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Ring-Chain Isomeric Conversions of Aldehydo-carboxylic and Keto-carboxylic Acids and Their Derivatives

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Ring-chain isomeric (including tautomeric) conversions of aldehydo- and keto-carboxylic acids and their chlorides, amides, hydrazides, esters, and mixed anhydrides are reviewed. The possibilities of using physical methods (ultraviolet, infrared, and proton magnetic resonance spectroscopy) for the identification and quantitative determination of isomers are discussed. The effect of structural factors on the relative stability of isomers is analysed. Conditions are elicited under which interconversion occurs or equilibrium is observed. A list of 207 references is included.

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I. INTRODUCTION

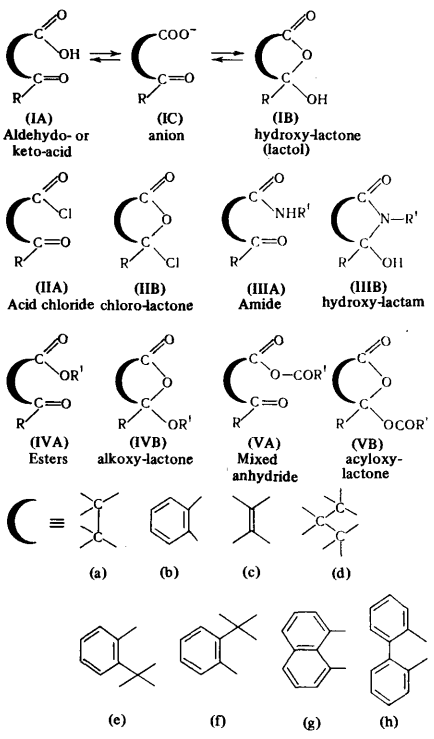
Ring-chain isomeric conversions are observed in organic molecules containing a multiple bond and a functional group capable of intramolecular addition at this bond. The structure of the molecule should enable the two groups to assume a relative arrangement suitable for the reversible intramolecular addition.

Ring-chain isomeric conversions are often termed ring-chain tautomerism [1]. Depending on the polarity of the bonds of the interacting functional groups, electronic and steric effects of substituents, and several other factors, however, three types of isomeric conversions may be observed. (1) In ring-chain tautomerism, equilibrium is rapidly established between open (A) and cyclic (B) forms in solution at room temperature. (2) In reversible ring-chain isomerism [2] both forms can be obtained separately, and are stable in neutral solvents at room temperature. The isomerisations A → B and B → A are effected by the action of acid or basic catalysts, by specific reagents, or on heating. (3) In irreversible ring-chain isomerism both forms are stable, but their interconversion can be achieved only in one direction (A → B or B → A).

Isomeric and tautomeric conversions must be clearly distinguished. Absence of tautomeric equilibrium can be reliably assessed, of course, only when both isomers have been isolated and it has been established that they are both stable in solution. If only one isomer has been isolated, e.g. A, and its stability in solution has been demonstrated, occurrence of the equilibrium A ⇌ B is still possible, displaced so far towards A that the concentration of the isomer B is below the limit of sensitivity of the method of identification used.

A previous review [1] did not differentiate between tautomeric and isomeric conversions. It had the defect of an uncritical approach to the results of early investigations, in which the structure of the isomers had been demonstrated only by chemical methods. The use of such methods to establish the structure of compounds capable of isomeric conversions is unreliable and a frequent source of error. As early as 1956 Hammond [3] wrote that, since spectroscopic methods had been developed after the period

Scheme 1



of the most active studies of ring-chain tautomeric conversions, there were grounds for expecting that in the near future a new stage would begin in the general investigation of these problems. Actually, quite a large number of investigations have been published during the last decade in which structures of open-chain and cyclic isomers and their interconversion have been examined by ultraviolet, infrared, and proton magnetic resonance spectroscopy.

The present Review summarises results only of those investigations, published mainly during the past decade,

in which the structure of the isomers was reliably established by spectroscopic methods. Attention has been paid mainly to—(i) spectroscopic characteristics enabling cyclic and open-chain forms to be identified and determined in mixtures, (ii) the relative stability of the isomers, i.e. the character of the equilibrium, (iii) the conditions under which isomeric interconversions occur, and (iv) the influence on the relative stability of the isomers exerted by the electronic and steric effects of substituents attached to the interacting functional groups and by the structure of the bridge connecting them. In order to analyse these questions in greater detail, we restrict our survey to aldehydo- and keto-carboxylic acids and their acid derivatives. Scheme 1 gives the general structures of the open-chain (A) and cyclic (B) forms examined (I)–(V) and the structures of the bridging units (a)–(h) joining the two functional groups. The structures (a)–(h) enable us to expect the existence of cyclic forms, but undoubtedly do not exhaust all possible cases.

II. ALDEHYDO- AND KETO-CARBOXYLIC ACIDS

γ-Aldehydo- and γ-Keto-carboxylic Acids (Ia–c)

Nucleophilic intramolecular addition of a carboxy-group to a carbonyl group is a rapid and reversible process[4], and the tautomeric equilibrium IA ⇌ IC ⇌ IB is established in solutions of γ-aldehydo- and γ-keto-acids. Independently of the structure of the molecule and of the substituent R, the carboxylate anion always has the open-chain structure (IC)[4–15]. Pascal[16] found that the equilibrium

$$\underset{\text{dimer of keto-acid}}{\text{IA...IA}} \rightleftharpoons \text{IA} \rightleftharpoons \underset{\text{associated lactol (C=O...H–O)}}{\text{IB...IB}} \quad (A)$$

is established in solutions of methyl-substituted γ-oxovaleric acids in solvents of low polarity.

It was suggested[16] that the tautomeric equilibrium constant $K_T = a_B/a_A$ of aldehydo- and keto-carboxylic acids in solution should be determined using the equation

$$\lg(K_T + 1) = pK_a - pK'_a \quad (1)$$

where K_a is the acid ionisation constant of the carboxylic acid determined potentiometrically, and K'_a the true (theoretical) acid ionisation constant of the carboxylic acid A in the absence of the tautomeric equilibrium IA ⇌ IB. Use of the method[4,16–18] is restricted by the fact that it is extremely difficult to determine accurately the constant K'_a from the acidity constants of model acids of similar structure that are incapable of cyclisation. This has been done most accurately for *cis*-β-acylacrylic acids from the experimental acidity constants of the corresponding *trans*-acids[19]. Bell[4] determined the constant K'_a of *o*-formylbenzoic acid from a kinetic investigation of its catalytic action in the decomposition of nitramide and the mutarotation of glucose, whence he calculated the tautomeric equilibrium constant in aqueous solution (K_T = 14.8). This method is claimed to be more accurate.

Bowden[20,21] solved the opposite problem by substituting in Eqn. (1) values of K_T determined by proton magnetic resonance and the constants K_a determined potentiometrically: he calculated the true acid ionisation constants K'_a of several *o*-acylbenzoic and *cis*-β-aroylacrylic acids in 80% aqueous 2-methoxyethanolic solution.

The ketonic carbonyl band disappears from the infrared spectrum in the tautomeric conversion IA → IB of γ-keto-acids. Owing to the bending stress on the >C=O bonds in the five-membered ring of IB, the lactonic carbonyl bond is shifted to higher frequencies (1800–1770 cm^{-1}) than in the carboxy-group in the open-chain form IA (Table 1).

Table 1. Frequencies (cm^{-1}) of C=O bands in infrared spectra of γ-keto-acids in solution.

