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γ-Formyl Acids

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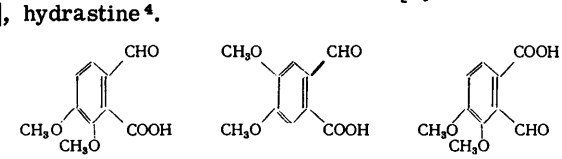
I. INTRODUCTION

The chemistry of γ-formyl acids and especially the problem of their structure has occupied the minds of many eminent investigators for over a century. It is sufficient to mention that Liebig and Wöhler, Gabriel and Libermann, Hans Meyer and Wilslicenus, Alder and Grove worked fruitfully in this field. The Soviet scientists V. M. Rodionov and M. M. Shemyakin also made a significant contribution to the study of the γ-formyl acids. Nevertheless the overwhelming majority of the studies completed up to the present time have been devoted to only an extremely limited number of γ-formyl acids, since the number of known representatives of this class of compound is generally small. They include principally the opianic and 2-formylbenzoic acids and their derivatives, halogenomucic acids, and β-formylpropionic and β-formylacrylic acids. We therefore did not set ourselves the aim of compiling an exhaustive review of all the investigations related to this problem, but have used from them only that part which, in our opinion, allows the contemporary state of the problem to be given with sufficient completeness.

II. METHODS OF PREPARING γ-FORMYL ACIDS

1. Aromatic and Heterocyclic γ-Formyl Acids

The first representative of the class of γ-formyl acids —opianic acid (I) was obtained as long ago as 1842 by Liebig and Wöhler[1-3] in oxidising one of the opium alkaloids—narcotine. Opianic acid (I) is also formed in the oxidation of the alkaloid of Canadian golden seal [*Hydrastis canadensis*], hydrastine[4].



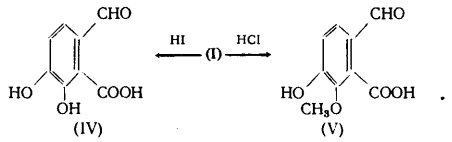
(I) (II) (III)

The structure of opianic acid was established by the work of Matthiessen and his coworkers (for example, see Ref. 5).

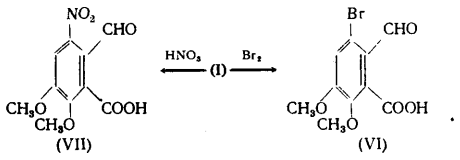
As well as opianic acid, γ-formyl acids isomeric with it are known: metaopianic (II)[6-8], which is formed in the

oxidation of the alkaloid cryptopine, and pseudo-opianic acid (III)[9], liberated in the oxidation of berberine.

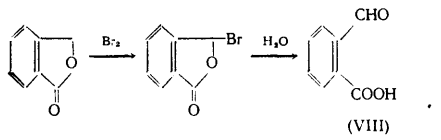
Noropianic acid (IV)[11] is obtained in the demethylation of opianic acid by hydrogen iodide[10], whereas when hydrochloric acid is used for this purpose a partial demethylation product is formed—methylnoropianic acid (V)[12,13]:



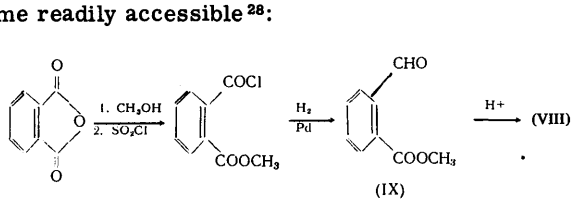
Of the derivatives of opianic acid, mention must be made of those obtained from it by the action of bromine or by nitration, the well-known 3-bromo-opianic (VI)[14-16] and 3-nitro-opianic (VII)[14,17,18] acids, and also the reduction products of the latter: 3-nitroso- and 3-amino-opianic acids[19]:



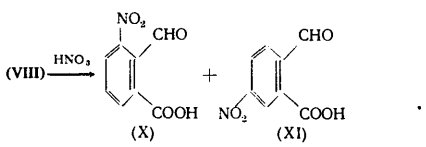
In their chemical and physical properties 2-formylbenzoic acids are very similar to opianic acid. The first method of obtaining 2-formylbenzoic acid itself (VIII), developed in 1886 by Racine[20-22], consists in the bromination of phthalide to bromophthalide and subsequent careful hydrolysis:



Another method of making 2-formylbenzoic acid which has been well studied is the oxidation of naphthalene with ozone[23,24] or potassium permanganate[25,26]. The best method of making this formyl acid is based on the Rosenmund reaction (yield reaches 60%, calculated on phthalic anhydride)[27]; in this way the normal methyl ester (IX) became readily accessible[28]:

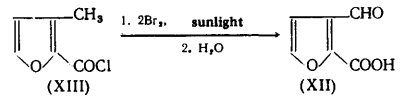


In the direct nitration[29,30] of 2-formylbenzoic acid a mixture of 3- and 5-nitro-2-formylbenzoic acids (X) and (XI) is formed, with the latter preponderating:

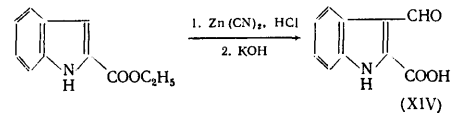


Several substituted 2-formylbenzoic acids were synthesised by Chakravarti and coworkers[31-34].

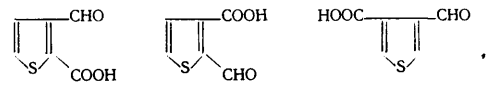
Several representatives of heterocyclic γ-formyl acids have been described. The first of these chronologically was probably 3-formylfuran-2-carboxylic acid (XII) obtained in 1924 by Japanese investigators[35] on brominating (with subsequent hydrolysis) elsholtzia acid chloride (XIII):



3-Formylindole-2-carboxylic acid (XIV)[36-38] can serve as an example of a γ-formyl acid of a nitrogen heterocycle:



In 1963 the Swiss scientist Gronowitz and his coworkers[39,40] synthesised three γ-formyl acids of the thiophen series:



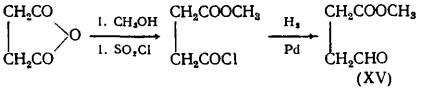
2. β-Formylpropionic Acids

The various β-formylpropionic or formylsuccinic acids which serve as the initial compounds for the synthesis of derivatives of the natural growth substance heteroauxin (β-indolylacetic acid)[41-46] are extremely interesting. In several instances these substances also exhibit antibiotic properties.

