine, purified by redistillation, the fraction boiling at 220-1°/18 mms. being used. Slight heat was generated on mixing the two liquids. The mixture was chilled and malonic acid (1 mol.) was added. The whole was at once very vigorously shaken to get good mixing, as the success of the reaction appears to depend largely on this. In some cases the reaction tended to proceed rather rapidly at this stage, and was slowed down by chilling the mixture in ice. After standing for 48 hours, the whole was finally heated under reflux on the steam until reaction had ceased (24 hours). The liquid was cooled, made acid to congo red with sulphuric acid (50% by weight) and then worked up as described in the case of the αβ-isomer. The rather viscous liquid left after the removal of the ether was carefully fractionally distilled in vacuo. In the first distillation, after the βγ-pentenoic acid had been removed boiling at 93°/13 mms., the distillation was continued.. On heating to above 100° the vacuum dropped owing to evolution of gas (decarboxylation?). After a time the vacuum was restored and a thick yellowish oil distilled over at 182°/22 mms. in quantity about 30% of the whole. The residue in the flask was a very viscous brown oil, smelling strongly of unsaturated hydrocarbons which, if present, had probably been formed by complex polymerisation and complete decarboxylation. The The high-boiling distillate slowly deposited needles and in time (3 months) became practically solid. The solid was drained on a tile and had m.p. 66° - 67°. Two recrystallisations

from benzene and light petroleum sufficed to yield the pure solid in colourless needles melting sharply at 74°. The solid had the following properties:

Equivalent by baryta 80.4; completely soluble in water; soluble, with evolution of carbon dioxide, in a saturated solution of sodium bicarbonate; completely unaffected by alkaline potassium permanganate solution even on long standing; does not absorb bromine from chloroform; nitrogen, sulphur, and halogens absent.

From the boiling point the acid would appear to be dibasic and would have a molecular weight of 160.8, which corresponds to an empirical formula of $C_7H_{12}O_4$ (M. = 160.1), and may be a glutaric acid, probably the symmetrical ethyl glutaric acid. Kommenos[55] obtained β-ethyl-glutaric acid by heating together propionaldehyde, malonic acid, and glacial acetic acid and records the melting point as 74°. A mixed melting point of the above solid with authentic β-ethyl-glutaric acid was 74°, and this shows the formation of a considerable portion of β-ethyl-glutaric acid during the above condensation.

The βγ-pentenoic acid was redsitilled carefully, and boiled very steadily at 93/13 mms., and had the following physical properties :

m.p.	0.5°	n.	1.4347
b.p.	93/13 mms.	d.	0.9848
J.	73.5	whence $[R_L]_D$	26.51

(iii) αβ-Butenoic acid; (trans-crotonic acid).

The modifications of Letch and Linstead[28] were applied to the original method of Staudinger as described by Henle[29] in

the following way:

A 200 ccs. round-bottomed flask was fitted with a reflux Liebig condenser and the whole tilted at 45° to the vertical. The top of the condenser carried a cork fitted with a dropping funnel and a lead-away tube, via a calcium chloride drying tube, to a vertical 50 cc. pipette which passed through a cork in the neck of a filter flask. This latter was cooled in ice and had the side tube fitted to a calcium chloride guard tube. Four drops of concentrated sulphuric acid were placed in the round flask and 30 c.c. of paraldehyde added. The flask was heated gently on the steam and the acetaldehyde formed by depolymerisation was collected in 300 c.c.s of ether (dried over sodium) in the filter flask. Paraldehyde was run in from the dropping funnel at the same speed as the acetaldehyde distilled over. About four mols. of paraldehyde were used. To the ethereal solution of pure aldehyde so obtained were added pyridine ($1^1/_3$ mols.) and malonic acid (1 mol.) and the whole allowed to stand under reflux in ice for 48 hours, at room temperature for 24 hours, and finally the ether was distilled off from the mixture on the steam and heating continued until no further evolution of gas occurred (15 minutes). A little water was added to the cooled liquid and it was made acid to congo red by addition of an excess of concentrated hydrochloric acid and cooled in ice. The solid acid separating was filtered off and a small amount more was obtained by extraction of the aqueous liquors with ether in the usual way. The acid was finally purified by recrystallisation from light petroleum (b.p. 60° - 80°) and

obtained in 80% yield.

m.p. 72.5° J. (bromine; 30 mins.) 1.3.

E. 86.2 (calc. 86.1)

(iv) βγ-Butenoic acid (Vinylacetic acid.)

This acid was synthesised by a method originally due to Bruylants,[30,31] but extensively modified and improved by Linstead and Noble.[23] The method depends on the hydrolysis of allyl cyanide in the cold by concentrated sulphuric acid. The reaction tends to proceed with violence, but if carefully controlled in its earlier stages it gives very consistent yields of pure βγ-butenoic acid. The method can be diagrammatically illustrated as shown:

$$\underset{(i)}{CH_2{=}CH{-}CH_2.OH} \xrightarrow[HCl]{CuCN} \underset{(ii)}{CH_2{=}CH{-}CH_2.CN} \xrightarrow{H_2SO_4} \underset{(iii)}{CH_2\ CH\ CH_2.CO_2H}$$

The allyl alcohol was prepared by the method of Kamm and Marvel,[56] from formic acid and glycerol in the usual way. No decription of the preparation is necessary here. Allyl cyanide (ii) was prepared directly from the allyl alcohol (i) by the method of Breckpot.[57] Equimolecular amounts of 70% alcohol, concentrated hydrochloric acid, and cuprous cyanide were mixed in a three litre flask fitted with a reflux condenser, using 260 g. of allyl alcohol. The whole was heated gently on the steam bath with good shaking, care being taken that the reaction did not get out of control. After 1½ hours' refluxing had practically ceased and the reaction had finished. The whole of the contents of the flask were then poured into a one-litre distilling flask fitted with a mercury-sealed stirrer, and the liquid completely distilled over from an oil

bath at 140-150°. The stirrer was essential, to stop the chlorides of copper formed during the reaction from clogging the flask and causing "bumping". The distillate formed two layers, the upper one consisting principally of allyl cyanide, and being distilled without further treatment, the fractions collected boiling below and above 102°. The fraction below 102° was chiefly unchanged alcohol and was used in subsequent preparations of the cyanide. The lower (aqueous) layer from the crude product was extracted four times with ether, the ether distilled off, and the residue distilled into the two fractions described above. The combined higher fractions were redistilled and that boiling over the range 112° - 120° was collected as pure allyl cyanide, in 67% yield (calculated on the cuprous cyanide).

The hydrolysis of the nitrile was carried out in the following manner. 30 g. of allyl cyanide (no more) were weighed out into 250 c.c. conical flasks and cooled in ice. To it was added, a little at a time, an equimolecular amount of concentrated sulphuric acid (24 c.c.s) cooling between the additions. Great care was necessary during the first four hours of the reaction as any excessive local overheating above about 40° promoted very vigorous, almost explosive, reaction, leading to carbonisation and ruination of the experiment. Cooling in ice at intervals was necessary, although prolonged cooling merely inhibited the reaction and postponed the danger. The viscous liquid formed was allowed to stand until all smell of nitrile had vanished and the whole had formed a hard glassy mass (four to five days). At the end of this period the mass

was treated with a weight of water equal to that of the sulphuric acid used and allowed to dissolve. The solution was then heated under reflux for 40 minutes on the steam. On cooling the top layer, of the βγ-butenoic acid mixed with a little sulphuric acid, was separated, and the lower, aqueous, layer was extracted with ether four times. The ethereal extracts were added to the top layer, the little sulphuric acid that separated was removed, the ethereal solution washed with water, dried over calcium chloride, and the ether distilled off. The residual liquid was twice fractionally distilled in vacuum, a slight low fraction being collected in the first distillation, consisting of unchanged nitrile, and a small undistillable residue remained in the flask which, according to Bruylants,[30,31] is crotonamide. The yield of the pure acid was very consistent at 29% to 30%, possessing the physical constants quoted below.

m.p.	-35.0°	n	1.4220	
b.p.	69°/10 mms.	d	1.0090	
J.	77.0.	whence $[R_L]_D$	21.66	(calc. 21.74)

Ethyl ester of the βγ-butenoic acid.

This ester has been prepared by Bruylants[66] by a method which seems rather unreliable, due to the great tendency of the βγ-acid to tautomerise to the αβ-acid under his conditions. The ester was consequently prepared by reaction between the silver salt of the pure acid and ethyl iodide. The silver salt was obtained by adding a slight calculated excess of silver nitrate solution to the acid (exactly neutralised with dilute ammonium hydroxide) and, in this particular case, by adding acetone to

the liquid to aid precipitation of the salt which appears to be somewhat soluble in water. The solid was obtained pure and dry in the usual way and boiled for 24 hours in sodium-dried ether with an excess of ethyl iodide. The silver iodide was filtered off, the ether removed, and the residue fractionally distilled under atmospheric pressure. The ester was found to have the following physical properties:-

b.p. 124°/764 mms. $\underline{n}_D$ 1.4102

$\underline{d}_4^{20}$ 0.9192

whence $[R_L]_D$ 30.74 (calc. 30.98)

(v) αβ-iso-Hexenoic acid.

This acid was obtained by condensing iso-butyraldehyde (redistilled b.p. 61° - 66°) with malonic acid in the presence of excess pyridine in an exactly similar manner to that described in the preparation of αβ-pentenoic acid (compare Goldberg and Linstead[27]). It was obtained as a colourless mobile liquid with the following physical constants:-

m.p. -32.0° E. 114.2 (calc. 114.1)

b.p. 105°/11 mms. J. (iodine; 5 mins.) 0.9.

(vi) βγ-iso-Hexenoic acid.

The equilibration of the αβ-isomeride by boiling caustic potash solution under the conditions of Linstead[1] was shown by Goldberg and Linstead[27] to give an acid with a high percentage of the βγ-isomer, and the method is based upon this fact.

αβ-iso-Hexenoic acid (1 mol.) was boiled under reflux in a copper flask with ten molecular proportions of 25% aqueous

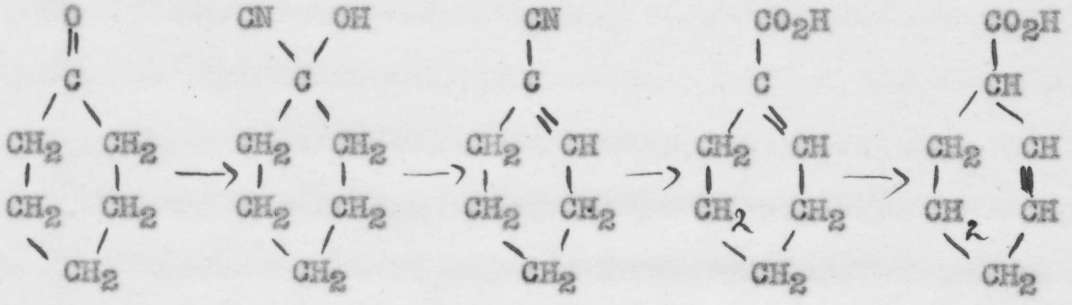
potassium hydroxide solution for 6½ hours. The liquid was cooled in ice, and very carefully acidified with a slight calculated excess of 15% hydrochloric acid, care being taken that the solution did not become warm, as the βγ-acid forms γ-iso-hexolactone with extraordinary ease in the presence of mineral acid. The acid was extracted immediately with ether in the usual way, the ethereal extracts washed with water, dried, the ether distilled off, and the residual acid distilled in vacuo. Apart from 1% of low fraction of pronouncedly lactonic odour, the acid boiled steadily over the range 100° - 106°/12 mms. The αβ -acid present was removed by partial esterification under Linstead's conditions as follows:- To the 100 gms of acid obtained from the above process were added 100 ccs. of N alcoholic hydrochloric acid solution and 400 ccs. of absolute alcohol. The well-mixed solution was allowed to stand at the temperature of the laboratory for 5½ hours. The mixture was then poured into at least three volumes of water containing an excess of sodium carbonate in solution, and the ester allowed to separated as an upper layer. A little ether was added to aid the separation but no attempt at extraction was made as this would introduce alcohol into the ester layer. The upper layer was removed, the alcohol present in the aqueous layer was distilled off in vacuo from a bath at less than 50°, and a small extra amount of ester obtained by ether extraction of the solution. The combined ethereal solutions of ester were dried, the ether removed, and the pure βγ-ester was distilled in vacuum, boiling at 70°-74°/17 mms. From this the

acid was obtained by alkaline hydrolysis in the cold. The ester was mixed with 10% aqueous caustic potash solution (2 mols.) and sufficient absolute alcohol added to render the two layers completely miscible. On standing overnight, hydrolysis was complete, there being no smell of ester, and no precipitation of the latter on dilution of the reaction mixture with water. This liquid was diluted with an equal volume of water and the alcohol removed at the pump as previously described. The residual aqueous liquid was acidified with hydrochloric acid, the precautions described above being taken. The upper acid layer was removed and the aqueous lower layer was extracted four times with ether, the combined top layer and ethereal extracts washed with water, dried, the ether distilled off, and the residual acid distilled without removal of lactone. The acid boiled at 88°/6 mms., It was freed from lactone by allowing to stand overnight with 50% excess of sodium bicarbonate solution, the resulting liquid thoroughly extracted with ether to remove all lactone, and the βγ-acid finally obtained pure by acidifying the ice-cold solution with cold 15% hydrochloric acid, immediately extracting the acid several times with ether, working up as above, and finally redistilling the acid. It was obtained in 50% yield from the αβ-acid, and had the following physical properties :-

m.p.	-2.0°	n.	1.4455
b.p.	84°/4 mms.	d.	0.9758
E.	114.2 (calc. 114.1)	$[R_L]_D$	31.15 (calc. 30.98).
J.	93.5		

(vii) Δ1-cyclohexene carboxylic acid.

The method used for the preparation of this acid was, as has been mentioned previously, of a new type for this series, the older methods of Aschan[32] and Einhorn[33] not being used. Various small test experiments were first performed and these indicated the general methods of procedure finally adopted. The method used was as follows:



(1) (ii) (iii) (iv) (v)

By this process the α/β-acid (iv) was obtained in large white overlapping plates melting at 38°. The cyanhydrin of cyclohexanone had been prepared many times, notably by Bucherer[58], Tarbouriech[59], Markownikow and Smirnow[60], Darzens[61], and Ruzicka and Brügger[34]; the method generally used being based on the acidification of a mixture of the ketone and a concentrated aqueous solution of potassium cyanide with mineral acid under various conditions. The method actually used was derived from the above experiments and was as follows. 262 gms of Cyclohexanone were weighed into a flask and to it added a concentrated aqueous solution of potassium cyanide (200 g. 95% single salt in c, 450 ccs. water). The flask was fitted with a dropping funnel and lead-away to the draught. The mixture was cooled in ice and 340 ccs. of concentrated hydrochloric acid, cooled in ice, were run in, in a thin

stream with shaking. Great care was taken to keep the liquid cold, as, if heat be generated in the presence of the acid, the ketone tends to condense to high-boiling oils. After a few hours' standing the liquid was filtered from the potassium chloride formed during the reaction and this latter well washed. The upper layer of crude cyanhydrin in the filtrate was removed, and the aqueous residue extracted three times with ether. The combined upper layer and ethereal extracts were thoroughly dried and the ether distilled off. A thick oily liquid was left; a sample of this was distilled in vacuum and boiled steadily at 101°/3mms., the distillate freezing in the receiver. As a certain amount of decomposition appeared to occur, it was decided not to distill the rest of the cyanhydrin, but to dehydrate the crude liquid. The method of Ruzicka and Brügger[34] was used here with slight modifications. The cyanhydrin obtained by the above process was dissolved in an equal volume of benzene and dried over sodium sulphate. The filtered solution was placed in a dry flask fitted with a reflux condenser and lead-away for the gases evolved. Ruzicka and Brugger recommend that the thionyl chloride used for the dehydration be added slowly over the space of three hours, the solution being mechanically stirred and cooled in a freezing mixture. These refinements were found to be unnecessary. 520 gms. of thionyl chloride were added to the benzene solution and the reaction allowed to proceed in the cold overnight. This was completed by heating on the steam until the reaction ceased (six hours). The flask was cooled in ice and ice added with good shaking to remove the last of the thionyl chloride. When this

had been completely destroyed, the top benzene layer was removed and washed free of acid with 10% aqueous caustic soda solution and then with water. The solution was dried and the benzene carefully removed at the pump from a bath at less than 50°. The residual crude unsaturated nitrile was then distilled in vacuo. The low fraction collected, that boiling below 100°/34 mms., consisted of mixed benzene, cyclo-hexanone, and unsaturated nitrile. The main fraction was collected at 96°/27 mms to 91°/17 mms., only a small residue being left in the flask. The main fraction was redistilled, and the $\alpha\beta$-unsaturated nitrile was obtained in 63% yield from cyclohexanone as a colourless liquid boiling steadily at 86°/17 mms. It resmbles benzonitrile in its odour, but possessed a sharper tang.

The unsaturated acid was obtained from the nitrile by alkaline hydrolysis. The nitrile was boiled with two molecular proportions of 10% aqueous potassium hydroxide solution under reflux condenser until the evolution of ammonia ceased. The nitrile dissolved in the liquid in three hours, (probably forming the amide) but seventeen hours boiling was needed to complete the reaction. On theoretical grounds, it was assumed that the acid obtained from the above would undoubtedly be the equilibrium mixture of the $\alpha\beta$ - and $\beta\gamma$-acids (iv) and (v), but that the ratio of $\alpha\beta$-acid to $\beta\gamma$-acid would be greatly in favour of the $\alpha\beta$-acid. The hydrolysis liquid was cooled, made slightly acid by addition of a calculated slight excess of sulphuric acid. The acids

separated as an oil on the liquid, and were distilled in steam to remove traces of hydroxyacid, etc, formed during the boiling with potash. The volatility of the acids in steam is small, 9 litres of distillate being collected for the acid from 100gms. of nitrile. This was neutralised with sodium carbonate, and the volume reduced considerably by evaporation on the steam (which also serves to remove volatile basic and neutral impurities), and the alkaline liquid then extracted twice with ether to remove the last traces of the last-named substances. The liquid was then made acid to congo red with concentrated hydrochloric acid under a layer of ether, with stirring. The ether serves to dissolve away an impervious skin of the unsaturated acid that otherwise forms on the solid double ("acid") salt which is formed. The top layer was removed and the residual solution extracted four times with ether. The combined ethereal extracts were washed with water, the solution dried, and the ether ditilled off. The acid was distilled in vacuum, there being no low fraction and very little high residue, the required fraction being that boiling at $107^{\circ}/3$ mms. ($138^{\circ}/14$ mms.). The distillate solidified to large overlapping plates of the Δ-1-cyclohexene carboxylic acid, although some oil was left, being mixed Δ-1-and Δ-2-acids. This substance had equivalent weight (by baryta) 126.8 (calc. for the acids required 126.1).