Formula (I)		Solvent	Form A		Form B, lactone	Ref.
	R		ketone, aldehyde	carboxyl		
CH_2	H	CCl_4	1749	1711	1795	22
	CH_3	CCl_4	1726	1758 (free) 1714 (bound)	—	16
CH_2	C_6H_5*	$CHCl_3$	1690	1710	—	23
	CCl_3	$CHCl_3$	1767	1724	1808	24
	H	dioxan	1699	1723	1778	20
	CH_3	dioxan	1706	1724	1776	20
	C_6H_5	dioxan	1681	1726	1781	20
	CCl_3	$CHCl_3$	1574 sh**	1721	1789	24
H	H	in KBr tablets	—	—	1795, 1761	25
	CH_3	dioxan	—	—	1763	19
H	C_6H_5	dioxan	1676	1713	1769	21
	CCl_3	$CHCl_3$	1786 sh	1715	1812	24

*β-Benzoyl-α-methylpropionic acid.
**sh = shoulder.

Determination of the tautomeric equilibrium constants of *o*-aroylbenzoic[26,27], *o*-acylbenzoic[20], and *cis*-β-aroylacrylic[21] acids from the infrared spectra is based on the postulated equality of the integrated intensities of the carbonyl bands in the spectra of esters of cyclic (IVB: νC=O = 1780 cm^{-1}) and open-chain (IVA: νCOOR = 1730 to 1720 and νC=O = 1700–1675 cm^{-1}) structure and the corresponding tautomeric forms (IA and IB) of keto-carboxylic acids. The reproducibility of the determination of the content of tautomeric forms is ±2–3%.[20,27] Satisfactory correlation is observed between the tautomeric equilibrium constants of *o*-*m*′(or *p*′)-X-benzoylbenzoic acids and the σ_m and σ_p constants of the substituents X respectively[26,27].

When proton magnetic resonance is used to analyse ring-chain tautomeric systems, it must be borne in mind that two cases are observed depending on the rate of the tautomeric conversion[28]: (i) with slow tautomeric conversions (on the p.m.r. time scale) the proton signals of the two forms are observed separately, and the tautomeric composition is determined from their relative intensities; (ii) with rapid conversions the proton signals of the two forms coalesce into a single signal, characterised by the mean chemical shift. Replacement of a less polar by a more polar solvent or additions of catalytic quantities of acids or bases may influence the rate of the tautomeric changes, and thereby change significantly the pattern of the p.m.r. spectrum[12,20,29].

The forms (IA) and (IB) are most often identified and determined by means of the signals from protons in the groups CH_3CO (IA) and $CH_3C(OH)O$ (IB: R = CH_3) (or in general AlkCO and AlkC(OH)O) for keto-carboxylic acids[13,16,17,20,29–32] and in the groups HCO (IA) and HC(OH)O (IB: R = H) for aldehydo-acids[9,11,12,14,15,18,22]. Signals of protons in other groups have been used more rarely[21,33]. In the p.m.r. spectrum of *o*-acetylbenzoic acid dissolved in hexadeuteriated dimethyl sulphoxide

Finkelstein[29] observed proton signals at 2.45 ppm† (CH_3CO) and 1.78 ppm ($CH_3C(OH)O$). The constant was determined from the signal intensities as $K_T = 2$. After catalytic quantities of hydrochloric acid had been added to the solution, the two signals coalesced into a single signal with a chemical shift of 2.02 ppm. In the p.m.r. spectra of keto-carboxylic acids, however, one common signal is most often observed, indicating the occurrence of rapid tautomeric conversions[16,17,20,31,32]. In the determination of the constant K_T it is assumed that the contents of the forms (IA) and (IB) in the tautomeric mixture are inversely proportional to the distances of their common signal from the corresponding signals in the spectra of fixed models, the esters (IVA) and (IVB)[20,31]. The constant K_T for β-formylpropionic acid[22] was determined from the intensity ratio of the signals of aldehydic and methine protons (9.54–9.66 and 5.66–5.83 ppm respectively).

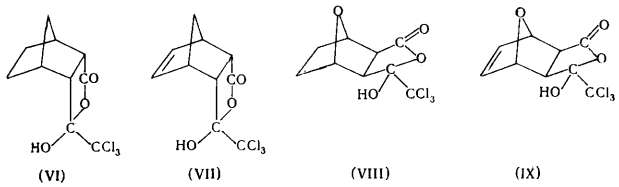
The disappearance of the chromophoric group (C=O) in the conversion of IA into IB is responsible for corresponding changes in the ultraviolet spectrum. However, absorption in the ultraviolet, governed by electron transitions in conjugated systems, cannot be interpreted as clearly as infrared absorption, where the presence of a particular multiple bond can be assessed unambiguously. The use of ultraviolet spectroscopy to determine the constants K_T in tautomeric systems of aldehydo- and keto-carboxylic acids is based on the postulate that the absorption by fixed models—the esters (IVA) and (IVB)—and the absorption by corresponding tautomeric forms of the acids (IA) and (IB) do not differ appreciably[22,31,34].

Little work has been done on the effect of the solvent on the tautomeric equilibrium. In more polar solvents the equilibrium is displaced towards the cyclic form[26,27,35]. However, contrary results have also been obtained[36]. The mechanism of the action of the solvent on the tautomeric system IA $\rightleftharpoons$ IB is complicated. Intermolecular hydrogen bonds may play an important part in stabilising a particular form, the cyclic isomer showing a greater tendency to form such bonds involving both carbonyl and hydroxyl groups. Dilution of the solution[6,7,22], the use of pyridine or triethylamine as solvent, or their addition to existing solutions displaces the equilibrium towards the open-chain form[15,22]. In acid media the equilibrium is shifted in favour of the less acidic cyclic form[7]. No correlation could be found between the structure of *o*-acylbenzoic acids and the temperature dependence of the ring–chain tautomeric equilibrium[36,37].

Structural factors promoting intramolecular nucleophilic addition of the carboxyl to the carbonyl group can be divided into three types—(i) factors that enhance the electrophilic character of the aldehydic or ketonic carbon atom (the presence of electron-accepting substituents R, the absence of conjugation between the carbonyl group and an aromatic ring, etc.), (ii) factors that enhance the nucleophilic character of the oxygen atoms in the carboxy-group, and (iii) factors that bring carboxyl and carbonyl groups closer together in space, which is most favourable for intramolecular attack.

The carbonyl carbon atom becomes less electrophilic with the squence of substituents R = H, Alk, Ar. The equilibrium IA $\rightleftharpoons$ IB is established in solutions of β-formylpropionic acid[22] and its chain-substituted derivatives[16,18,38]. The cyclic form is not detected in solutions of γ-oxovaleric acid[16]. The accumulation of two or three methyl groups in the chain brings about a steric approach of carboxyl and carbonyl groups (the *gem*-dimethyl effect[3,39]), and for $\alpha\alpha\beta$-trimethyl-γ-oxovaleric acid[16] in 80% aqueous 2-methoxyethanol $K_T = 7.7$. Infrared spectroscopy provides evidence that β-aroylpropionic acids[23,40,41] and several of their more complicated analogues[42] have the open-chain structure in the crystalline state and in solution.

An increased tendency to form the cyclic modification has been observed[10,24] in a series of β-trichloroacetylcarboxylic acids. The $-I$ effect of the trichloromethyl group is obviously operating here. The relatively high stability of the ring forms of the bicyclic keto-carboxylic acids



(VI) (VII) (VIII) (IX)

is due to the completely protected conformations of the *cis*-substituents (COOH and CCl_3CO) attached to the second and third carbon atoms of 1,4-*endo*-methylene- and 1,4-*endo*-oxo-cyclohexanes and -enes, which create the most favourable conditions for intramolecular nucleophilic attack.