The first representatives of this class of compound, β-formylpropionic and β-formyl-α-methylpropionic acids were obtained in 1899 by Perkin Jnr. and Sprankling[47], by the condensation of sodiomalonic ester and, respectively, sodiomethylmalonic ester with bromoacetaldehyde acetal with subsequent hydrolysis and decarboxylation. Later[48,49] a large number of alkyl-substituted β-formylpropionic acids was synthesised by this method. β-Formyl-α-methylpropionic acid was also obtained from ketomethylglutaric acid[50].

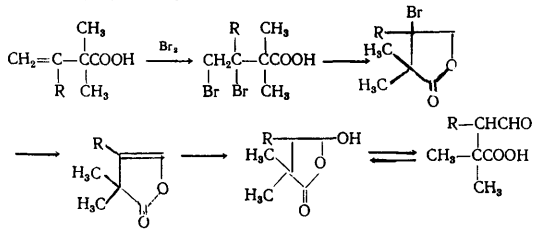
Wilslicenus and coworkers[51] effected the synthesis of β-formylpropionic acid by starting from formylsuccinic acid, which they subjected to hydrolysis by heating with water in a sealed ampoule at 120–130°C. The hydrolysis of formylsuccinic ester by an aqueous solution of oxalic acid has also been described[52,53]. β-Formyl-α-phenylpropionic acid was synthesised in a similar manner[54].

Johnson and coworkers[55] proposed a good method for the synthesis of methyl β-formylpropionate (XV) with the aid of the Rosenmund reaction:



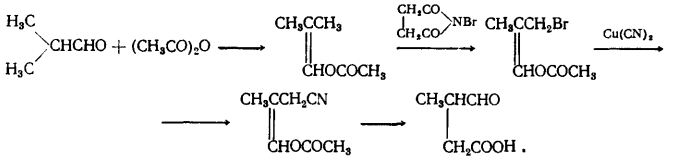
Application of the Rosenmund reaction to monoesters of various dicarboxylic acids is evidently a promising path to a variety of γ-formyl acids and also to γ-formyl acids of another structure.

Blaise and Kourtot[56,57] obtained trisubstituted β-formylpropionic acids from the corresponding trisubstituted βγ-unsaturated acids:

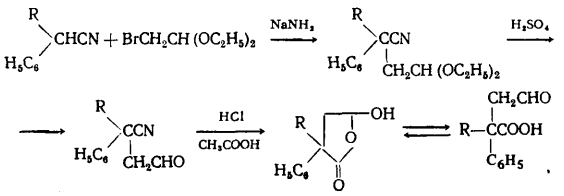


where R = CH_3, C_6H_5.

A new synthesis of β-formylbutyric acid was recently[58] effected according to the following scheme:

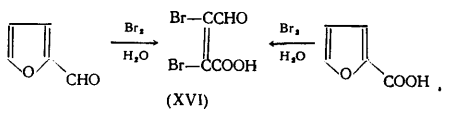


In 1963 Salmon-Legagneur and Paulain[59,60] developed a general method for the preparation of αα-disubstituted β-formylpropionic acids based on the condensation of the nitriles of alkyl aryl carboxylic acids with bromoacetaldehyde acetal in the presence of sodium amide, followed by hydrolysis:



3. β-Formylacrylic and β-Formylcrotonic Acids

Of this type of γ-formyl acid, the halogenomucic and dihalogeno-β-formylacrylic acids have long been known and have been well investigated. These compounds are usually obtained by starting from furan derivatives. For example, in the vigorous bromination of furfural or pyromucic acid in aqueous solutions bromomucic acid (XVI) is obtained in excellent yield[61-63]:



(XVI)

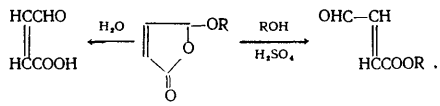
Chloromucic acid was synthesised in an analogous manner[61].

The halogen atoms and the double bond in the halogenomucic acids are distinguished by extremely low reactivity, because of which these compounds have not been used for the synthesis of new representatives of γ-formyl acids to any significant extent. Only the products of the replacement of the bromine atom at the α-carbon atom of bromomucic acid by hydroxy-, phenoxy-, and arylaminogroups[64-66] and also the replacement of the chlorine atom of chloromucic acid by the hydroxyl group[64] are known.

Of great interest for synthetic organic chemistry are the β-formylacrylic and β-formylcrotonic acids which do not contain halogen atoms; they were, for example, used for the synthesis of carotenoids by the Wittig reaction[67].

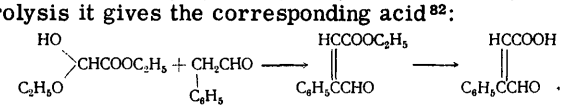
The use of ψ-esters of β-formylacrylic acid as dienophiles in the diene condensation allowed a series of representatives of a previously unknown class of alicyclic γ-formyl acids to be obtained[68-74].