At the time that this preparation was being investigated the pure $\beta\gamma$-acid had not been obtained, and so any halogen additions could be expected to give only an approximate value for the amount of the $\beta\gamma$-acid present.

However, the semi-solid acid was separated into its two parts by filtration, and the solid acid drained on a tile, and iodine additions done on the three samples for one hour. (J_1).

Mixture from the preparation. . . .	E.	127.6	J_1	2.7	J_2 21.3
Solid acid, filtered and tiled . .	"	126.8	"	1.1	" 13.2
drainings from the solid. . . .	"	127.5	"	4.5	" 31.2

Owing to the small iodine additions, the addition of bromine in chloroform was then tried, and the values from these addenda are given in the above table as J_2. These indicate that the amount of the $\beta\gamma$-acid at equilibrium does not exceed 20%, as this acid can be considered almost certainly to add bromine in chloroform to very nearly 100% in 30 minutes, the time used, while the $\alpha\beta$-acid may also add it, but to a much less extent in this time. The method of filtering off the solid from the distillate and draining it on a tile did not seem to give perfect results as the last traces of liquid could not be removed by this method, while the acid (m.p.35.5°) could not be recrystallised from any solvent owing to its tendency to supercool and form an oil. Eventually the $\beta\gamma$-acid present was removed by partial esterification according to the method of Linstead[1] but using smaller proportions of the esterifying agents. The esterifications performed were rather drastic, and removed some of the $\alpha\beta$-acid, but ensured the removal of all of the $\beta\gamma$-acid and yielded the $\alpha\beta$-acid in a high state of purity. The acid was mixed with an equal volume of N alcoholic hydrochloric acid and twice this volume of absolute alcohol. In the case of the solid portion of the product, the mixture was allowed to stand for three hours, heated on

the steam for thirty minutes under reflux, and the mixture poured into three volumes of an aqueous solution of excess sodium carbonate. The upper layer of ester was removed; the alcohol present in the aqueous layer removed at the pump, and the last traces of ester extracted with ether. The pure acid was obtained on acidifying the aqueous solution as described previously, under ether, separating, extracting the acid with ether, washing the combined ethereal extracts with water, drying the solution over calcium chloride, and distilling off the ether. The acid was finally distilled in vacuo. More pure $\alpha\beta$ -acid was obtained from the drainings by esterifying them with the same proportions of alcohol and acid for eight hours in the cold and for one hour on the steam. The liquid was worked up in the same way and yielded an acid identical in properties with that from the solid portion. Pure Δ-1-cyclohexene carboxylic acid is characterised by :-

	Pure acid from solid portion	Pure acid from drainings.
E. (calc. 126.1)	126.1	126.1
J. (Bromine; 5 mins.)	1.8	1.7

The pure acid has m.p. 38° C.

The acid impurity that had been removed as ester was recovered from the distilled ester by alkaline hydrolysis in the cold in the manner described for $\beta\gamma$-iso-hexenoic acid (p. 57.) The acid was distilled (b.p. 139° - 145°/13 mms.) and dissolved in three volumes of dry chloroform and the liquid cooled in a freezing mixture. To it was added drop by drop, a solution of bromine in the same solvent (10% by volume) until the colour of the bromine in the reaction mixture was

just permanent, a white solid having commenced to separate towards the end of the reaction. The chloroform was removed at the pump, and the white solid residue was recrystallised from benzene and petroleum ether. This had m.p. 167.5°, both alone an admixed with pure dibromoacid obtained in a similar way from the βγ-acid. This shows that the αβ-acid has equilibrated to the βγ-isomeride under the influence of boiling alkaline solution. The amount of βγ-acid so formed, however, was small and could not be conveniently used as as preparative method.

Ethyl ester of Δ-1-cyclohexen carboxylic acid.

This was made from the silver salt of the pure acid and ethyl iodide as described for the case of the ester of βγ-butenoic acid (p. 54), although it was not found necessary to use acetone as a precipitating agent in this case. The overall yield of the ester was 73%, a mobile liquid with the usual odour of unsaturated esters combined with the odour of ethyl benzoate, and possessing the physical properties given below.

b.p. 96°/16 mms. n_D 1.4700

d_4 0.9999

whence $[R_L]_D$ 42.98 (calc. 42.63)

(viii) Δ -2-cycloHexene carboxylic acid.

For the preparation of this acid several methods were tried, the first being that of Aschan.[36] His conditions were reproduced as accurately as possible in the following way : 50 gms. of benzoic acid were dissolved in 250 c.c.s of 10% caustic soda solution, and heated on the steam under an

air reflux condenser, with passage of carbon dioxide through the liquid by a wide glass tube. 1200 gms of sodium amalgam were added in three equal portions, the reaction being allowed to finish in each case before adding the next portion. The liquid was cooled, the mercury removed, and the residual liquid acidified by addition of sulphuric acid, the organic acid being obtained by four extractions with ether. The ether was distilled off from the combined extracts, the acid remaining being dissolved in the above amount of caustic soda solution and the process repeated with a second 1200 gms. of amalgam. On recovery of the acid in the usual way, Aschan claims that he obtained an oil, permanently liquid. The result obtained by the process was a semi-solid mass, still conataining a considerable proportion of unchanged benzoic acid. The reductions were continued in this way until a permanent oil was obtained. After using about 10 kgs. of amalgam this stage was reached, but the oil contained only a little of the $\beta\gamma$-acid, extensive change having occurred to the $\alpha\beta$-isomer. The method was tried repeatedly, but with disappointing results. Slight variations were also introduced as, for instance, the boiling of the solution over a flame, but no appreciable amount of the desired acid was obtained.

The next attempt to obtain the acid was based on the work of Herman[62] and also Mettler,[63] on the reduction of aromatic compounds in cells. The apparatus finally adopted was as follows: the anode, a corrugated lead sheet, was supported in a porous pot containing the anolyte, a 10%

aqueous solution of sodium sulphate, which was kept neutral during the passage of the current by occasional addition of concentrated caustic soda solution. The pot and its contents were supported in a beaker, the bottom of which was covered by a layer of mercury. This was the kathode, connection being made in the usual way via a piece of platinum wire fused through the bottom of a glass tube, and dipping into the mercury. The katholyte was a normal solution of caustic soda in which was dissolved the benzoic acid. This was stirred vigorously during the reaction and was also provided with a thermometer for use at elevated temperatures.

At first the strictly kathodic-hydrogen method of reduction was tried, working at 18 volts with a steady current of 5 amperes over a mercury surface of 300 sq. cms. No reduction was detected even after long passage of current in the cold. The whole cell was warmed to 80° but still no reduction occurred. Also the effect of passage of carbon dioxide was tried in both cases, but with no result. The current density was then increased by reducing the size of the mercury surface to 10 sq. cms., and the new current density was tried under all the conditions described above. No reduction occurred, the only difference between the two sets of conditions being that at the higher current density solid lumps of sodium amalgam formed in the mercury. In the face of the above results, attempts at electrolytic reduction were then abandonned and attention once more directed to reductions by sodium amalgam. No reductions in acid

solution, of course, are possible due to the fact that under these conditions the -COOH group of the benzoic acid is preferrentially reduced to $-CH_2.OH$. After three test experiments, the method described below was adopted. 15 gms. of benzoic acid were dissolved in 75 ccs. of 10% aqueous sodium hydroxide solution (which is a very slight excess over the amount required to neutralise the acid) and the solution placed in a 250 cc. flat-bottomed flask fitted with a reflux air condenser and a wide tube dipping well into the liquid through which a steady stream of carbon dioxide was passed. 5% sodium amalgam was prepared by plunging 150 gms of sodium in one lump into 2850 gms of warmed, dry mercury in an iron mortar, and immediately covering the latter with a heavy weighted lid. The reaction was very violent. The amalgam was allowed to cool and broken up to pieces the size of a large pea. The aqueous solution of sodium benzoate was heated in a steam bath and 150 gms of the amalgam added. After the reaction had ceased (about five hours) the mercury remaining was removed and a second addition of 150 gms of amalgam was made together with 50 ccs. water. The process was repeated three times, after which the mixture was semi-solid with crystals of sodium carbonate. It was cooled, carefully acidified with sulphuric acid (50% by volume) and the silica allowed to settle. The organic material was extracted four times with ether, the ether distilled off, and the residue, which had the consistency of butter, was dissolved in 75ccs. of the caustic soda solution and the above process repeated, the exhausted mercury being removed each

time before the addition of a fresh portion of amalgam. When 900 gms. of amalgam had been used, the acid recovered was a permanent oil and the reductions were stopped. Continuation would undoubtedly have produced more βγ-acid, but there would also have been a notable increase in the amount of the αβ-acid formed by tautomeric change. The liquid was dried in ethereal solution, the ether distilled off, and the crude oil dissolved in three volumes of dry chloroform, the solution so obtained being cooled in a freezing mixture. To this was added slowly and with shaking, a 20% (by volume) solution of bromine in chloroform, the whole being kept quite cool to inhibit substitution in the ring by the bromine , and also the formation of dibromide from any αβ-acid present. The solid 2.3-dibromo-cyclohexane carboxylic acid soon began to separate as a white crystalline solid, addition of bromine being continued until the colour of the halogen was permanent for a few minutes. The solvent was removed at room temperature at the pump, and the white solid remaining was washed out with petroleum ether and filtered. One recrystallisation of this solid from benzene and petroleum sufficed to yield the pure 2.3-dibromo-acid, m.p. 167.5° (cf. Aschan[36]; from this solvent, m.p. 163°; from glacial acetic acid m.p. 166°). Equivalent found 285.6, (calc. 286. 0). Fifteen runs of the above process produced , from 225 gms. benzoic acid, 160 gms of pure recrystallised dibromide.

The pure βγ-acid was obtained from this as follows: 80 gms. of the solid were dissolved in 800c.c.s of absolute

alcohol in a flask fitted with a reflux condenser and inlet tube to allow the flask to be filled with nitrogen, as the acid appears to be sensitive to atmospheric oxygen. 30 gms. (2 molecular proportions) of zinc dust were added and the whole allowed to stand with occasional hand shaking for 30 minutes. During this time the temperature of the reaction mixture rose to about 60°. It was then heated (in an inert atmosphere) on the steam for 45 minutes to ensure completion of the reaction. The liquid was cooled, filtered from excess zinc, and the filtrate poured in to three volumes of a solution of excess sodium carbonate. The precipitated zinc carbonate was filtered at the pump, and thoroughly washed by shaking several times with water. The filtrate and washings were extracted twice with ether to remove basic and neutral impurities, and filtered again from the zinc carbonate thrown down by the ether extraction. It was acidified with hydrochloric acid, and extracted five times with ether. The combined extracts were washed twice with brine to remove alcohol, dried, the ether distilled off in an inert atmosphere, and the residual acid distilled in vacuum in an atmosphere of nitrogen, having a boiling point 124°/12 mms. Equivalent of the acid (by baryta) 126.2 (calc. 126.1). It was obtained in 84% yield as a colourless liquid, smelling like the pentenoic acids, but not so strongly.

Trial experiments were made to find the best method of halogen addition. The percentage addition of iodine in potassium iodide solution to the acid in sodium bicarbonate was too small for practical purposes, and so the addition of

bromine in chloroform solution was tried, as this depends on direct addition with formation of the dibromo-acid, and not of the γ-iodolactone (or γ-bromolactone in this case) as does the addition of iodine in alkaline solution. Additions performed for five minutes were found to be satisfactory. The following are the physical properties of two samples of the acid from two different runs of the preparation :-

m.p.	7.0°	6.5°
b.p.	120°/10 mms.	130°/18 mms.
J.	92.4	93.2
n.	1.4814	1.4813
d.	1.0820	1.0814
$[R_L]D$.	33.19 (calc. 33.40).	33.19

(ix) 3-Methyl Δ-1-cyclohexene carboxylic acid.

This acid was prepared by a method very similar to that used for Δ-1-cyclohexene carboxylic acid, several minor differences will, however, be noticed.

The cyanhydrin of the ketone, m-methyl cyclohexanone, was not prepared by the method previously used, as this ketone shows a very great tendency to condense in the presence of strong mineral acids to form high-boiling oils and gums. Test experiments showed that the following procedure gave very good results. Sodium bisulphite (1 mol.) was prepared in saturated aqueous solution from 227 gms. of crystalline sodium carbonate by passing in sulphur dioxide until the pale apple-green colour appeared. The liquid was cooled in ice and 170 gms. (1 molecular proportion) of m-methyl cyclohexanone

were added, the whole being very vigorously shaken until the bisulphite compound of the ketone suddenly commenced to separate in white crystals. The pasty mass was allowed to stand overnight to complete the reaction and then broken up with a glass rod. To this was added potassium cyanide (one molecular proportion; 104 gms. in 200 ccs. water) and 300 ccs. of ether. The ether was found to be necessary to remove a protective coating of the oily cyanhydrin that formed on the bisulphite compound and tended to inhibit the reaction. The flask was stoppered, shaken in ice for 30 minutes, and then in the mechanical shaker overnight. At the end of this time no solid was left and the reaction was complete. The ethereal layer was removed and the aqueous residue extracted three times with ether, the combined ethereal layers washed with water, dried thoroughly, and the ether removed in vacuum at room temperature, as the cyanhydrin is reputed to decompose at 100° to reform the ketone and hydrocyanic acid (cf. Markownikow and Smirnow[60]). The cyanhydrin could be distilled in small quantities if stabilised by the addition of a few drops of concentrated sulphuric acid, the b.p. being 133°/16 mms. There was, however, appreciable decomposition and the bulk of the cyanhydrin was dehydrated undistilled, this having been shown by test experiment to be the best method. The dehydration was done exactly as described for the nitrile of the unsubstituted cyclohexene acid see p. 59. The nitrile was distilled in vacuo. There was no low fraction, any free ketone having apparently, condensed completely to form oils, found in the high fraction. The fractions collected were

those boiling over the ranges 88-93/17 mms., the bulk of which boiled at 92-93/17 mms. (90 gms.) and some high fraction which, on refractionation yielded a further 13 gms. of nitrile boiling at 90-95/16 mms. Redistillation of the nitrile does not yield a steadily boilng fraction, but this may be due to the existance of two forms of the nitrile in the liquid.

The pure nitrile so obtained was hydrolysed by boiling it with two mols. of 10% aqueous potash solution under reflux condenser . The reaction was much slower than that previously described, the nitrile being dissolved in 11 hours although about 50 hours boiling were then needed to complete the reaction. The liquid was then cooled in ice and very carefully acidified with hydrochloric acid, keeping cool, as the $\beta\gamma$-acid shows a great tendency to form lactone (cf. $\beta\gamma$-iso hexenoic acid). For the same reason, the acids were not distilled in steam from the solution, as tests have shown that by this method considerable lactone was produced. Perkin also obtained some lactone by steam distillation of the $\beta\gamma$-acid that he had prepared by dehydrobromination of the γ-bromoacid. The acidified solution was extracted with ether four times, the combined extracts washed with water, dried, the ether distilled off, and the residual oil fractionally distilled in vacuo. There was obtained a fraction (12 gms) boiling over the temperature range 57 - 70/16 mms. (mixed acid, ketone, and nitrile) and the bulk distilled at 126-8/7 mms. (145-6/15 mms.) This was the acid required, of equiv. 141.0 (calc. for the methyl cyclohexene carboxylic acids: 140.1) and was obtained in 77% yield. There was a negligeable high fraction and

residue. The acid so obtained was tested for the presence of βγ-acid by addition of bromine in chloroform solution under analytical conditions for five minutes, and J was found to be 23% indicating the presence of about 22% of the βγ-acid in the mixture. The proposed method of separation was by a long partial esterification to remove all the βγ-acid as ester and subsequent purification of the αβ-acid by recrystallisation of the calcium salt. This was applied as follows.

The acid was partially esterified in the cold for twenty hours using 100 ccs. of N-alcoholic hydrochloric acid and 200 ccs. of absolute alcohol to every gm. mol. of the acid. The reaction was stopped in the usual way, the ester extracted with ether and set aside, the alcohol removed from the aqueous liquid at the pump, and the αβ-acids obtained by acidification of the residue and ether extraction in the usual manner. The crude acid remaining after distilling off the ether was dissolved in a slight excess of ammonium hydroxide solution, (1 part ammonia s.g. 0.880 ; 1 part water), and ten volumes of very concentrated calcium chloride solution added. The whole was well stirred and allowed to stand, on the steam for 30 minutes and finally overnight. The solid was filtered off, washed with calcium chloride solution, and the solvent removed by pressing or rubbing on a tile. From the accumulated mother liquors more salt can be salted out by the addition of calcium chloride The substance was recrystallised from dilute calcium chloride solution in long shining white needles of the calcium salt of the Δ-l- acid, which were filtered off, washed with calcium chloride solution, and dried. The pure acid was obtained by

acidifying a suspension of this salt in water with hydrochloric acid. The liquid was extracted four times with ether, the combined ethereal extracts washed with water, dried over calcium chloride, the ether distilled off, and the acid finally distilled in vacuum. This was very pure, there being neither high nor low fraction. 50 gms of the pure 3-methyl-Δ-1-cyclohexene carboxylic acid were obtained boiling at 130°/7 mms. The acid was obtained solid on freezing or seeding and remained so at room temperature. Perkin was unable to obtain his acid completely solid and claimed that the method of purification through the calcium salt was not satisfactory, due to the presence of the Δ-6-acid. To check the purity of the above acid a small amount was "purified" as follows :-. The acid was dissolved in carbon disulphide (equal volume), cooled in ice, and the theoretical amount of bromine in three volumes of the same solvent were added, slowly. If the bromine be added all at once, the reaction becomes very vigorous and substitution probably occurs. The liquid was then heated under reflux on the steam for three hours to complete the formation of the $\alpha\beta$-dibromo-compound, the solvent was removed in vacuo, and the residual oil soon formed a hard, crystalline mass. This would not recrystallise from the usual solvents but was eventually obtained pure from formic acid (s.g. 1.2) or formic acid-water. Pure 1.2-dibromo-3-methyl cyclohexane carboxylic acid formed clusters of small white plates melting at 119° C. Equivalent: 300.0 (calc. 300.0). Bromine found 53.2% (calc. 53.3%). The pure $\alpha\beta$-acid was obtained from this in the same way as Δ-2-cyclohexene carboxylic

acid was obtained from the corresponding dibromide (p. 68) and was shown to be identical with the original acid from the coincidence of the melting points (26°). Hence the acid from the calcium salt appears to be the pure acid and was used without further treatment. It possessed the following physical constants:

m.p.	26° - 27.0°	n.	1.4917
b.p.	130°/7 mms.	d.	1.0501
J(bromine; 5 mins.)	2.0	$[R_L]_D$	38.62 (calc. 38.02).