Because of the steric approach of carboxyl and carbonyl groups, *o*-acylbenzoic acids (Ib), and especially *cis*-β-acylacrylic acids (Ic), show a greater tendency than do β-acylpropionic acids (Ia) to form the cyclic modifications. Three-dimensional models show that the open-chain forms of these acids (Ib–A and Ic–A) are able to exist only in the energetically disadvantageous non-coplanar form, which excludes conjugation of the π-bonds[43].

In solutions of *o*-formylbenzoic (Ib: R = H)[4,8,11,12,15,44,45] *o*-acylbenzoic (Ib: R = Alk),[5,20,29,31,32,35,45–50] and especially *cis*-β-acylacrylic (Ic: R = H, Alk)[17,19,25] acids the tautomeric equilibrium is displaced towards the cyclic form. The ketonic carbon atom in *o*-aroylbenzoic acids (Ib: R = Ar) is less strongly electrophilic owing to conjugation with both aromatic rings. In the absence of specific structural factors stabilising the ring form, *o*-aroylbenzoic acids have predominantly the open-chain structure in the crystalline state and in solution[20,27,31,34,45,51–56]. The tautomeric equilibrium constants of *o*-*m*'- or *o*-*p*'-X-benzoylbenzoic acids[26,27] in dioxan have values of 0.03–0.10, and those of *cis*-β-*p*-X-benzoyl-α(or β)-methylacrylic acids[21] lie in the range 1–26, the higher values being observed with acids having electron-accepting substituents X.

A methyl group in the 3- or 6-position of a 2-aroylbenzoic acid exerts a steric effect on the carboxyl and carbonyl groups, so that the equilibrium is shifted in favour of the ring form, with a 6-methyl group having the stronger effect. Methyl groups in the 2'- and 6'-positions of the aroyl substituent shield the carbonyl group sterically, and hinder cyclisation[34,52,57]. Predominance of the cyclic form has been noted in 2-benzoyl-3,4,5,6-tetrachlorobenzoic acid[27,31].

The series of 2-acetyl-6-X-benzoic acids shows[29] increase in the stability of the ring form with strengthening of the electron-donating power of the substituent X, i.e. with enhancement of the nucleophilic character of the oxygen atoms in the carboxy-group. Nitro-groups, independently of their position in the phthaloyl ring,

†Chemical shifts are always indicated on the δ-scale relative to TMS.

stabilise the open form [27,29,31,56]; the reason for this is not entirely clear.

Infrared spectroscopy has been used to investigate the structure of *o*-acylbenzoic acids in the crystalline state [31,45,58]. The isolation of one tautomeric form of an aldehydo- or keto-carboxylic acid in the crystalline state does not prove that this same form predominates in solution [3,31,35,49]. Interpretation of the infrared spectra is complicated by the presence in the lattice of stable intermolecular hydrogen bonds O–H...O=C (lactol), which split the carbonyl band of the lactol and shift it to lower frequencies than in solutions [31,42,45]. The spectra of concentrated solutions of keto-carboxylic acids in weakly polar solvents contain, besides the free carbonyl band of the lactol (1780–1770 cm^{-1}), also a band at 1750 cm^{-1} due to a bound carbonyl group [16,32,35]. The latter becomes less intense with dilution of the solutions, which distinguishes this band from absorption by monomeric carboxyl observed [16] in the same region. The main evidence of the ring structure (IB) in the spectra of crystalline compounds is the presence [6,31,58] of an intense, broad band due to a bound hydroxy-group (OH...O=C) at 3350–3150 cm^{-1}. In the spectra of crystalline keto-carboxylic acids (IA) the hydroxy-absorption of the dimeric carboxy-groups is apparent as a diffuse band at lower frequencies (3000 to 2600 cm^{-1}).

o-Formylbenzoic [44,45,58] and *o*-acetylbenzoic [29,31,32,45,58] acids have the ring structure in the crystalline state. Some *o*-acylbenzoic acids (Ib: R = Alk or more complicated substituent) have been obtained in the crystalline state as the cyclic modification [5,10,24,59], and others in the open form [35] or as a mixture with one form predominating [35,47–50,60]. Both isomers of benzil-*o*-carboxylic acid



(XA) (XB)

have been obtained in crystalline form [58,61], and the thermal isomerisation XB → XA has been accomplished.

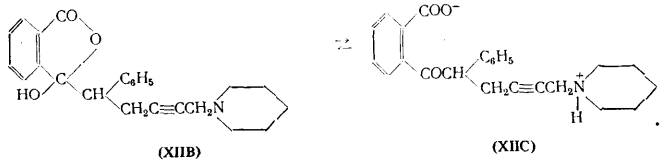
Three crystalline modifications of *o*-β-*N*-t-butylcarbamoyl-α-phenylpropionylbenzoic acid have been described which differ in their content of the tautomeric forms



(XIA) (XIB)

and in the involvement of the various carbonyl groups in the formation of intermolecular hydrogen bonds [50].

It is interesting that the acid (XII) can be isolated, depending on the conditions, as the lactol (XIIB) or the betaine (XIIC)[62]



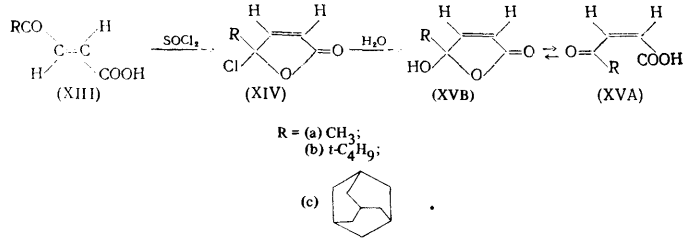
(XIIB) (XIIC)

The effect of the conditions of isolation on the isomeric composition of crystalline aldehydo- and keto-carboxylic acids has not yet been adequately studied. It is of interest to ascertain the effect of the temperature régime of crystallisation, the nature of the solvent, the temperature of the alkaline solution from which the acid is isolated by acidification, the pH of the medium after acidification, etc. These conditions probably play an important role, neglect of which makes nonsense of the search for rules relating the structure of the acids to their isomeric composition in the crystalline state.

cis-β-Formylacrylic acid [25,63,64], its αβ-substituted derivatives [9,15,65–68], and *cis*-β-acetylacrylic acids [13,17,69–71] in the crystalline state have the cyclic structure, which predominates even in solution. *cis*-β-Aroylacrylic acids have been isolated in the crystalline state either as the cyclic or as the open-chain isomer [6,7,72–75].

The geometrical isomerism of β-acylacrylic acids complicates the study of their ring–chain tautomerism. It is necessary to distinguish not only open-chain and cyclic forms but also *cis*- and *trans*-isomers of the form (IA). This problem is solved by proton magnetic resonance: the spin–spin interaction constant of the olefinic protons for αβ-unsubstituted *cis*-β-acylacrylic acids is 5.5–7 Hz, and that for the *trans*-isomers 16 Hz. [13,17,70,71] The *trans*-configuration has been identified [36,37] also from the infrared band due to out-of-plane deformation vibrations of the carbon–hydrogen bond at 980 cm^{-1}.

Scheffold [17] obtained the cyclic chloride, 5-chloro-2,5-dihydro-5-methylfuran-2-one (XIVa), by the action of thionyl chloride on *trans*-β-acetylacrylic acid (XIIIa):



(XIII) (XIV) (XVB) (XVA)

R = (a) CH_3; (b) $t\text{-}C_4H_9$; (c)

Careful hydrolysis of the chloride yields *cis*-β-acetylacrylic acid in the ring form (XVa–B). This compound is converted back to the thermodynamically more stable *trans*-isomer (XIIIa) on sublimation. Crystalline *cis*-β-acetylacrylic acid could not be obtained in the open-chain form (XVa–A).