The methods described earlier for obtaining *cis*-β-formylacrylic acid (XVII) were based on the oxidation of pyromucic acid[75,76] or furfural[77] by various oxidants. Later Shenk[78-80] developed a convenient method for obtaining the ψ-esters of *cis*-β-formylacrylic acid (XVIII) by the photochemical oxidation of furan derivatives. Hydrolysis of the ψ-esters with boiling water leads to the corresponding *cis*-acid (XVII)†, whereas on boiling alcoholic solutions of the ψ-esters in the presence of catalytic amounts of sulphuric acid esters of the *trans*-isomer (XIX) are obtained:

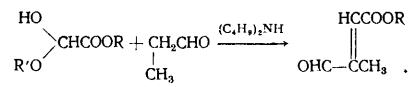


(XVII) (XVIII) (XIX)

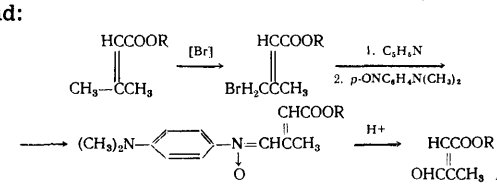
Photochemical oxidation was not used for the synthesis of substituted β-formylacrylic acids, although there are undoubted prospects for its use for such purposes. A few well-known representatives of γ-formyl acids of this type are obtained by other methods. Thus in the condensation of the hemiacetal of ethylglyoxalate with phenylacetaldehyde, ethyl β-formyl-β-phenylacrylate is formed, and on hydrolysis it gives the corresponding acid[82]:



Esters of β-formylcrotonic acids are obtained in good yields in the condensation of the hemiacetals of the esters of glyoxalic acid with crotonaldehyde in the presence of dibutylamine[67]:

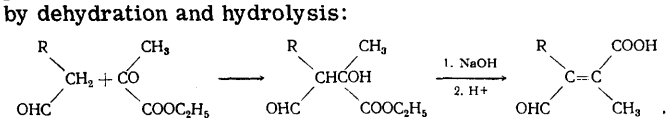


In another method[83] various esters of ββ-dimethylacrylic acid were subjected to bromination by *N*-bromosuccinimide, then the γ-bromo-β-methylcrotonic esters produced were treated (in the form of pyridinium salts) with *NN*-dimethyl-*p*-nitrosoaniline. Careful hydrolysis of the nitrones thus obtained led to the corresponding esters of β-formylcrotonic acid:



Ethyl β-formylcrotonate was also synthesised from β-methylcrotonic ester[84].

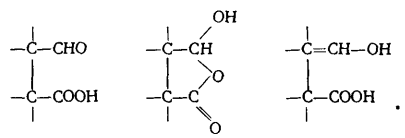
Recently Schreiber and Wermuth described[85] the production of a series of *trans*-β-formyl-β-alkyl-α-methylacrylic acids and their esters by condensation of esters of pyrotartaric acid with various aliphatic aldehydes, followed by dehydration and hydrolysis:



† *cis*-β-Formylacrylic acid is also obtained from 2-acetoxyfuran by bromination and subsequent hydrolysis[81].

III. REACTIONS OF γ-FORMYL ACIDS

The characteristic property of all the γ-formyl acids is their ability to react in two tautomeric forms[86]: the α-form (aldehydic) (XX) and the ψ-form (hydroxy-lactone) (XXI). The aliphatic and alicyclic γ-formyl-acids, although having one unsubstituted hydrogen atom at the β-carbon atom, are capable in some instances of also reacting in a third tautomeric form—enol (XXII)[86]:



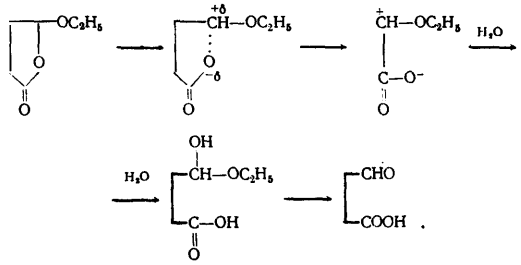
(XX) (XXI) (XXII)

Between these forms there is a mobile chemical equilibrium, therefore the establishment of the structure of γ-formyl acids in the isolated state acquires a special significance. Furthermore, it is very important to investigate the conditions under which displacement of the equilibrium to one of the tautomeric forms takes place, since such a displacement can be determined not only by the influence of the external medium but also by the structure of the γ-formyl acids.

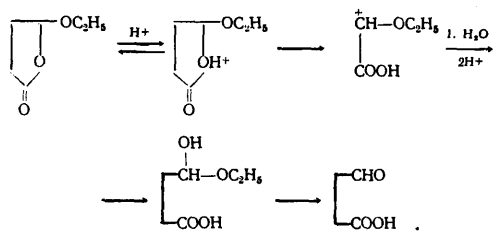
The problem of the structure of isolated γ-formyl acids was presented to chemists immediately after the discovery of the first of their representatives and more than a century later it still remains the subject of lively discussion[87,88]. In order to discriminate in this question it is necessary to first consider in detail the chemical behaviour of γ-formyl acids and to try to understand which factors determine their ability to react in any particular tautomeric form. Above all, it can be assumed as a working hypothesis that in the conditions of a medium which does not facilitate tautomeric transformations aldehydo-acids will react in that form in which they exist in the pure state and form a compound corresponding to this form. Thus it appears that crystalline γ-formyl acids are formed with astonishing ease even when alcoholic solutions of the corresponding ψ-esters, that is, ethers of the hydroxy-lactone form are kept for prolonged periods[89-91]. This conversion takes place more rapidly on heating[7,29,86,92,93] or in the presence of mineral acids[2,86,91,94-96]. A similar reaction has been described for many γ-formyl acids and is evidently a typical feature of those which are incapable of showing tautomerism in alcoholic solution. If the γ-formyl acids exist as a mixture of tautomeric forms then they would be expected to form a mixture of α- and ψ-esters in alcoholic solution. This occurs, for example, with β-formylpropionic, β-formyl-α-methylpropionic, and other α-alkyl-β-formylpropionic acids[47,50,52-58], which are liquids under ordinary conditions. The mercaptans behave like alcohols; they readily react with crystalline γ-formyl acids[97] to form compounds corresponding to their ψ-forms. For a long time examples have been known when either only the ψ-esters or their mixture with the corresponding α-esters are formed in the esterification of γ-formyl acids, depending upon the reaction conditions. Such a phenomenon was, for example, observed on heating 2-formylbenzoic acid with methanol in the presence of sulphuric acid[91]. These facts found explanation in the work of Kirpal and Zieger[98], who showed that normal formyl esters are products of the isomerisation of the ψ-esters formed initially, which takes place under the influence of the mineral acid. A similar isomerism is well known for esters of γ-keto-acids[99,100].