(x). 3-methyl Δ-2-cyclohexene carboxylic acid.

This acid has only been previously made by Perkin[37] in an impure form from the corresponding γ-bromo acid. In the present case the acid has been obtained from the Δ-1-isomer by equilibration of this acid by boiling caustic alkali solution. Part of the acid used was that obtained from the ester resulting from the purification of the acid from the alkaline hydrolysis of the unsaturated nitrile as described above. The ethereal solution of the ester was dried, the ether distilled off, and the ester distilled in vacuo. 24 gms of this liquid boiling at 84°-9°/5 mms. was obtained and was hydrolysed in the cold by alkali in the way described on p. for the βγ-iso-hexenoic acid. The acid so obtained was distilled and prepared for iodine addition experiments in the usual way (p. 101), but, immediately on addition of the iodine solution to the solution of the acid there was formed a solid precipitate, undoubtedly the β-iodo-γ-lactone. Occlusion of iodine by this solid rendered the results unrepeatable and

consequently the addition of bromine in chloroform was used, for the space of five minutes, although other times were tried. The physical properties and halogen additions appertaining to this acid are quoted here.

b.p.	123°/7 mms.	n.	1.4839
E.	140.9	D.	1.0508

whence $[R_L]_D$ 38.11 (calc. 38.02)

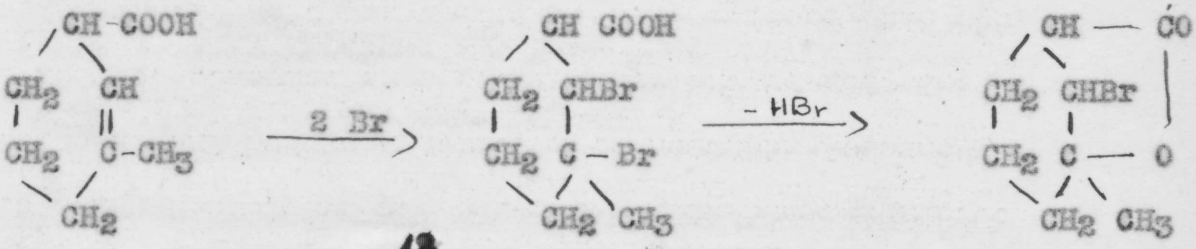
Time.	Additions of iodine	Additions of bromine.
5 minutes.	61.2	79.4
10 "	63.9	80.0
30 "	66.4	82.0

Hence there still appears to $\alpha\beta$-isomer present in the acid, so it was partially esterified for four hours and the reaction mixture worked up as usual. The recovered acid was again esterified to recover more $\beta\gamma$-acid, for six hours. The acids obtained by this "fractional partial esterification" were distilled and bromine additions performed on them

First "fraction".	7.1 gms.	J.	96.1
Second "fraction".	4.1 gms.	J.	95.1

This would hence appear to be the pure $\beta\gamma$-acid, or, at any rate, the acid in a form as pure as it is possible to obtain it by this method. Several attempts were made to obtain a solid dibromoide from the various samples of the acid by careful addition of a solution of bromine in chloroform to a solution of the acid in the same solvent, (carbon disulphide was also used). The solution was then either allowed to stand; or the solvent allowed to evaporate spontaneously; or removed at the pump. In all cases much evolution of hydrogen

bromide occurred, and an oil was left. This is doubtless the bromolactone formed by the following reaction from the dibromide first formed :-



(cf. Fittig and Kraft [13] who found the same phenomenon in the case of teracrylic acid).

The acid also was only available in limited amount and so other methods of purification by methods that involved considerable loss, as, for example, regeneration from the p-toluidide, could not be used. However the acid undoubtedly contained, as a minimum, 95% of the required acid and was used as such.

The p-toluidide of the acid was made in order to characterise it, and was obtained as follows:- the olefinic was allowed to stand in a small Claisen flask fitted with a reflux condenser with two molecules of thionyl chloride for 30 minutes, and the reaction completed by heating on the steam for 45 minutes. The thionyl chloride remaining was removed at the pump and the residual acyl chloride distilled in vacuo, b.p. 90°/16 mms. This was dissolved in 10 volumes of ether, cooled in ice, and twice the molecular proportion of pure p-toluidine dissolved in an equal volume of ether was added. After standing for one hour, the liquid was shaken with a slight excess of dilute hydrochloric acid to remove all uncombined

p-toluidine as hydrochloride, the ethereal layer removed the ether evaporated off, and the residual p-toluidide allowed to solidify. Recrystallisation from petroleum (b.p. 60° - 80°) yielded the pure p-toluidide in tufted clusters of needles. m.p. 108-109°.

(b) Preparation of the reference compounds needed.

Lactones and associated compounds.

(i) γ-Valerolactone.

This lactone was obtained by the reduction of laevulic acid to γ-hydoxyvaleric acid, which ring-closes with great readiness to form the lactone. The preparation is based on the work of Wohlgemuth[47], Wolff[40], and Neugebauer[39].

Laevulic acid was prepared in the following way:- Sucrose (900 gms.) was dissolved in warm water (2 Litres) and 600 ccs. of concentrated hydrochloric acid added, The mixture was heated on the steam with occasional shaking for 48 hours. (Starch was also used in the place of sucrose in one attempted preparation according to Vanino[43], but was found to give rise to very extensive charring, sucrose being by far the more satisfactory starting material). The very dark liquid was filtered from the masses of charred material and these well washed with water. The filtrate and washings were evaporated on the steam for 24 hours to drive off all hydrochloric, formic, etc. acids present. The syrup so obtained was filtered again after dilution with an equal volume of water, and the solid washed. The filtrate and washings were exhaustively extracted with ether, the ether

distilled off, and the residual liquid distilled in vacuo. The laevulic acid boiled quite steadily at 161°/24 mms., and solidified readily to beautiful crystalline masses. 138 gms. of the acid were obtained, which could not be further purified by fractional fusion.

The acid was reduced to the corresponding hydroxy-acid by sodium amalgam (5%). The amalgam was made as described on p. 67, and this appeared to be the best reagent as it did not carry the reduction too far. The 138 gms of laevulic acid were dissolved in 440 ccs. of water and exactly neutralised by the addition of sodium hydroxide. 3 kgms. of sodium amalgam were added to the solution in the course of four days, the solution being stirred occasionally. Also, hydrochloric acid was added at intervals to reduce the concentration of the alkali present, although care was taken to keep the solution always strongly alkaline. After the amalgam had ceased reacting the mercury was removed, the solution made strongly acid by the addition of sulphuric acid, and boiled under reflux for fifteen minutes to complete the conversion of the γ-hydroxy-valeric acid to the γ-valero-lactone:

$$CH_3.CO.CH_2.CH_2.CO_2H \rightarrow CH_3.CH(OH).CH_2.CH_2.CO_2H \rightarrow CH_3.CH(O{-}CO).CH_2.CH_2$$

Laevulic acid. γ-Hydroxy-valeric acid. Lactone.

The lactone separated as an upper layer on cooling the solution and was obtained from this by extraction with ether five times. The ethereal solution was washed with sodium carbonate solution dried over calcium chloride, the ether distilled off, and the

lactone distilled in vacuum. This was apparently a very pure product and practically all distilled at the required temperature, 102°-103°/28 mms. in 46% yield.

The liquid was further slightly purified by allowing it to stand in contact with powdered anhydrous potassium carbonate in a vacuum desiccator overnight, but the original product was so pure that very little reaction occurred. Redistillation gave pure γ-valerolactone, a colourless, mobile liquid possessing the smell characteristic of lactones, that of coco-nuts, and having the following physical constants:

m.p.	-36°	n.	1.4322
b.p.	102° - 3°/28 mms.	d.	1.0529
M. (by baryta) 100.1 (calc. 100.1). whence		$[R_L]_D$	24.67
		Calc.	24.75)

The lactone, at low temperatures, formed a mass of shining white leaflets. It was characterised by conversion into a solid derivative, the one chosen being the amide of γ-hydroxy-valeric acid. Neugebauer[39] originally prepared this by a somewhat drastic reaction (in a sealed tube) between the lactone and concentrated aqueous ammonia, but Linstead,[1] showed that, in the case of the hexolactones, the reaction proceeded in the cold with this reagent. His method was tried as follows: the lactone was allowed to stand with half its volume of aqueous ammonia (saturated at 0°), until miscible, and then allowed to stand in a vacuum desiccator over concentrated sulphuric acid. This gave a very poor yield of the amide, a large amount of unchanged lactone being present. The next

attempt was by using alcohol as a solvent, but either cold or hot treatment gave no better results. Ether was also used, but negative results were obtained. The final method adopted was to dissolve the lactone in one half of its volume of aqueous ammonia solution, and to saturate the whole at 0°. The reaction vessel was stoppered and after 24 hours the liquid was again saturated with ammonia at 0°. The whole was allowed to stand for 24 hours and finally left in a vacuum desiccator over sulphuric acid until solid (2 - 3 days). It was triturated with ether, washed with ether, and dried on a tile (in a desiccator as the amide appeared to be very deliquescent). It was then recrystallised. Several of the usual solvents were tried, but from all or them the amide came out as an oil. It was finally obtained pure by recrystallising from chloroform under reduced pressure, the solvent being slowly removed at the pump. γ-Hydroxy-valeramide was obtained in large white glistening plates, in 92% yield, m.p. 52° C.

(ii) γ-Butyrolactone.

The first preparative methods tried were based on those of Fittig and Strom[42] as follows.

Sodium ethoxide was made as usual from 28.4 gms of sodium and 280 ccs alcohol and to it were added 162 gms. of acetoacetic ester, the mixture being heated on the steam under reflux for one hour to assure complete formation of the complex. The liquid was cooled and 100 gms of ethylene chlohydrin were run in. The reaction soon commenced with precipitation of sodium chloride and was completed by heating

on the steam for 23 hours. The alcohol was distilled off and the residue was divided into two halves, these being treated in different ways. The first half was treated as advised by Vanino[43] and Fittig and Strom.[42] The salt was filtered off, the solid well washed with ether, and the ether distilled off. The residual liquid was then run in a thin stream into a boiling solution of baryta (1½ molecular equivs.) in 33% aqueous solution. The whole was boiled for one hour under reflux, and for a further three hours in a dish to volatalise any ketones formed. The excess baryta was removed by passing in carbon dioxide until precipitation was complete. The mass was filtered, the barium carbonate well washed with water, and the combined filtrate and washings concentrated by evaporation until the volume of the liquid had been reduced to about 60 ccs. Concentrated caustic soda solution was added until all the barium present had been thrown out of solution, the liquid again filtered, and the filtrate and washings evaporated down on the steam, and refiltered. This solution of, presumably, the sodium salt of γ-hydroxy-butyric acid was acidified with fuming hydrochloric acid, the liquid boiled underreflux for a few minutes to aid lactonisation, and the liquid extracted continuously with ether for 24 hours. The ethereal extract was dried, the ether distilled off, and the residue distilled. 0.2 gms of impure lactone were obtained.

The second half of the condensation product was then taken and water added to dissolve the salt present, the liquid being thoroughly extracted with ether to obtain the

organic material present. The ether was distilled off and the liquid was run into the same amount of boiling baryta solution as was the first half, and treated in the same way down to the stage of evaporating in a basin to drive off ketones. The liquid was then treated with a slight excess of sulphuric acid and the precipitated barium sulphate filtered off and washed. The filtrate and washings were boiled under reflux for ten minutes and the liquid exhaustively extracted with ether. The ethereal solution was dried, the ether distilled off, and the residue distilled to yield 0.5 gm. of lactone.

The final successful method used was based on the work of Fruhling.[44] Trimethylene chlohydrin was made from trimethylene glycol by the method of Marvel and Calvery[45]. A large hard-glass test-tube was fitted with a rubber stopper carrying a dropping funnel, a thermometer, a lead in tube, (both of the latter reaching to the bottom of the vessel) and a lead-away tube from the top of the apparatus connected to a Liebig condenser. This was attached by a cork to a distilling flask, to the side arm of which was connected a small reflux condenser to trap any vapour spray in the stream of gas. About 20 ccs. of trimethylene glycol were placed in the test-tube and heated to 150-165° in an oil bath, while a very rapid stream of dry hydrogen chloride was blown through the liquid. More trimethylene glycol was run into the flask at the same speed as the chlorhydrin distilled over. The red distillate collected consisted of trimethylene glycol and chlorhydrin, water, and hydrochloric acid, and was heated on the steam for

one hour to drive off the hydrochloric acid. It was then distilled in vacuo and the fractions collected were those boiling at : below 72°/29 mms. ; 72°/29 mms. - 89°/14 mms. ; 89°/14 mms. - 108°/13 mms. The residue was small and was discarded. The high fraction was mostly unchanged glycol, while the low fraction was saturated with potassium carbonate and the upper layer of chlorhydrin that separated was removed, dried over potassium carbonate, added to the main fraction, and the whole redistilled. The fraction collected was that boiling over the range 64°/14 mms - 68°/ 12 mms., the bulk of which boiled at 64°/12 mms.

The cyanhydrin was obtained from this chlorhydrin by a method similar to that used by Jacobsen and Heidelberger[102] for ethylene cyanhydrin. 53 gms. of trimethylene chlorhydrin were dissolved in 200 ccs. of rectified spirit and boiled gently on the steam while a solution of potassium cyanide (41 gms of 95% single salt i.e. 10% excess over the theoretical amount, in 60 ccs. water) was run in. The formation of solid soon commenced and the reaction was considered to be complete after boiling on the steam under reflux for 23 hours. The trimethylene cyanhydrin (γ-hydroxy-butyronitrile) so formed was not isolated, but was hydrolysed by the addition of 41 gms. of potassium hydroxide in 45 ccs. water, and boiling the mixture for 12 hours, at the end of which time evolution of ammonia had ceased. The alcohol was distilled off at atmospheric pressure, and the aqueous solution of the potassium salt of γ-hydroxy-butyric acid was extracted twice with ether to remove neutral and basic impurities. The

residual aqueous liquid was made strongly acid to congo red with concentrated hydrochloric acid, and extracted continuously for 40 hours with ether. The practically colourless ether solution was dried over calcium chloride, the ether distilled off, and the liquid remaining was distilled at atmospheric pressure in order to eliminate water from the γ-hydroxy-acid and produce the lactone. The water was allowed to fractionate off and the crude lactone distilled over boiling at 200-210°. The liquid was completely dried and freed from traces of acid by two treatments with potassium carbonate in the usual way, and finally distilled in vacuo to give pure γ-butyrolactone in 30% yield calculated on the chlorhydrin. It had the normal lactone odour and appearance when solid, and the physical properties given here.

m.p.	-48.0°	n_D	1.4354
b.p.	83.5°/12 mms.	d_4	1.1299
M.	86.2 (calc. 86.1)	whence $[R_L]_D$	19.88 (calc. 20.1)

(iii) γ-iso-Hexolactone.

This was prepared very simply by the method of Linstead[1], recently discovered.

βγ-iso-Hexenoic acid was boiled in a Geisler flask for five hours under reflux, at the end of this time conversion to the lactone was practically complete. The residual acid was removed by washing the ethereal soution of the product with potassium carbonate, distilling off the ether, and allowing the residual lactone to stand with a little anhydrous potassium carbonate in a vacuum desiccator for 24 hours. The lactone was finally distilled in vacuo, b.p. 94°/20 mms.

The liquid had the typical lactonic odour of coco-nuts, and was obtained solid in long flat needles by slightly super-cooling and scratching with a glass rod. It had m.p. 9.0° M. 114.1 (calc. 114.1).

(iv) cycloHexanolide 1:3.

As mentioned in section 2, this was prepared by the method of Perkin and Tattersall,[38] the complete synthesis being performed as follows:

m-Hydroxy-benzoic acid was prepared in the classical way according to the method of Offerman.[46] 500 gms. of benzoic acid were placed in a 3-litre flask with 1000 gms. of fuming sulphuric acid (20% SO_3), and heated to 210° (registered, on a thermometer in the liquid). At about 50° the solution of the benzoic acid was complete. After five hours a test portion of the mixture gave no precipitate of benzoic acid on adding to water and the reaction was complete. The liquid was cooled and poured onto 2 litres of ice and water, and the resultant clear brown liquid added to 5 litres of boiling saturated salt solution, at the same time adding 250 gms of salt. On cooling, the mono-sodium salt of the m-sulphonic acid of benzoic acid crystallised out in a fairly pure state. It was not further purified but was filtered off, washed with brine, dried in the steam oven and powdered. It was converted into the disodium salt by stirring it into a mixture of 400 gms of caustic soda and 250 ccs. of a concentrated solution of the latter, heated on the steam. It was allowed to cool, broken up, and added with stirring to a fused mass of 500 gms. each of sodium and potassium hydroxides. The

temperature was raised to 210° - 215° and kept at this level for 2 hours, the melt being continually stirred. At the end of this time reaction was complete and the melt was cooled, leached out with water and partially neutralised with concentrated hydrochloric acid. The solid that separated was filtered off, the filtrate made acid to Congo red by addition of hydrochloric acid, and the solid that separated from the cooled solution was recrystallised from water to yield pure m-hydroxy-benzoic acid in glistening plates.

Two chief methods of reduction of the acid to the fully saturated cyclohexane acid have been described. The first was that of Perkin and Tattersall[36] by sodium in boiling alcohol; the second that of Balas and Srol[64] by reduction with gaseous hydrogen using the platinum catalyst of Adams.[65] The latter was found to be unsuitable for the preparation of large quantities of the acid and thus the original method of Perkin was adopted. 50 gms. of m-hydroxy benzoic acid were dissolved in one litre of absolute alcohol and the liquid boiled on the steam under a good reflux condenser. 155 gms. of sodium were added as quickly as possible and the reduction allowed to proceed vigorously. The precipitate of the sodium salt of the unreduced acid soon dissolved. When the reaction slowed down, more alcohol was added and heating continued until the sodium had been completely dissolved. The clear liquid was poured into an equal volume of water and a slight defficiency of concentrated hydrochloric acid was added, leaving the liquid slightly alkaline. The solution was evaporated on the steam bath

until the alcohol had been completely removed and the volume was reduced to about one fifth of the original. The cooled liquid was made acid to Congo red by addition of hydrochloric acid, the sodium chloride filtered off and washed, and the aqueous liquid exhaustively extracted with ether. The extract was dried, the ether distilled off, and the residual gum allowed to stand in a vacuum desiccator when, after a short time, it solidified. The solid was cis-3-hydroxy-cyclohexane carboxylic acid, and was mixed with a little of the trans-isomer. From 150 gms of the benzenoid acid were obtained 100 gms. of the fully reduced acids.

