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Methods of Synthesis of β-Substituted Furan Derivatives

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The review describes the methods of synthesis of β-substituted furan derivatives. Particular attention was devoted to the methods based both on furan itself and its α-monosubstituted derivatives. This approach to the problem arises from the fact that at the present time compounds of the furan series, for example furfural, furan, silvan, etc. are readily available and are manufactured on a commercial scale. The bibliography includes 202 references.

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I. INTRODUCTION

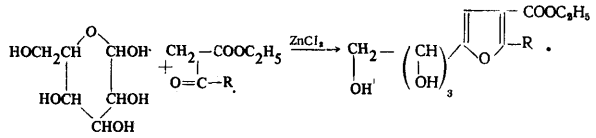
The most important distinctive feature of the furan system consists in its vigorously defined mode of interaction with electrophilic and nucleophilic agents: in all cases, when at least one α-position in the ring is free and the second α-position is not substituted by a very active group, for example a keto-group, the new substituent enters the α-position whatever its nature [1]. This gave rise to a definite trend in the development of the chemistry of furan. As a result α-mono- and αα'-di-substituted furan derivatives constitute so far the main bulk of the synthesised and investigated compounds of the furan series. At the same time many β-substituted derivatives have been obtained by an "indirect" method involving, in particular, the ring closure of the corresponding open-chain derivatives, which are frequently not readily available. However, it is evident that the interest in β-substituted furan derivatives will increase, since they are often encountered in natural products and sometimes exhibit physiological and other activity different from that of the isomeric compounds with substituents in the α-positions. As an example, one may quote the importance of the position of the nitro-group as a factor responsible for antibacterial activity [2].

II. METHODS OF SYNTHESIS OF TRI- AND TETRA-SUBSTITUTED FURAN DERIVATIVES

Since tri- and tetra-substituted furan derivatives (mainly tri-substituted) are the starting materials in the synthesis of β-mono-, 2,3-di-, and 2,4-di-substituted furan derivatives, it is desirable to describe in the first place the general methods for the preparation of these compounds.

1. Syntheses Based on Aliphatic β-Dicarbonyl Compounds

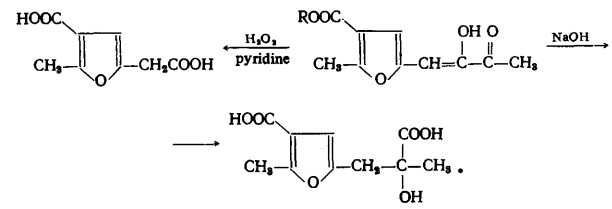
α-Substituted esters of furan-3-carboxylic acid (II) have been obtained by the reaction of acetoacetic ester, benzoylacetic ester, or the ester of acetonedicarboxylic acid with aldoses (I):[3,4]



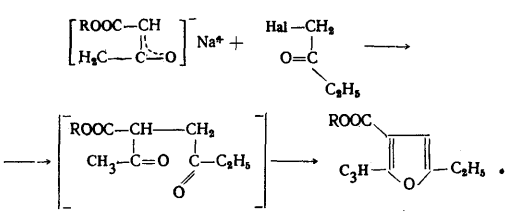
(I) (II)

Compound (II, R = CH_3) has been oxidised with potassium permanganate to 5-methylfuran-2,4-dicarboxylic acid and with periodic acid to the ester of 2-formyl-5-methylfuran-carboxylic acid.

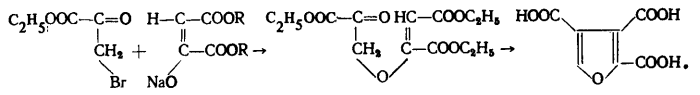
Recently Dalton [5] showed that, when compound (II) is heated in an ethanolic solution of hydrogen chloride, an α-diketone is formed. Under the action of hydrogen peroxide, the diketone is converted into 2-carboxymethyl-5-methylfuran-4-carboxylic acid, while in the presence of alkali it undergoes a benzilic acid rearrangement:



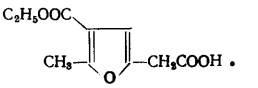
Tri-substituted furan derivatives are also obtained in the interaction of sodioacetoacetic ester and similar compounds with α-halogeno-ketones:[6-8]



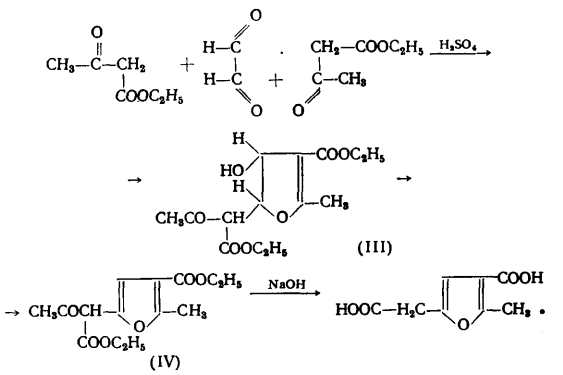
At the same time there are reactions regarded as examples of the interaction of an α-halogenocarbonyl compound with the sodio-derivative of a β-dicarbonyl compound via the oxygen atom. For example, Reichstein[9] described the reaction of the sodio-derivative of the oxaloacetic ester with monobromopyruvic acid, which was converted into furan-2,3,4-tricarboxylic acid:



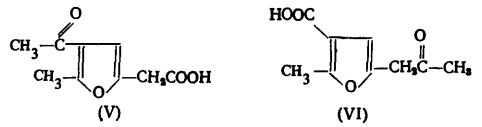
If the process proceeded via a 1,4-dicarbonyl compound, as suggested by Sutter[10], the reaction product would have been furan-2,3,5-tricarboxylic acid. When the acetoacetic ester is heated with the disodium salt of succinic acid in acetic anhydride, the monoethyl ester of 4-carboxy-5-methylfuran-2-acetic acid is formed:



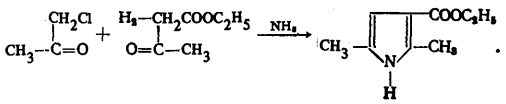
This synthesis was achieved for the first time by Fittig[11] and then by Reichstein and Grüssner[12]. Patent data published in 1959 show[13] that 4-carboxy-5-methylfuran-2-acetic acid can also be obtained by the condensation of acetoacetic ester with glyoxal in an acid medium:



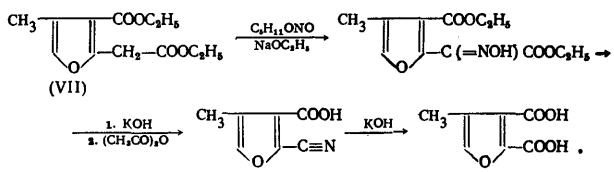
It has been shown that the process takes place via stages involving the formation of compounds (III) and (IV). The Fittig reaction was repeated in 1963 with acetylacetone by Suverkropp and Wynberg[14], who obtained 4-acetyl-5-methylfuran-2-acetic acid (V), which was then converted by decarboxylation into 3-acetyl-2,5-dimethylfuran. It proved to be identical with the product formed in the acylation of 2,5-dimethylfuran[15]. It is noteworthy that the structure of the isomeric 5-acetonyl-2-methylfuran-3-carboxylic acid (VI) was previously incorrectly attributed to compound (V):[16]



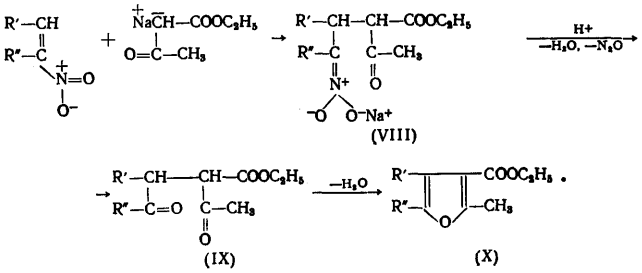
The syntheses of Feist[17] and Benary[18] are very close to the reactions of the sodio-derivatives of β-dicarbonyl compounds with α-halogeno-ketones. They consist in the interaction of β-dicarbonyl compounds with α-halogeno-ketones[17] or with α-chloroacetaldehyde[18] in ammonia. These reactions usually result in a mixture of pyrrole and furan derivatives, the relative amounts of which depend on the nature of the β-dicarbonyl compound employed. Thus, when acetoacetic ester is used, pyrrole derivatives are mainly obtained (the Hantzsch reaction):



With acetonedicarboxylic acid, the formation of the furan derivative (VII) predominates[17,19]. Starting with compound (VII), Rinkes[20] and Reichstein[19] achieved almost simultaneously the synthesis of 4-methylfuran-2,3-dicarboxylic acid, which can be illustrated by the following scheme:



Boberg and Schultze[21] synthesised a number of tri- and tetra-substituted furan derivatives by the reaction of sodioacetoacetic ester with α-nitro-olefins:

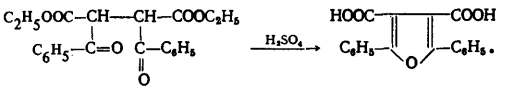


The sodium salt of the nitronic acid (VIII) underwent the Nef reaction under the influence of cold mineral acid[22] and was converted via the 1,4-dicarbonyl compound (IX) into esters of furan-3-carboxylic acid (X). By hydrolysing compound (X) and decarboxylating the acid, it is possible to obtain 2,3,5-trisubstituted furan derivatives.

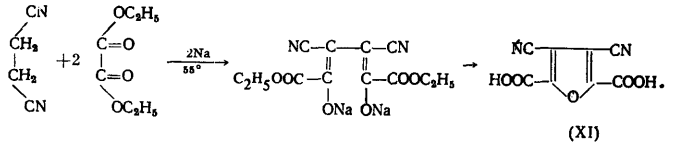
2. Syntheses from Saturated and Unsaturated 1,4-Diketones and 1,4-Keto-alcohols

The oldest method for the preparation of furan derivatives from aliphatic compounds is the cyclodehydration of the dienol forms of 1,4-diketones. As early as 1884, Bayer and Perkin[23] converted dibenzoylsuccinic ester into

2,5-diphenylfuran-3,4-dicarboxylic acid by refluxing for 20 h with 30% sulphuric acid:



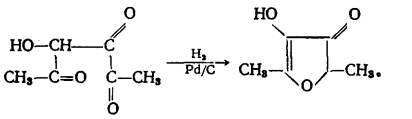
3,4-Diacetyl-2,5-dimethylfuran was obtained similarly by the action of hydrochloric acid on tetra-acetylethane [24,25]. In 1941 Trefil'ev and Lifanov [26] repeated this synthesis using hydrobromic acid. Subsequently an American patent was published, in which the preparation of the acid (XI) according to the scheme



(XI)

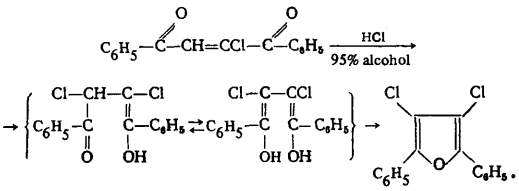
was described [27].

In 1956 Hoffmann and Eugster [28] synthesised the principal aromatic components of the pineapple fruit—3-hydroxy-2,5-dimethyl-4,5-dihydrofuran-4-one (XII):

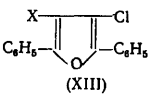


(XII)

The synthesis of tetrasubstituted furan derivatives from unsaturated 1,4-diketones was investigated in detail by Lutz and McGinn [29] using dibenzoylethylenes. They assumed that probably ring closure precedes the addition of the reagent in the 1,4-positions favouring cyclisation. Both *cis*- and *trans*-dibenzoylchloroethylenes react with hydrogen chloride in 95% alcohol forming 3,4-dichloro-2,5-diphenylfuran:



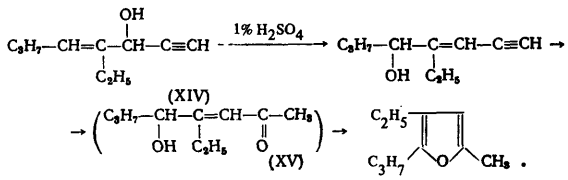
The reaction of *cis*-dibenzoylchloroethylene with acetyl chloride or acetic anhydride in the presence of sulphuric acid yields chloro- or acetoxy-furans (XIII):



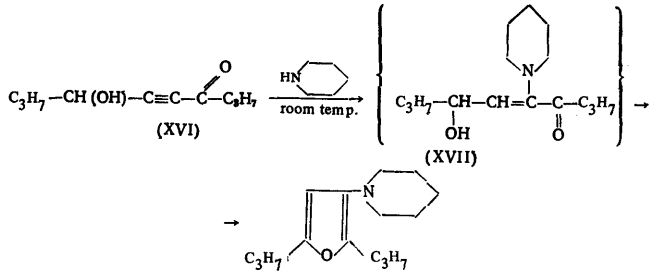
(XIII)

where X = Cl or $CH_3C(=O)-O-$.