A characteristic property of the ψ-esters of γ-formyl acids is also the exceptional ease of their saponification: many of these are converted into the initial γ-formyl acids even on simple heating with water[29,67,69,86,88]. In the presence of acid catalysts this reaction takes place more rapidly.

On the basis of kinetic investigations of the hydrolysis of the ethyl ψ-ester of β-formylpropionic acid, Fife[101] concluded that a neutral medium is much more favourable for the hydrolysis of such bifunctional compounds of acylal-acetal structure than for ordinary acetals or esters. He proposed the following mechanism for the hydrolysis of a ψ-ester in neutral medium, which is a first-order reaction:

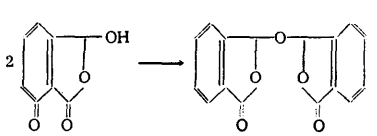


In the presence of mineral acids, in his opinion, the hydrolysis of a ψ-ester takes place by a somewhat different scheme:



On heating γ-formyl acids with acetic anhydride (in some instances in the presence of sodium acetate or sulphuric acid), acetyl derivatives of their hydroxy-lactone form are always produced[21,62,102,103]. The reaction of γ-formyl acids with phosphorus(V) chloride or thionyl chloride also leads to cyclic derivatives[104-108].

When heated above their melting point, aromatic γ-formyl acids are converted into ψ-anhydrides[21,29,103,107,109], for example:



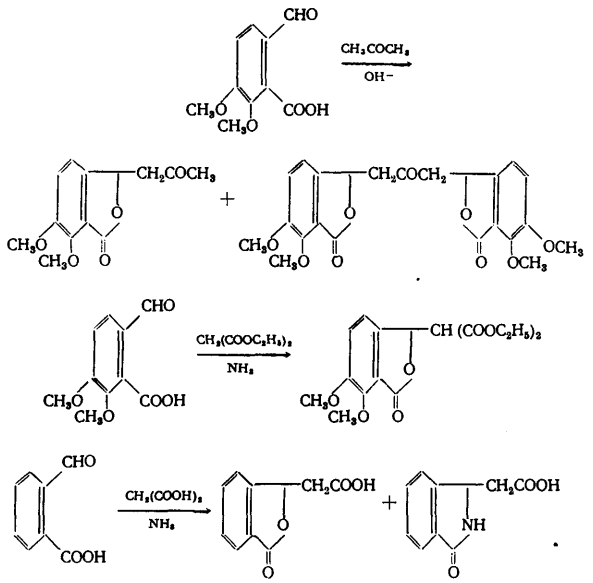
Finally, derivatives of the ψ-form are obtained by the action on γ-formyl acids of such weak bases as aromatic amines[12,110-117].

Since the α-form of the γ-formyl acids exhibits incomparably more reactive functional groups than the hydroxy-lactone form, in all those instances when the α-form arises in a reaction medium, it specifically takes part in the chemical conversion. In this, when the reaction product is insoluble (semicarbazone, and also other analogous derivatives) or is incapable of further conversion under the given conditions (for example, a methyl ester formed under the action of diazomethane), the tautomeric equilibrium is completely shifted to the side of the α-form. When the derivative of the α-form which is produced can undergo secondary transformations, for example, be cyclised into a

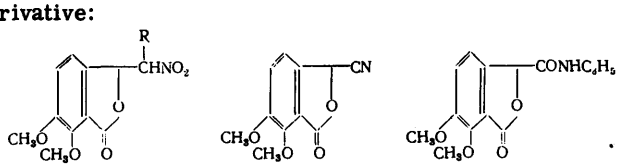
lactone, then the final reaction products are derivatives of the ψ-form of the original γ-formyl acid. Thus, most formyl acids react with Schiff's reagent in alcoholic solutions[86,117] and smoothly form crystalline derivatives with hydroxylamine, hydrazine, and substituted hydrazones[76, 111,112,118-120].

Reactions in which the pure α-form of γ-formyl acids are produced are the reactions of their neutralisation, leading to the corresponding metal salts[1,3,121]. By starting from the potassium opianate it is possible to obtain compounds corresponding to the normal form with yields of ~ 80%; for example, with benzyl chloride it gives the α-benzyl ester, and with chloroacetone, the α-acetonyl ester[121,122].

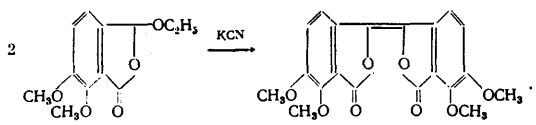
A series of conversions of the γ-formyl acids is known in which the nature of the reagents employed, the conditions of the medium, or the presence of bases would lead us to expect the formation of derivatives of the α-form but nevertheless the final products are derivatives of cyclic structure. Thus, the condensation in the presence of alkali or ammonia of opianic and certain other formyl acids with ketones[123-126], malonic ester, and malonic acid[127-129] leads to compounds corresponding to the ψ-form:



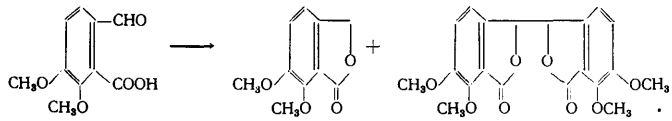
The reaction of γ-formyl acids with nitromethane and other aliphatic nitro-compounds[130-132], potassium cyanide[128,129], or phenyl isocyanide[133] also leads to a cyclic derivative:



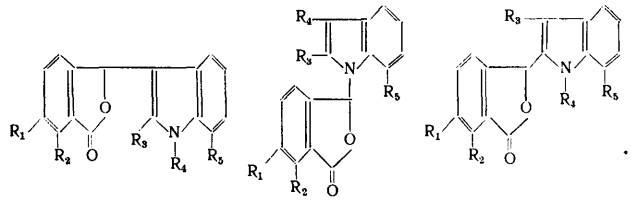
The action of anhydrous potassium cyanide on ethyl ψ-ester of opianic acid in absolute alcohol leads to the formation of meconilidenemeconine[134]:



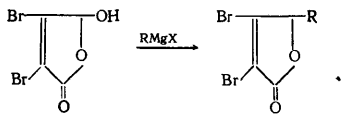
Meconin[5,6-dimethoxyphthalide (Ed. of Translation)] is obtained by the reduction of opianic acid with zinc and sulphuric acid[135] or sodium amalgam[135,136]. Electrolytic reduction of potassium opianate in an apparatus without a diaphragm but with a mercury cathode[136-138] leads to a mixture of meconine and other stereoisomeric dimeconyls (racemic and meso):



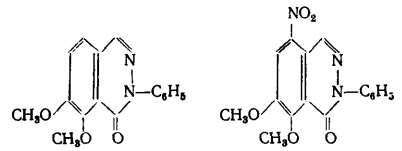
In the condensation of aromatic γ-formyl acids with indole and its derivatives[139-142], various meconylindoles are obtained, the structure of which depends on the position of the substituents in the pyrrole ring:



This reaction was later[142] studied also for chloromucic acid and also extended to other heterocyclic systems: substituted pyrroles, carbazole, indazole, and benzotriazole. For 2-formylbenzoic acid a reaction mechanism was established[141,142] which included the intramolecular catalytic activation of the aldehyde groups by the carboxyl group. The reaction of γ-formyl acids with alkyl (or aryl) magnesium halides leads to compounds which contain a γ-lactone grouping[143-147], for example:



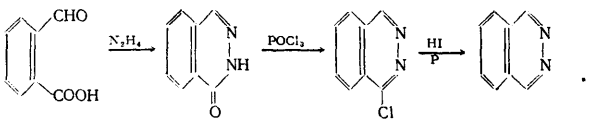
Finally, many reactions of γ-formyl acids are known in which the interaction takes place simultaneously at the aldehyde and carboxyl groups. γ-Formyl acids react in this way with various nitrogen compounds (aromatic o-diamines, hydrazine, substituted hydrazines), leading to derivatives of pyridazine, phthalazine, isocarbostyril, and other heterocyclic systems. Thus as long ago as 1886, in an attempt to obtain phenylhydrazones from opianic and nitro-opianic acids, Liebermann[148] unexpectedly isolated the products of the removal of two water molecules from them. To these compounds, named opiazone (XXIII) and nitro-opiazone (XXIV), Liebermann ascribed the structure of heterocyclic derivatives with two adjacent nitrogen atoms, this being based on the work of Roser[149] who obtained analogous products by the condensation of phenylhydrazine with σ-carboxybenzoylacetic acid and related acids:



(XXIII) (XXIV)

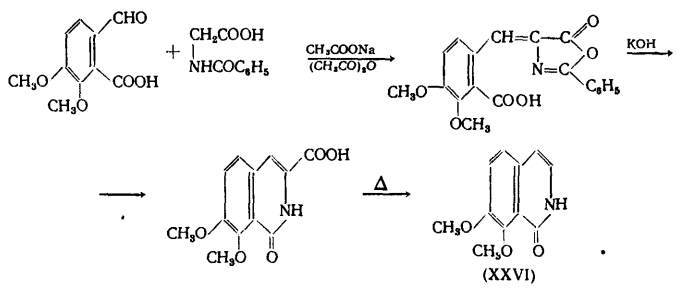
Later the same reaction was studied by the examples of 2-formylbenzoic[21,150], bromo-opianic[119], and bromomucic[151] acids and in every instance analogously constructed heterocyclic compounds were formed.

In 1897 Gabriel and Eschenbach[152] studied the condensation of phthalaldehydric acid with hydrazine itself and developed a method of reduction of the keto-groups formed therein, which preceding workers could not do. In this way a general method of synthesis of the derivatives of a new heterocyclic system, which Liebermann[148] named phthalazine (XXV), was discovered:



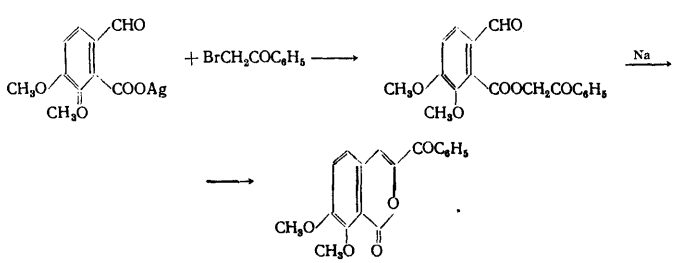
(XXV)

In their classical investigations of the alkaloids of the berberine group, Perkin, Jnr. and his coworkers[153] cleverly used the condensation of opianic acid with hippuric acid to synthesise the 7,8-dimethoxyisocarbostyril (XXVI) which they needed:

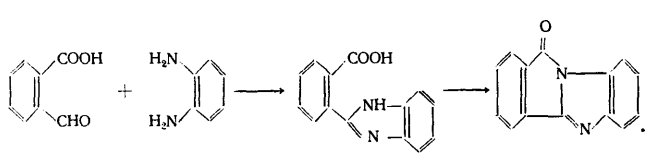


(XXVI)

In an analogous way[153] isocarbostyril itself was obtained from phthalaldehydic acid. 3-Benzoyl-7,8-dimethoxyisocoumarin was synthesised[153] by the reaction of silver opianate with ω-bromoacetophenone and the subsequent cyclisation of the intermediate ester:



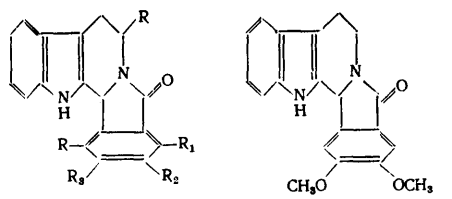
Complex polycyclic nitrogen-containing compounds of alkaloid type can also be obtained on the basis of γ-formyl acids. Even as long ago as the eighteen-nineties Bistrzycki[154,155] showed that 2-formylbenzoic and opianic acids react in the cold with *o*-phenylenediamine and *o*-toluylenediamine, forming cyclic amidines (XXVII), which on boiling with acetic anhydride give the corresponding amidones (XXVIII), for example:



(XXVII) (XXVIII)

Later, Stephenson[156,157] described products of the condensation of phthalaldehydric acid also with other aromatic diamines: with ωω'-diamino-*o*-xylene. 2,2'-diaminobiphenyl, 1,8-diaminonaphthalene, and *o*-aminobenzylamine.