This mixture was converted into lactone by dry distillation in vacuo. The mixture was first heated to 170° at ordinary pressure for 30 minutes to allow water, that is formed by the dehydration of the hydroxy-acid to the lactone, to fractionate off, and the remaining liquid was distilled through a column under reduced pressure. The lactone distilled over at 120° - 140°/20 mms. and solidified in the receiver. A further small high fraction was collected at 177° - 190°/20 mms., which deposited crystals of the trans-3-hydroxy-cyclo-hexane carboxylic acid. The lactone was redistilled, and finally purified by recrystallisation from petroleum ether (b.p. 60° - 80°). The needles of the lactone so obtained were always very sticky, but repeated recrystallisation would not change the melting point, and it was hence conidered to be pure. It had a faint odour of coco-nuts, and boiled steadily at 120°-123°/19 mms. The m.p. was 119°; molecular weight(by baryta), 126.0 (calc. 126.1).

(v) 1-Methyl-cyclohexanolide 1:3.

The method of Perkin and Tattersall[38] was used, with a few modifications to improve the purity of the product. The starting point in the synthesis was cis-3-hydoxy-cyclo-hexane carboxylic acid, and was obtained by the reduction of m-hydroxy-benzoic acid as described in the previous preparation. Perkin obtained his pure cis-acid by tiling the crude solid reduction product, and recrystallising from ether. In the following preparation, the acid was obtained very pure by distilling the mixed cis and trans acids to obtain the pure lactone as described above, and subsequently heating the lactone with a slight calculated excess of 10% aqueous caustic soda solution under reflux on the steam for 15 minutes. This formed the sodium salt of the cis-hydroxy-acid in quantitative yield, being the direct reversal of the ring-closure of this latter acid to the lactone. The solution was cooled in ice and carefully acidified by the addition of a slight calculated excess of hydrochloric acid , exhaustively extracted with ether, the extract dried, the ether distilled off, and the hard solid which was left was recrystallised from ethyl acetate to give pure cis-3-hydroxy-cyclo-hexane carboxylic acid, melting at 132° (perkin: 130-2° from ether).

43 gms. of this acid were dissolved in 172 ccs. of water and oxidised to the corresponding keto-acid in the following manner: the aqueous liquid was heated to a temperature of 45°, and throughout the oxidation it was kept at between 43° and 47°. To it was added, a little at a time, a solution

of 60 gms. of potassium dichromate and 43 ccs. of concentrated sulphuric acid in 258 ccs. of water, each addition being allowed to become completely reduced before adding any more. After eight hours the oxidation was complete and the liquid was cooled, saturated with ammonium sulphate, the alum filtered off and washed, and the residual aqueous liquid very thoroughly extracted with ether. The ethereal solution was dried, the ether removed, and the crude residual acid (40 gms.) immediately esterified by addition of 103 ccs. of N-alcoholic hydrochloric acid and 48 ccs. of absolute alcohol. The liquid was well mixed and allowed to stand at room temperature for three days, and finally heated on the steam for one hour under reflux. The use of such dilute hydrochloric acid was necessitated by the tendency of the keto-acid to condense in the presence of stronger acid. The reaction mixture was poured into four volumes of water, the ester obtained by extraction of the liquid several times with ether, and the solution dried after being washed with sodium carbonate solution and water, and the ether distilled off. The ester so obtained was very carefully purified by repeated fractional distillation in vacuo, particularly to remove any hydroxy-ester present (b.p. 140°/9 mms.). The final fraction collected was that boiling at 120°/10-8 mms. in 31% yield (16 gms). The final stage of the synthesis was the introduction of the methyl and hydroxyl groups by subjecting the above ester to the Grignard reaction with methyl iodide. The usual apparatus for Grignard reactions was used, the mercury-sealed stirrer being of the "scraper" type. 5 gms. of dry magnesium turnings

were placed in the flask and 15ccs. of a solution of 30 gms. of redistilled methyl iodide in 15 ccs. ether (dried over sodium) were added. The vigorous reaction started immediately. 100 ccs. of dry ether were added and then the rest of the methyl iodide solution. When the magnesium had all dissolved, 16 gms. keto-ester, in 16 ccs. of ether, were added drop-wise to the well stirred liquid. After all had been added and refluxing had ceased, the liquid was boiled on the steam for two hours to complete the reaction. The thick oil gradually solidified, and after standing overnight it was decomposed under the tap, acidified with hydrochloric acid and the ether layer removed. The residual aqueous layer was very thoroughly extracted with ether, the combined ethereal extracts washed with a little sodium thiosulphate to remove iodine, then with water, and the solution finally dried and the ether distilled off. 16 gms of crude ester were obtained. This was boiled under reflux on the steam with two molecular proportions of potassium hydroxide in 10% methyl alcoholic solution for one hour. The liquid was the diluted with twice its volume of water and the alcohol, together with a little unidentified oil, was removed at the pump. The residual solution was extracted twice with ether to remove neutral and basic impurities; made acid to Congo red with hydrochloric acid, and the hydroxy-acid obtained by exhaustive extraction with ether after saturation with ammonium sulphate. The ethereal extracts were dried and the ether distilled off. The residual oil containing the hydroxy-acid required, was converted into lactone in an analogous

manner to that previously described (p. 88), by slow dry distillation in vacuum. The fraction boiling at 128°/22 mms. was collected (Perkin gave 145°/20 mms.), weighing 4,6 gms. This was dissolved in ether, washed with sodium bicarbonate and water, dried, the ether distilled off, and the last trace of acid removed in the usual way by potassium carbonate in a vacuum desiccator. The lactone was finally distilled at 120° - 1°/20 mms. This was a solid of m.p. after draining on a tile, 45°. Perkin's product was an oil, due probably to the presence of some neutral oil that he failed to remove. The solid had the usual lactonic odour, and formed over-lapping plates on freezing.

Bromo-acids and associated compounds.

(i) β-Bromovaleric acid.

Dry αβ-pentenoic acid was weighed into a tube and the whole cooled in ice. A stream of pure dry hydrogen bromide (see p. 109) was passed into the liquid, slowly as to avoid overheating the acid, until a slight calculated excess had been absorbed. The tube was lightly stoppered, and after a few minutes the liquid suddenly solidified with evolution of uncombined gas. The white solid was recrystallised from light petroleum and the pure β-acid was obtained in long white needles. (Found: E., 180.8; %Br, 44.3% : calc. E., 180.9; %Br, 44.2%). It had m.p. 58.5° - 59°. This method of preparation is much more convenient than that of Fittig and Spenzer[67]; and Fittig and Mackenzie[68].

(ii) γ-Bromovaleric acid.

The method of Wohlgemuth[47] was used, a product being

obtained that appeared to be slightly purer than his acid. 12.25 gms. of γ-valerolactone were mixed with 3.6 ccs. of water and the mixture saturated with hydrogen bromide at 0°. It was allowed to stand in the cold for 24 hours and then heated to 100° for one hour under a ground in condenser. The liquid was cooled and the process repeated. The cooled liquid was poured into a large test-tube containing ice and water, and the oily drops of the bromo-acid that collected in the bottom of the tube soon solidified as the temperature dropped considerably. This solid was powdered and dried by standing in a vacuum desiccator containing sulphuric acid for two days, being kept in an ice chest to stop the acid melting. The solid was dissolved in light petroleum, decolourised by standing for ten minutes with recently activated charcoal, and obtained as a white, crystalline solid by cooling in a freezing mixture of solid carbon dioxide and ether, the crystals being finally dried in vacuo.

Yield 77%. m.p. 22.5° (cf. Wohlgemuth; 21°)

Equiv. 182.4 (calc 181.0).

(iii) β-Bromobutyric acid.

αβ-butenoic acid (trans-crotonic acid) was fused in a bath at 80° and treated with dry hydrobromic acid gas for two hours, the oily liquid being allowed to cool in a stream of the gas. After standing overnight it was again saturated, and the excess gas removed in a vacuum desiccator over potash in the usual way, until a constant, (calculated) weight was attained. The pale yellow liquid solidified at

-15° to a mass of white plates of β-bromo-butyric acid. This had m.p. 17° - 17.5°. (cf. Brulé,[49] who obtained the acid by a more vigorous reaction, and who quotes m.p. 17° - 18°). Equivalent by baryta, 169.2 (calc. 167.0).

Ethyl β-bromobutyrate.

The ethyl ester was obtained by the method that Wohlgemuth[47] used for the ester of γ-bromovaleric acid. 6.85 gms. of pure β-bromobutyric acid were poured slowly into an ice-cooled mixture of 0.7 ccs. concentrated sulphuric acid and 5.5 ccs. absolute alcohol. The mixture was allowed to stand in ice for a few hours, and then at room temperature for 48 hours. After six hours a large amount of ester had separated out at the bottom as an oil. The liquid was poured onto four volumes of ice and water, the lower ester layer run off, and the residual aqueous layer extracted three times with ether. The combined ester and ethereal extracts were thoroughly washed with a saturated solution of sodium bicarbonate to remove any acid present, then with water, dried, the ether distilled off, and the ester distilled in vacuo. Ethyl β-bromobutyrate (cf. Lespieau[70]) so obtained in 75% yield boiled at 81°/17.5 mms. without trace of decomposition. The physical properties are given below, together with the amount of bromine found present in the ester. This latter figure shows that no gross decomposition had occurred during the esterification. Any attempt to freeze the ester to a crystalline solid merely resulted in the formation of a glass.

b.p. 81°/17.5 mms. n_D 1.4485

% Br. 40.90%, (calc. 40.99%). d_4 1.3214

whence $[R_L]_D$ 39.75 (calc. 40.31).

(iv) γ-Bromobutyric acid.

This was obtained by the method of Henry[48] as follows:- Equal weights of lactone(γ-butyrolactone) and water were mixed and saturated with hydrogen bromide at 0°. The liquid was sealed in a thick-walled tube and heated to 100° for 7½ hours. The dark brown liquid was extracted with ether, the solution dried, and the ether removed at the pump. The dark oil remaining froze at -15° and was further purified by dissolving in light petroleum, the solution decolourised and purified from impurities by shaking with calcium chloride, and the bulk of the solvent removed at the pump. The acid was obtained as a solid, white flattened needles. The m.p. of γ-bromobutyric acid was 32° - 33°; (Henry[48] quotes the same); equiv. 166.5 (calc. 167.0).

Ethyl γ-bromobutyrate.

This ester was obtained from γ-bromobutyric acid by an exactly similar process to that used for the β-isomer. The ester so obtained boiled steadily without decomposition, and had the following physical constants:

b.p. 94°/18 mms. n_D 1.4569

d_4 1.3540

whence $[R_L]_D$ 39.41 (calc. 40.31).

The ester would not yield a crystalline solid at -80°.

(v) β-bromo-iso-hexoic acid.

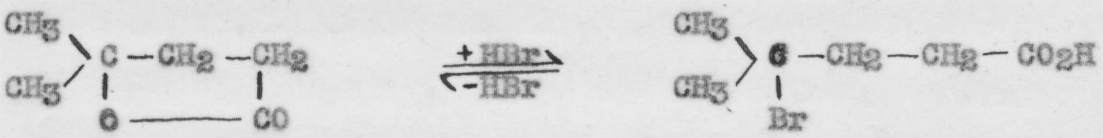
The usual method for β-bromoacids was used in this

case, pure α-β-iso-hexenoic acid being saturated with hydrogen bromide in absence of solvent, and the excess gas removed by standing in a vacuum desiccator to constant weight. A pale yellow liquid resulted which could not be obtained solid at -80° but yielded a glass at this temperature. The acid, however, would appear to be the pure β-bromoacid from the following figures:

Equiv. 195.1 (calc. 194.9). Br, 41.05 (calc. 40.95)%.
(cf v. Braun.[11])

(vi) γ-bromo-iso-hexoic acid.

This acid has been obtained by Fittig and Geisler[9,49] in an impure form as an oil, by the action of aqueous hydrobromic acid on γ-iso-hexolactone, but could not be obtained solid. It was considered that the presence of water militated against a successful preparation owing to the facilitation, by water, of the reverse reaction:



A method was then devised that did not involve the use of water. The lactone was heated to 100° and dry hydrogen bromide was passed in for 30 minutes, the liquid being allowed to cool in a stream of the gas. The light brown oil was allowed to stand in a closed vessel overnight, then dissolved in light petroleum and a little impurity removed. The oil remaining after sucking of the solvent at the pump solidified on cooling for some time in a freezing mixture to the typical burr-like clusters of flattened needles of the

γ bromoacid. The melting point was found to be at -4.0° with previous softening at -6.0°. This acid was considered to be the purest obtainable by fission of the very stable lactone ring. The percentage of bromine present in the acid was found to be 35.1% while the theoretical amount is 40.95%, showing that some lactone is still present. The pure acid was finally obtained by another method during the study of addition of hydrogen bromide to the unsaturated acids (see p. 139).

(vii) 2-bromocyclohexane carboxylic acid.

This was obtained from Δ-1-cyclohexene carboxylic acid by addition of hydrogen bromide, various solvents being used.

Passage of hydrogen bromide into the pure αβ-acid led to very slow absorption and yielded a sticky solid. After draining on porous earthenware and several recrystallisations from petroleum ether (b.p. 60° - 80°), a pure compound of m.p. 108° was obtained. This method being unsatisfactory, the addition was next performed in toluene solution. The toluene was removed from the addition product at the pump, and the oil remaining soon solidified, the crude solid after draining on a tile having m.p. 93°. One recrystallisation produced rosettes of flattened needles, m.p. 107-8°. The melting point mixed with the acid obtained by addition without solvent was 108°. The third solvent tried was glacial acetic acid, the unsaturated acid being used in 50% solution. The liquid was cooled to 0° and a large excess of hydrobromic acid gas passed in. After standing for a few hours the

solution commenced to deposit white crystals. The acetic and excess hydrobromic acids were removed in a vacuum desiccator over soda-lime and potash, and the crude residue, which melted at 103°, was recrystallised from the above solvent. A practically theoretical yield of 2-bromo-cyclo-hexane carboxylic acid was thus obtained. Melting point both alone and mixed with the acid obtained by addition to the undiluted olefinic acid: 108° C. E, 206.6 (calc. 207.0). The addition in acetic acid is thus the best method of preparing the acid. Aschan,[72] by heating the αβ-acid with a large excess of acetic acid saturated with hydrogen bromide in a sealed tube for some time obtained an acid m.p. 108-9°. The two acids are probably identical and, considering the drastic conditions of Aschan, the acid he obtained was probably the trans- acid. Proof of this was sought by attempted malonation of the corresponding ester, but this was inconclusive due, as described on p. 157, to the unexpected decomposition of the ester.

Ethyl 2-bromocyclohexane carboxylate.

This ester was obtained from the acid just described by esterification by a modification of Wohlgemuth's[47] method. 6 gms. of the acid were dissolved in 12 ccs. of absolute alcohol, and 1.7 ccs. of concentrated sulphuric acid added carefully with cooling. The vessel was corked and allowed to stand. The times of standing were varied, and it was found that 7 days gave 87% yield; 4 days gave 85%; 2 days gave 87%. Thus two days appears to be ample time for the reaction, indeed, even after six hours there was always

a large amount of heavy oily ester separated to the bottom of the tube. The mixture was worked up as described for the bromobutyric esters (p. 94), except that the liquid was not distilled, as decomposition occurs, but was allowed to stand in a vacuum desiccator for two days to remove all traces of ether and alcohol. The ester obtained in this way was a slightly yellow, mobile liquid. It contained 33.9% of bromine the calculated amount being 34.0%. Thus the method yields the pure ester required.

(viii) cis-3-bromo-cyclohexane carboxylic acid.

This acid was obtained by opening the ring of the corresponding lactone with hydrobromic acid, such a reaction yielding the cis- acid. The method of Perkin and Tattersall [36] was modified to improve quality and quantity or the yield. cycloHexanolide 1:3 was mixed with 1½ volumes of water and saturated with hydrobromic acid at 0°. The liquid was allowed to stand in the cold in a closed vessel for 24 hours, during which time an oil had separated up to the top of the liquid and had commenced to solidify. The liquid was again saturated with hydrogen bromide at 0° and the whole allowed to stand in a closed tube for three days, when the top layer had formed a hard solid mass. Water was added, the solid crushed, filtered off and washed with water. It was dried on a tile in vacuum over sulphuric acid and was obtained in 85% yield. The m.p. of this solid was 60-65° (Perkin: 62°). The acid was recrystallised from light petroleum and formed the typical burr-like clusters of needles formed by γ-bromoacids, and melted sharply at 65°; E., 207.0 (calc. 207.0).

Ethyl cis-3-bromocyclohexane carboxylate.

This was obtained from the pure acid by esterification exactly as described in the case of the β-bromo-isomer. It was obtained as a mobile liquid, containing 34.2% bromine (calc. 34.0%), in 96% yield. This ester could be, and was, distilled without decomposition; it boiled steadily at 143°/25mms

(ix) trans-3-bromocyclohexane carboxylic acid.

An attempt was made to prepare this by Perkin's[38] method from trans-3-hydroxy-cyclohexane carboxylic acid (see p. 88), but owing to the scarcity of material the pure acid could not be obtained.

PART 2: METHODS OF ANALYSIS AND IDENTIFICATION.

The mixtures of acids and lactones obtained from the various experiments to be described were all analysed by the same method, that of Linstead.[1] About M/500 of the acid-lactone mixture was weighed into a flask and dissolved in water, or neutral water-rectified spirits. The free acid was determined by direct titration with standard N/10 barium hydroxide solution. A known excess of the baryta was then added and the liquid heated under reflux, with a soda-lime guard tube, on the steam for fifteen minutes to assure quantitative conversion of the lactone to the barium salt of the corresponding hydroxy-acid. The solution was cooled and the remaining alkali estimated by back titration with standard sulphuric acid. The results obtained are all expressed to the nearest ½%. In all cases the accuracy of the method was demonstrated by test experiments before it was adopted for general use.

In some cases the acid and lactone were separated semi-quantitatively and weighed. The mixture was allowed to stand with a fifty per cent excess of sodium bicarbonate solution overnight and the lactone extracted with ether in an extracting apparatus for 24 hours. The ethereal extract was dried, the ether distilled off, and the residue left until of constant weight in a vacuum desiccator over calcium chloride and wax, being finally weighed. The acid was recovered by making the aqueous residue acid to Congo red with a slight calculated excess of hydrochloric acid and immediately extracting with ether. It was worked up in the usual way and weighed.