Heilbron et al. [30] showed that enyne alcohols (XIV) are cyclised into a furan system during distillation with 1% sulphuric acid, probably via an intermediate keto-alcohol (XV):

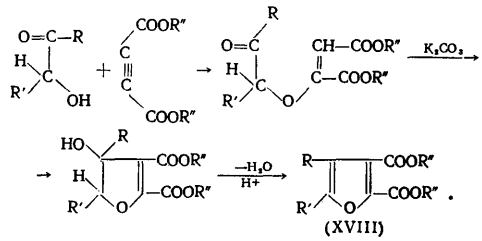


Cyclisation also takes place when piperidine is allowed to act upon the keto-alcohol (XVI), evidently also via an ethylenic 1,4-keto-alcohol (XVII):[31]



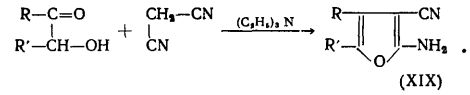
3. Other Syntheses of Aliphatic Compounds

Furan derivatives with the structure (XVIII) have been obtained by the condensation of the esters of acetylenedicarboxylic acid with an α-hydroxy-ketone [32]:



(XVIII)

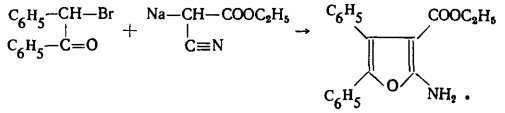
In 1966 Gewald [33] stated that the dinitrile of malonic acid readily reacts with α-hydroxy-ketones in the presence of bases, forming 2-amino-3-cyanofurans (XIX):



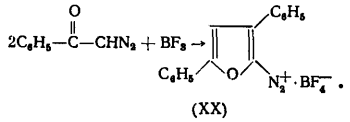
(XIX)

4-Acetyl-2-amino-3-cyano-5-methylfuran, analogous to compounds (XIX), had been synthesised earlier [34] from the dinitrile of malonic acid and 3-chloroacetylacetone. In contrast to the unsubstituted 2-aminofuran, these aminofurans are relatively stable. Only compounds (XIX) with a free α-position are sensitive to oxygen.

2-Amino-3-ethoxycarbonyl-4,5-diphenylfuran was obtained by the reaction of α-bromodeoxybenzoin with the sodio-derivative of cyanoacetic ester in ethanol [35]:



The first compound with a diazo-group in the furan ring, 2,4-diphenylfuran-5-diazonium fluoroborate (XX), was synthesised in 1963 by Reid and Bodenstedt [36], who allowed benzoyldiazomethane to react with boron trifluoride-ether:



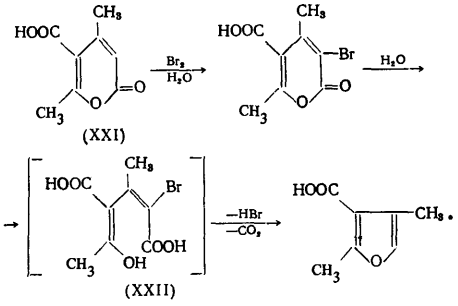
(XX)

It is noteworthy that the mechanisms of most of the reactions described above have an inadequate basis and the equations quoted must be regarded as only approximate.

The syntheses involve certain difficulties: frequently mixtures difficult to separate are formed and the yields of the desired products are as a rule low.

4. Syntheses from Other Cyclic Systems

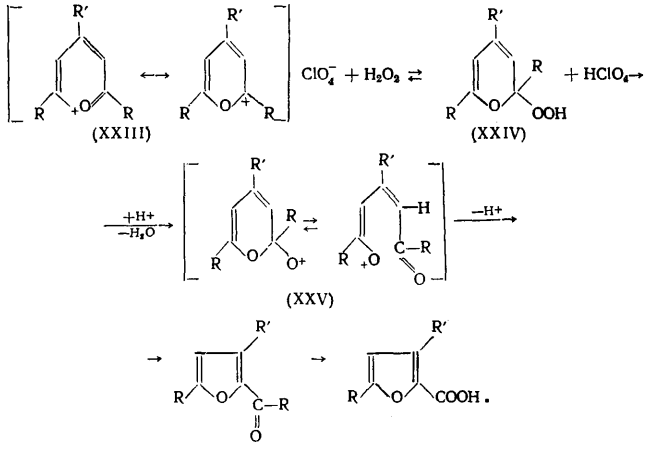
In his study of the bromination of α-pyrone derivatives Feist observed [37] that in some cases the reaction can be used to synthesise furan compounds. According to the suggested mechanism, dimethylcoumalic acid (XXI) gives rise to 2,4-dimethylfuran-3-carboxylic acid, probably via the intermediate (XXII):



(XXI)

(XXII)

In 1960 Balban and Nenitzescu [38] published a paper in which the synthesis of trialkyl-substituted furan derivatives from pyrylium salts is proposed. Earlier only one similar case of the contraction of the pyran ring in the hydrolysis of 2,4,5,6-tetraphenylpyrylium bromide had been described [39]. It was found [38] that, under the action of hydrogen peroxide, the readily available trialkylpyrylium perchlorates (XXIII) are converted into 3,5-dialkyl-2-acylfurans. These ketones were oxidised to the corresponding 3,5-dialkylfuran-2-carboxylic acids, whereby their structure was confirmed:



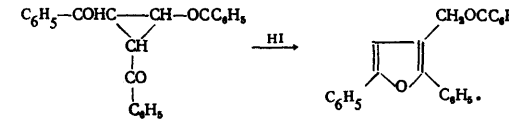
(XXIII)

(XXIV)

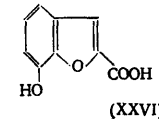
(XXV)

In this reaction the α-position of the pyran ring is subjected to nucleophilic attack by hydrogen peroxide and this gives rise to the peroxy-analogue of the pseudo-base (XXIV), which decomposes under the action of the acid formed. The formation of the furan ring favours the irreversible stabilisation of the cation (XXV).

Certain trisubstituted furan derivatives can be obtained from cyclopropane derivatives. For example, when concentrated hydriodic acid is allowed to act on *cis*- and *trans*-tribenzoylcyclopropanes, 2,5-diphenyl-3-phenylacetylfuran is formed [40]:

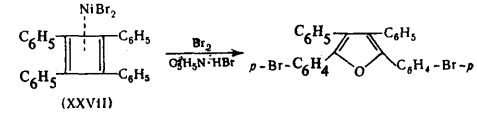


Furan-2,3,5-tricarboxylic acid was obtained from 7-hydroxycoumarone-2-carboxylic acid (XXVI) by oxidation with hydrogen peroxide in an alkaline solution [41]. In compound (XXVI) the benzene ring becomes sensitive to oxidation by virtue of the presence of the hydroxy-group, but the furan ring is stable [42] with respect to the action of hydrogen peroxide in an alkaline medium, particularly when it contains a carboxy-group:



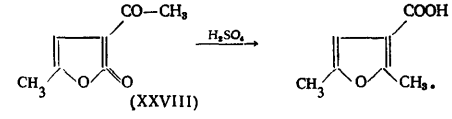
(XXVI)

Comparatively recently it has been established [43] that substituted furans may be obtained in high yield from the nickel bromide complex of tetraphenylcyclobuta-1,3-diene (XXVII) by treatment of the latter with bromine in the presence of pyridine hydrobromide which had been kept in moist air:



(XXVII)

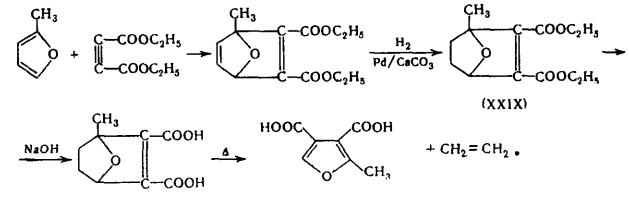
βγ-Unsaturated α-acyl-lactones can be readily converted into furancarboxylic acids. For example, 2,5-dimethylfuran-3-carboxylic acid is obtained smoothly from α-acetylangelicalactone (XXVIII):[44]



(XXVIII)

5. Preparation from α-Monosubstituted Furan Derivatives by Successive Diene and Retrodiene Syntheses

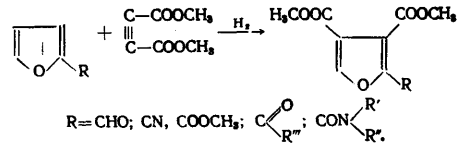
Adler and Rickert [45] showed that the adduct obtained by the addition of the diester of acetylenedicarboxylic acid to silvan can be partially reduced with hydrogen over a palladium catalyst. The product (XXIX) is converted into 2-methylfuran-3,4-dicarboxylic acid on hydrolysis and heating (retrodiene synthesis):



(XXIX)

Similarly the corresponding 2,3,4-trisubstituted furan derivatives were obtained from 1-acetamido-1-(fur-2′-yl)-ethane [46] and the acetal of furfural [47]. Recent investigations [48,49] revealed the capacity of furan derivatives substituted in the α-position by electron-acceptor groups to

react as dienes with the dimethyl ester of acetylenedicarboxylic acid:

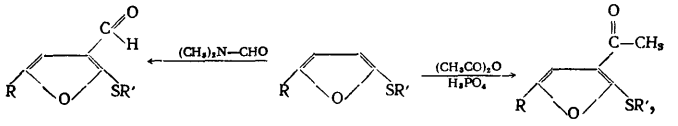


The method of consecutive diene and retrodiene syntheses is used[50] to identify the α- and β-furyl residues in natural products since furan-3,4-dicarboxylic acid is formed from mono-β- or $\beta\beta'$-disubstituted derivatives[51,52] as a result of the reactions described above, while mono-α-derivatives yield trisubstituted furan.

6. Substitution Reactions of α-Monosubstituted Furan Derivatives

The vast majority of known trisubstituted furan derivatives have been obtained by the electrophilic substitution of readily available mono-α-substituted furans: silvan, furfural, and pyromucic acid and its esters. It is generally known that, regardless of its nature, a new substituent enters into the second α-position in the ring of an α-monosubstituted furan. The possibility of further substitution in the β-position depends on the type of substituents already present in the α- and α'-positions and on the nature of the attacking reagents.

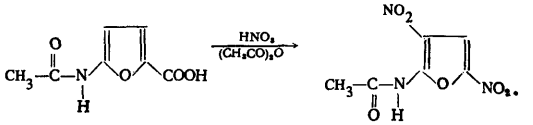
If the α-positions of the ring are substituted by two identical electron-donor groups, the introduction of a third substituent, although possible, is hindered as a result of the competing reaction involving the opening of the furan ring or the displacement of one of the existing groups by the attacking reagent[53]. For example, 2,5-dimethylfuran may be nitrated[54], chloromercurated[55], sulphonated[56], and acylated[7] in the β-position, but it does not undergo the Gattermann–Koch reaction[57]. In this case the ring is opened and acetonylacetone is formed. For furan derivatives with two electron-donor non-identical substituents in the α-position, only isolated examples of the introduction of β-substituents are known, since the reaction is usually accompanied by the opening of the furan ring. Examples are the acylation and formylation of 2-alkyl-5-alkylthiofurans (XXX).[58] The new substituent occupies the β-position adjacent to the alkylthio-group:



(XXX)

where R and R′ = alkyl.