Recently[158], with the aim of synthesising new hypertensive preparations, analogues of reserpine, condensations were effected with the aid of the Pictet–Spengler reaction between 2-formylbenzoic, opianic, metaopianic, and 3,4,5-trimethoxyphthalaldehydric acids and tryptophan and tryptamine. Among the series of pentacyclic compounds thus obtained which contain the β-carboline nucleus, weakly hypertensive activity appeared only in the derivative of metaopianic acid (XXIX):



(XXIX)

IV. INVESTIGATION OF THE STRUCTURE OF γ-FORMYL ACIDS BY PHYSICAL METHODS

Hence, as is evident from the preceding chapters, the study of the chemical behaviour of γ-formyl acids did not provide a conclusive solution for the perennial controversy about their structure‡. A revolutionary role in this sense was played by spectroscopy, the credit for the first use of which for solving the complicated problem of the structure of the γ-formyl acids belongs to Buu-Hoi and his coworkers[163–165]. In 1939–1941 they studied the ultraviolet spectra of 2-formylbenzoic, opianic, 6-bromo-opianic, 6-nitro-opianic acids. It was shown that all these γ-formyl acids in the crystalline state and in chloroform solutions exist in the hydroxy-lactone form. In aqueous solution 2-formylbenzoic and opianic acids have an acyclic form, whereas 6-bromo- and 6-nitro-opianic acids in alcoholic and aqueous–alcoholic solutions exist as equilibrium mixtures of both tautomeric forms. The last two acids, which contain substituents in the *ortho*-position to the aldehydic group, seemed capable of existing in the acyclic form only in strongly alkaline aqueous solutions.

After the ultraviolet spectra, infrared spectra were also used successfully for studying ring–chain tautomerism of γ-formyl acids. Thus with the aid of infrared spectra it was shown that 2-formylbenzoic acid is in a cyclic form in the crystalline state[166]. The extremely thorough work of Wheller and coworkers[167] appeared later. These authors synthesised over fifty derivatives of 2-formylbenzoic acid, the study of the infrared spectra of which in liquid paraffin showed that they exist solely in cyclic form. The absorption spectra of a series of other γ-formyl acids, studied in recent years, also show that these compounds are found exclusively in the cyclic form in the crystalline state, but in solutions they are in the form of equilibrium mixtures of both tautomeric forms, and the position of the equilibrium depends on the dielectric constant of the solvent, its pH, and many other external factors[58,168–174].

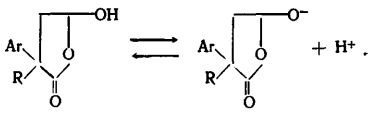
On the other hand, thiophen analogues of 2-formylbenzoic acid (see p. 255) have been shown by Gronowitz and

‡ It must be emphasised that a correct solution of this problem is important not only for the theoretical organic chemistry alone; it also has biological importance, since keto-lactol tautomerism evidently determines the physiological activity of certain antibiotics[159–162].

coworkers[39,40]—on the basis of the NMR spectra in chloroform, dioxan, acetone, and water and also with the aid of ultraviolet and infrared spectra—to exist solely in the acyclic form and it was even found that on esterification in the presence of sulphuric acid 3-formylthiophen-2-carboxylic acid gives a normal ester. The reasons for such a phenomenon are evidently purely geometrical: the incapability of formyl acids of the thiophen series to form lactol tautomers is probably due to differences in the C–C distances and in the values of the valence angles in the benzene and thiophen molecules.

Study of the structure of halogenomucic acids with the aid of NMR showed that they were completely free from an acyclic form, but in the presence of an equivalent quantity of potassium hydroxide halogenomucic acids are converted completely into the acyclic form[170]. According to the ultraviolet and infrared spectra, *cis*-β-formylacrylic acid also has the lactol structure[175].

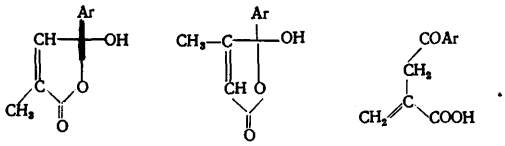
It is interesting to note that for certain substituted β-formylpropionic acids the cyclic form is so stable that it even exhibits a slight acidity, owing to the weak dissociation of the hydrogen of the lactol hydroxyl. These properties are exhibited by αα-disubstituted β-formylpropionic acids which contain not less than one aromatic substituent[176]:



It is necessary to mention here, though briefly, the information about the structure of the nearest relatives of the γ-formyl acids, among which belong above all the γ-keto-acids, with chemical properties very reminiscent of them. The structure of the γ-keto-acids has been extensively studied by spectroscopic methods. Various *o*-benzoylbenzoic acids have been investigated in considerable detail in this respect[177–181]. It was found that most of the methyl-substituted *o*-benzoylbenzoic acids studied exist in the crystalline state and in chloroform or carbon tetrachloride solutions as acyclic tautomers[177–180]. Only acids with a methyl group in the *ortho*-position to carboxyl are an exception, especially 2-benzoyl-3,6-dimethylbenzoic acid, which even in methanol contains only 7% of the keto-acid form[179]. Functional derivatives of *o*-benzoylbenzoic acid (containing halogens, CN, NO_2, and other groups), also have, according to the infrared spectra, an acyclic structure (18 compounds were studied) in the solid state, but form equilibrium mixtures in solutions, with the predominance of the tautomer with an open chain[180]. A well-expressed linear relationship between the free energy and Hammett constant (σ) of the substituents is observed for these compounds.

o-Acetylbenzoic acids have predominantly cyclic structure[178,180]. The increased stability of the tautomers with an open chain in the example of *o*-benzoylbenzoic acid may be connected with the gain in energy due to the formation of a conjugated system.