The acids, both pure and recovered from the experiments, were analysed with respect to their $\alpha\beta$- and $\beta\gamma$-constituents by one of the two halogen addition methods mentioned previously, after having checked the purity of the acid by determination of its equivalent by baryta. Iodine additions were done by the method of Linstead and May[50] as follows. A slight excess over M/300 of the acid was weighed out into a 50 cc. standard flask and allowed to dissolve without heating in about 40 ccs. of a saturated solution of sodium bicarbonate by leaving overnight. The volume was then adjusted to 50 ccs. by addition of bicarbonate solution, and the calculated volume of the same solution required to make the concentration of the acid exactly M/15 was run in from a burette. After thorough mixing 10 cc. portions of this were pipetted into stoppered bottles and treated with the theoretical amount (j) of a solution of iodine in potassium iodide (the amounts present in

this solution being 12.7 gms. of iodine and 28 gms. of potassium iodide in two litres of solution), which had been standardised immediately before use by standard sodium thiosulphate solution. The mixture was allowed to stand in the dark for a definite time, and the excess iodine was then estimated by addition of 2 ccs. concentrated hydrochloric acid and 200 ccs. of water, and titration with thiosulphate solution.

If t_{25} be the thiosulphate titre of 25 ccs. of the iodine solution, and F the factor of the thiosulphate, then the quantity of iodine solution theoretically equivalent to 10 ccs. of the M/15 acid solution is $j = \frac{100}{3.t_{25}.F}$

Also, if T be the back titration after addition has taken place, the % of unchanged iodine, $U = \frac{2500.T}{t_{25}.j}$, and hence the amount of iodine absorbed, J = (100 - U)%. The iodine additions were all done at a temperature of 20°, as Linstead and Noble[23] have shown that the temperature coefficient is considerable. This method was used in the case of the pentenoic acids (for 60 mins.) and the iso-hexenoic acids (for 5 mins.).

Additions of bromine were done when the above method was not satisfactory. These were done as follows according to the method of Linstead and Noble.[23] The acid to be analysed was weighed out, a slight excess over M/600 being placed in a 25 cc. standard flask, and the solution made up in chloroform to be exactly M/15 by addition of the solvent from a burette. The M/20 solution of bromine in chloroform

was made up immediately before use , and was standardised by allowing 25 ccs. of it to stand for the standardised time with 10ccs. of chloroform in the dark in a stoppered bottle. The bromine present was estimated by the addition of 10 ccs. of 10% potassium iodide solution and 200 ccs of water, the liberated iodine was then titrated with thiosulphate solution with vigorous shaking. (j) was calculated in the way described for iodine addenda, and this volume of the bromine solution was added to 10 cc. portions of the M/15 solution of the acid in stoppered bottles. These were subsequently treated as the standardisation experiments. U and J were calculated from the back-titration figures in the same way. Owing to the escape of the bromine from the chloroform solution it was necessary to check the value of j every 30 minutes. For the reason quoted in the other method of halogen addition, the experiments were conducted at 20°, and were used for the butenoic acids (for 30 mins, and for the cyclohexene and 3-methyl-cyclohexene carboxylic acids (for 5 minutes).

The methods of analysis described above were the only ones used in the lactonisation work.

The analyses performed on the bromo-acids varied with the acids under investigation. The equivalent weights of the acids were determined whenever possible, by titration with baryta, the end-points being quite sharp, but fading rapidly due to the liberation of hydrobromic acid from the acids. The only case where this failed was in that of the γ-bromo-iso-hexoic acids whose great instability in water

rendered the determination of equivalents by baryta impossible. In many cases the purity of the bromoacids was proved by estimation of the percentage of bromine present. It was considered unnecessary to do the estimations by the Carius method, and two other methods were tried on β-bromovaleric acid, which had been obtained in a very pure state.

(a). Modified Carius method. The bromoacid was boiled for 15 minutes with concentrated nitric acid and silver nitrate, the silver bromide formed being filtered off, dried and weighed in the usual analytical manner. This method gave results that were slightly low.

(b) The bromoacid was dissolved in an excess of dilute, halogen free sodium hydroxide solution, and the liquid boiled gently. Various times of boiling were tried, the best being between 20 and 15 minutes. It was made slightly acid with concentrated nitric acid and silver nitrate solution immediately added. The liquid was boiled gently with stirring (to stop "bumping") for 15 minutes, and the silver bromide filtered off on a glass gooch crucible, washed with hot water, alcohol, and ether and dried to constant weight in the steam oven. This was found to give very good results, eg in the case of bromovaleric acid the amount of bromine found was 44.26%, the calculated amount being44.18%. This method was then adopted for analysis. It was later modified for the analysis of bromoesters. The ester was weighed into a flask and boiled under reflux with excess of dilute halogen free sodium hydroxide solution for 2 hours. At the end of this time hydrolysis of the ester was always found to be complete and

the resulting acid had been decomposed into sodium bromide. The solution was washed into a beaker, acidified with nitric acid, and the analysis concluded as in the case of the acids. This method was always found to give good results.

As the methods of analysis of the bromoacids were so varied, a description will not be given here, but will be found in detail under the relevant headings in "Additions of hydrogen bromide".

Methods of identification of the products obtained.

The lactones that were formed in the various experiments conducted, were separated from the acids as described on p. /0/ , and identified, in the case of liquid lactones, by comparison of values of M., n, d, m.p., mixed m.p., b.p., of the recovered liquid with the corresponding values of the pure reference lactone. In the case of the first lactone studied, γ-valerolactone, the formation of the solid γ-hydroxyvaleramide from it was used for identification, by its m.p. and m.p. mixed with amide from the pure reference lactone. In the case of the solid lactones (i.e. solid at ordinary temperatures), the melting points and the mixed melting points were used, together with values of M.

The acids recovered from the experiments were identified by E., and if pure, by values of J, n, d, b.p. m.p., and mixed m.p. with the reference acid, in the case of liquids; and by values of J, b.p. and the two melting points if solid at ordinary temperatures. In one case, the preparation of a solid derivative, the p-toluidide was utilised to prove the identity of several samples of the acid in question.

The evidence quoted above was considered to be sufficient to prove the identity, or otherwise, of two compounds.

In the few cases where pure bromo-acids were obtained by the addition of hydrobromic acid to the unsaturated acids, the proof of their structures rested on their melting points, both alone and mixed with the pure reference bromoacids. In the one case where a bromoester was to be identified, the evidence of the physical properties was used to establish its constitution, together with the evidence of a chemical method of analysis (see p. 137).

Note on the determination of melting points at low temperatures. The liquid whose melting point was to be determined was introduced into a thin-walled capillary tube sealed at one end, the liquid shaken down to this end, and the other end sealed. This was attached by a rubber band to a toluene thermometer of range -120° to 30°, and the liquid frozen *in situ* by immersion in a freezing mixture of solid carbon dioxide and ether in a Dewar vessel. The crystalline form of the "liquid" was examined, and the melting point determined by immersing the tube and the bulb of the thermometer in a bath of ether, cooled by the addition of solid carbon dioxide. This was supported in a beaker acting as an air bath. The ether was stirred if required, and the temperature allowed to rise spontaneously, note being taken of the temperature of fusion recorded on the thermometer, and also of the room temperature, and the reading corrected for the exposed stem. In this way the melting points of many substances normally liquids was accurately determined.

PART 3: LACTONISATION METHODS IN USE.

Three main methods of obtaining lactones from unsaturated acids have been studied.

(i). Boiling sulphuric acid; 50% by volume. The olefinic acid (x gms.) was added to the lactonising agent (5x ccs. measured from a burette) and the whole heated rapidly over a free flame to boiling. The liquid was boiled under reflux for a certain set time, note being taken of the time required for complete miscibility and of the general condition of the solution. At the end of the required time the boiling was stopped. If the acids and lactone were fairly volatile in steam the reulting liquid was diluted and distilled in steam, 50 x ccs. of distillate being collected. This was saturated with ammonium sulphate and extracted continuously with ether for 24 hours. The extract was dried, the ether distilled off, and the residue taken down to constant weight in a vacuum desiccator over calcium chloride and wax , when it was ready for analysis. If the acids were not very volatile in steam, the solution was diluted with three volumes of water, saturated with ammonium sulphate, and extracted 6-8 times with ether. The ethereal extracts were washed with a solution of ammonium sulphate saturated at 20°, dried, the ether distilled off, and the residue distilled to free the product from a certain amount of impurity that had formed in the reaction. In the case of each acid, one lactonisation was always performed under the conditions used by Fittig. This was to boil the solution in 50% sulphuric acid for 5 minutes, then it was diluted with 10 x ccs. of water, and boiled for

10 minutes. The product was then worked up in one of the ways just described, depending on the volatility of the acids in steam.

(ii) Cold sulphuric acid; 60% by volume. The unsaturated acid (x gms.) was added to the sulphuric acid (5 x ccs.) and the liquids shaken together until miscible, unless miscibility was never complete. Note was taken of the time for the two layers to become completely miscible, and also of any change in temperature. The mixture was allowed to stand in a stoppered vessel at about 20° for the requisite time, and the reaction stopped by pouring onto three volumes of ice and water. This liquid was saturated with ammonium sulphate, extracted 6 - 8 times with ether, the ethereal extract dried over calcium chloride after being washed once with saturated ammonium sulphate solution, and the ether distilled off. The residue was either taken down to constant weight in vacuo, or, as was invariable in the case of the βγ-acids, distilled in vacuum.

In the above cases the percentage recovery was noted, and also the residue on distillation, and the boiling point, if distilled.

(iii). Heat alone. The unsaturated acid was placed into a bulb on the end of a tube acting as an air condenser, and the atmosphere rendered inert by repeated evacuation and filling with nitrogen or carbon dioxide. Back-diffusion of air into the flask during the experiment was prevented by passage of a slow current of the gas along the top tube of a T-piece attached to the top of the condenser. The acid was boiled under atmospheric pressure on a sand-bath for a known time,

the liquid being then analysed for acid and lactone, being if possible, distilled to remove polymeric etc. impurities. In the cases where an acid was boiled in a solvent, the resulting liquid was stirred with 100% excess of a saturated solution of sodium bicarbonate, the liquids allowed to stand in contact overnight, and finally shaken thoroughly together. The alkaline liquid was separated off and the residue shaken with more sodium bicarbonate solution to complete the extraction of the acid. The combined aqueous liquids were extracted several times with ether to remove solvent and lactone, and the residual aqueous solution was made acid to congo red with hydrochloric acid and the acid obtained by thorough ether extraction, and weighed as usual. The lactone was estracted from the solvent used by shaking it in the machine with an excess of 10% caustic soda solution overnight, and working this up by acidification and extraction of the hydroxy-acid with ether, and weighing. Test experiments showed that this method worked quite well.

PART 4: GENERAL METHODS FOR THE ADDITION OF HYDROGEN BROMIDE.

The hydrobromic acid gas used for these addenda was prepared in an apparatus made entirely of "Pyrex" glass to avoid contamination of the gas by contact with rubber. Naphthalene was placed in the bulb of a flask fitted with a side-arm perpendicular to the neck, and a ground-in dropping funnel. From the latter dry bromine was dropped onto the naphthalene and the hydrogen bromide thus evolved was scrubbed quite free of bromine by passage through a U-tube filled with

naphthalene attached to the side arm. It was dried by passage over phosphorus pentoxide in a second U-tube and freed from all dust by a plug of glass wool in the second tube. The substance with which the hydrobromic acid was to react was placed in a third U-tube ground on to the end of the train. Provision was made for shaking this tube, and also for cooling in water or ice . A sulphuric acid bubbler was used as a guard on the end of the apparatus.

The unsaturated acid under investigation was weighed into the last U-tube and hydrogen bromide bubbled slowly through it (with cooling or shaking as required) until a slight excess over the amount required was absorbed. After standing, in most cases overnight, the stoppers of the U-tubes were removed and any excess hydrobromic acid gas was removed by allowing the addition product to stand in a vacuum desiccator until the tube had attained constant weight, at that calculated for the experiment. The acid was then analysed. In the case of the acids containing ½% water the additions were done in exactly the same way. When additions were done to the acids in solvents a larger U-tube with bulbs, of the Péligot type, was used, the whole being cooled in ice. After an excess of the gas had been absorbed, and the usual time allowed for reaction, the solvent was removed at as low a temperature as possible, the last traces of solvent and excess hydrobromic acid removed in a vacuum desiccator, and the residue analysed.

In the case of the additions to esters, these were done in the same way as additions to the dry acid, the ester

being distilled after removal of excess hydrogen bromide in the vacuum desiccator.

In all the above addenda the liquids were not allowed to become warm as this would facilitate decomposition and lead to incorrect results.

PART 5:PROPERTIES OF LACTONES: METHODS OF INVESTIGATION.

(i). Hydrolysis of the lactones by water. The conditions used in this portion of the work were standardised as much as possible in the following way:-

About M/500 of the pure lactone was weighed into a 100 cc. conical flask and the calculated amount of distilled water added, from a burette, to make the solution exactly M/25. The flask was fitted with a small Davis reflux condenser and heated to 100° for 24 hours to attain equilibrium. The free acid formed was estimated by titration with N/10 baryta. A similar experiment was then performed for 48 hours to prove that equilibrium had been reached, and in this case both acid and lactone were estimated in the usual way to show that no gross decomposition had occurred. In the case of the aliphatic lactones, equilibrium was always reached in 24 hours, but the dicyclic lactones required longer heating as will be seen from the experimental figures. The results were expressed as % of lactone changed.

(ii). Velocity of formation of lactones from hydroxy-acid. In this series of measurements the standard conditions used were based on those of Hjelt[19,20] as mentioned in a previous section and were as follows :-

About M/200 of the pure lactone was weighed into a

flask, and heated on the steam under a reflux condenser and soda-lime guard tube with the theoretical amount of standard N/10 baryta, for 15 minutes. The solution of the barium salt of the hydroxy-acid so obtained was cooled in ice and 95% of the amount of N/10 hydrochloric acid required to neutralise the amount of baryta used was added. This liberated the bulk of the hydroxy-acid, but ensured that there was no free mineral acid present, as these have a marked catalytic effect on the change. The solution was made exactly N/20 by addition of water, and kept in ice. 10 cc. portions of this solution were used for analysis, the free acid being estimated by titration with N/100 baryta. One titration was done on the liquid before heating at all. The portions used in the estimations were pipetted into dry flasks and fitted with dry reflux condensers, and heated for certain times at 100° in a bath of boiling water. The reaction was stopped by pouring the liquid into three volumes of ice-cooled water and titrating the residual free acid with the N/100 baryta. For the purposes of plotting a curve, the zero time was taken as after five minutes heating, the velocity being expressed as "% of the acid lactonised in t minutes". The curves for the lactones studied were plotted and are given opposite p. 149. The times for the half change times were determined and used as a comparison between different lactones.

(iii) Parachor measurements. No detailed description of the method need be given here. The densities were determined by the method of Sugden[73] using the U-type pycnometer

a slight modification being introduced (viz., the slow introduction of the liquid with a pipette) to eliminate his "draining error". The densities were found over a range of temperature and the values were in all cases found to be in linear relation to the temperature. For that reason, the graphs of the density-temperature figures for the lactones will not be given. The surface tensions were determined by the method of maximum bubble pressure, (Sugden[74]). Two bubbling cells were used, and each result quoted is the mean of many concordant figures. Both cells and the pycnometer were accurately calibrated using pure benzene as advised by Sugden.

PART 5: LACTONISATION EXPERIMENTS PERFORMED.

αβ-Pentenoic acid.

Hot sulphuric acid, 50% by volume.

The two acids were immediately miscible in all proportions. Only very slight charring occurred during the boiling even the 60 minute experiment being only a dark yellow. No sulphur dioxide could be detected. The products were all distilled in steam, the results appear in the table:

Time.	% Recovery	% Acid.	% Lactone.
Fittig's.	73	63.5	35.0
30 mins.	60	6.5	93.0
60 mins.	58	1.5	97.0

The experiment performed under Fittig's conditions was separated semi-quantitatively into acid and lactone, and yielded 63.5% acid; 31.0% lactone. This is in fairly good agreement with the titration figures. These are repeatable as was shown by two titrations on the sample from the 30 minute experiment, the results of which were identical.

Identification. Lactone from the 60 minute experiment was freed from acid by potassium carbonate and distilled. The physical properties show it to be pure γ-valerolactone.

m.p. - 37° n. 1.4320

b.p. 96° - 7° / 19 mms. d. 1.0538

M. 100.9 (calc 100.1) Whence $[R_L]_D$ 24.67 (calc. 24.75)

m.p. of hydroxyamide 51.5° - 52°

m.p. of hydroxyamide mixed with reference amide 51°

The acid from the combined experiments was isolated and distilled. Itwas proved to be very pure, unchanged αβ-pentenoic acid.

m.p.	8.0 - 8.5°	n.	1.4513
J.	1.0	d.	0.9903
		whence $[R_L]_D$	27.16

Cold sulphuric acid, 60% by volume.

The acids were all immediately miscible with no change of temperature. The recovered acids were analysed to yield the following figures:

Time.	% Recovery.	% Acid.	% Lactone.
2 days.	91	95.0	4.0
7 days.	-	96.5	4.0
7 days.	-	97.0	2.5

The high percentage of ψ-acid in the two day experiment appears to be fortuitous, as in the longer times the amount formed is less. There was not enough of it formed to identify. but the acid was obtained free from lactone in the usual way and identified as the pure starting material, αβ-pentenoic acid

Identification.

m.p.	8.5 - 9.5°	n.	1.4507
J.	0.5.	d.	0.9908
		whence $[R_L]_D$	27.18

βγ-Pentenoic acid.

Hot sulphuric acid, 50% by volume.

The only experiment done was that under the condition of Fittig, in which lactonisation was practically complete,

there being practically no gross decomposition.

% Recovery, Overall.	Pure distillate.	% Acid.	% Lactone.
55	54	4.5	94.5

The acid was removed from the mixture by potassium carbonate in the usual way, and the lactone distilled. This was shown to be pure γ-valerolactone by the following data:

m.p. -34.5° n. 1.4326

b.p. 94°/15 mms. M. 100.4 (calc. 100.1)

γ-hydroxyamide, mixed m.p. 51.5°.

Cold sulphuric acid, 60% by volume.

The acids were all miscible immediately with no discernable change in temperature. The products were all distilled in vacuo to remove a small amount of polymer and then analysed. The results are given below, the five hour experiment being performed twice to show that the methods in use gave repeateble results.

Time.	% Recovery, of product, Total.	Pure distillate.	b.p. (°)	%Acid.	% Lactone.
1 hour.	81	79	92-7/14	84.5	15.0
3 hours.	79,	77	90-3/14	41.0	57.5
5 hours.	-	-	-	40.5	56.5
8 hours.	60	58	94-5/16	19.5	79.5
48 hours.	-	-	90-3/17	5.5	95.5

The products were all mixed and separated into acid and lactone through bicarbonate solution. The two portions were distilled, and shown to be pure γ-valerolactone and βγ-pentenoic acid by the following physical properties:

Acid.

m.p. 0.5° n. 1.4346

b.p. 89.5°/11.5 mms. d. 0.9869

J. 73.2 whence $[R_L]_D$ 26.45

Lactone.

m.p. -36.5° n. 1.4326

M. 100.8 d. 1.0546

m.p. of hydroxyamide 52° $[R_L]_D$ 24.65

m.p. mixed with reference hydroxyamide 51.5°

γ-Valerolactone. This was treated under the most drastic of each type of method used to see if any reversal of the change had occurred with the production of acid.