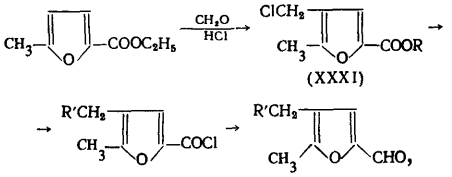
Examples of the formation of trisubstituted furan derivatives when the α- and α'-positions of the ring are occupied by different electronegative groups are encountered rarely; in the main they occur with compounds having two identical electron-acceptor groups. For example, the diethyl ester of furan-2,5-dicarboxylic acid can be mercurated[59] and chlorinated[60] but not brominated[61–63]. Furan-2,5-dicarboxylic acid is inert with respect to reagents such as aqua regia, fuming nitric acid, bromine, and concentrated sulphuric acid[55]. The greatest number of β-substitution reactions is known for $\alpha\alpha'$-disubstituted furans in which one group is an electron donor and the other an electron acceptor. These are mainly substituted esters of furan-2-carboxylic acid[64–77]. The work of Sasaki[78] on the nitration of 2,5-disubstituted furan derivatives with substitution should be mentioned:



The replacement of the carboxy-group by a nitro-group takes place with best yields in the case of electron-donor groups in the α'-position of the furan ring.

The introduction of two substituents into the furfural molecule[79] or silvan molecule[56,80,81] has been described, but such cases are rare; they include, in particular, the syntheses[82,83] of 4,5-dibromofurfural and 2-acetyl-4,5-dibromofuran in one stage using aluminium chloride without solvent. Under the conditions of the bromination of furfural[84] or its acylal[85,86] in a solvent without aluminium chloride, 5-bromofurfural is formed. Apart from the procedures described above, there are also others leading to trisubstituted furans, for example from 3,4-disubstituted[87,88], 2,3-disubstituted[88,89], and 2,4-disubstituted[79,90,91] derivatives, but these are of limited applicability.

A series of papers dealing with the synthesis of new tri- and tetra-substituted furan derivatives via the reactions of groups already present in the furan ring have been published. Among these one should mention the investigation of Mndzhoyan et al. of the synthesis of the chloroacetyl-, β-chloropropionyl-, and p-nitrobenzoyl-amides of 4,5-disubstituted furan-2-carboxylic acid[95] and of the preparation of the ethyl ester of 4-chloromethyl-5-methylfuran-2-carboxylic acid[67] (XXXI) and its conversion into 4,5-dimethylfuran-2-aldehyde[68], 5-bromoethyl-4-chloromethylfuran-2-carboxylic acid[92], 2-dimethylaminoethyl ester of 4-benzyl-5-methylfuran-2-carboxylic acid[92], and 4-benzyl-5-methylfuran-2-aldehyde[94], from which the nitrile, amide, and amine were obtained:



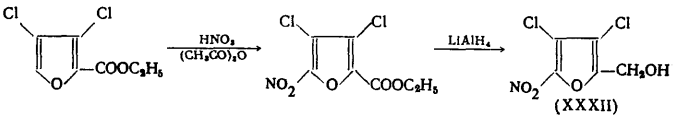
(XXXI)

where R = H or C_2H_5 and R′ = H or C_6H_5.

Janda and coworkers[96,97] synthesised the methyl ester (XXXI) from 5-acetylsilvan and replaced the chloromethyl group by an aldehyde group.

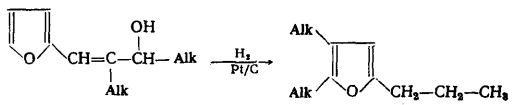
In a study of the possibility of the allyl rearrangement in certain tetrasubstituted furans, for example in 3,4-dichloromethyl-2,5-dimethylfuran under the action of sodium cyanide, Novitskii et al.[98] obtained certain new tetrasubstituted furans. They also synthesised[99] a number of trisubstituted furans.

Michels[100] described the conversion of the ester of 3,4-dichlorofuran-2-carboxylic acid into the alcohol (XXXII):

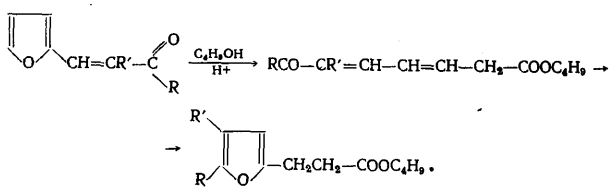


(XXXII)

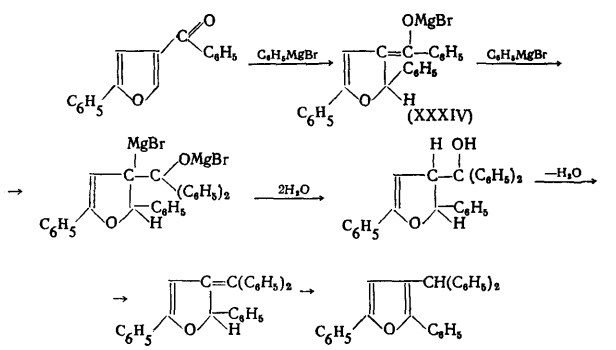
There exist patent data [101] concerning the synthesis of trialkylfurans (XXXIII) by a procedure involving a catalytic hydrogenation stage over platinum:



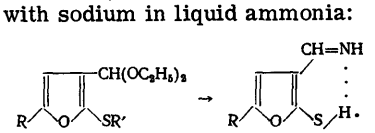
Esters of 4,5-dialkylfuran-2-propionic acids were obtained from fur-2-ylalkenones by acid-catalysed alcoholysis [102]:



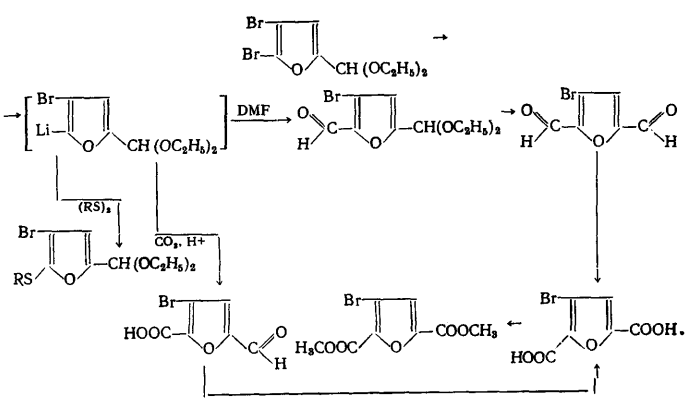
An example of the synthesis of a trisubstituted furan from a 2,4-disubstituted derivative, 4-benzoyl-2-phenylfuran, has been described [103]. In this case probably one phenylmagnesiumbromide molecule adds initially to the 1,4-positions of the conjugated system and the second molecule to the double bond of compound (XXXIV):



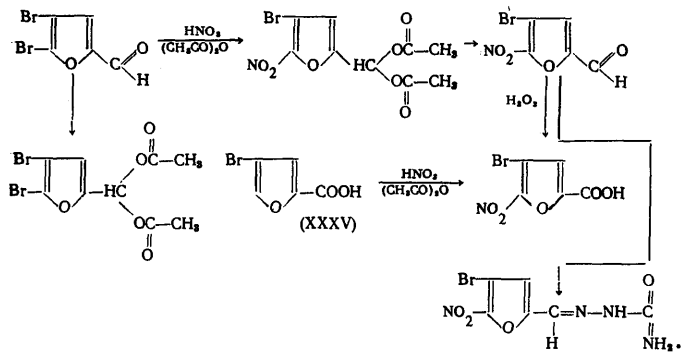
Like the corresponding acetals of the thiophen series [104], the acetals of 5-alkyl-2-alkylthiofuran-3-aldehydes are converted [105] into 5-alkyl-2-mercaptofurfurylideneimines on treatment with sodium in liquid ammonia:



By virtue of the inertness of the acetalised aldehyde group to the action of butyl-lithium, it proved possible to synthesise from 4,5-dibromofuran-2-aldehyde [82,83] the previously unknown sulphides, dialdehydes, and diesters with a bromine atom in the β-position of the ring [106]:



New nitro-derivatives, which may prove of interest as antibacterial agents, were also obtained by the substitution of a bromine atom in the α-position by a nitro-group [106]. The substitution of bromine in the α-position [84,107] by a nitro-group in the furan series is not always possible.



It is noteworthy that the present authors were able to nitrate the acid (XXXV) with formation of 4-bromo-5-nitrofuran-2-carboxylic acid. Judging from the literature data [72], in the nitration of compound (XXXV) the furan ring cleaves to form bromofumaric acid.

III. METHODS OF SYNTHESIS OF MONO-β-SUBSTITUTED FURAN DERIVATIVES

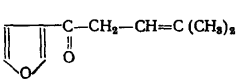
The information about the preparation of β-monosubstituted furan derivatives is extremely limited; this is undoubtedly because of the difficulties associated with their synthesis. In fact up to 1933 not a single mono-β-substituted furan had been obtained. Only isolated cases of the introduction of a substituent in the β-position of an unsubstituted furan molecule were described. When furan is alkylated with propene in the presence of boron trifluoride-ether, a very small amount of the isomeric mono-β-alkyl derivative is formed together with the α-isomer [108]. By alkylating furan with isobutene and pentene in the presence of phosphoric acid on kieselguhr, it is possible to obtain [109] β-alkylfurans with acceptable yields, but containing an admixture of α-isomers. It is interesting to note that 2-t-butylfuran isomerises [109] over this catalyst to 3-t-butylfuran. Nevertheless these data have no value when the aim is to synthesise β-monosubstituted furans.

We shall now examine the methods available at present for the preparation of β-monosubstituted furan derivatives.

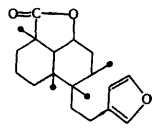
1. Isolation from Natural Products

The first known 3-monosubstituted furan, furan-3-carboxylic acid, was not synthesised but was isolated from plants [110,111]. The principal component of perilla oil is 3-furyl isopentyl ketone [112,113]. The oil also contains 3-(4'-methylpent-3'-enyl)furan [113,114]. Each year there is an increase in the number of β-monosubstituted furan derivatives discovered as constituents of natural materials [50,115-118].

In 1962 a ketone with the following structure was obtained from perilla oil [119]:

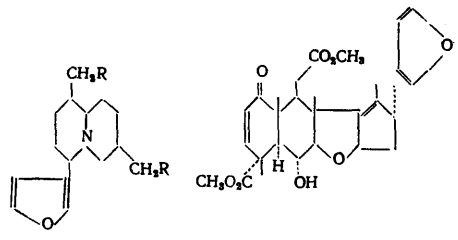


The following structure has been proposed for marrubiin, which incorporates a non-condensed 3-substituted furan ring[120]:

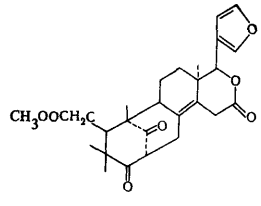


The structure of this compound was confirmed[121] by additional data.