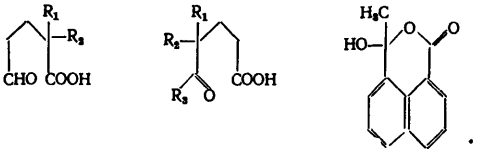
Lutz and coworkers[182] showed with the aid of ultraviolet spectra that various *cis*-β-aroyl-α-methyl- and *cis*-β-aroyl-β-methyl-acrylic acids (XXX) and (XXXI) in alcoholic solutions exist predominantly in the lactol form§. On the other hand, saturated analogues of these compounds—β-aroylbutyric acids, and also β-aroyl-α-methyleneacrylic acids (XXXII) have an open structure:



(XXX) (XXXI) (XXXII)

The structure of the β-acylacrylic acids is closely connected with their stereochemistry. Thus, on the basis of spectroscopic data it was found that β-acetylacrylic acid, with the *trans*-configuration, and also the *trans*-isomer of β-pivaloylacrylic acid are true keto-acids, whereas *cis*-β-acetyl-α-methylacrylic and *cis*-β-pivaloylacrylic acids are lactols[175,184,185]. The solution of the problem of the configuration of the stereoisomeric β-pivaloylacrylic acids on the basis of an examination of their tautomeric structure with the aid of NMR spectra[184] is probably the first example of the use of spectra for such a purpose¶.

Aliphatic mono- and di-substituted δ-formyl acids (XXXIII), recently synthesised by Salmon-Legagneur and coworkers[186,187], are, according to their infrared spectra, tautomers with an open chain. The aliphatic δ-keto-acids (XXXIV) also have an analogous structure[188–190]:

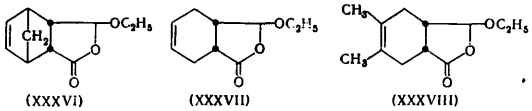


(XXXIII) (XXXIV) (XXXV)

However, 8-acetyl-1-naphthoic acid (XXXV) exists only in the lactol form[191].

V. ALICYCLIC γ-FORMYL ACIDS

γ-Formyl-acids of the cycloaliphatic series remained unknown until very recently, becoming accessible only in 1958, thanks to the work of Alder and Fariña[68], who found that the ethyl ψ-ester of β-formylacrylic acid (XVIII) is capable of undergoing a diene condensation with cyclopentadiene, bivinyl, and 2,3-dimethylbutadiene, forming the corresponding adducts (XXXVI)–(XXXVIII)†:

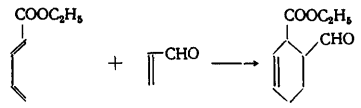


(XXXVI) (XXXVII) (XXXVIII)

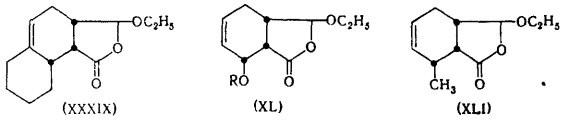
§ For *cis*-β-(4-bromophenyl)-β-methylacrylic acid this was established even earlier by polarograph[183].

¶ See p.262 for the analogous use of infrared spectroscopy in several alicyclic-formyl acids.

† In 1965 the synthesis of an α-ester of an alicyclic γ-formyl acid effected by another path was described[192]:



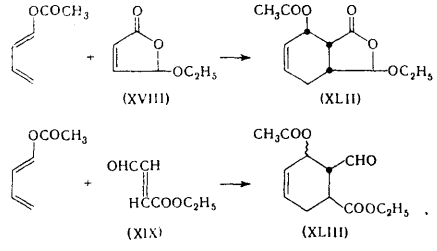
It was found later that an analogous condensation also takes place with 1-vinylcyclohex-1-ene[72], 1-acetoxybutadiene[69], and *trans*-piperylene[74], leading to the adducts (XXXIX)–(XLI):



(XXXIX) (XL) (XLI)

Furan and dienes, like styrene, do not react with the ψ-ester (XVIII)[68]. Instead of the ψ-ester of β-formylacrylic acid the corresponding *cis*-acid (XVII) and also the normal ethyl ester of its *trans*-isomer (XIX) can be used in the diene synthesis[68,69]. The adducts of the diene synthesis obtained with the ψ-ester (XVIII), are readily converted into the corresponding acids or normal esters, which contain a free formyl group and are capable of entering into the Knoevenagel reaction[68,69,73].

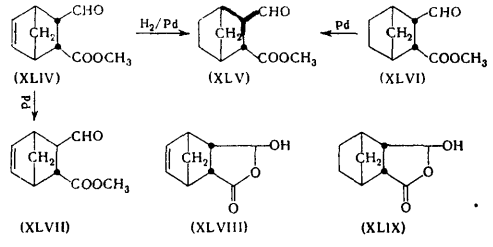
In studying the diene condensation of 1-acetoxybutadiene with the ethyl ψ-ester of β-formylacrylic acid and also 1-acetoxy and 1-methoxy-butadiene with the ethyl α-ester of *trans*-β-formylacrylic acid, Farina and coworkers[69] observed an interesting fact. It appeared that the adducts (XLII) and (XLIII) obtained from the *cis*- and *trans*-dienophiles have not only different configuration but also different structure, which is evidently due to the different orientation abilities in the diene synthesis of the functional groups of the dienophiles:



(XVIII) (XLII)

(XIX) (XLIII)

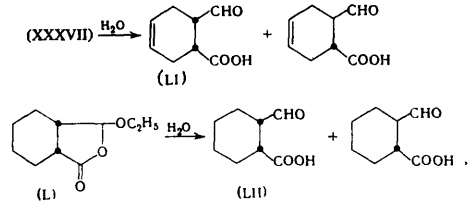
The synthesis and stereochemical conversions of the adducts of the diene condensation of the ethyl ψ-ester of β-formylacrylic acid (XVIII) with cyclopentadiene, 2,3-dimethylbutadiene, and bivinyl were subsequently subjected to a more detailed study[70,71]. Here in particular it was found that the hydrogenation of the unsaturated *cis*-γ-formyl ester (XLIV) is accompanied by the simultaneous isomerisation, leading to the saturated *trans*-γ-formyl ester (XLV), which is obtained also in the simple shaking of the saturated *cis*-formyl ester (XLVI) with reduced palladium catalyst. The unsaturated *cis*-γ-formyl ester (XLIV) is isomerised in an analogous manner, giving the *trans*-isomer (XLVII). Such astonishingly easy isomerisation of the α-esters (XLIV) and (XLVI) and the incapability to isomerisation under the same conditions of the corresponding γ-formyl acids (XLVIII) and (XLIX) are chemical proofs of the lactol structure of the latter[70]:



(XLIV) (XLV) (XLVI)

(XLVII) (XLVIII) (XLIX)

In contrast to Alder and Farina's results[68], it was shown that saponification of the adduct (XXXVII)[71] with boiling water and also saponification of its hydrogenation product (L) (contrary to the behaviour of the analogous derivatives obtained from cyclopentadiene[70]) is accompanied by isomerisation and leads to mixtures of *cis*- and *trans*-γ-formyl acids:



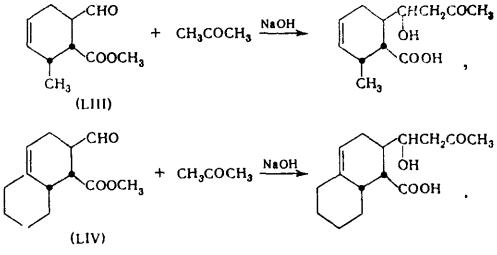
(LI)

(L) (LII)

On this basis it can be suggested that the γ-formyl acids (LI) and (LII) exist in aqueous solution as mixtures of tautomeric forms.

The γ-formyl acids and their derivatives obtainable with the aid of the diene condensation of the ethyl ψ-ester of β-formylacrylic acid (XVIII) with piperylene[74] and 1-vinylcyclohexene are distinguished by a considerable tendency to epimerisation[72,193]. Diene reactions in which these unsymmetrical dienes participate proceed with structural and spatial selectivity, leading mainly to the adducts mentioned above (XXXIX) and (XLI). Hydrolysis of the latter even in neutral conditions is accompanied by partial isomerisation and the *cis*-γ-formyl acids which are formed contain the *trans*-isomers as impurity. Therefore the preparation of the pure γ-formyl acids and their derivatives by these means is practically unattainable. The especially ready isomerisation is observed in the bicyclic series[193]. The catalytic hydrogenation of adducts (XXXIX) and (XLI) takes place readily and in the case of adduct (XXXIX) is stereo-directed—to the side opposite the lactol ring. From the saturated ψ-esters obtained in this manner the corresponding *cis*- and *trans*-formyl acids have been synthesised; these, and also their normal esters, are distinguished by a somewhat smaller tendency to *cis*–*trans*-isomerism than their Δ^4-unsaturated analogues.

The esters of the alicyclic γ-formyl acids of the cyclohex-4-ene series are characterised by considerable inertness in nucleophilic additions at the aldehyde group. Thus, the *cis*-*trans*-formyl ester (LIII) is only saponified, and does not form an acetylenic alcohol under the action of sodium acetylide in liquid ammonia‡[74]. The condensation of the *cis*-*trans*-γ-aldehydo-esters (LIII) and (LIV) with acetone under the influence of dilute sodium hydroxide§ takes place to only 10–15% extent[74,193].



(LIII)

(LIV)

Such behaviour of the formyl group was explained by its participation in an intramolecular interaction with the π-electrons of the double bond (supra-annular effect)[194,195],

‡ The corresponding *cis-cis*-formyl ester in this is isomerised into the *trans*-isomer.

§ Hydrolysis of the ester group takes place simultaneously.

which is confirmed also by diminished reactivity of the double bond in such compounds as was shown by determination of the thiocyanate numbers[74,193].

Interesting regularities were observed in studying the infrared spectra of γ-formyl acids[74,193], derivatives of the adducts of the ψ-esters (XVIII) with 1-vinylcyclohexene and *trans*-piperylene (XXXIX) and (XLI). It was found that unsaturated γ-formyl acids of both the *cis*- and *trans*-series exist in carbon tetrachloride solution as equilibrium mixtures of almost equal amounts of the two tautomeric forms. On the other hand, the corresponding unsaturated γ-formyl acids of *cis*-configuration have under these conditions the structure of lactols, whereas the *trans*-acids are true γ-formyl acids. Evidently infrared spectroscopy is a rapid and reliable method of demonstrating the configuration of stereoisomeric alicyclic γ-formyl acids (especially in the presence of pairs of isomers[85,168].

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Progress in the Chemistry of the 1,3-Dioxans

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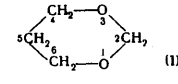
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I. INTRODUCTION

In recent years there has been a considerable increase in interest in the 1,3-dioxans. There has been a review of the chemistry of these compounds[1] but it is incomplete and contains references to the literature only up to 1955. The present review fills some of the gaps in this earlier review and surveys the literature for 1955–1965. Furthermore, the present article examines the problem of the stereochemistry of the 1,3-dioxans, which was not considered systematically earlier. In this the authors consider it necessary to express their viewpoint on some of the complicated stereochemical problems relating to works they have carried out.

The first information on 1,3-dioxans appeared in 1865, however, the simplest of them, 1,3-dioxan itself[1], was synthesised only in 1902.[2] Compounds of this type were named 1,3-dioxans (or *meta*-dioxans) only by the external similarity in structure to 1,4-dioxans. However, the latter are simple ethers, whereas 1,3-dioxans are cyclic acetals (ketals).


(I)

There is no great industrial production of most 1,3-dioxans. However, there are now great possibilities for their rational use. Many substituted derivatives of (I) were found to be good solvents. Some of the compounds of this type are physiologically active and have found application as effective spasmolytic and antihistamine preparations, depressants of the central nervous system, and even antibiotics. A series of 1,3-dioxans seemed an important intermediate product in organic synthesis, particularly in the synthesis of isoprene and other conjugated dienes.