Hot acid. 1 hour. The recovered liquid had:

% Acid, 1.0. % Lactone, 99.0. The trace of acidic material formed was removed by potassium carbonate and the lactone distilled. This was the pure starting material:- of M. 100.L., b.p. 102°/28 mms., n. 1.4322.

Cold acid. 7 days. The recovered liquid contained:-

% Acid, 0.5. % Lactone, 99.5. No identification was done on this as it was unlikely that change would have occurred in the cold while none occurred on heating.

Hence, γ-valerolactone is quite unaffected by all the lactonising conditions that produce lactone from the pentenoic acids.

dβ Butenoic acid.

The acid (m.p.72.5°) was finely powdered before use to aid solution. Only one of the hot sulphuric acid experiments was distilled in steam as the acid was found to be

very involatile under these conditions. All the products were distilled, as a dimeric form of the acid is formed (as also in the case of the βγ-acid) which is also pseudo-acidic and can be removed by distillation.

Hot sulphuric acid, 50% by volume.

Time.	% Recovery, Total.	% Recovery, Pure distillate.	b.p.(°)	% Acid.	% Lactone.
Fittig's.	43	43	(steam distilled).	99.0	1.0
1 hour.	77	54	85/9.	97.5	1.5
3 hour.	-	-	75-8/8.	-	-

The three hour experiment was done in an attempt to isolate lactone if possible and was not analysed accurately. However, no lactone was formed. The recovered acids in each case were practically the pure starting material as seen from the m.p.s and values of J.

Time.	m.p.	J.
Fittig's.	71 - 72°	2.5
1 hour.	69 - 70°	3.0
3 hour.	70 - 71°	4.5

the small drop in melting point and the slight increase in J is probably due in each case, to the formation of a little allo- (cis-) crotonic acid.

Cold sulphuric acid, 60% by volume.

One experiment was done for seven days. Solution was complete in 20 minutes with a slight fall in temperature. The recovered compound was pure αβ-acid (in 94% recovery) % Acid 99.0; % Lactone 0.5; m.p. 72°; J. 1.3., and is obviously identical with the starting material.

βγ-Butenoic acid.

Hot sulphuric acid, 50% by volume.

Very little charring occurred during these experiments although a considerable residue was left on distilling the products from the longer boilings, consisting of products of gross decomposition and polymeric change.

Time.	% Recovery		b.p.(°).	% Acid.	% Lactone.
	Total.	Pure distillate.			
Fittig's.	77	51	85-90/12	98.0	1.5
60 mins.	76	51	80/9.	97.0	2.0

The acids so recovered were both hard solids and a it appeared that the βγ-acid had been completely converted into the isomeric αβ-acid under the lactonising conditions, and this was proved by the melting points and bromine additions.

Time.	m.p.	J.
Fittig's.	69 - 70°	2.5
1 hour.	68 - 69°	2.5

Cold sulphuric acid, 60% by volume.

The acids were miscible immediately with no temperature change. A certain amount of impurity was formed, especially in the cases of long standing, and was removed by distillation.

Time.	% Recovery,		b.p.	% Acid.	% Lactone.	J.
	Total.	Pure distillate.				
4 hours.	92	90	66-7/8.	98.0	2.0	73.1
2 days.	89	71	68/5.	98.0	2.0	74.1
7 days	78	51	-	97.5	1.5	70.3

Hence the amount of lactone formed even over a long

period was negligeable. The recovered acids however, deposited no solid, and were seen by the halogen additions to be practically unchanged βγ-acid, very little tautomeric having occurred.

(iii) Heating the acid in a solvent.

Owing to the unexpected nature of the addition of hydrogen bromide to βγ-butenoic acid in hydrocarbon solvents, (p. 135), it was considered possible that the acid might form lactone under similar conditions if activated suufficiently. A hydrocarbon was chosen whose boiling point was about equal to that of the acid under ordinary pressure. This was trans-dekalin, dried over sodium, twice fractionated very carefully through a column of Lessing rings, and finally distilled from sodium. A 10% by weight solution of butenoic acid in this solvent was boiled gently under reflux for 24 hours. A few drops of immiscible liquid formed. This was acid, but was not included in thegeneral recovery. The acid present was extracted as previuosly described, and in 91% yield. The lactonic content of the mixture was 0.4%. The recovered acid resembled βγ-butenoic acid very closely in its general properties, and obviously did not contain much of the isomeric acid. Hence it may be stated definitely that the acid does not form any lactone if boiled in an inert solvent for a long time.

γ-Butyrolactone.

As usual, the two most drastic lactonising conditions were imposed on the lactone, with the result that no change at all was detected in either case, the lactone appearing to

be very stable to sulphuric acid under the conditions used.

Hot sulphuric acid, 50% by volume. 3 hours:

67% recovered, b.p. 77°/3.5 mms. 1.5% acid and 98.5% lactone.

Cold sulphuric acid, 60% by volume. 7 days:

b.p. 69° - 70°/6 mms. 1.5% acid and 95.5% lactone.

Δ-1- cyclohexene carboxylic acid.

All lactonisations done on this acid and also the Δ-2- acid were done in an atmosphere of nitrogen in an a attempt to keep down the general decomposition of the acids.

Hot sulphuric acid, 50% by volume.

The acid was rather badly attacked after some time, a slow evolution of sulphur dioxide was noticed together with the formation of a certain amount of charred material. The products were not distilled in steam. As far as could be observed, the two acids never became completely miscible in the times of boiling used. Lactone appeared to be formed slowly as will be seen from the figures appended, but, owing to the slowness of the change and the amount of decomposition occurring, there was not obtained enough for identification.

Time.	% Recovery, Total.	Pure distillate.	b.p.(°)	% Acid.	% Lactone.
Fittig's	98	92	130-4/13.	97.5	1.5
30 mins.	69	46	132-6/13.	90.0	8.5

The acid was recovered, and had m.p. 37° - 38°, and melting point mixed with the reference αβ-acid 37°. This effectively shows that the acid recovered was the pure αβ-acid

Cold sulphuric acid, 60% by volume. One experiment only was done, for three days. The olefinic acid did not dissolve completely in the sulphuric acid, although the mixture was kept well shaken. Recovery was 59% with b.p. 137°-8°/15 mms. there being little residue on distilling. It contained 97.5% acid and 2.0% lactone. Thus, the acid is practically identical with the starting material, and had m.p. 37° - 38° and m.p. in admixture with the pure α/β-acid 37°.

Δ-2-cyclohexene carboxylic acid.

Hot sulphuric acid, 50% by volume.

Any attempt to boil the mixture for longer than the time used by Fittig resulted in complete destruction of the acid. The result from the one successful experiment is : 73% recovered boiling at an unknown temperature. % Acid, 35.0 % Lactone, 63.0.

The lactone and acid were separated in the usual way and identified if possible. The amount of the acid recovered was so small as to render identification impossible. The lactone was obtained as a white crystalline solid of m.p. 122°, and m.p. mixed with the pure reference lactone of 120°, showing that the lactone formed in this way was cyclohexanolide 1:3.

Cold sulphuric acid, 60% by volume.

The two acids were always found to be miscible in 42 minutes, and consequently the shortest time used was 45 minutes. There was very considerable formation of polymeric material (cf. Nametkin and Abakumuvskaja[75]), but no charring or evolution of sulphur dioxide was detected.

Time.	% Recovery, Total.	% Recovery, Pure distillate.	b.p.(°).	% Acid.	% Lactone.
45 mins.	51	46	124-8/15.	89.5	10.0
2 hours.	44	33	122/15.	73.5	26.0
4 hours.	37	25	125/12	11.0	88.5

For any time greater than four hours the product isolated in very poor yield was practically pure lactone. From the very bad recoveries and large residues on distillation, the βγ-acid appears to be removed by side reactions as well as by lactonisation, which appear to obey the fairly general rule that such reactions are autocatalytic. The lactone was isolated in the usual way: It had M. 126.2 (calc. 126.1). m.p. 120°. m.p. mixed with the reference lactone, 119°.

Boiling alone.

A few gms. of the acid were boiled gently at atmospheric pressure in an inert atmosphere for one hour. The product was distilled from about 5% of gummy residue and contained 99.0% acid and 0.5% lactonic material. The recovered acid was quite mobile and closely resembled the starting material.

Cyclohexanolide 1:3.

Hot sulphuric acid, 50% by volume. The experiment was done for thirty minutes , in which time the lactone was completely destroyed except for a small amount of undistillable gum.

Cold sulphuric acid, 60% by volume. The experiment was done for 7 days, the lactone being recovered in60% yield with acid content 2.0%, lactone97.0%, The lactone was

recrystallised from light petroleum and proved to be identical with the starting material by its m.p. (120°) and its melting point mixed with the original solid (118°).

From the above results it would appear that this lactone is not so stable to the lactonising conditions as the aliphatic lactones, but that no trace of olefinic acid can be obtained from it.

3-methyl-Δ1-cyclohexene carboxylic acid.

Hot sulphuric acid, 50% by volume.

There was considerable charring and evolution of sulphur dioxide during these experiments, while, as far as could be seen, the acids were never completely miscible in all proportions. The figures from the two experiments performed are given below and it will be seen that the amount of lactonic material formed was very small.

Time.	% Recovery		b.p. (°).	% Acid.	% Lactone.
	Total.	Pure distillate.			
Fittig's	84	81	129-35/8.	98.0	2.5
15 mins.	79	69	133-4/8.	96.5	2.0

Cold sulphuric acid, 60% by volume.

The acids were never miscible in all proportions during the times studied. Results:

Time.	% Recovery		b.p.(°)	% Acid.	% Lactone
	Total.	Pure distillate.			
2 days.	100%(not distilled.)			99.0	0.0
7 days.	83	80	130-6/7.	99.5	1.0

The distilled liquid from the longer experiment

had melting points, both alone and admixed with the pure $\alpha\beta$-acid, at 25°, conclusive proof that the acid is quite untouched by cold sulphuric acid (60% by volume).

3-methyl Δ-2-cyclohexene carboxylic acid.

Hot sulphuric acid, 50% by volume.

In this case charring and evolution of sulphur dioxide set in rapidly and vigorously, and in one minute the liquid was worked up. There was obtained one drop of a liquid highly lactonic in nature. The acid is obviously very unstable to hot dilute sulphuric acid.

Cold sulphuric acid, 60% by volume.

The two layers were always miscible after 55seconds, with a rise in temperature of about 5°. The figures from several experiments are quoted in the table:-

Time.	% Recovery, Total.	% Recovery, Pure distillate.	b.p.(°)	% Acid.	% Lactone.
5 mins.	96	89	118/18.	15.5	86.0
15 mins.	95	86	-	12.5	88.5
60 mins.	90	83	-	8.5	92.5

The products were mixed and the acid and lactone separated as usual. It can be seen that the amount of acid was not sufficient for identification, all that could be done was a bromine addition which showed that J was c. 96.0 i.e. the recovered acid was $\beta\gamma$-acid.

The lactone had M. 139.8 (calc. 140.1) and m.p. 44°. The m.p. mixed with the reference lactone was 44-5°, showing it to be 1-methyl-cyclohexanolide 1:3.

Boiling alone.

The acid was boiled gently in the usual apparatus in an inert atmosphere, and samples withdrawn at intervals and analysed as usual for acid and lactone. Owing to the scarcity of material it was not possible to distill the liquid before analysis, and consequently the results from the longer boilings are rendered slightly different by the appearance of a little neutral substance. Unfortunately, this was unavoidable. A second experiment was done on a further sample of acid and was ditilled. The figures for this are given in the last column of the table.

Time of boilng:-	30 mins.	90 mins.	300 mins.	120 mins.
% βγ-acid left.	74.0	68.0	65.0	72.0
% lactone formed.	26.0	31.5	30.5	32.0

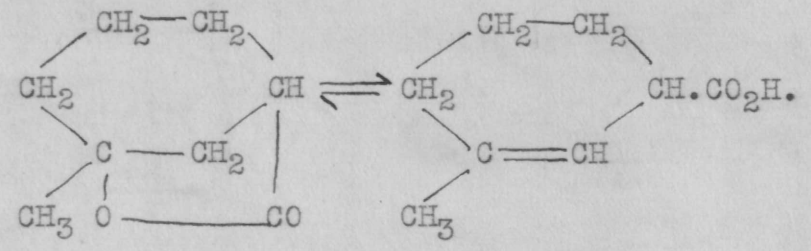
There thus appears to be an equilibrium between βγ-acid and γ-lactone at 32% acid and 68% acid. The lactone formed was isolated and identified as 1-methyl-cyclohexanolide 1:3 by its m.p. (@43° - 44°). Mixed with the reference lactone it melted at 44°.

1-methyl-cyclohexanolide 1:3.

Hot sulphuric acid, 50% by volume.

On boiling the mixture of lactone and sulphuric acid charring and evolution of sulphur dioxide occurred and after five minutes no distillable product was obtained. The lactone was totally destroyed except for a little gum, but not nearly so quickly as was the βγ-acid under similar conditions.

LACTO-ENOIC TAUTOMERISM.



% ACID

% LACTONE

100 90 80 70 60 50 40 30 20 10 0

0 10 20 30 40 50 60 70 80 90 100

20 40 60 80 100 200 300 400 MINUTES

Cold sulphuric acid, 60% by volume.

After two days treatment the lactone was recovered in 85% yield and contained 0.5% acid and 101% lactone, having m.p., both alone and with the reference lactone, of 44°.

Heat alone.

The pure γ-lactone was boiled in the same apparatus and under the same conditions as the isomeric βγ-acid, and the analyses gave the following figures (of the undistilled liquid):-

Time of boiling:-	15 mins.	75 mins.	255 mins.	375 mins.
% βγ-acid formed.	13.0	42.5	61.5	57.5
% lactone left.	94.0(?)	58.0	36.5	36.5

This again appears to have proceeded to an equilibrium at 36% lactone. There is a slight difference between this and the figure obtained from the acid side, but, as explained, the acid may have contained some few per cent of impurity, and consequently the conclusion is drawn that the two equilibria are the same.

The acid was isolated from the mixture and found to have a bromine addition of about 94%. A p-toluidide has been prepared from it in the usual way but, owing to the very small quantity available, only sufficient solid was obtained for a mixed melting point, with the p-toluidide of the pure βγ-acid. This was 107° - 108°, and indicates that the acid formed by such fission of the lactone ring is the βγ-acid. Further work is being carried out on this subject at the present time.

Part 6: HYDROGEN BROMIDE ADDITIONS TO THE βγ-ACIDS.

including various associated experiments on bromoacids and este:

(1). βγ-Pentenoic acid.

Additions were done to this acid in the apparatus described above. Two additions were done to the pure, dry acid, and two to the acid containing ½% water. One of each of these was analysed twice to ascertain if the method was giving repeatable results, and a bromine estimation was also donc in each case to see if the method of taking down to constant weight in a vacuum desiccator over potash was giving reliable bromoacids. Actually the weight was never obtained constant. After the big loss of weight due to the removal of unccmbined hydrobromic acid there followed a very slow loss due to the loss of hydrogen bromide from the δ-bromo-acid with the formation of lactone. This will be seen from the amounts of bromine present in the acids. Actually the bromo-acid was removed from the desiccator when the speed of losing weight changed and the amount of hydrogen bromide left in the acid was that calculated as required to saturated the double bond.

The addition to the dry acid was slow, the mixture of acid and excess hydrogen bromide being left in the stoppered U-tube overnight to ensure complete reaction. The moist acid reacted much faster, no standing overnight being necessary, and actual absorption of hydrogen bromide by the liquid being faster.

The following experiments were performed on the pure reference β-bromovaleric acid during attempts to find a

method of analysis of mixed bromoacids.

(a). 3 gms of the acid were boiled with water under a reflux condenser for two hours, at the end of which time all smell of unsaturated hydrocarbon (amylene?) had disappeared and decomposition of the bromoacid was assumed to be complete. The liquid was saturated with sodium bicarbonate and extracted with ether continuously for 24 hours. The ethereal extract was dried, the ether distilled off, and the residue left in a vacuum desiccator over calcium chloride and wax to constant weight. This (lactonic material) represented 0.4% of the β-bromovaleric acid taken, showing that no γ-lactone was formed from the β-bromoacid. This indicates that the decomposition proceeded to the β-hydroxyacid, probably via the β-lactone, together with a little unsaturated hydrocarbon. This gas was bubbled into chloroform and shown to be unsaturated by its absorbing bromine in the same solvent, but this absorption was too slow to have been of any use as an analytical method.

(b). An aqueous-alcoholic solution of β-bromovaleric acid was made up and samples allowed to stand in the cold for times of 0, 15, 30, and 60 minutes and 16 hours. Addition of silver nitrate solution always produced a slow precipitation, commencing after 4 seconds in all cases, irrespective of the time of standing. Boiling the solution a few minutes before adding silver nitrate caused immediate and copious precipitation with this reagent; also boiling the solution with silver nitrate caused immediate decomposition.

An experiment conducted on γ-valeric acid as (a)

above produced a 75% yield of pure γ-valerolactone. This liquid had m, 101.1 (calc. 101.1); b.p. 88°/14 mms.; m.p. -35°.

The method of analysis tried and found satisfactory was as follows, being based on the fact that the β-bromoacid treated as above (a) forms no lactonic material, while the γ-bromoacid yields γ-valerolactone.

c. 0.2 gms. of a bromoacid were weighed into a flask and dissolved in 100 volumes of neutral 50% alcohol-water, and titrated with N/10 baryta using phenolphthalein as indicator. From this, of course, one obtained the equivalent. The liquid was heated under a small reflux condenser on the steam bath until decomposition in the sense shown above was complete (not less than 80 minutes). The solution was cooled and titrated with baryta to neutralise any free acid formed by decomposition of the β-bromoacid to the β-hydroxy-acid. The lactone present (formed from the γ-bromoacid quantitatively) was then estimated in the usual way by addition of excess baryta, heating on the steam for fifteen minutes, and back-titrating the cooled solution with standard sulphuric acid. . From this last figure the amount of γ-bromoacid present is obtained. the method was tested on various synthetic mixtures, and it was shown that the γ-bromoacid formed γ-lactone quantitatively with the greatest of ease without forming any free acid.