It is suggested[122,123] that the β-furyl residue is a structural component of the castoramine molecule and "nimbinic acid", to which the following structures are attributed respectively:

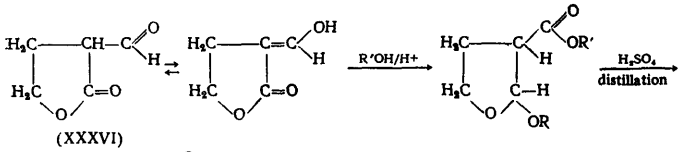


The following structure has been assigned to mexicanolide, a natural lactone[124]:

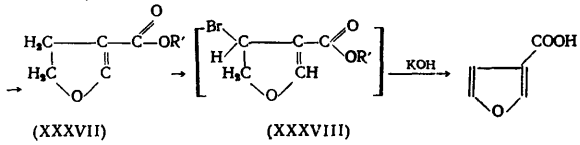


2. Cyclisation of Aliphatic Compounds

There are very few examples of the preparation of β-monosubstituted furan derivatives by direct ring closure of aliphatic compounds. The method of synthesis of furan-3-carboxylic acid, proposed fairly recently, is interesting. α-Formyl-γ-butyrolactone (XXXVI) is obtained from the readily available γ-butyrolactone formed[125] by the dehydration of butane-1,4-diol and subsequent condensation with formic ester[44]:

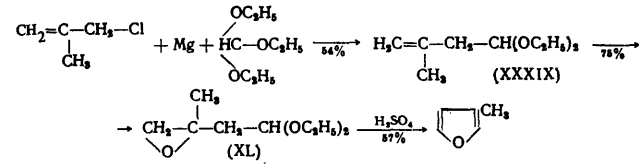


(XXXVI)

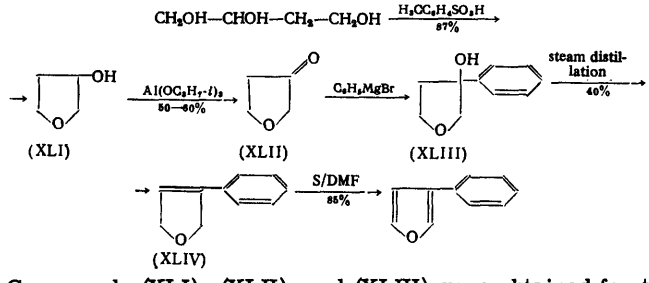


(XXXVII) (XXXVIII)

The rearrangement[44] of this lactone to the ester of 4,5-dihydrofuran-3-carboxylic acid (XXXVII) and bromination[126] of the latter by *N*-bromosuccinimide leads to an unstable product (XXXVIII), which is converted by treatment with aqueous alkali into furan-3-carboxylic acid with 58% yield[126]. A convenient three-stage synthesis of 3-methylfuran has been described[127]. The diethyl acetal of 3-methylbut-3-enal (XXXIX), formed by the reaction of methylallyl chloride, magnesium, and orthoformic ester, is converted by oxidation with perphthalic acid into the epoxide (XL), the hydrolysis of which yields 3-methylfuran:



Wynberg[128] synthesised 3-phenylfuran from 1,2,4-trihydroxybutane:



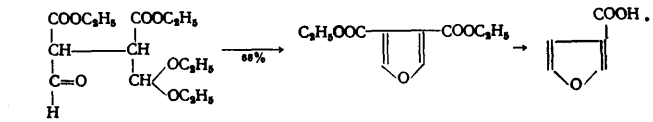
Compounds (XLI), (XLII), and (XLIII) were obtained for the first time by Yur'ev and Korobitsyn[129,130].

The last stage in the conversion of 3-phenyl-2,5-dihydrofuran (XLIV) into 3-phenylfuran, in 2–3% solution of sulphur in dimethylformamide, requires special attention. When 3-hexyl-2,5-dihydrofuran is treated similarly[128] with a solution of sulphur in dimethylformamide, the expected results are not achieved. This method is particularly interesting, since the attempt[128] to prepare 3-phenylfuran from 3-phenylfuran-2-carboxylic acid, synthesised by a standard method[131], proved unsuccessful.

3. The Removal of Two or One Substituents from Tri- and Di-substituted Furan Derivatives

The structure of furan-3-carboxylic acids isolated from a natural product was confirmed in 1932 by Reichstein[132], who obtained it by the decarboxylation of furan-2,3-dicarboxylic acid (see p. No. 401). A year later Reichstein prepared it[133] by the decarboxylation of furan-3,4-dicarboxylic acid. When furantetracarboxylic acid is heated to 270°C, furan-2,3,4-tricarboxylic and furan-3,4-dicarboxylic acids are formed. On heating with copper in quinoline, the latter yields furan-3-carboxylic acid.

Gilman showed[134] that furan-3-carboxylic acid can be obtained by the decarboxylation of furan-2,4-dicarboxylic acid. In connection with the development[135] of a relatively simple method for the synthesis of furan-3,4-dicarboxylic acid, consisting in the cyclisation of the diethyl ester of 2-diethoxymethyl-1-formylsuccinic acid (XLV), there arose the possibility of the direct synthesis[136] of furan-3-carboxylic acid:

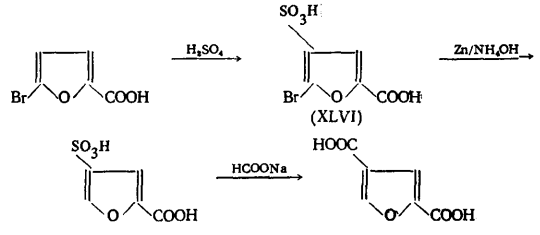


(XLV)

Probably this method is the most convenient preparative procedure.

3-Methylfuran has been obtained[19,20] by the decarboxylation of 4-methylfuran-2,3-dicarboxylic acid and also 3-methylfuran-2-carboxylic acid[131,137,138].

3-Nitrofuran was prepared by Rinkes[65] from 5-methyl-4-nitrofuran-2-carboxylic acid. Its decarboxylation yielded[77] 2-methyl-3-nitrofuran, which was oxidised to 4-nitrofuran-2-carboxylic acid, the latter being decarboxylated to 3-nitrofuran in 18% yield. Furan-3-sulphonic acid was also obtained[139] by the elimination of substituents from the α-positions of a trisubstituted furan, namely 5-bromo-4-sulphofuran-2-carboxylic acid (XLVI). The latter was synthesised for the first time by Hill and Palmer[140] by treating 5-bromofuran-2-carboxylic acid with fuming sulphuric acid. However, they did not establish which of the two β-positions was substituted by the sulpho-group. The structure of the acid (XLVI) was confirmed by Gilman[69] by means of reactions leading to the formation of the known furan-2,4-dicarboxylic acid:

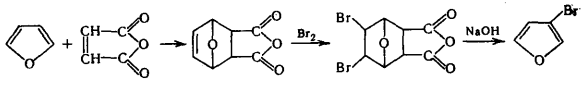


Treatment of compound (XLVI) with an equimolar amount of bromine by a standard method[141] yielded 2,5-dibromofuran-3-sulphonic acid[139], which was converted into furan-3-sulphonic acid by Hills method[140].

β-Halogenofurans may be obtained[53,142] by the removal of three halogen atoms from tetrahalogenofurans. However, this method cannot be regarded as convenient because of the difficulty of synthesising the starting materials and because the reaction products are obtained in low yields. 3-Bromofuran and 3-chlorofuran were obtained[143] from 4,5-dibromo-, 4,5-dichloro-, and 3,4-dichloro-furan-2-carboxylic acids by the action of zinc in aqueous ammonia followed by decarboxylation in quinoline in the presence of copper.

Certain doubts have been expressed about the method of preparation of 3-bromofuran[144]. They concerned the reproducibility of the yields in the bromine elimination stage. Consequently Gronowitz and Sorlin suggested that 3-halogenofuran, namely 3-iodofuran, be obtained from furan-2-carboxylic acid via 3-chloromercurifuran (see p. 397).

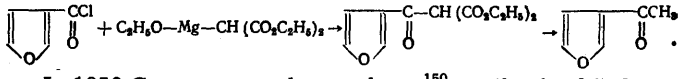
There exist also other indirect methods for the introduction of a halogen into position 3 of the furan ring, for example by the bromination of the adduct of furan and maleic anhydride[145]:



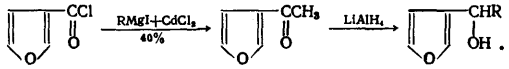
4. Syntheses Based on Furan-3-carboxylic Acid

Among the β-derivatives of furan, furan-3-carboxylic acid is the most readily available and the most frequently used starting material in various syntheses. The preparation from it of 2,4-disubstituted furan derivatives is described below (see p. 399). The syntheses of a number of β-monosubstituted furan derivatives, consisting in the conversion of the carboxy-group, will be examined here. Gilman obtained[134] furan-3-aldehyde by the Rosenmund reduction of the chloride of furan-3-carboxylic acid and the reduction of furan-3-aldehyde by the Wolff–Kishner method gave 3-methylfuran. Monosubstituted β-ketones, individual representatives of which are encountered in natural products[112,113,119], remained inaccessible for a very long time. Information[146] about their preparation included no data concerning the experimental conditions and the constants and analyses of the desired products. This made it difficult for other investigators to repeat the syntheses[147].

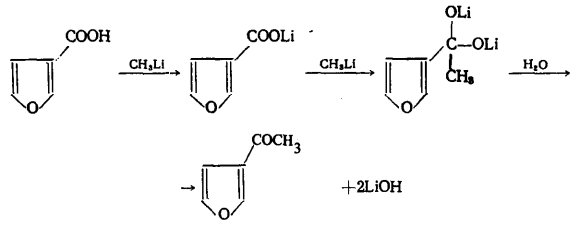
Kubota and Naya[148] obtained in 1956 3-acetylfuran in 86% yield by the Reynolds method[149] from the chloride of furan-3-carboxylic acid:



In 1959 Grunanger and coworkers[150] synthesised in low yields a number of alkyl 3-furyl ketones by the reaction of the chloride of furan-3-carboxylic acid with organocadmium compounds. The ketones were reduced to the corresponding alcohols in high yields:

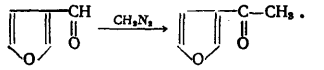


Somewhat later Gronowitz and Sorlin[147] obtained 3-acetylfuran from furan-3-carboxylic acid by Tegner's reaction[151] consisting in the interaction of methyl-lithium with carboxylic acids:

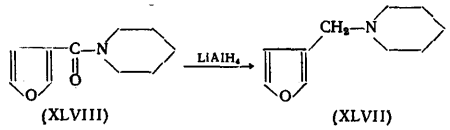


The constants of 3-acetylfuran (a crystalline compound) and its semicarbazone, quoted in these papers, agree, but differ from the data of Gilman et al.[146], who described 3-acetylfuran as liquid.

The work of Capuano[152], which has hardly any preparative value for the synthesis of 3-acetylfurans because its yield is too low, should also be mentioned:

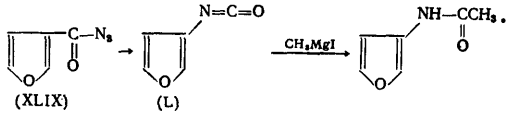


In connection with studies on the alkaloids of the yellow lily, *N*-(fur-3′-ylmethyl)piperidine (XLVII) was synthesised[136] by the reduction of *N*-(3-furoyl)piperidine (XLVIII):



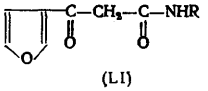
The history of one synthesis based on furan-3-carboxylic acid, namely the preparation of 3-acetamidofuran, is interesting. When this investigation was undertaken[153], the author could hardly suppose that subsequently it might prove to be of value for the demonstration of the structure

of a natural product. It was found that, when *N*-acetyl-D-glucosamine and *N*-acetyl-D-galactosamine, which form part of the polysaccharides of chitin and cartilage, were treated[154] with a solution of sodium carbonate, furan compounds were formed, one of which is 3-acetamidofuran. Its structure was confirmed[155] synthetically by repeating the Burtner synthesis[153]. Furan-3-carboxylic acid was converted into its chloride in 60% yield. Under the conditions specified by Naegeli and Stefanovitsch[156], the latter reacted with sodium azide to give 3-furoyl azide (XLIX) in 80% yield. Subsequently this azide was subjected to the Curtius rearrangement and was converted in 60% yield into the isocyanate (L), from which 3-acetamidofuran was obtained in 41% yield by the action of methylmagnesium iodide:



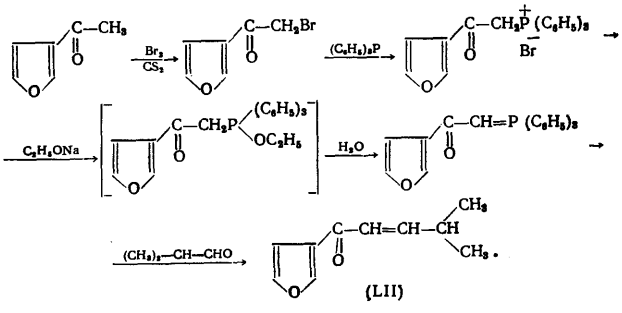
(XLIX) (L)

Starting from furan-3-carboxylic acid, Wul'fson and Kolchin[157] synthesised the substituted amides (LI) of 3-furoylacetic acid:



(LI)

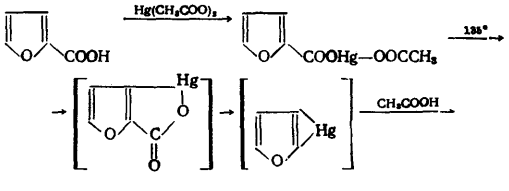
The synthesis of the ketone (LII) should also be mentioned[158]:

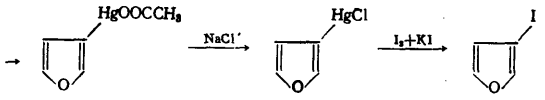


(LII)

5. Syntheses Based on Furan-2-carboxylic Acid

In 1933 Gilman and coworkers[53] showed that the reaction of mercuric chloride with the sodium salt of pyromucic acid results in decarboxylation, the chloromercuri-group entering the furan ring. When mercuric acetate is allowed to act on pyromucic acid under the conditions described by Pesci[159] with subsequent pyrolysis of the resulting mixed salt, 3-acetoxymercurifuran is obtained instead of the expected 2-acetoxymercurifuran. Thus here we are dealing with the *ortho*-rearrangement characteristic of aromatic mercury salts, although the reaction is in this case more complex and its mechanism cannot be regarded as established:





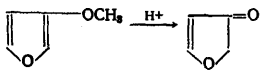
This synthesis is interesting because it permits the introduction of a substituent into the β-position of the furan ring, while leaving the α-positions free. In furan-3-carboxylic acid the carboxy-group cannot be replaced by the chloromercuri-group. The yield of 3-chloromercurifuran amounts to 15%, which was recently comparatively confirmed by other investigators[147,160], 3-Chloromercurifuran is an infusible compound insoluble in all solvents, which can be converted by treatment with an aqueous solution of iodine and potassium iodide into 3-iodofuran in 46% yield. Gilman also noted[53] that the attempt to prepare 3-acetylfuran by the action of acetyl chloride on 3-chloromercurifuran was unsuccessful. Gilman characterised 3-iodofuran as a much more stable compound than 2-iodofuran; it was shown that the iodine in this compound is not very labile. 3-Iodofuran did not react even with activated magnesium or lithium and underwent only partial exchange for the metal when acted upon by a sodium–potassium alloy.

The reactions of 3-chloromercurifuran were investigated in greater detail fairly recently by Gronowitz and Sorlin[147,160], who found that it is impossible to obtain 3-substituted furan derivatives by treating 3-chloromercurifuran with bromine, thiocyanogen, or acetyl chloride in benzene solution. In bromination experiments it was impossible to isolate the reaction products but it was established that the substitution takes place at a carbon–hydrogen bond and not an organometallic bond. Treatment with thiocyanogen gave a low yield of a mixture of 2- and 3-isomers in proportions of 4 : 1, which the authors also explained by the competition of reactions at the C–H bond in the active α-position and the C–Hg bond at the β-position in the ring. The product of the interaction of 3-chloromercurifuran with acetylchloride in benzene is 2-acetylfuran (yield 17%). Consequently 3-substituted furan derivatives can be obtained from 3-chloromercurifuran only by reaction with iodine and, as established by Bak et al.[161], with deuterium chloride.

The fact that in some cases an electrophilic agent attacks the reactive α-position of the five-membered heterocyclic compound more readily than the organometallic bond in the β-position was first discovered in the thiophen series. Namely, Gronowitz found[144] that, when 3-thienyl-lithium was acted upon by cadmium chloride and zinc chloride with subsequent treatment with acetyl chloride, a mixture of 55% of 2-acetylthiophen and 31% of 3-acetylthiophen was obtained.

Gronowitz and Sorlin also confirmed[147] and improved Gilman's results; in experiments designed to synthesise 3-iodofuran it proved possible to increase the yield from 46 to 75%; the scope of syntheses based on 3-iodofuran was also extended. In particular, it was shown that the iodine atom in 3-iodofuran is not as inert as was suggested by Gilman. It is sufficiently labile to undergo exchange for lithium in the reaction with alkyl-lithium in ethereal solution at −70°C. This permits the synthesis of new 3-substituted furan derivatives. When carbon dioxide, *NN*-dimethylformamide, and dimethyl disulphide were allowed to react with this organolithium compound, furan-3-carboxylic acid (yield 72%), furan-3-aldehyde (yield 38%), and fur-3-yl sulphide (yield 75%) were obtained respectively. Furthermore, it was shown[147] that, in contrast to 2-bromo- and 2-iodo-furan[162], 3-iodofuran

reacts with sodium methoxide in methanol in the presence of copper(II) oxide, forming 3-methoxyfuran in 65% yield. 3-(2*H*)-furanone (LIII) was synthesised by the acid hydrolysis of 3-methoxyfuran [163]:



(LIII)

The reaction of 3-iodofuran with copper cyanide in quinoline gave [147] 3-cyanofuran in 50% yield.

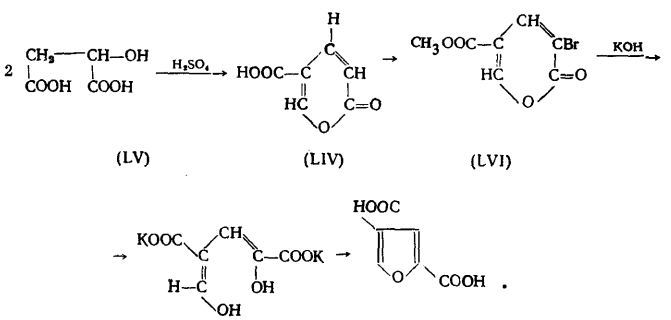
IV. METHODS OF SYNTHESIS OF 2,4-DISUBSTITUTED FURAN DERIVATIVES

The methods discussed below are mainly used to obtain 2,4-disubstituted furan derivatives.

1. Cyclisation of Certain Aliphatic Compounds

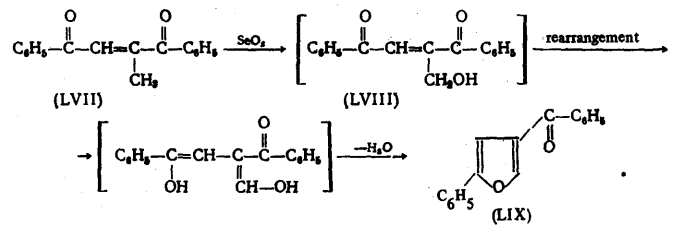
2,4-Disubstituted furans of various types are difficult to obtain, since the second electrophilic substituent usually enters the α'-position in the ring, forming 2,5-disubstituted furans regardless of the directing capacity of the group already present in the α-position. Only one rather difficult to explain case is known where in the reaction of isopropyl chloride with furfural in the presence of aluminium chloride the alkyl group enters the β'-position [79,164,165] (yield of 4-isopropylfurfural 11%). However, this is not a typical example and there is no doubt that it cannot be classified as a general method for the synthesis of 2,4-disubstituted furan. Usually, in order to obtain 2,4-disubstituted furans as well as the mono-3-substituted derivatives and 2,3-disubstituted derivatives, it is necessary to use rather inefficient "indirect" procedures. One of these is cyclisation by a suitable method of selected aliphatic compounds, the synthesis of which is often associated with considerable difficulties. We shall quote as an example the synthesis of furan-2,4-dicarboxylic acid [134] from malic acid via coumalic acid.

There exist also other methods [41] for the preparation of this acid, but they are used more rarely. Gilman [134] obtained coumalic acid (LIV) from malic acid (LV) by Pechman's synthesis [166], consisting in the treatment of malic acid with sulphuric acid; the acid (LIV) was then obtained in 60% yield. The methyl ester of the acid was further converted by the Feist reaction [167] into the ester of bromocoumalic acid (LVI) in 65% yield and the latter into furan-2,4-dicarboxylic acid in 50% yield:



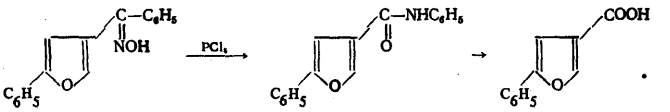
(LV) (LIV) (LVI)

The cyclisation of 1,2-dibenzoylprop-1-ene (LVII) in its oxidation with selenium dioxide also leads [168] to a 2,4-disubstituted furan—4-benzoyl-2-phenylfuran. The authors [168] suggest that initially the methyl group at the double bond is oxidised to an alcoholic group and the ketone (LIX) is formed from the alcohol (LVIII) as a result of a prototropic rearrangement with subsequent elimination of water:

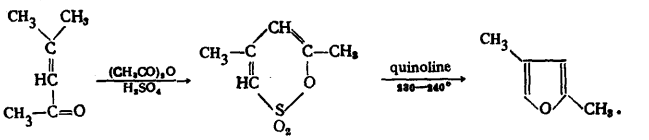


(LVII) (LVIII) (LIX)

The same workers [168] achieved the Beckmann rearrangement of the ketone oxime, which leads to 5-phenylfuran-3-carboxylic acid, a compound otherwise difficult to obtain:

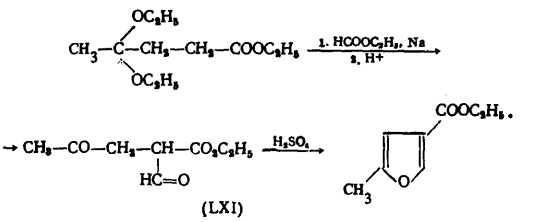


In 1948 Morell proposed [169] a novel synthesis of 2,4-disubstituted furans consisting in the heating of 3,5-dimethylsultone (LX) in quinoline. However, in view of the low availability of compound (LX) (low yields), this method can hardly be regarded as preparative:



(LX)

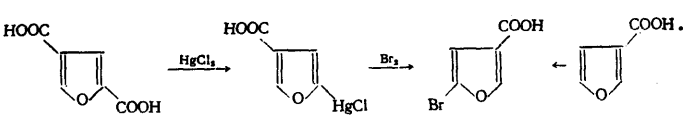
The synthesis of 5-methylfuran-3-carboxylic acid from levulinic acid [170] consists in the condensation of the diethyl ketal of levulinic acid with formic ester and subsequent cyclisation of the ester (LXI) by treatment with sulphuric acid:



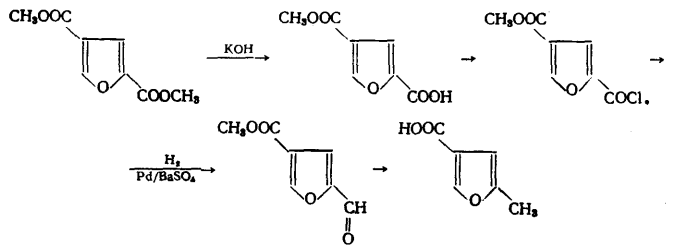
(LXI)

2. Reactions of Furan-2,4-dicarboxylic Acid

Despite the difficulties in its preparation, furan-2,4-dicarboxylic acid is regarded as the most readily available in the series of 2,4-disubstituted furans. A number of other 2,4-disubstituted derivatives were obtained by the conversion of its carboxy-groups. For example, by selective substitution of the α-carboxy group by a chloromercuri-group, Gilman and Burtner synthesised [134] 2-bromofuran-4-carboxylic acid in order to confirm the structure of the product formed on bromination of furan-3-carboxylic acid:

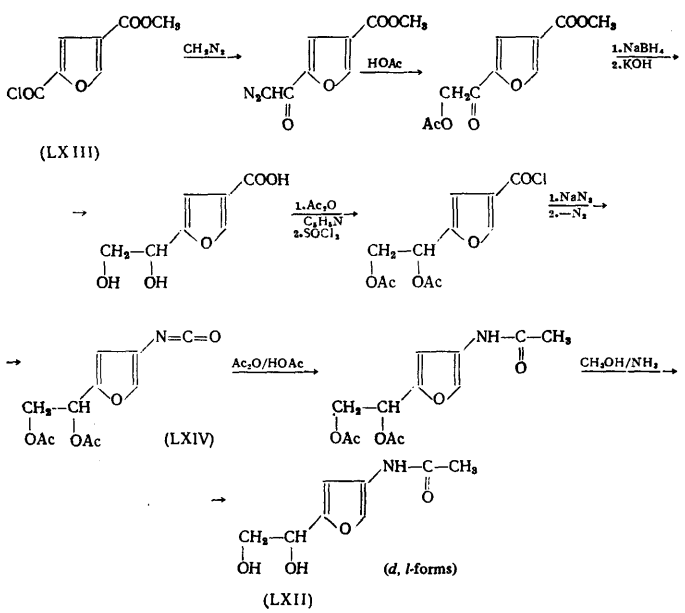


5-Methylfuran-3-carboxylic acid was also obtained[171] from furan-2,4-dicarboxylic acid:



This method is based on the more ready hydrolysis of the ester group of the diester in the α-position.