Sugiyama [71] accomplished the isomerisation XIIIa → → XVa–B by exposing *trans*-β-acetylacrylic acid to a mercury lamp. An attempt to obtain the open-chain *cis*-isomer by the isomerisation of *trans*-β-pivaloylacrylic acid (XIIIb) was also unsuccessful. These experiments confirm the extraordinary stability of the cyclic forms of *cis*-β-acylacrylic acids.

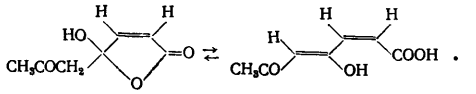
Kuchař [76] obtained a mixture of three isomers—(XIIIc), (XVc–A), and (XVc–B)—on acidifying an alkaline solution of 4-adamant-1'-yl-4-oxobut-2-enoic acid, but the evidence for the presence of the open-chain *cis*-form (XVc–A) was not entirely rigorous. Equilibria between cyclic and open forms were observed in acid and alkaline solutions of the 2- or 3-halogenated acids [33,37], but unfortunately the configurations of the open-chain isomers were not established.

Bowden [19] obtained unexpectedly high tautomeric equilibrium constants for *cis*-β-pivaloylacrylic acid (K_T = 94 ± 11) and *cis*-4-adamant-1'-yl-4-oxobut-2-enoic acid (70 ± 8) in 80% aqueous 2-methoxyethanol solution.

The introduction of methyl groups [6,7,17,19,21] and also of halogen atoms [33,77] as substituents attached to the olefinic carbon atoms in *cis*-β-acylacrylic acids stabilises the

cyclic form, a substituent having a greater effect in the β than in the α position.

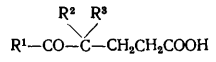
Simultaneous ring–chain and keto–enol tautomerism has been observed [78] in maleoylacetone:



(XVIB) (XVIA)

δ-Aldehydo- and δ-Keto-carboxylic Acids (Id–g)

Pentin [40,79–81] used infrared and ultraviolet spectroscopy to investigate the series of saturated δ-keto-carboxylic acids



(XVII)

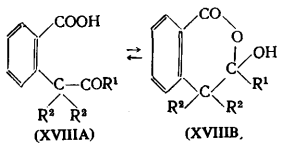
(R^1 = Alk, Ar; R^2 = H, Alk, Ar; R^3 = H, Br)

and found that they had the open-chain structure in the crystalline state, and when dissolved in chloroform and in carbon tetrachloride the cyclic form was not detected. The chain of three sp^3 carbon atoms evidently does not create sterically suitable conditions for the cylic form to be produced. Unfortunately, δ-keto-carboxylic acids having *gem*-dialkyl substituents on the chain carbon atoms were not examined, although they might be expected, by analogy with γ-keto-carboxylic acids [16], to form the cyclic isomers.

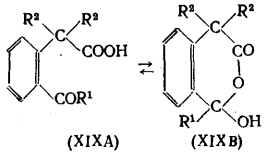
Table 2.

Compound	R^1	R^2	Structure in cryst.	Compound	R^1	R^2	Structure in cryst.
XVIII a	C_6H_5	H	A	XIX a	CH_3	H	A
XVIII b	CH_3	CH_3	B	XIX b	C_6H_5	H	A
XVIII c	C_6H_5	CH_3	B	XIX c	CH_3	CH_3	B
				XIX d	C_6H_5	CH_3	A

Infrared spectroscopy has been used to investigate the structure of crystalline *o*-acetonylbenzoic and *o*-phenacylbenzoic acids (XVIIIa–c in Table 2) and *o*-acylphenylacetic acids (XIXa–d) [82–85]



(XVIIIA) (XVIIIB)



(XIXA) (XIXB)

The state of equilibrium IA ⇌ IB was analysed [82,83] only from the results of chemical reactions. The acids (XVIIIb, c) and (XIXc), which contain a *gem*-dimethyl fragment, have the cyclic structure in the crystalline state. The acid (XIXd), in which the keto-group is conjugated with two aromatic rings, has the open structure, in spite of the presence of a *gem*-dimethyl fragment. Among the acids (XVIIIa–c) and (XIXa–d) only *o*-αα-dimethylacetonylbenzoic acid (XVIIIb) reacts with diazomethane to form a cyclic ester, 3-methoxy-3,4,4-trimethylisochroman-1-one. In solutions of the acid (XVIIIb) the equilibrium is supposed [83] to be displaced completely in favour of the cyclic form, owing to the absence of conjugation between the keto-group and the aromatic ring.

Spectroscopic [30] and indirect chemical [57,86,87] evidence indicates that tautomeric equilibrium is established in the 8-acylnaphthoic acids (Ig) and is absent from *o'*-acylbiphenyl-*o*-carboxylic acids, which have the open structure (Ih–A). Data on the possible formation of cyclic isomers by completion of a seven-membered ring are contradictory [88,89].

III. ACID CHLORIDES

Chlorides of γ-Aldehydo- and γ-Keto-carboxylic Acids (IIa–c)

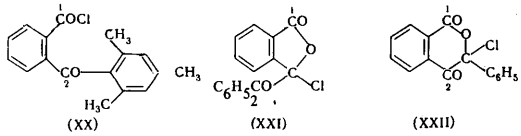
Formation of the cyclic modification of chlorides of keto-carboxylic acids is favoured by factors making the carbon atom of the COCl group more strongly electrophilic and the oxygen atom of the keto-group more strongly nucleophilic. Because the former is so strongly electrophilic, owing to the $-I$ effect of the chlorine atom, chlorides of β-acylpropionic [22,90–94], *o*-acylbenzoic [45,51,55,56,95–101], and *cis*-β-acylacrylic [6,7,17,25,75,76] acids have exclusively the cyclic chloro-lactone structure (IIB) in the crystalline state and in solution.

The infrared spectra of γ-chloro-lactones (IIa–c–B) are characterised by an intense lactonic carbonyl band at 1820–1805 cm^{-1} (IIa–B), 1810–1790 cm^{-1} (IIb–B), and 1800–1760 cm^{-1} (IIc–B, the band sometimes being split [17]) and the absence of absorption by the ketonic or aldehydic carbonyl in the range 1725–1660 cm^{-1}. The state of aggregation of the compound has little effect on the carbonyl frequency of γ-chloro-lactones.

γ-Chloro-lactones form two series of derivatives with nucleophilic reagents [6,98,102]. Since it has been demonstrated spectroscopically that the tautomeric equilibrium IIA ⇌ IIB is not present in solutions, the formation of two series of derivatives can be explained by the presence of two electrophilic centres—the carbon atoms of the C=O and C–Cl groups—in the chloro-lactone molecule. Stronger nucleophiles polarise the carbonyl group and attack its carbon atom preferentially; weaker nucleophiles attack the carbon of the C–Cl group. Reactions with primary amines, for example, yield *N*-monosubstituted amides (IIIA or IIIB) in the former case; in the latter case amino-lactones are obtained, for which in solution the tautomeric equilibrium amino-lactone ⇌ imino-acid is established [6,102].

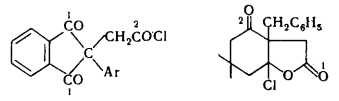
o-2′,4′,6′-Trimethylbenzoylbenzoyl chloride has the open structure (XX) owing to steric shielding of the keto-group [55,57,96], and is almost the sole exception [57] in the series of *o*-acylbenzoyl chlorides. It has recently been established [101] that, contrary to early investigations [61], both chlorides of benzil-*o*-carboxylic acid have cyclic

structures, 3-benzoyl-3-chlorophthalide (XXI) and 3-chloro-1,4-dioxo-3-phenylisochroman (XXII).