Results of tests:

% γ-acid (true):	100	46.5	93.5
% γ-acid (found):	101	46.8	92.8

As a rough check, the amount of β-bromoacid (as well as being obtained by difference from the above figures for the γ-bromoacid) can be obtained from the fact that under the conditions used, the β-bromoacid appears to decompose with formation of 76 ± 1% of free acid.

The results of the analyses on the addition products of βγ-pentenoic acid and hydrogen bromide are given in the table below. It will be noticed that the equivalents as determined are always slightly high and that the percentage of bromine present in the acids is correspondingly low. These facts point to the loss of hydrogen bromide from the γ-bromoacid with formation of lactone as mentioned previously. The lactone, however, is estimated in the appropriate place and so the slight decomposition that has occurred makes very little difference to the accuracy of the results.

Condition of acid.	Equivalent (calc. 180.9)	% Br. (calc. 44.2)	% γ-bromoacid.
Dry.	182.4	43.6	92.8
"	183.8	-	91.8
"	187 (?).	-	91.4
+½% water.	185.7	-	93.2
"	185.6	43.5	92.4
"	185.0	-	92.5

The product from the dry addition was converted into γ-valerolactone by neutralising with sodium hydroxide, and boiling under reflux for a short time, to complete the formation of the lactone by fission of NaBr. The liquid

was continuously extracted with ether and worked up as in (a). The liquid had M, 100.4 (calc. 100.1), m.p. -55.5°, b.p. 92-3°/11 mm. The lactone was also obtained from the "wet" addition and had similar properties, proving it to be γ-valerolactone, and shows the presence of considerable quantities of γ-bromo-valeric acid in the addenda.

(ii). βγ-Butenoic acid.

The additions in this case were rather numerous and were done in a variety of ways. The first to be done were according to the conditions that had been standardised for this work i.e. to the dry acid and to the acid containing ½% water. The rate of addition was found to be very slow indeed, particularly in the case of the dry acid, several saturations with hydrobromic acid being necessary (allowing to stand 24 hours between each) before the correct amount of gas could be absorbed.

Great difficulty was experienced in finding a satisfactory method of analysis of mixed β- and γ-bromo-butyric acids. The method as used for the valeric acids was tried but was found to be unsatisfactory as the β-bromo-acid gave rise to about 5% of ψ-acidic material which resulted in high results for the γ-acid. Distillation of the bromo-acids in steam, and also of the sodium salts of the bromoacids, before and after heating under reflux, was tried, but with no success. An attempt was then made to find a base that would discriminate between this pseudo-acid and γ-butyrolactone. This was dropped after many trials. Finally the method used was standardised as follows:

The bromoacid (known weight), was dissolved in neutral alcohol-water, and neutralised with N/10 baryta, the solution boiled under reflux for fifteen minutes, an excess of baryta added and the whole boiled for a further fifteen minutes. Any solid was filtered off, the liquid made acid by addition of an excess of sulphuric acid, and boiled for fifteen minutes to lactonise any γ-hydroxy-acid (from any γ-bromoacid) present. The lactone was then estimated as usual. In this way the amount of γ-bromoacid present in the addendum was found by comparison of the figures with those for the pure bromo acids and synthetic mixtures.

Pure β-bromo-butyric acid: Found 4.7% " γ "-bromoacid.

Pure γ-bromo-butyric acid: Found 100% γ -bromoacid.

For confirmation of the results obtained, any γ-bromoacid was converted to lactone as described in the cases of the addenda to the pentenoic acid and weighed. Results obtained.

Condition of acid.	Equivalent (calc. 167.0).	% γ-bromoacid.
Dry	168.6	1.9
"	167.2	1.5
+½% water	164.0	0.0
"	165.0	0.0
"	164.2	0.0

The five hydrobromides so obtained were united and neutralised with aqueous baryta, boiled for fifteen minutes under reflux, the liquid neutralised with sodium bicarbonate, and the liquid extracted continuously with

ether. The ether extract was dried, the ether distilled off, and the residue taken down to constant weight in a vacuum desiccator. 7.11 gms of hydrobromide yielded .15 gms of ψ-acidic material, from which only 0.016 gms of "γ-butyrolactone" could be removed by distillation in vacuo. Hence it is stated that the addition of hydrogen bromide proceeds in the same way both in the presence and absence of water, the amount of γ-bromoacid formed being certainly less than ½%.

Additions to βγ-butenoic acid in solvents.

These were done in view of the results obtained by Walker and Lumsden[16] on the addition of hydrogen bromide to undecenoic (undecylenic) acid in ether and toluene. The following solvents were used.

(a) Ether.

The ether used was shaken in the machine with calcium chloride solution, twice dried with sodium, and very carefully fractionated to remove water and alcohol. The unsaturated acid was treated in 50% solution in the ether with hydrogen bromide, being cooled in ice to stop , or inhibit, loss of solvent. The liquid was allowed to stand with excess of hydrobromic acid in a stoppered tube overnight (although this was probably not necessary), the ether and hydrobromic acid removed at the pump and finally in a vacuum desiccator over potash-wax. The liquid would not freeze in a freezing mixture and smelled strongly of ester; there was a considerable residue insoluble in alkaline solution that was ester. It was then discovered that this esterification of

of acids in ethereal solution is connected with the phenomena discovered by Fenton,[76] and, later, Fenton and Gostling.[77] They showed that many acids, among them acetic acid, if dissolved in pure alcohol-free diethyl ether and treated with hydrogen bromide, gave good yields of the ethyl ester of the acid. As the addition of hydrobromic acid to βγ-butenoic acid in ether appears to be almost instantaneous, the ester formed was that of the bromoacid present, and so the mixture was analysed by the attempted separation of γ-lactone from any γ-bromocompound there, as described above. The ψ-acidic substance isolated corresponded to 0.4% of γ-bromobutyric acid.

(b). Glacial acetic acid.

The ordinary reagent was used, the olefinic acid being in 50% solution. Addition was rapid, and the acetic and excess hydrobromic acids were removed in a vacuum desiccator over potash and soda-lime . The residual light yellow oil was examined. It had M. 168.0, and the amount of γ-bromoacid present was shown to be less than one per cent by isolation of lactone. The acid froze in a freezing mixture to the typical round masses of crystals of β-bromobutyric acid. It had m.p. 8.0°, and m.p. mixed with the reference β-bromoacid, 12° - 13°. This slight lowness in m.p. may be due to traces of impurity, e.g. ψ-acid and acetic acid in the final product. The addition in both these solvents appears to proceed to 100% β-addition.

(c) Toluene.

This was purified by long standing over sodium

wire and distillation from the same metal. The acid was first used in 50% solution, and after allowing the solution, saturated with hydrogen bromide, to stand overnight, the toluene was removed at the pump from a bath at40° - 45°. The residue readily solidified at -15° leaving a few drops of a purple liquid. This impurity, unlike both the pure bromoacids, was insoluble in light petroleum (b.p. 60° - 80°) and was removed by extraction with this solvent. On removing the petroleum at the pump, a white crystalline solid came out which, after draining on a tile from residual toluene, had m.p. 32°.

The experiment was repeated using a 20% solution of the acid in toluene. The bromoacid so obtained was freed from the trace of impurity as before, and had m.p. 32°, and m.p. mixed with authentic γ-bromo-butyric acid, 32°. M. was found to he 167.1, and analysis as for the bromo-valeric acids (see p. 130) showed it to be 99% γ-bromobutyric acid. Treatment to isolate lactone in the usual manner yielded 95% of γ-butyrolactone, identified by:- M. 86.6 (calc. 86.1), m.p.- 48.0°; m.p. mixed with pure γ-butyrolactone, -48.5°.

(d). Petroleum.

The petroleum used was purified from unsaturated compounds by shaking it with concentrated sulphuric acid, drying over sodium, and fractionally distilling, that fraction boiling at 40° - 60° being used. The additions were done to the acid in 20% ice-cooled solution in the petrol, the gas being readily absorbed, and the bromoacid commenced to separate from the solution as an oil. Removal of the

solvent at the pump after a few hours, and chilling the residue in ice, soon yielded a permanent solid. This had m.p.s both alone and mixed with authentic γ-bromobutyric acid 33°; M. 167.1; found 99.3% of γ-bromoacid. The acid was converted into the lactone in the usual way and gave 41% yield of pure γ-butyrolactone identified by the following figures:- M. 86.3 (calc. 86.1); m.p. -48.0°; m.p. mixed with authentic γ-butyrolactone, -48.5°. The bromoacid so obtained was free from the oily impurity that was formed when toluene was used, and can be obtained in this way far more conveniently than by any of the previously known methods.

On theoretical grounds it was next decided to perform additions on the ethyl ester of βγ-butenoic acid. For analysis of the addition products two methods were used :-

(a). The evidence of the physical properties of the ester so formed in comparison with those of the two pure reference bromoesters.

(b). A method of chemical analysis. The method finally chosen was tried on ethyl β-chlorpropionate at first and was found to give good results and was then tried on the two reference β- and γ-bromobutyric esters. with equal success.

About five gms of the ester were weighed accurately into a specimen tube, and a weight of clean sodium exactly equivalent to this was weighed out, cut into small pieces, and pressed out under sodium-dried petroleum into very thin sheets, and dropped into about 30 ccs. of benzene (dried over sodium). A 10% excess of the molecular equivalent of pure redistilled diethyl malonate was added to the mixture and the

the flask closed by a calcium chloride tube. The whole was allowed to stand with occasional hand shaking for six hours, at the end of which time the sodium had almost completely dissolved with the formation of a thick gelatinous mass of the sodio-compound. The flask was corked and shaken vigorously overnight in the machine to complete the reaction and to break up the solid into a fine paste. The halogen ester was then added, and washed in with a little dry benzene, and the whole boiled under reflux guarded by a calcium chloride tube on the steam for 24 hours to ensure complete reaction; at the end of this time (and usually long before) the solution was neutral. The benzene was removed at the pump, care being taken to remove it completely, as any remaining interfered with the hydroysis of the ester at a later stage. Water was added and the ester obtained in the usual way by extraction of the aqueous layer with ether, and the ester washed into a tared Geisler flask without distillation. It was boiled for 20 hours with two volumes of concentrated hydrochloric acid to completely hydrolyse the ester and also to decarboxylate it, this being completed by heating the liquid to 150° - 170° for a short time after removal of the hydrochloric acid at the pump. The acid was finally dried in a vacuum desiccator and weighed, and recrystallised if necessary. The test experiment on the chlorpropionic ester yielded an 85% of glutaric acid (calculated on the bromo-ester).

The method was then tried out on the reference bromoesters and these gave the following results :-

β-Bromobutyric ester gave 85% yield of β-methyl glutaric acid; m.p. crude, 75 - 77°, after recrystallisation from benzene-petroleum ether the m.p. was 86° both alone and mixed with an authentic specimen of β-methyl glutaric acid. γ-Bromobutyric ester gave a 72% yield of adipic acid, m.p. "crude", 149.5°, and with authentic adipic acid, 150°. The addition ester was obtained and distilled in the usual way. It distilled very steadily with no decomposition at all and practically a theoretical yield was obtained, a very small high residue being left. The ester was submitted to the above method of analysis with the following results: 86% yield of adipic acid; m.p. "crude" 149°, mixed with authentic specimen, 150°.

The ester had the following physical constants.

n. 1.4558 b.p. 96°/18.5 mms.

d. 1.3577

whence $[R_L]_D$ 39.35.

From the evidence of these figures, together with the fact that adipic acid was obtained in such good yield in a practically pure condition, the conclusion may be drawn that βγ-butenoic ester reacts with hydrogen bromide to yield pure γ-bromobutyric ester.

(iii) βγ-iso-Hexenoic acid.

The additions in this case were done under the two standard wet and dry conditions, i.e. to the acid alone and to the acid with ½% water. The gas was absorbed with very great ease, and the solutions were cooled in ice. The

addenda were allowed to stand in vacuo over potash until the correct amount of hydrogen bromide was present. This method was shown to give good results by bromine estimations. If the bromoacids were left in the desiccator over potash, the weight steadily dropped due to decomposition of the acid to lactone with loss of hydrogen bromide.

It was shown that the β-bromoacid was quite stable to water by silver nitrate tests as applied to bromovaleric acids. The γ-bromoacid however, was seen to be very unstable in the water solution, as it dissolved completely in cold water in less then a minute and the solution gave an immediate precipitate with silver nitrate solution. It was also found impossible, on account of this decomposition, to estimate the equivalents of the acids by this method. The method then tried was to add the theoretical amount of N/10 baryta equivalent to the weight of acid taken, and then to carry out the analyses exactly as described for the bromo-valeric acids on p. 130. Test experiments showed that the γ-bromoacid was converted rapidly and quantitatively into the lactone as usual, while the β-bromoacid yielded small but varying amounts of ψ-acid. It was, however, considered possible that this latter would not be formed to any noticeable extent in the presence of a large amount of the γ-bromoacid. and test analyses showed this to be so:

% γ-acid (true):	100	94.0
% γ-acid (found):	101	94.2

This method was adopted for the analyses and the results so obtained are given in the table below.

Condition of acid.	% Bromine (calc. 40.93)	% γ-bromoacid.
Dry	41.55	100.0
"	-	100.2
+½% water	-	100.2
"	-	99.3

The product of addition to the dry acid was found to solidify easily and gave a hard solid mass of needles, m.p. 10°. A mixture of this and the impure reference compound melted at 4°. This method of addition thus appears to yield pure γ-bromo-iso-hexoic acid, and is the best (and possibly the only) method of obtaining the pure acid.

The compositions of the dry and wet adducts were confirmed by conversion into the lactone as follows: the hydrobromide was neutralised with the theoretical amount of caustic soda solution, boiled under reflux for five minutes, acidified and boiled for a further similar period to lactonise any hydroxy acid remaining. The solution was cooled, saturated with sodium bicarbonate , and exhaustively extracted with other. The lactones were recovered from the ethereal solutions and distilled and identified as γ-iso-hexolactone by the following:

Source.	Yield.	b.p.	m.p.	mixed m.p.	M.
"dry" addn.	92%	93°/19 mms.	8.4°	8.2°	113.9
"wet" addn.	87%	97°/22 mms.	8.5°	8.2°	113.8
Reference.	-	94°/20 mms.	8.5°	-	114.1

The ψ-acidic material from the β bromoacid was

proved not to be γ-lactone in the following way. The β-bromoacid was exactly neutralised with sodium hydroxide solution and boiled under reflux for 30 minutes to complete the reaction. This was extracted with ether and a small amount of liquid was obtained. This was dissolved in saturated sodium bicarbonate solution and the aqueous liquid thoroughly extracted with ether. From the ethereal extract was obtained 0.2 gms. of a gum (from 5.41 gms. of bromoacid) which was obviously not γ-iso-hexolactone.

(iv) Δ-2-cyclohexene carboxylic acid.

By addition of hydrobromic acid to this acid there are theoretically four possible bromo-acids to be obtained. They are the cis- and trans- forms of both the β- and the γ-bromoacids. The first aim of the analyses was to estimate the amounts of β- and γ- acid present as such and to leave the consideration of the proportions of the cis- and trans- forms until later.

Various trial and test experiments on the bromoacids showed that the following method was the best. The acid was dissolved in 20 volumes of neutral alcohol and 40 volumes of water, and titrated with N/10 baryta. The liquid was heated under reflux for fifteen minutes, and neutralised again with baryta. It was found that in this time the β-bromoacid had undergone complete decomposition to 77 ± 1% of the hydroxy-acid, some cyclohexene, and a little pseudo acid, whereas the cis-γ-bromoacid had been converted into the γ-lactone with no liberation of acid, and the trans-isomer

had remained apparently unaffected, the bromine atom in this being very stable indeed. Excess baryta was then added and the estimation concluded as for a lactone except that the heating on the steam was for one hour to cause complete decomposition of the trans-γ-bromoacid, A second estimation was them done as a check, in which the amount of the β-bromoacid present had been artificially increased by about 25%- 30%.

The Δ-2 acid absorbed hydrogen bromide very slowly indeed, although a considerable increase was noticed with the moist acid. The adducts were worked up as usual, the correct amount of hydrogen bromide being present at constant weight as shown by a bromine estimation done in a test case.

Condition of acid.	E. (calc 207.0)	Direct %β	Direct %γ	Indirect. %β	Indirect. %γ	% Br
Dry	207.5	17.5	86.5(?)	18.0	82.0	38.6
"	205.4	13.0	81.0	19.0	81.0	-
+½% water.	210.0	16.5	82.0	18.5	82.0	-
"	205.0	17.0	83.0	18.0	82.0	-

In the above results the values for the β-acid are those calculated on the amount of hydroxy-acid formed and are of necessity not so accurate as the other figures, but have been included in the above table for the sake of completeness. It would appear from the figures that the addition has proceeded with the formation of 82% of the γ-bromoacid, and 18% of the β-acid. If the addenda were allowed to stand for several weeks solidification

commenced, The solid that first separated was drained on a tile and washed with petroleum ether, and then had m.p. 153° - 157° and was doubtless slightly impure trans-3-bromo cyclohexane carboxylic acid (cf. Perkin[38]). The acid was then allowed to stand until no further solidification occurred and the solid was recrystallised from petroleum ether and had m.p. 65°, both alone and admixed with pure cis-3-bromocyclohexane carboxylic acid. This shows that both cis- and trans- γ-bromoacids were formed, but, from the relative amounts of each isolated, the cis- form appeared to preponderate.

The results obtained by titration as given above were checked by experiments on the esters. β-Bromocyclohexane carboxylic ester had been shown to decompose, under the conditions of semiquantitative malonation as described on p.137 for the bromo-butyric esters, quantitatively to the αβ-unsaturated ester (cf. Cocker, Lapworth and Peters[52]). Test experiments were done under the same conditions on the pure cis-3-bromoester and this was found to be completely unchanged by the treatment, even on long boiling (72 hours) and was recovered unchanged in good yield. The aqueous liquors from the working up of the experiment contained no inorganic bromine, showing that no decomposition had occurred. This being so, it was considered that the trans-bromoester certainly would remain unchanged by similar treatment.

The analysis was performed by esterifying the addition products by the method used in the preparation of the reference cis-3-bromocyclohexane carboxylic ester (p.98)

and the purity of the final product proved by a bromine extimation on it. The ester was then treated under the semi-quantitative malonation conditions previously described for 24 hours. The liquid did not become neutral, nor was the liquid clear owing to the presence of sodiomalonate. Water was added and the free alkali carefully neutralised with hydrochloric acid, and the mixed esters recovered in the usual way by extraction with ether. The ethereal extracts were dried, the ether distilled off, the benzene removed at the pump at less then 50 °C, and the residue fractionally distilled in vacuum. The method was subsequently tested by taking the unchanged mixed 3-bromoesters from the analyses on the addition esters, adding a known amount of pure 2-bromoester, and repeating the estimation. In all cases where there was 2-bromoester present the low fraction from the distillation was highly unsaturated (for the reason explained above), and the aqueous liquors from the working up of the experiment contained sodium bromide owing to the decomposition of the 2-bromoester; while in the test on the pure cis-3-bromoester the reverse was the case.