The difficulties which must be overcome in the synthesis of 2,4-disubstituted furans may be demonstrated by means of the following example: in order to confirm[154] the structure of "chromogen III" (LXII), isolated from natural products (chitin and the polysaccharides of cartilage), it was necessary to undertake a seven-stage synthesis. The seven stages, starting with malic acid and proceeding via coumalic and furan-2,4-dicarboxylic acids to the chloride of 4-methoxycarbonylfuran-2-carboxylic acid (LXIII), were described earlier[171]. Further stages[154] are illustrated by the following scheme:



In this synthesis the isocyanate (LXIV) was converted into 3-acetamido-5-diacetoxyethylfuran by a standard method[172] —by the action of a 1 : 1 mixture of acetic anhydride and acetic acid.

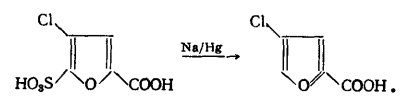
3. Electrophilic Substitution Reactions in the Series of Furans Substituted in the β-Position by *Meta*-directing Groups

Reactions of this kind are extremely rare. In 1933 Gilman[134] formulated the directing rule operating when a substituent enters the furan ring with an electronegative group in the β-position. For the nitration and bromination of furan-3-carboxylic acid and also furan-3-aldehyde as examples, it was shown that the site of substitution is the further removed α-position in the ring, as a result of which 2,4-disubstituted furans are produced.

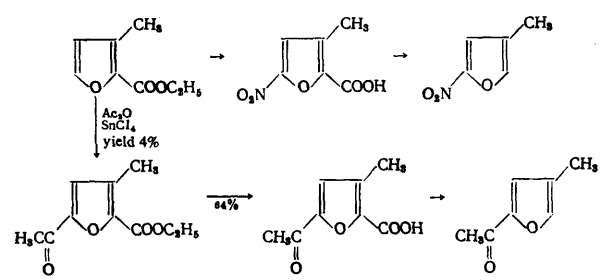
4. Elimination of One Substituent from Trisubstituted Furans

Probably the most widely used procedure employed in the synthesis of 2,4-disubstituted furans is the removal of certain groups, usually halogen atoms[62,69-71,73,74] and a carboxy-group[41,81,173] from trisubstituted furans. The reagents most often used to eliminate halogen atoms are zinc in acetic acid, alcoholic ammonia, or aqueous ammonia solutions, and sodium amalgam.

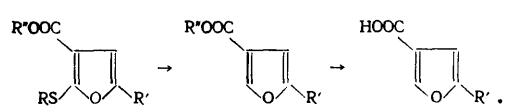
An example of the synthesis of a 2,4-disubstituted furan, namely 4-chlorofuran-2-carboxylic acid, by the elimination[70] of a sulpho-group has also been described:



It is noteworthy that 4-methyl-2-nitrofuran[81] and 2-acetyl-4-methylfuran[173] were obtained via a trisubstituted derivative starting with the relatively readily available 2,3-disubstituted derivative:

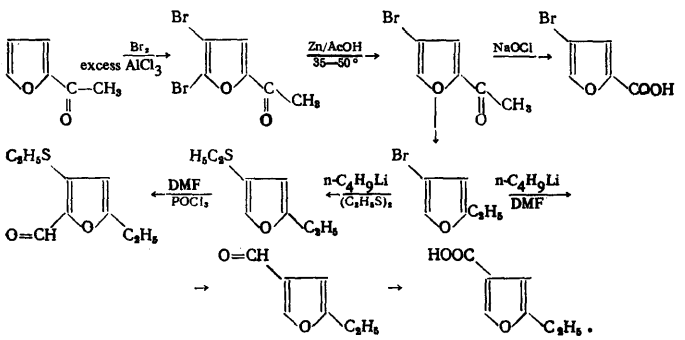


Recently a series of 2,4-disubstituted furans were prepared[58,174] by the elimination of a sulphide group from trisubstituted furans with the aid of Raney nickel:



The authors of the present review demonstrated for the first time the possibility of eliminating sulphide sulphur from furan derivatives by Raney nickel with preservation of the ring double bonds in the synthesis of 2,3-disubstituted furans[175] and proposed a method for the selective elimination of a bromine atom from the α-position in 2-acetyl-4,5-dibromofuran with zinc in acetic acid[176]. Under the conditions discovered, the keto-group and the bromine atom in the β-position do not undergo any changes. We were unable to find any literature data concerning the possibility of the elimination of a halogen atom from the furan ring while retaining the carbonyl group. Usually the latter, in particular in an aldehyde, is reduced to an alcoholic or a methyl group under the action of zinc in acetic acid[177] (a modification of the Clemmensen reaction).

Only Lutz and coworkers mention in one of their communications [178] the elimination by zinc in acetic acid of two bromine atoms from 3-(ω-dibromoacetyl)-2,5-diphenylfuran with retention of the keto-group. 2-Acetyl-4-bromofuran, which we obtained, is a key compound for the synthesis of many 2,4-disubstituted furans (bromides, sulphides, etc.):

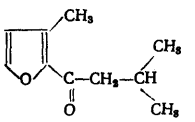


V. METHODS OF SYNTHESIS OF 2,3-DISUBSTITUTED FURAN DERIVATIVES

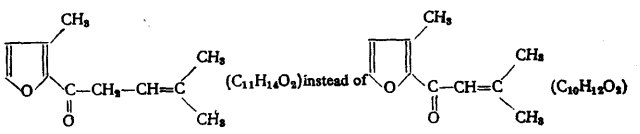
The known 2,3-disubstituted furans were obtained from certain natural products, by the cyclisation of aliphatic compounds into a furan system, the conversion of the carboxy- or methyl groups in 2-methylfuran-3-carboxylic and 3-methylfuran-2-carboxylic acids, by the elimination of one substituent from trisubstituted furans, mainly by the decarboxylation of acids, and by substitution of the available β-monosubstituted furans, mainly 3-methylfuran.

1. Isolation from Natural Products

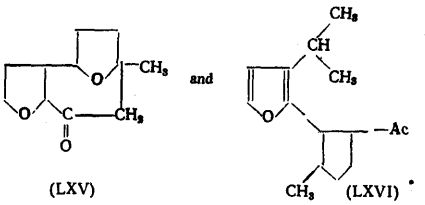
Most of the furan compounds encountered in nature are terpenoids [179]. Together with mono-β-substituted derivatives, a number of 2,3-disubstituted furans were isolated from natural products: 2-isovaleroyl-3-methylfuran [180],



"naginata ketone", and others. The "naginata-ketone" was detected for the first time in the essential oil of *Elsholtzia oldhami* by Fujita [181], who incorrectly attributed to it the structure

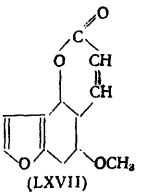


as established by Naves and Ochsner [182]. The structures of ipomeamarone [183] (LXV) and pelargone [184] (LXVI) from the essential oil of *Bourbon geranium*, which are also 2,3-disubstituted furan derivatives, were likewise elucidated:

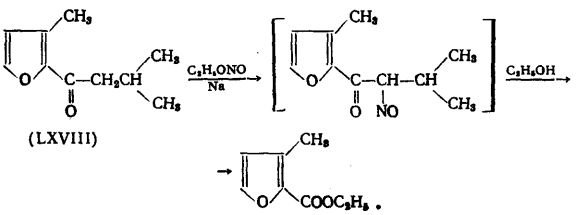


Isomaltol, isolated for the first time from bread by Back [185] and obtained recently by Hodge and coworkers [186] by appropriate treatment of lactose, is also a 2,3-disubstituted furan, namely 3-hydroxyfur-2-yl methyl ketone, as shown by Fischer and coworkers [187].

A substance called isobergaptene (LXVII) was isolated from the roots of *Pimpinella saxifraga* [188]. Its oxidation with hydrogen peroxide in alkaline solution gave furan-2,3-dicarboxylic acid:

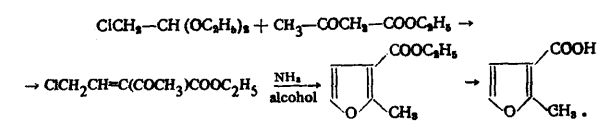


When ethyl nitrite and sodium were allowed to react with isobutyl 3-methylfur-2-yl ketone (LXVIII), isolated from the essential oil of a member of the labiatae (*Elsholtzia Cristata wild*), the ketone decomposed with formation of the ester of 3-methylfuran-2-carboxylic acid [137]:



2. Cyclisation of Aliphatic Compounds into the Furan System

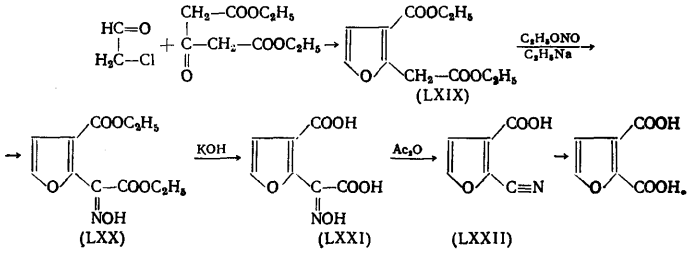
There exist several methods of synthesis for 2-methylfuran-3-carboxylic acid. The method of Plancher and Albini [189] is inconvenient, since the interaction of chloroethylideneacetoacetic ester with alcoholic ammonia was carried out in a sealed tube; the authors did not state the yield:



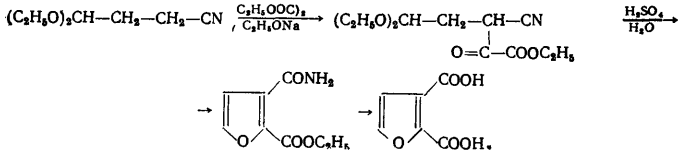
Benary [18] obtained the ester of this acid as an admixture with the ethyl ester of 2-methylpyrrole-3-carboxylic acid by the reaction of chloroacetaldehyde with acetoacetic ester in an ammoniacal medium. Gilman, who repeated the study [89], notes that the yield of 2-methylfuran-3-carboxylic acid is 40%.