(XX) (XXI) (XXII)

1) $\nu_{C=O}$ 1797, 1733‡ 1) $\nu_{C=O}$ 1808 (4,6) 1) $\nu_{C=O}$ 1764 (3,6)
2) $\nu_{C=O}$ 1673 2) $\nu_{C=O}$ 1694 (1,2) 2) $\nu_{C=O}$ 1726 (1,7)



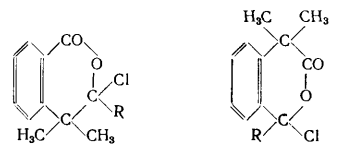
(XXIII) (XXIV)

1) $\nu_{C=O}$ 1740, 1700 1) $\nu_{C=O}$ 1818 (4,0)
2) $\nu_{C=O}$ 1800-1770 2) $\nu_{C=O}$ 1720 (1,7)

2-Aryl-1,3-dioxoindan-2-ylacetyl chlorides (XXIII) [42] have the open structure, whereas 2-benzyldimedon-2-ylacetyl chloride [103], in which conjugation of the keto-groups with the aromatic ring is absent, has the cyclic structure (XXIV).

Chlorides of δ-Aldehydo- and δ-Keto-carboxylic Acids (IId–g)

These compounds have been insufficiently studied [104]. The action of thionyl chloride on γγ-dimethyl-δ-oxo-δ-phenylvaleric acid yields a mixture of chlorides of open and cyclic structure [105]. The chlorides of the acids (XVIIIb, c) and (XIXc, d) have the cyclic structure (XXV) and (XXVI) [82,83].



(R=CH_3, C_6H_5)

(XXV) (XXVI)

$\nu_{C=O}$ 1750 cm^{-1} (CCl_4) $\nu_{C=O}$ 1770 cm^{-1} (CCl_4)

8-Acylnaphthoyl chlorides [57,87] have the cyclic structure (IIg–B), whereas chlorides of o'-acylbiphenyl-o-carboxylic acids [57] have the open structure (IIh–A).

IV. AMIDES AND HYDRAZIDES

Amides and Hydrazides of γ-Aldehydo- and γ-Keto-carboxylic Acids (IIIa–c)

Amides of aldehydo- and keto-carboxylic acids, whether unsubstituted or substituted on the nitrogen atom, are more stable than the acids themselves, which in solution undergo the tautomerisation IA ⇌ IB. There are a few reports [37,106–108] that the tautomeric equilibrium IIIA ⇌ IIIB is established in solution, but in most cases both isomeric forms (IIIA) and (IIIB) are stable in neutral solvents at room temperature. Aldehydo- and keto-amides are most often obtained only in a single form—(IIIA) or (IIIB)—and only rarely can both isomers be isolated [99,106,109–113].

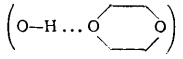
‡Infrared bands (cm^{-1}) of solutions in dioxan. Integrated intensities in practical units of measurement 10^4 M^{-1} cm^{-2} (ln) indicated in parentheses.

The true structure of β-acylpropionamides and o-benzoylbenzamides could not be established by chemical methods. Erroneous conclusions were reached also from polarographic examination [114], the use of which to establish the structure of compounds capable of isomeric or tautomeric conversions requires caution [115]. The structures of these compounds, first prepared long ago, have since been refined by spectroscopic methods [102,106,116–118].

Infrared spectroscopy is most often used to establish reliably the structures (IIIA) and (IIIB) (general frequency data will be found in Refs. 99 and 106). The main evidence of the open structure (IIIA) in N-monosubstituted keto-amides is the presence [55,99,106,110,117,119,120] of the amide-II band (νC-N + δN-H) at 1570–1520 cm^{-1}. In the spectra of the crystalline compounds [99,120], moreover, comparatively narrow N–H bands at 3500–3150 cm^{-1} (IIIA) are easily revealed and distinguished from the broad O–H bands (IIIB) in the same region. Because of angular strain of the >C=O bonds in the five-membered ring the C=O band of the lactam in the spectra of solutions of (IIIa–c–B) is shifted to higher frequencies than the amide-I band in the spectra of the open isomers (IIIa–c–A). The integral intensities of these bands have been measured [91,100,101,103,109,110,121].

The use of carbonyl bands to establish the structure of crystalline keto-amides is complicated by the presence of stable intermolecular hydrogen bonds O–H...O=C (lactam) in the lattice of the cyclic isomers (IIIB). [17,55,99–103,110,121] This displaces the carbonyl band to lower frequencies (than in the spectra of solutions) or even splits it into two bands representing absorption by bound and by free C=O groups. The band due to a bound carbonyl group in the spectra of crystalline o-benzoylbenzamides, which actually have the cyclic structure [99,102,106,118], was wrongly accepted [98] as the total band ($\nu_{C=O}$ ketone + $\nu_{C=O}$ amide) in the form (IIIb–A). This led to the erroneous conclusion [27,98] that these amides have the open structure in the crystalline state. For the same reason the infrared spectra of crystalline *cis*-β-aroylacrylamides were wrongly interpreted [122].

The frequencies and intensities of the carbonyl bands of hydroxy-lactams (IIIB) must be measured in dioxan. As a result of the formation of intermolecular hydrogen bonds with the solvent

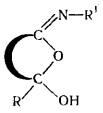


only the absorption due to free carbonyl groups is observed in the spectrum. A shift to lower frequencies, increase in intensity, and splitting of the carbonyl bands in the spectra of hydroxy-lactams (IIIB) due to intermolecular hydrogen bonds have been observed [110,118] also in solvents of low polarity. They were incorrectly explained [119] by the equilibrium IIIA ⇌ IIIB.

The infrared spectra of crystalline amides having the open structure (IIIA) exhibit [35,55,99,110] a decrease in frequency and splitting of the amide-I band with an increase in frequency of the amide-II band. This indicates the presence of intermolecular hydrogen bonds N–H...O=C (in the amide). Complications in interpreting the infrared spectra of the open isomers (IIIA) in solution sometimes arise from the coalescence of the two carbonyl bands (ketone and amide) [55,56,99,117,119]. In such cases it is advisable to measure the integrated intensity of the whole band [99]. It has been possible in this way to explain the infrared spectra of o-benzoyl-N-t-butylnitrobenzamides [56]. In these spectra the two carbonyl bands appear together and, furthermore, the amide-II band overlaps the band due to antisymmetric stretching vibration of the nitro-group.

In addition to infrared spectroscopy, ultraviolet spectroscopy [6,51,107,117,119,123-125], proton magnetic resonance spectra [37,106,108,111-113,119,123,124], and mass-spectrometric data [113] have been used to establish the structure of keto-amides.

It has recently been reported [108] that the presence of a third tautomeric form



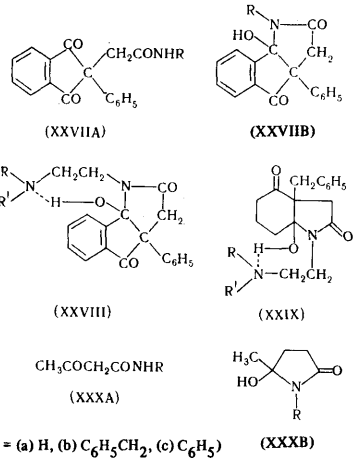
(IIIC)

in solutions of $\beta\beta$-dimethyl-γ-oxovaleramides [125] has been confirmed by proton magnetic resonance. However, formation of this isomer is improbable, so that more rigorous proof, using different spectroscopic methods, is necessary for its confirmation.