Results:-

Test on cis-3-bromoester. Recovered 89% of the ester.

Synthetic mixture.

% γ-bromoester(true)	78
% γ-bromoester(found)	79

The results from the actual addition esters are given overleaf.

Addendum from which

the ester was obtained.	% γ-acid found
Dry	83.5
Wet	83.0

These figures, although of necessity not so accurate as the titration results, are an added proof that the addition produces about 82 - 83% of 3-bromo-acid.

PART 7: PROPERTIES OF LACTONES.

1. Hydrolysis of γ-Lactones.

The lactones were studied exactly as described on p. /// , with the following results. The aliphatic lactones have been kept separate from the dicyclic lactones as the former were all found to have attained a steady state after 24 hours heating in the bath, while the latter needed longer heating. Also, in the case of the first dicyclic lactone used, the corresponding hydroxy-acid was available in a pure state and this was also heated under the standard conditions to show that the equilibrium was reached from both sides.

Lactone.	% change to acid in: 24 hours.	48 hours.	% lactone remaining after 48 hours.
γ-Butyro-	25.2	25.1	75.1
γ-Valero-	7.1	7.0	92.7
γ-Hexo-	6.6	6.8	92.3
γ-iso-Hexo-	3.5	3.5	95.1

Dicyclic lactones:

(see over)

cycloHexanolide 1:3

Time of heating	% Acid formed.	% Lactone left.
24 Hours.	74.7	25.5
48 "	86.8	14.6
96 "	90.1	12.6
144 "	89.5	13.5

cis-3-Hydroxy-cyclohexane carboxylic acid.

Time of heating	% Acid left.	% Lactone formed.
24 Hours	88.0	12.0
72 Hours	87.3	14.2

1-methyl-cyclohexanolid 1:3

Time of heating	% Acid formed.	% Lactone left.
24 Hours	21.6(?)	74.0
48 "	27.1	75.2
72 "	28.7	69.3

In these longer heating experiments there has been formed in the solution some impurity that interferes slightly with the figures in the analyses. It is probable that the figure for the amount of acid present as determined by direct titration with baryta (N/10) is the more accurate in each case, as the lactone figure would include the amount of any ψ-acidic material present.

For purposes of comparison the value in each case of the ratio lactone/acid has been calculated and they are given in the table below.

Lactone	Ratio Lactone/Acid (L/A)
γ-Butyrolactone	2.97
γ-Valerolactone	13.1
γ-Hexolactone	13.9
γ-iso-Hexolactone	27.6
cycloHexanolide 1:3	0.136
1-Methyl-cyclohexanolide 1:3	2.57

2. Velocity of formation of γ-Lactones from γ-Hydroxyacids.

The determination of velocities for the two hexolactones had already been determined by Linstead by the same method (as described on p. ///), while it was considered that the very large proportion of acid present at equilibrium in the case of cyclohexanolide 1:3 rendered the determination of velocity useless. The tables for the velocity determinations of the three lactones are given here. The three curves have all been plotted on the same axes for comparison, and these curves use the "five minute zero" as advocated by Hjelt and Linstead.

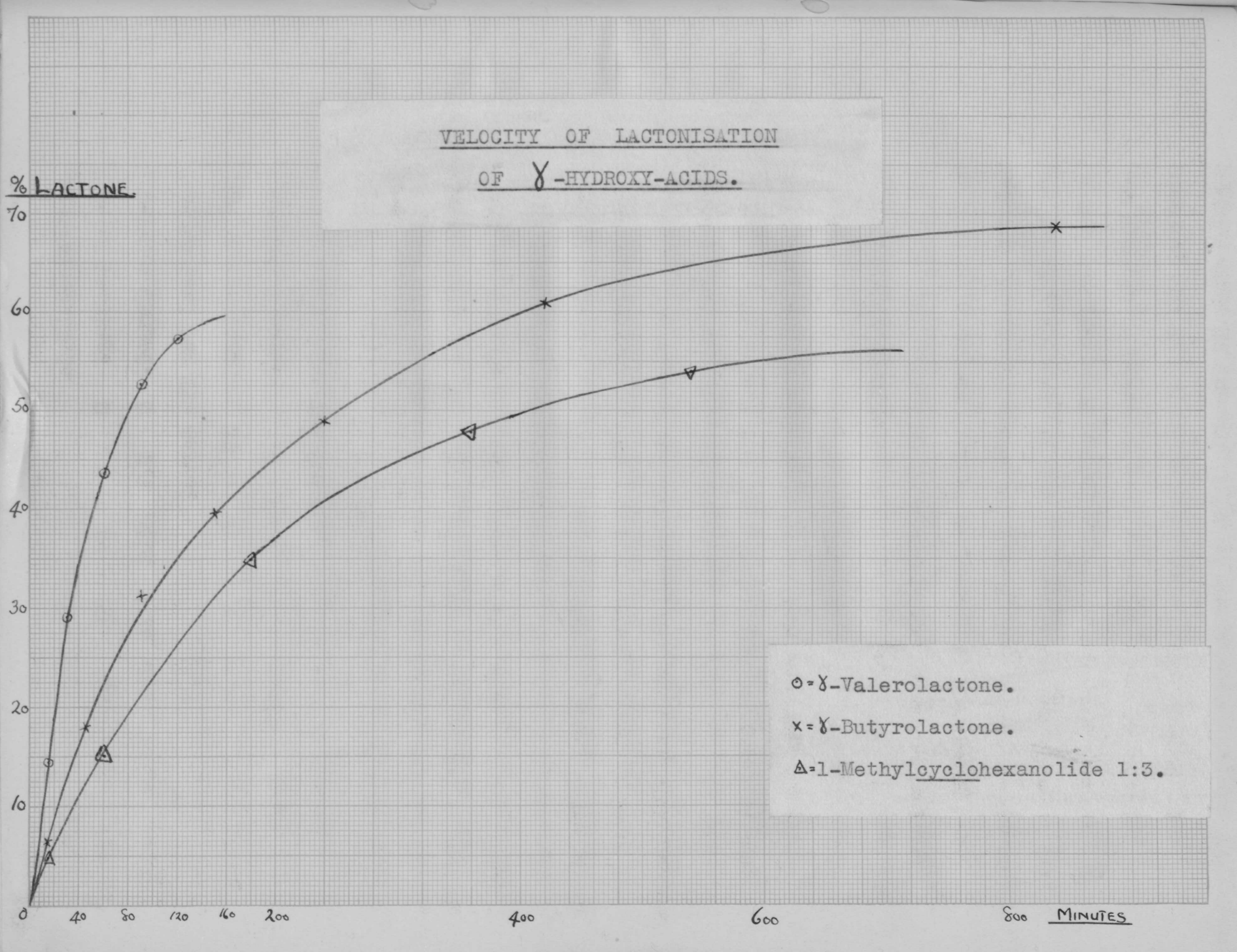
γ-Butyrolactone

Time of heating.	0	5	20	50	95	155	245	425	845 m.
% Lactone formed.	0.0	2.1	8.3	19.6	32.6	40.9	50.0	62.0	69.4.

Figures used for the curve.

Time of heating.	0	15	45	90	150	240	420	840 m.
% Lactone formed.	0.0	6.4	17.9	31.2	39.6	48.9	61.1	68.7

The time for half-change (i.e. to 37.4% lactone) is seen to be from the top table, 135 minutes.


VELOCITY OF LACTONISATION
OF γ-HYDROXY-ACIDS.
% LACTONE.
70
60
50
40
30
20
10
0
40
80
120
160
200
400
600
800
MINUTES
⊙=γ-Valerolactone.
×=γ-Butyrolactone.
△=1-Methylcyclohexanolide 1:3.

γ-Valerolactone.

Time of heating.	0	5	20	35	65	95	125 m.
% Lactone formed.	0	5.9	22.4	34.1	48.2	56.6	61.5

Figures used for the curve.

Time of heating.	15	30	60	90	120 mins.
% Lactone formed.	17.0	29.1	43.6	52.6	57.3

The time for the half change, with a lactone content of 46.5%, is 64 minutes.

1-Methyl-cyclohexanolide 1:3.

Time of heating.	0	5	20	65	185	365	545 m.
% Lactone formed.	0	0.3	5.2	15.2	35.1	47.7	54.1

Figures used for the curve.

Time of heating.	15	60	180	360	540 mins.
% Lactone formed.	4.9	15.0	34.9	47.9	54.0

The time of half-change is198 minutes, with lactone content 36.0%.

The curves for these three sets of results face this page, and it will be noticed that they are all of the same general type.

3. Parachor measurements on γ-Lactones.

The method of determining the parachor valuesof of the lactones was that of Sugden.[73,74] As this method was followed exactly, a detailed description is not needed here. One remark, relevant to the determination of the densities by the U-shaped pycnometer, may be made. The lactone was introduced into the pycnometer by means of a small pipette, the tip of which was placed right down on the constriction in the side tube of the pycnometer, and the

liquid allowed to flow slowly in. This was found to eliminate the moistening of the sides of the tube by liquid and to remove a possible source of error.

The densities were determined over three temperatures and the graphs which were plotted were in each case very accurately linear. The figures only for the temperature-density changes are given here.

The actual measurement of parachors was done at two temperatures as widely separated as possible, and repeated in a second bubbling cell. Each reading recorded was checked several times to reduce error, and every reading was done three times. The values found are given below.

γ-Butyrolactone.

Data for temperature-density change.

Temperature.	17.8°	34.5°	82.6°
Density.	1.1284	1.1123	1.0643

Parachor values; two cells.

Temperature.	16.6°	90.5	90.5	20.7°	90.0	90.0
Surface tension.	43.93	35.29	35.36	43.82	36.10	36.29
Parachor, P.	196.6	198.4	198.6	196.6	198.5	198.2

Mean of P. at low temperatures.	196.3
Mean of P. at high temperatures.	198.4
P. calculated on Sugden's values	190.3
P. calculated on Mumford and Phillip's values . . .	194.2

The theoretical value of P. obtained from the atomic and structural parachors of Mumford and Phillips agrees well with actual value found.

γ-Valerolactone.

Data for temperature-density change

Temperature.	18.9°	33.3°	86.0°.
Density.	1.0563	1.0420	0.9917

Parachor values : two cells.

	Cell 2.		Cell 1.	
Temperature.	21.4	91.0	19.7	90.5
Surface tension.	37.37	30.06	37.96	31.50
Parachor, P.	234.8	237.4	235.4	237.6

Mean of P. at low temperatures. 235.1

Mean of P. at high temperatures 237.6

P. calculated on Sugden's values 229.3

P. calculated on Mumford and Phillip's values. . 234.2

Here also the agreement between the experimental figures and the theoretical value as calculated on the atomic and structural parachors of Mumford and Phillips is fairly good.

From these results the γ-lactone ring does not appear to possess a structural parachor apart from the normal ring value.

PART 8: OTHER EXPERIMENTS CONDUCTED.

(i). Determination of the position of the three carbon tautomeric equilibrium in the case of the cyclohexene carboxylic acids. This was done by a modification of the method of Linstead and Noble,[23] no attempt being made to determine the mobility of the change in either direction.

The acid to be equilibrated was dissolved in 10 molecular equivalents of 25% aqueous potassium hydroxide solution (the alkali used being that purified by alcohol) and the solution sealed in special bulbs of "Monax" glass in an inert atmosphere. This was then heated to 100° in a bath of boiling water for 14 hours. The method of working up the liquid was modified slightly owing to the tendency of the βγ-acid to undergo various destructive changes if heated in the atmosphere. The alkaline solution was extracted twice with ether to remove neutral and basic impurities, the liquid carefully made acid to Congo red with a calculated small excess of sulphuric acid (25% by volume), the liquid extracted with ether five times, the combined extracts washed with water, dried over calcium chloride, the ether distilled off and the residue distilled in vacuo in an inert atmosphere. The proportions of αβ - and βγ - acids present were estimated by bromine addition in the way described on p. 102, and the final figures found from a reference curve. Equilibrium had been attained in 14 hours, and both the acids obtained solidified to the large overlapping plates of the αβ-acid, The acid obtained by equilibrating

the βγ-acid was separated into its two constituents and the αβ-acid had m.p. 37°. Mixed m.p. with the pure αβ-acid, 37°. This shows that the βγ-acid forms the αβ-acid on equilibration, while the fact the the βγ-acid is obtained from the αβ-acid by the same process has been previously proved (see p. 64)

Figures for the reference curve:

% βγ-acid.	0.0	4.4	9.1	12.9	16.7
J.	1.7	6.5	10.8	14.0	18.2

Acids recovered from the equilibrations:

	% Recovery.	E. (calc. 126.1).	J.	% βγ acid
From αβ-acid.	78	126.1	5.9	4.1
From βγ-acid.	74	126.4	6.2	4.4

Hence the three carbon equilibrium in the case of Δ-1- and Δ-2-cyclohexene carboxylic acids lies at c. 4.2% Δ-2-acid.

(ii) Determination of the position of the three carbon tautomeric equilibrium for the 3-methyl-cyclohexene carboxylic acids. In this case the determination was combined with a preparative method and the equilibrations were done on large quantities of the αβ-acid. The mobility of the change seems remarkably low as will be seen from the following results. Two experiments were run in parallel, one always being treated more drastically than the other to ascertain whether equilibrium had been reached or not. The two series of experiments, with the treatment used and results obtained, are given in parallel:

A

The acid was boiled for 16 hours under reflux in a copper flask with two molecular equivalents of 25% caustic potash solution

B

The acid was boiled for 9 hours under reflux in a copper flask with 10 molecular equivalents of 25% caustic potash solution

The liquids were cooled, very carefully acidified in ice cold solution with hydrochloric acid, the acids extracted with ether the ethereal extracts washed, dried, the ether distilled off, and the residue distilled in vacuo. Bromine addition experiments were done on the acids thus obtained.

90% recovered; E. 140.4; J. 6.2.

83% recovered; E. 140.0; J10.

The recovered acid was dissolved in two molecular equivalents of 40% potash, (concentration of free KOH, 20%), boiled for 24 hours, and heated for 40 hours on the steam under reflux. Worked up as above.

The recovered acid was dissolved in 2 molecular equivalents of 40% potash, and boiled under reflux for 63 hours. It was worked up as described above.

84% recovered; E. 141.0; J. 13.0.

83% recd.; E. 140.0; J. 18.5

The recovered acid was boiled for 90 hours with 3 molecular equivalents of 33% caustic potash, and worked up as above,

The recovered acid was boiled for 114 hours with 3 molecular equivalents of 33% caustic potash and worked up as above.

84% recovered; E. 141.1; J. 27%

81% recd.; E. 140.4; J. 26.0.

Thus equilibrium has been reached in the last two cases, and appears to be at 25.2% of βγ-acid. Unfortunately, scarcity of material prevents a study of the reverse reaction from the βγ-acid, but the above is good evidence of the approximate position of the equilibrium.

The βγ-acid formed in the above way was purified by partial esterification as described previously and the p-toluidide prepared; this on recrystallisation from petroleum, formed clusters of needles m.p. 109°. These in admixture with the p-toluidide from the βγ-acid from the preparation, melted at 108° - 109°. This shows that the two acids are identical.

(iii). Michael addition to the △-1-cyclohexene carboxylic ester.

The first attempt to do this was after the classical method of Michael. one sixth of the amount of sodium equivalent to the amount of ester to be used was converted into sodium ethoxide using the smallest amount of alcohol possible, this latter having been dried over calcium. The unsaturated ester with an equimolecular amount of redistilled malonic ester were added, and enough sodium-dried ether to cause a slight opalescence in the liquid. This was then heated on the steam under a reflux condenser guarded by a calcium chloride tube for twelve hours, cooled, the solution washed free from sodium with dilute hydrochloric acid, the ethereal layer dried, the ether distilled off, and the

residue fractionally distilled in vacuo. No condensation had occurred, as the liquid distilled completely over the temperature range 87° - 93°/11 mms. and was a mixture of the unsaturated ester and malonic ester.

The recovered liquid was then allowed to stand for three days in the cold with one molecular equivalent of sodium ethoxide, and then heated on the steam for 12 hours. The liquid was dissolved in ether, the solution washed with hydrochloric acid as before, the solution dried, the ether distilled off, and the residue fractionally distilled in vacuum. A 45% yield of condensation product boiling at 176° - 183°/9 mms. was obtained. (cf. Helfer,[79] who by a similar experiment on a larger scale obtained 40%).

In order to hydrolyse this ester it was found necessary to boil it for 28 hours with two volumes of concentrated hydrochloric acid in a Geisler flask. The aqueous liquid was removed at the pump and the residual acid dried in a vacuum desiccator. Heating to 170° did not cause any further decarboxylation. Yield: 98%. The acid was recrystallised from water, the uncrystallisable residues being collected and hence the amount of pure acid was determined. This was proved to be pure trans-hexahydrohomophthalic acid by the following:- E. 93.0 (calc. 93.05), m.p. 158°; m.p. mixed with pure hexahydrohomophthalic acid, 158-9°. This pure acid was obtained in 92% yield from the tricarbethoxy-ester.

The Michael addition was repeated, the only difference being that the time of heating on the steam was

24 hours instead of 12 as in the first case. The yield of condensation ester was 38%, and from this was obtained 95% of the pure recrystallised dicarboxylic acid, of m.p.158° and mixed m.p. 158°.

These two results indicate clearly that the very great part of the condensation reults in the production of the trans configuration.

(iv) Attempted malonation of 2-bromocyclohexane carboxylic ester.

The pure bromoester (see p. 98) was submitted to the semi-quantitative malonation conditions as described on p. 137. and used for the analysis of bromobutyric esters. The reaction mixture soon became neutral and the product was worked up in the normal manner. The whole of the liquid distilled at about 95°/15 mms., there being no high fraction. As the reaction mixture was neutral before it was worked up, this indicated the quantitative loss of hydrogen bromide from the bromoester to form the unsaturated ester. Consequently the ester fraction that had distilled was put up for condensation by the Michael method just described and worked up as the first addition that was successful. In this way a 43% yield of an ester boiling at 185° - 187°/13 mms. was obtained. This was hydrolysed in the usual way with concentrated hydrochloric acid (two volumes) and gave a 93% yield of pure hexahydrohomophthalic acid (trans) identified by its m.p., 158°, and the mixed m.p. with an authentic sample, 158°. This proved that the

2-bromocyclohexane carboxylic ester decomposed quantitatively into the corresponding Δ-1-unsaturated ester as would be expected from the work of Cocker, Lapworth and Peters[52].

SECTION 5.

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