There is also mention [69,96] of other methods of synthesis of the acid. As a rule, they consist of many stages and

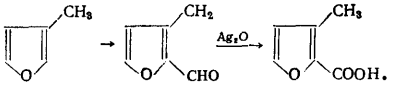
reduce to the decarboxylation of 5-methylfuran-2,4-dicarboxylic acid. Reichstein [132] also used the Benary method to prepare furan-2,3-dicarboxylic acid. He synthesised in 18% yield the ethyl ester of 3-ethoxycarbonylfuran-2-acetic acid (LXIX) by the condensation of chloroacetaldehyde with the diethyl ester of acetonedicarboxylic acid in the presence of ammonium hydroxide. Further reactions of the ester (LXIX) reduced to the synthesis of the oxime (LXX) and its subsequent conversion via compound (LXXI) and the nitrile (LXXII) into furan-2,3-dicarboxylic acid:



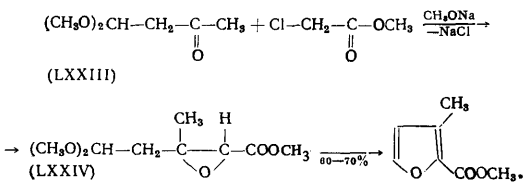
Later furan-2,3-dicarboxylic acid was obtained [170] from 4,4-diethoxybutyronitrile [190]:



As already mentioned above, 3-methylfuran-2-carboxylic acid was obtained for the first time from the natural ketone (LXVIII). Reichstein synthesised this acid from 3-methylfuran [90]:



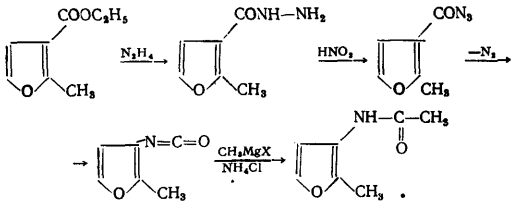
In 1956 Burness [131,138] proposed a new synthesis for 3-methylfuran-2-carboxylic acid whereby the latter became quite readily available. In this procedure the starting compound is the dimethyl acetal of formylacetone (LXXIII), which is converted quantitatively by the Darzens method, by the reaction with methyl monochloroacetate, into the glycidic ester (LXXIV), the distillation of which at 160°C leads to the methyl ester of 3-methylfuran-2-carboxylic acid:



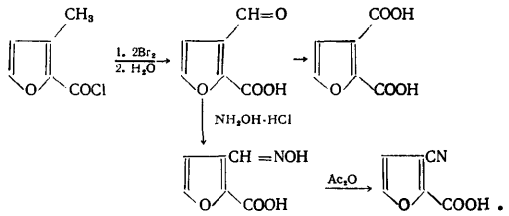
3-Phenylfuran-2-carboxylic acid was obtained similarly [138].

3. Reactions of 2-Methylfuran-3-carboxylic and 3-Methylfuran-2-carboxylic Acids

Although 2-methylfuran-3-carboxylic acid is essentially rather difficult to obtain, certain important studies have been carried out on its basis. Here we shall mention the synthesis [153] of 3-acetamido-2-methylfuran:

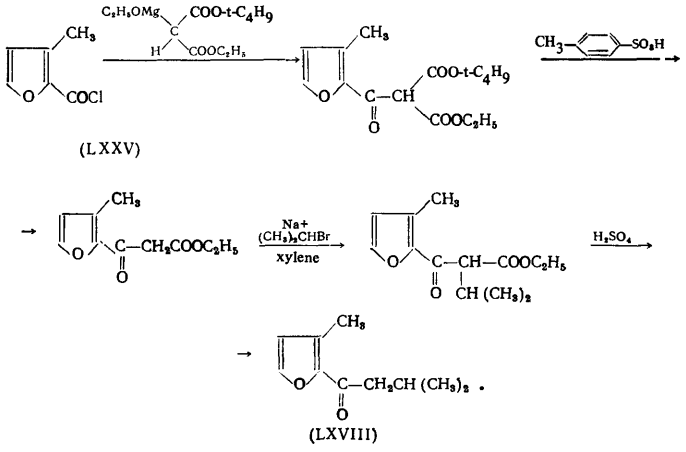


The isomeric 3-methylfuran-2-carboxylic acid has been much more widely used as a starting material for a wide variety of reactions. Asahina and Murayama [137], who obtained 3-methylfuran-2-carboxylic acid for the first time, synthesised from it certain 2,3-disubstituted furans. By the reaction of two moles of bromine with the chloride of this acid in direct sunlight at 130°C and subsequent hydrolysis, they obtained 3-formylfuran-2-carboxylic acid. On oxidation with silver oxide, the latter yielded furan-2,3-dicarboxylic acid:



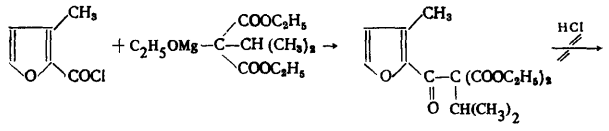
3-Cyanofuran-2-carboxylic acid was synthesised from the aldehydo-acid via the oxime.

In recent years there has been a considerable increase of interest in 3-methylfuran-2-carboxylic acid as a starting material. Ketones detected in natural products have been prepared from it. In 1963 Finan and Forthergill [191] synthesised the "Elsholtzia ketone" (LXVIII) in 50% yield using the acid chloride (LXXV) as the starting material:

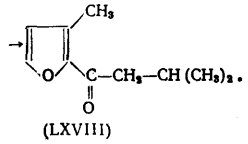


The attempts [191] to modify somewhat this synthesis in connection with data [192] concerning a new method for the preparation of the "perilla ketone" proved to be fruitless. Following the procedure of the Japanese investigators but using the acid chloride (LXXV) instead of the chloride of furan-3-carboxylic acid, Finan and Fothergill [191] condensed the acid chloride with the ethoxymagnesium derivative of

the diethyl ester of α-isopropylmalonic acid, but the ester (LXXVI) could not be cleaved to yield the ketone (LXVIII):

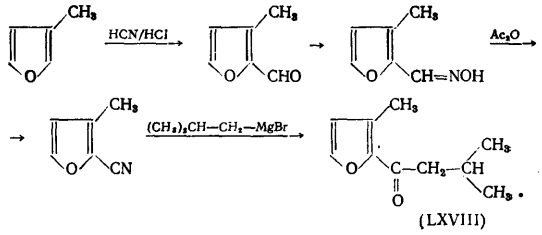


(LXXV) (LXXVI)



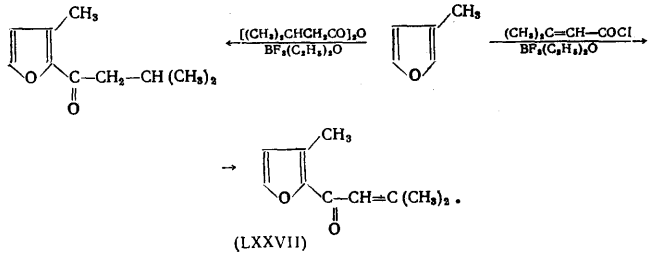
(LXVIII)

This finding is consistent with the observations of some workers [193,194], who showed that on treatment with an acid the diethyl esters of alkylated α-acylmalonic acid are not split with the formation of ketones. The structure of the "Elsholtzia ketone" (LXVIII) was confirmed for the first time in 1931 by Reichstein, who obtained it from 3-methylfuran in a low yield by the following procedure [90]:



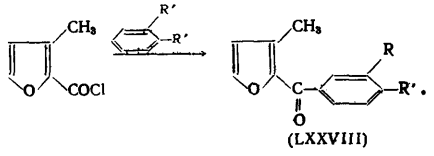
(LXVIII)

We may also mention here the formation of this ketone [173] in 30% yield when 3-methylfuran, which has become quite readily available, is acted upon by the anhydride of isovaleric acid. Some of its homologues have been synthesised similarly. The same workers obtained the "naginata ketone" (LXXVII) in 40% yield [195]:



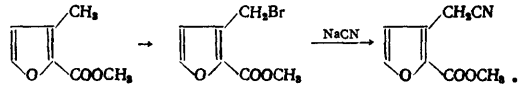
(LXXVII)

Leditschke [196] synthesised the hitherto unknown aryl 3-methylfur-2-yl ketones (LXXVIII) by the acylation of aromatic hydrocarbons with the chloride of 3-methylfuran-2-carboxylic acid:



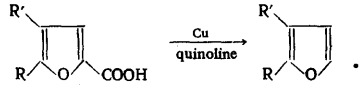
(LXXVIII)

Fairly recently the methyl ester of 3-bromomethylfuran-2-carboxylic acid was obtained [197] in a satisfactory yield by the reaction of *N*-bromosuccinimide with the methyl ester of 3-methylfuran-2-carboxylic acid in the presence of a radical-reaction initiator:

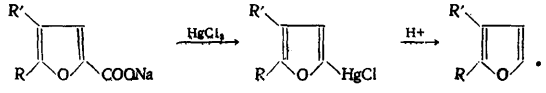


4. Elimination of One Substituent from Trisubstituted Furan Derivatives

The syntheses of 2,3-disubstituted furans from trisubstituted derivatives reduce to the reductive elimination of a halogen atom from certain trisubstituted furans [73,89] and decarboxylation [65,67,69,79,80,88,89,96,134,198–200] of the corresponding furan-2-carboxylic acid:



In the decarboxylation the authors [134] employed a method involving the intermediate replacement of the carboxy-group by a chloromercuri-group, which was subseqently eliminated by treatment with acid:



5. Substitution Reactions of Certain β-Monosubstituted Furan Derivatives

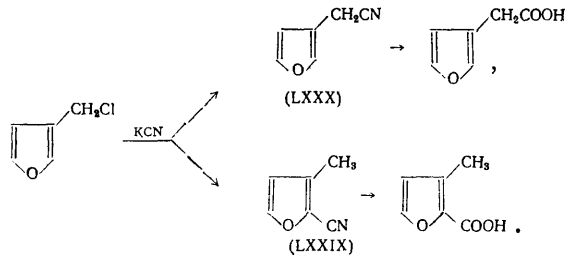
Until Gilman formulated the directing rule for mono-β-substituted furans in reactions involving the introduction of an electrophilic substituent into the ring [134,201], there existed only one example of reactions of this kind: the formylation [90] of 3-methylfuran by the Gattermann–Koch method. Having somewhat extended the number of mono-β-substituted furan derivatives, Gilman showed [134] that, when the existing β-group is *ortho*, *para*-directing in the benzene series, the new substitutent is directed to the adjacent α-carbon atom, forming 2,3-disubstituted furan; on the other hand, if the β-group is *meta*-directing, the new group forms a 2,4-disubstituted furan.

Gilman achieved the nitration of 3-methylfuran [134] and the chloromercuration of 3-methylfuran [201] and 3-isopropylfuran [79] with formation of the corresponding 2,3-disubstituted furans.

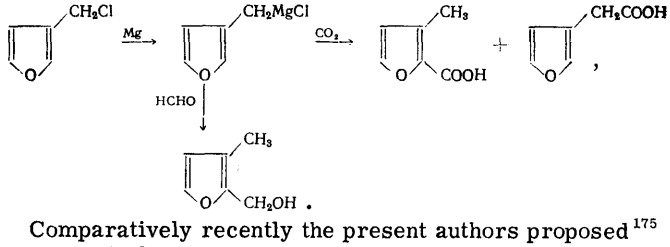
In view of the ready availability of 3-methylfuran, recently electrophilic substitution reactions with this compound have been carried out again, namely acylation [173] and bromination [197]. When 3-methylfuran was brominated with one mole of *N*-bromosuccinimide without a radical-reaction initiator, 2-bromo-3-methylfuran was obtained. When the amount of the brominating agent was varied, then, depending on the presence or absence of a radical-reaction initiator, various bromination products were obtained: with bromine either in the α-position of the furan ring or in the methyl group.

Sherman and Amstutz [202] made an interesting observation, namely that 2,3-disubstituted furan is formed as a result of the allyl rearrangement of certain β-monosubstituted furans of 3-chloromethylfuran under the action of

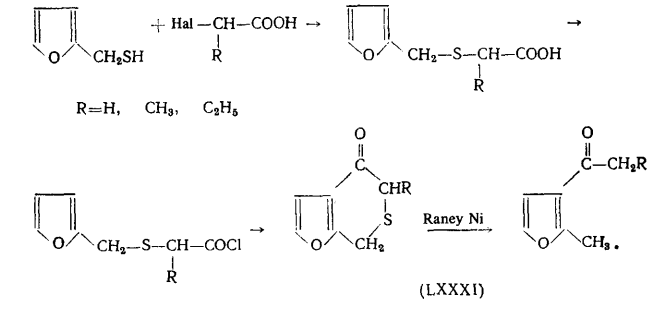
an aqueous solution of potassium cyanide and of fur-3-yl-methylmagnesium chloride under the action of carbon dioxide and formaldehyde. In the first case the product of the allyl rearrangement—3-methyl-2-furonitrile (LXXIX) —is formed only as an impurity in the main product fur-3-ylacetonitrile (LXXX):



In the second case the main product is 3-methylfuran-2-carboxylic acid (90% yield) or 3-methylfurfuryl alcohol (33% yield) is obtained as the sole product:



Comparatively recently the present authors proposed[175] a new method for the synthesis of 2,3-disubstituted furans —allyl 2-methylfur-3-yl ketones. It consists in the formation from the readily available 2-substituted furans of bicyclic condensed systems with a "bridge" between the second and third positions in the furan ring incorporating a sulphur atom in one of the units. This unit, separated from the ring by carbon atoms, is eliminated in the next stage by Raney nickel. The elimination of sulphite sulphur from the side chain by Raney nickel takes place without appreciable reduction of the furan ring to the tetrahydrofuran derivative:



In the course of the synthesis of 2,3-disubstituted furans a new condensed bicyclic compound (LXXXI) was obtained and some of its properties were investigated.