Formation of the cyclic modification of keto-amides (IIIB) is favoured by factors tending to make the ketonic carbon atom more strongly electrophilic, make the nitrogen atom more strongly nucleophilic, and bring the two groups closer together in space. *N*-Unsubstituted β-formyl-β-R-butyramides have the ring structure [126,127]. β-Acylpropionamides have either the cyclic or the open structure depending on the substituent R attached to the keto-group and the substituent R′ on the nitrogen atom, and also on the presence or absence of alkyl substituents on the chain carbon atoms [48,50,93,106,111-113,116,117,119-121,124,128-138].

Chiron [119] has found that, among a broad group of β-aroylpropionamides, only the *N*-methylamides§ have the ring structure, which he explains by hyperconjugation. Another explanation has been suggested [139]: the stability of the cyclic form improves with increase in the $+I$-effect of the substituent R′ on the nitrogen atoms ($H < CH_3 < C_2H_5 <$ iso-C_3H_7). On the other hand, increase in the effective steric volume of R′ destabilises the ring form [48,99,110,140]. Aggregating these effects—electronic and steric—may lead to enhanced stability of the cyclic forms of *N*-methylamides. As would be expected, the introduction of methyl groups at the α and β carbon atoms in β-acylpropionamides improves the stability of the cyclic forms [120,124].

Both isomers stable in solution were first obtained [110,141] in a series of *N*-alkyl-1,3-dioxo-2-phenylindan-2-yl-acetamides (XXVIIA) and (XXVIIB). The isomerisation XXVIIB → XXVIIA is accomplished by heating [37,106], and the isomerisation XXVIIA → XXVIIB by the catalytic action of bases. Owing to thermal isomerisation several hydroxylactams (XXVIIB) have two melting points: i.e. after fusion the substance crystallises again, and then melts at the melting point of the corresponding open isomer (XXVIIA). Sometimes it is quite impossible to determine the true melting points. The presence of bulky s- or t-alkyl groups on the nitrogen atom prevents the isomerisation XXVIIA → XXVIIB. [48] The cyclic forms of the *N*-2-dialkylaminoethylamides (XXVIII) and (XXIX) are stabilised by an intramolecular hydrogen bond [109,121,142].



(XXVIIA) (XXVIIB)

(XXVIII) (XXIX)

(XXXA)

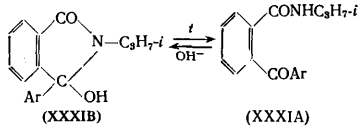
(R = (a) H, (b) $C_6H_5CH_2$, (c) C_6H_5)

(XXXB)

Both isomers have been isolated in the case of the γ-oxovaleramides (XXXa) [106], (XXXb) [111,112], and (XXXc) [113]. Flitsch [106] used proton magnetic resonance to detect the equilibrium A ⇌ B in a solution of the amide (XXXc–A) in hexadeuteriated dimethyl sulphoxide. Later Prelog [113], having isolated both isomers (XXXc–A) and (XXXc–B), established that they were stable at room temperature in the crystalline state and in neutral solvents. Equilibrium was observed between the two forms in the presence of acidic (trifluoroacetic acid) or basic (pyridine) catalysts and also on the surface of silica gel. Isomerisation of the open into the ring form (XXXc–A → XXXc–B) was effected by passing a solution in chloroform through a column packed with an acid ion-exchange resin (Dowex-50W).

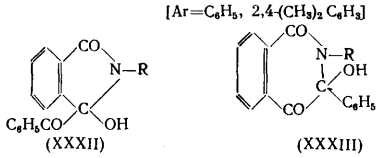
N-Monosubstituted and unsubstituted *o*-formylbenzamides [97,106,111,143,144] and *o*-acylbenzamides [50,51,55,56,99-102,106,111,118,145-152] exist, both in the crystalline state and in solution, in the cyclic form as 3-hydroxy-3-R-2-R′-isoindolinones. Exceptions are *N*-t-alkyl-*o*-acylbenzamides [55,56,99,100] and unsubstituted and *N*-substituted *o*-2′,4′,6′-trimethylbenzoylbenzamides [55], which have the open structure because of steric shielding of the nitrogen atom or the ketonic carbon atom, and are incapable of the transition IIIA → IIIB under the conditions of basic catalysis.

3-Aryl-3-hydroxy-2-isopropylisoindolinones (XXXIB) isomerise thermally into the *N*-isopropylamides (XXXIA) [55,99]. The reverse isomerisation is effected by the action of bases. Increase in the bulk of the substituent on the nitrogen atom facilitates the isomerisation B → A, for thermal isomerisation cannot be achieved in the case of 2-n-alkyl-3-hydroxy-3-phenylisoindolinones [99].



(XXXIB) (XXXIA)

[Ar = C_6H_5, 2,4-$(CH_3)_2C_6H_3$]

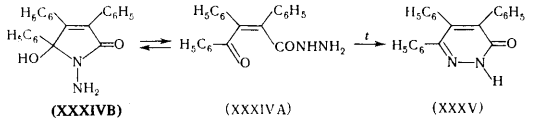


(XXXII) (XXXIII)

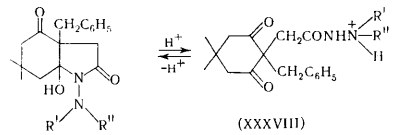
Amides of benzil-*o*-carboxylic acid [101] have been obtained in the cyclic forms (XXXII) and (XXXIII). The six-membered rings are easily isomerised into the more stable five-membered forms (XXXIII → XXXII).

§This relates to *N*-methylamides only of those acids in which the substituted aromatic ring does not possess a strong $+C$-effect.

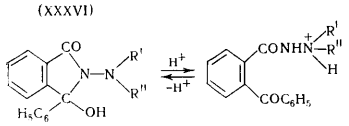
All known *cis*-β-acylacrylamides, whether *N*-substituted or unsubstituted, have the cyclic structure of 5-hydroxy-5-R-1-R′-$\Delta^{3,4}$-pyrrolin-2-ones both in the crystalline state and in solution [6,17,75,123,125,153–159]. Conclusions on the open form of the amides [122,156,160–162] need to be reconsidered.



(XXXIVB) (XXXIVA) (XXXV)

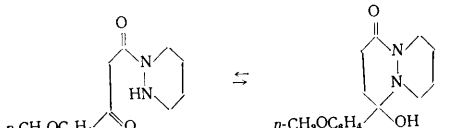


(XXXVI) (XXXVIII)

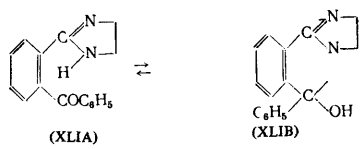


(XXXVII) (XXXIX)

cis-β-Benzoyl-αβ-diphenylacrylohydrazide [75], which has the cyclic structure (XXXIVB), is converted thermally into the dihydro-oxopyridazine (XXXV). *N′N′*-Dialkyl-1,3-dioxo-2-phenylindan-2-ylacetohydrazide (XXVII: R = NR′R″) have been obtained in both isomeric forms A and B [107]. Their interconversion has been accomplished. It is curious that isomerisation of the open into the ring form is effected merely on boiling solutions in ethanol by the autocatalytic action of the basic group NR′R″. Slow establishment of the equilibrium A ⇌ B was observed in solution. *N′N′*-Dialkylhydrazides of 2-benzyldimedon-2-ylacetic and *o*-benzoylbenzoic acids [104] have the cyclic structure (XXXVI) and (XXXVII). When the dialkylamino-group is protonated, the strong $-I$ effect of the substituent on the nitrogen atom effects ring opening with formation of the protonated hydrazides (XXXVIII) and (XXXIX). Deprotonation is accompanied by the reverse process.



(XLA) (XLB)

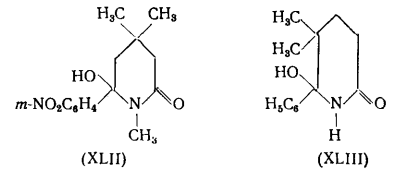


(XLIA) (XLIB)

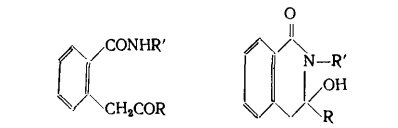
Little study has been made of the structure of *NN′*-dialkylhydrazides of γ-keto-carboxylic acids, where a six-membered ring may be formed. The open form (XLA) predominates [163] in the case of the hexahydropyridazide of β-*p*-methoxybenzoylpropionic acid. The tautomerism XLIA ⇌ XLIB is observed [164] in solutions of *o*-benzoyl-benzamidine.

Amides of δ-Keto-carboxylic Acids (IIId–g)

Spectroscopic examination of a wide range of γ-acyl-butyramides, their *N*-monosubstituted derivatives [120,165], and amides of more complex δ-keto-carboxylic acids [35] has shown that they all have the open structure (IIIA). Only two δ-keto-amides, with a chain of three sp^3 carbon atoms between the carbamoyl and ketone groups, are known in the ring form (XLII) [120] and (XLIII) [166]; both compounds have *gem*-dimethyl groups.



(XLII) (XLIII)



(XLIVA) (XLIVB)

(R=C_6H_5, R′=iso-C_3H_7; R=*p*-$CH_3OC_6H_4$, R′=C_2H_5, *n*-C_3H_7, *n*-C_4H_9, $C_6H_5CH_2$) (R=C_6H_5, R′=CH_3, C_2H_5, *n*-C_3H_7, *n*-C_4H_9, $C_6H_5CH_2$; R=*p*-$CH_3OC_6H_4$, R′=CH_3)

N-Monosubstituted *o*-phenacylbenzamides [139,167,168], with the exception of the *N*-isopropylamide, have the ring structure (XLIVB). Among *o*-*p*′-methoxyphenylbenzamides, in which the ketonic carbon atom becomes less strongly electrophilic under the influence of the +*C*-effect of the methoxy-group, only the *N*-methylamide has the cyclic structure (XLIVB). The isomers (XLIVA) and (XLIVB) are stable in solution. Among *N*-monosubstituted *o*-acylphenylacetamides (IIIf) α-*o*-benzoylphenyl-α-phenylacetanilide has been prepared [169], and exists in the open form.

The structure of the amides (IIIg, h) has not been studied, but it may be supposed that the amides (IIIg) will have the cyclic structure, and (IIIh) the open structure.

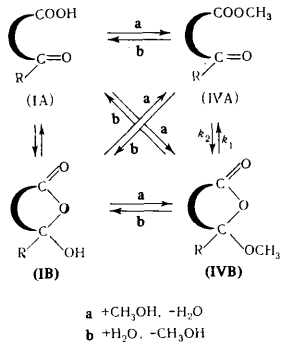
V. ESTERS

Esters of β-acylpropionic [18,22,94,170], *o*-acylbenzoic [27,31,34,51,52,57,61,98,171–175], *cis*-β-acylacrylic [6,7,13,19,21,69,74,75,176–178], and δ-keto-carboxylic [30,82,83,179,180] acids are obtained both in open (IVA) and in cyclic (IVB) forms. Both isomers are stable in neutral solvents at room temperature. The equilibrium IVA ⇌ IVB is established in acid and alkaline media [52,74,94,171] or on heating [177]. Isomers are identified by ultraviolet spectroscopy [7,22,31,34,69,125,177], infrared spectroscopy [7,13,21,22,27,30,34,51,58,69,70,75,82,83,98,171,177], and proton magnetic resonance [21,22,30,31,52,69,70,92,171,177,181], and are determined by gas–liquid chromatography [171], infrared spectroscopy [34], and proton magnetic resonance [31,52,171].

Methods are known [1] for esterifying keto-carboxylic acids to obtain predominantly a certain isomer. Open isomers are formed by the action of alkyl halides on the silver salts [7,25,69] or by esterification of the acids with diazomethane [7,22,30,34,69,75,82,177]. Exceptions have been observed [83] in the latter reaction. Beška [177] found that the esterification of β-formyl-αβ-dihalogenoacrylic acids with diazomethane at 0°C yields predominantly the open isomers, but at higher temperatures the proportion of cyclic isomers in the reaction mixture increases. Thermal isomerisation IVA → IVB of the open esters of these acids has been accomplished. Esters of open structure are obtained by esterifying *o*-formyl- and *o*-acetyl-benzoic acids with methyl iodide in the presence of potassium carbonate [174,182].

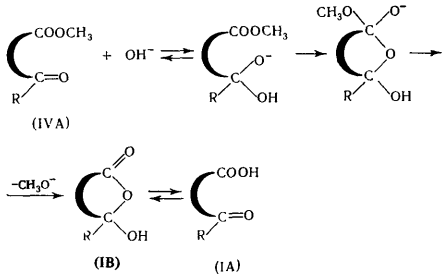
Cyclic esters are formed predominantly by the alcoholysis of chloro-lactones (IIB), which is usually conducted in the presence of pyridine [6,7,27,51,57,75,82,83,98,170,180], though urea has also been suggested [183] as base. Cyclic γ-oxovaleric esters are obtained by the alcoholysis of α-angelica lactone [170].

Scheme 2



The esterification of keto-carboxylic acids by alcohols in the presence of hydrogen chloride (Fischer–Speyer method) or other acid catalysts usually leads to mixtures of the two isomers. Their content in the mixture depends on the duration of the reaction (kinetic or thermodynamic control) and is determined by the equilibria [31,52,171,184] in Scheme 2 (intermediate stages not indicated). This scheme shows the possibility of nucleophilic attack at both electrophilic carbon atoms in the molecules (IA) and (IB). Kinetic investigations show [173,174,178,185–191] that a neighbouring carbonyl group accelerates the hydrolysis of esters (IVA). The reason for this effect is that the nucleophilic reagent first attacks the ketonic carbon atom, and the mechanism of alkaline hydrolysis is represented by Scheme 3.

Scheme 3



In thermodynamically controlled Fischer–Speyer esterifications, in the presence of a large excess of methanol, the equilibrium IVA ⇌ IVB plays a decisive role in determining the isomeric composition of the products. Bowden [171] has studied this reversible isomerisation of methyl *o*-acylbenzoates (IVb: R = CH_3, C_2H_5, iso-C_3H_7, t-C_4H_9, $C_6H_5CH_2$, and C_6H_5) under conditions of acid and alkaline catalysis. The equilibrium constants (K = [IVB]/[IVA] = 1.7–8.1 with R = Alk and 0.02 with R = C_6H_5) are almost equal for acid and alkaline catalysis. They increase with the size of the substituent R (CH_3 < C_2H_5 < < iso-C_3H_7 < t-C_4H_9). The explanation is that a bulky substituent destabilises the open form, since the COR group is forced out of the plane of the aromatic ring [43]. The equilibrium constants correlate with the Taft steric constants E_S of the substituents ($\delta = -0.35 \pm 0.05$). The isomerisation rate constants k_1 and k_2 (rates of formation of IVA and IVB) have been measured under conditions of acid catalysts, and are found to fall with increase in the volume of the substituent R, while $k_2 > k_1$. Increase in the volume of R has a greater effect on k_1 than on k_2 (δ = 0.9 and 0.5 respectively).

Unfortunately, such detailed investigations are lacking for esters of other keto-carboxylic acids. However, the equilibrium constant of the reversible isomerisation of keto-carboxylic esters and the tautomeric equilibrium constant K_T of the free acids are determined in general by the same structural factors. There is thus a correlation between the predominant tautomeric form of keto-carboxylic acids and the predominant isomer in the products of thermodynamically controlled Fischer–Speyer esterifications [31]. This explains the preferential formation of open isomers (IVA) in the esterification of γ-oxovaleric [94,170], *o*-aroylbenzoic [27,31,34,52,57,173], *cis*-β-aroylacrylic [21,178], and γ-benzoylbutyric [180] acids. *o*-Acylbenzoic (Ib: R = H, Alk) [20,31,171], *cis*-β-acylacrylic (Ic: R = H, Alk) [69,176,177], and 8-acetylnaphthoic [30] acids, for which the tautomeric equilibrium IA ⇌ IB is displaced towards the cyclic form, on esterification yield predominantly the ring isomers (IVB). The isomerisations IVA → IVB (*cis*-β-formylacrylic esters [177]) and IVB → IVA (γ-oxovalerates [94,170], *o*-aroylbenzoates [51], and *cis*-β-aroylacrylates [7,74]), catalysed by acids or alkalis, are explained by displacement of the equilibrium IVA ⇌ IVB towards the thermodynamically more stable isomer.

VI. MIXED ANHYDRIDES

Mixed anhydrides of keto-carboxylic acids (VA) and their more frequently encountered cyclic isomers—acyloxy-lactones (VB)—are easily identified by infrared spectroscopy. The infrared spectra of the former (VA) are characterised by anhydride carbonyl bands at ~1820 and 1750 cm^{-1} and carbonyl absorption of the aldehydo- or keto-group at 1725–1660 cm^{-1}. Absence of absorption in the range 1725–1660 cm^{-1} is the main evidence for the ring structure (VB). The infrared spectra of (Va–c–B) contain a lactonic carbonyl band at 1810–1775 cm^{-1} and a carbonyl band of the acyloxy-group at 1770–1745 cm^{-1}; [7,22,25,35,69,75,192] sometimes the two bands overlap [35].

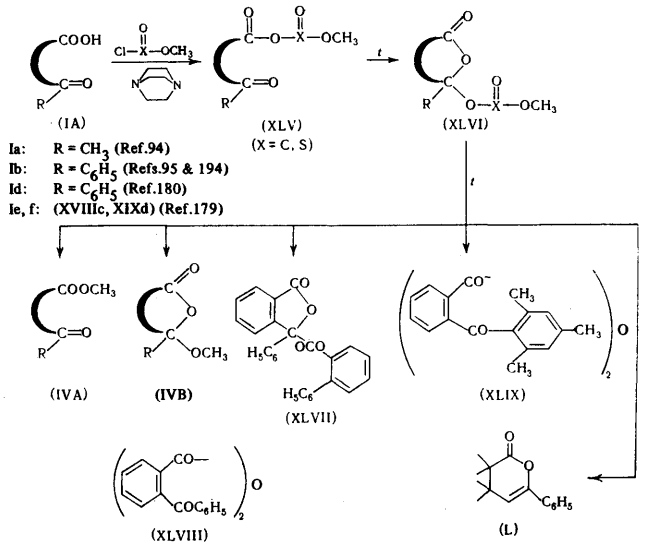
The acylation of β-formylpropionic [22], *o*-acylbenzoic [35,57,59,192,193], *cis*-β-acylacrylic [7,25,69,75,176], and α-*o*-benzoylphenyl-α-methylpropionic [84] acids by means of acetic anhydride [22,59,69,176,193] or mixtures of the anhydride with pyridine [35,57,75,84,192], sodium acetate [192], acetic acid in the presence of sulphuric acid [7], or acetyl or benzoyl chloride [25] gives acyloxy-lactones (VB). A specific method for their preparation is the reaction of cyclic chloro-anhydrides (IIB) with silver acetate [7,193].

Mixed anhydrides of open structure (VA) are obtained by the action of a keten on β-formylpropionic acid [22], by the acetylation of β-benzoyl-αβ-diphenylpropionic acid with acetic anhydride [75], and by the action of acetyl chloride on silver benzil-*o*-carboxylate [193].

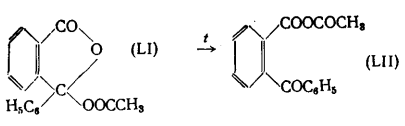
Newman [94–96,180,194] prepared mixed anhydrides of γ- and δ-keto-carboxylic acids (XLV) by the action of methyl chloroformate or chlorosulphite on the acids in the presence of a base, 1,4-diazabicyclo[2,2,2]octane, or directly on their sodium salts.

Heating converts the mixed anhydrides (XLV) into the cyclic isomers (XLVI) (not in all cases isolated). At higher temperatures the latter undergo pyrolysis to form a mixture of esters (IVA) and (IVB). Pyrolysis of the mixed anhydride (XLV: X = C) obtained from *o*-benzoylbenzoic acid yields not only IVA and IVB but also *o*-benzoylbenzoyl anhydride (XLVII), in which one acid radical has the cyclic structure, and the other the open structure. The anhydride (XLVII) is obtained also by the action of ethoxyacetylene on *o*-benzoylbenzoic acid, by the reaction of 3-chloro-3-phenylphthalide (IIb–B: R = C_6H_5) with *o*-benzoylbenzoic acid in the presence of pyridine [95], and by the action of sodium nitrite on 3-chloro-3-phenylphthalide [98]. The structure (XLVIII) (Scheme 4) had previously been attributed to the anhydride (XLVII) on the basis of ultraviolet spectroscopy [193] and polarographic results [195]. Pyrolysis of the mixed anhydride of *o*-2′,4′,6′-trimethylbenzoylbenzoic acid (XLV: X = C) gives as sole product the anhydride (XLIX). The mixed anhydrides of γ-benzoylbutyric acids and their *gem*-dimethyl derivatives yield unsaturated lactones (L) as well as the corresponding esters (IVd–B).

Scheme 4



Schmid [193] showed that 3-phenylphthalid-3-yl acetate (LI) undergoes thermal isomerisation into the mixed anhydride (LII):



in the opposite direction to that of the mixed anhydrides of methoxyformic acid studied by Newman.

Published information does not reveal the effect of the structure of the acyl residue (the substituent R′ in formula V) on the stability of the mixed anhydrides (VA) and (VB) or the conditions of their isomeric interconversion.

ADDENDUM

Several papers were published while this Review was being prepared for the press, and are briefly surveyed below.

The electronic and steric effects of substituents near the keto-group and in the ring on the position of ring–chain tautomeric equilibrium in a series of aromatic *o*-ketocarboxylic acids have been discussed [196]. The relative reactivities of ring and chain isomers of α-*gem*-disubstituted β-formylpropionic acids and their esters have been studied [197].

The presence of an intramolecular hydrogen bond has been established [198] in *N*-aryl-β-aroylpropionamides. A study has been made of the chemical properties of several *m*-acylbenzamides existing in the ring form [199,200]. Both isomers (IIIA and IIIB) of the 3,4-dimethoxyphenethylamide of 3-oxocycloheptanecarboxylic acid have been isolated [201].

A review [202] lists papers on the use of nuclear magnetic resonance spectroscopy for the study of ring–chain tautomeric phenomena.

Structure and ring–chain isomerism have been studied in amides of β-formylpropionic [203,204] and $\beta\beta$-dimethyl-γ-oxovaleric [205] acids. Both isomers of phenyl *o*-benzoylbenzoate have been prepared [206]. The cyclic isomers of *cis*-β-formylacrylic acids exhibit an extraordinarily strong tendency to associate [207].

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