REFERENCES

1. H. Gilman and G. F. Wright, Chem. Rev., **11**, 323 (1932).
2. M. C. Dodd, D. E. Cramer, and W. C. Ward, J. Amer. Pharm. Assoc., **39**, 313 (1950).
3. E. S. West, J. Biol. Chem., **74**, 561 (1927); Chem. Zentr., I, 485 (1928).
4. F. G. Gonzales, J. Fernandez-Bolanos, and A. M. Perez de Gozman, Anal. Real. Soc. Espan. Fis Quim (Madrid), **60** (B), 339 (1964); Chem. Abs., **62**, 7714b (1965).
5. L. K. Dalton, Austral. J. Chem., **17**, 1174 (1964); Chem. Abs., **62**, 3991h (1965).
6. T. Reichstein and A. Grüssner, Helv. Chim. Acta, **16**, 6 (1933).
7. C. D. Hurd and K. Wilkinson, J. Amer. Chem. Soc., **70** 739 (1948).
8. V. A. Barkhash and O. I. Andreevskaya, Dokl. Akad. Nauk SSSR, **166**, 1343 (1966).
9. T. Reichstein, Helv. Chim. Acta, **16**, 276 (1933).
10. H. Sutter, Annalen, **499**, 47 (1932).
11. R. Fittig, Annalen, **250**, 166 (1883).
12. T. Reichstein and A. Grüssner, Helv. Chim. Acta, **16**, 6 (1933); quoted after R. C. Elderfield (Editor), "Heterocyclic Compounds" (Translated into Russian), Inostr. Lit., Moscow, 1953, Vol. I, p. 102.
13. H. Gault, E. Gordon-Ginette, and M. Selim, French P. 1 185 403 (1959).
14. G. H. Suverkropp and H. Wynberg, Chem. Ind., 1803 (1963).
15. R. Levine, J. V. Heid, and M. W. Farrer, J. Amer. Chem. Soc., **71**, 1207 (1949).
16. Z. F. Stefanovskaya, V. V. Dorofeev, and I. A. Trefil'ev, Zhur. Obshch. Khim., **11**, 518 (1951).
17. F. Feist, Ber., **35**, 1548 (1902).
18. E. Benary, Ber., **44**, 493 (1911).
19. T. Reichstein and H. Zschokke, Helv. Chim. Acta, **14**, 1270 (1931).
20. I. J. Rinkes, Res. Trav. chim., **50**, 1127 (1931); Chem. Abs., **26**, 1279 (1932).
21. F. Boberg and I. R. Schultze, Ber., **90**, 1215 (1957).
22. A. R. Surrey, "Name Reactions in Organic Chemistry" (Translated into Russian), Gos. Nauch.-Tekh. Izd. Khim. Lit., Moscow, 1962, p. 195.
23. A. Bayer and W. H. Perkin, Ber., **17**, 61 (1884).
24. S. P. Mulliken, Amer. Chem. J., **15**, 523 (1893); Chem. Zentr., II, 562 (1893).
25. C. U. Zanetti, Atti R. Accad. Lincei Roma (5), **2** (1), 564 (1893); Chem. Zentr., II, 568 (1893).
26. I. A. Trefil'ev and E. V. Lifanov, Zhur. Obshch. Khim., **11**, 182 (1941).
27. D. Weis, U. S. P. 3 125 584 (1964); Chem. Abs., **61**, 6991 (1964).
28. A. Hoffmann and C. H. Eugster, Helv. Chim. Acta, **49**, 53 (1966).
29. R. E. Lutz and C. E. McGinn, J. Amer. Chem. Soc., **64**, 2585 (1942).
30. I. M. Heilbron, E. R. H. Jones, P. Smith, and B. C. L. Weedon, J. Chem. Soc., 54 (1946).
31. K. Bowden, E. A. Braude, E. R. H. Jones, and B. C. L. Weedon, J. Chem. Soc., 45 (1946).
32. J. B. Hendrickson, R. Rees, and J. E. Templeton, J. Amer. Chem. Soc., **86**, 107 (1964).
33. K. Gewald, Chem. Ber., **99**, 1002 (1966).
34. G. Westöö, Acta chem. Scand., **13**, 692 (1959).
35. T. I. Temnikova and R. N. Kovalevskaya, Zhur. Obshch. Khim., **1**, 612 (1965).
36. W. Reid and W. Bodenstedt, Annalen, **667**, 96 (1963).
37. F. Feist, Ber., **26**, 747 (1893).
38. A. T. Balaban and C. D. Nenitzescu, Ber., **93**, 599 (1960).
39. F. Quint, R. Pütter, and W. Dilthey, Ber., **71**, 356 (1938).
40. C. Paal and H. Schulze, Ber., **36**, 2425 (1903).
41. T. Reichstein and A. Grüssner, Helv. Chim. Acta, **16**, 555 (1933).

42. F. Wessely and E. Nadler, Monatsh. Chem., 60, 141 (1932); Chem. Zentr., II, 2196 (1932).
43. H. H. Freedman and G. A. Doorkian, Tetrahedron, 20, 2181 (1961).
44. F. Korte and K. H. Büchel, Angew. Chem., 71, 709 (1959).
45. K. Adler and H. F. Rickert, Ber., 70, 1354 (1937).
46. N. Elming, J. T. Nielsen, and N. K. F. W. Clauson-Kaas, U. S. P. 2 839 539 (1958); Chem. Abs., 53, 9248e (1959).
47. M. Lamant, L. M. Gomes, and O. Riobe, Compt. rend., 259, 1740 (1964).
48. M. L. Mavoungou-Gomes, Bull. Soc. chim. France, 1764 (1967).
49. M. L. Mavoungou-Gomes, Compt. rend., 265, 677 (1967).
50. T. Kubota and T. Tokoroyama, Chem. Ind., 1298 (1957).
51. C. D. Weis, J. Org. Chem., 27, 3520 (1962).
52. T. Kubota and T. Matsuura, Proc. Chem. Soc., 262 (1957); Chem. Abs., 52, 10114c (1958).
53. H. Gilman and G. F. Wright, J. Amer. Chem. Soc., 55, 3302 (1933).
54. H. Gilman and R. R. Burtner, Rec. Trav. chim., 51, 667 (1932).
55. H. Gilman and R. V. Young, Rec. Trav. chim., 51, 761 (1932).
56. A. P. Terent'ev and L. A. Kazitsyna, Dokl. Akad. Nauk SSSR, 55, 625 (1947).
57. R. C. Elderfield (Editor), "Heterocyclic Compounds", Vol. 1, "Three- Four-, Five-, and Six-membered Monocyclic Compounds Containing one O, N, and S Atom" (Translated into Russian), Inostr. Lit., Moscow, 1953, p. 120.
58. Ya. L. Gol'dfarb, Ya. L. Danyushevskii, and M. A. Vinogradova, Dokl. Akad. Nauk SSSR, 151, 331 (1963).
59. H. Gilman, "Organic Chemistry", New York, John Wiley, 1944, p. 551.
60. H. Gilman and R. J. V. Wal, Rec. Trav. chim., 52, 267 (1933); Chem. Abs., 27, 2952 (1933).
61. A. Klinkhardt, J. prakt. Chem., 25, 41 (1882); Chem. Zentr., 167 (1882).
62. I. K. Phelps and W. I. Hall, Amer. Chem. J., 25, 445 (1901).
63. H. B. Hill, Amer. Chem. J., 25, 439 (1901).
64. I. J. Rinkes, Rec. Trav. chim., 51, 349 (1932); Chem. Abs., 26, 2455 (1932).
65. I. J. Rinkes, Rec. Trav. chim., 57, 390 (1938); Chem. Abs., 32, 4980 (1938).
66. H. B. Hill and W. L. Jennings, Amer. Chem. J., 15, 158 (1893).
67. A. L. Mndzhoyan and M. T. Grigor'yan, "Sintezy Geterotsiklicheskikh Soedinenii" (Syntheses of Heterocyclic Compounds), Izd. Akad. Nauk Arm. SSR, Erevan, 1957, Vol. 2, pp. 30, 32, 47.
68. A. L. Mndzhoyan, V. T. Afrikyan, et al., Izv. Akad. Nauk Arm. SSR, Khim. Nauki, 15, 391 (1962); Ref. Zhur. Khim., 9Zh173 (1963).
69. H. Gilman, N. O. Calloway, and E. W. Smith, J. Amer. Chem. Soc., 56, 220 (1934).
70. H. B. Hill and W. S. Hendrickson, Amer. Chem. J., 15, 145 (1893).
71. H. Gilman and R. R. Burtner, J. Amer. Chem. Soc., 57, 909 (1935).
72. H. B. Hill and C. R. Sanger, Annalen, 232, 67 (1885).
73. H. B. Hill and L. L. Jackson, Amer. Chem. J., 12, 22 (1890).
74. T. Okusumi, J. Chem. Soc. Japan, 79, 1366 (1958); Ref. Zhur. Khim., 13401 (1960).
75. H. Gilman and G. F. Wright, Iowa State Coll. J. Sci., 5, 85 (1931); Chem. Zentr., I, 3687 (1931).
76. W. W. Beck and C. S. Hamilton, J. Amer. Chem. Soc., 60, 620 (1938).
77. I. J. Rinkes, Rec. Trav. chim., 51, 349 (1932); Chem. Abs., 26, 2455 (1932).
78. T. Sasaki, Bull. Inst. chem. Res., 33, 39 (1955); Chem. Zentr., 13340 (1957).
79. H. Gilman, N. O. Calloway, and R. R. Burtner, J. Amer. Chem. Soc., 57, 906 (1935).
80. M. Janda and P. Novak, Coll. Czech. Chem. Comm., 29, 1731 (1964).
81. I. J. Rinkes, Rec. Trav. chim., 51, 981 (1931); Chem. Zentr., I, 66 (1932).
82. Ya. L. Gol'dfarb and L. D. Tarasova, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 1304 (1960).
83. Ya. L. Gol'dfarb and L. D. Tarasova, Izv. Akad. Nauk SSSR, Ser. Khim., 1079 (1965).
84. Z. N. Nazarova, Zhur. Obshch. Khim., 24, 575 (1954).
85. H. Gilman and G. F. Wright, J. Amer. Chem. Soc., 52, 1170 (1930).
86. H. Bauer, J. Amer. Chem. Soc., 73, 5862 (1951).
87. H. Gilman and R. R. Burtner, J. Amer. Chem. Soc., 71, 1213 (1949).
88. T. Reichstein and A. Grüssner, Helv. Chim. Acta, 16, 28 (1933).
89. H. Gilman, R. R. Burtner, and E. W. Smith, Rec. Trav. chim., 51, 407 (1932); Chem. Zentr., I, 3177 (1932).
90. T. Reichstein, H. Zschokke, and A. Georg, Helv. Chim Acta, 14, 1277 (1931).
91. H. B. Hill and A. W. Palmer, Amer. Chem. J., 10, 373 (1888).
92. A. L. Mndzhoyan, V. T. Afrikyan, and G. A. Papayan, USSR P. 157695 (1963); Chem. Abs., 60, 6827b (1964); Byull. Izobret., No. 19, 22 (1963).
93. A. L. Mndzhoyan, V. T. Afrikyan, A. E. Kalaidzhyan, L. Z. Kazaryan, and E. A. Markaryan, Izv. Akad. Nauk SSSR, Ser. Khim., 175 (1963).
94. A. L. Mndzhoyan, E. A. Markaryan, L. P. Solomina, and A. E. Kalaidzhyan, Izv. Akad. Nauk Arm. SSR, Ser. Khim., 17, 89 (1964).
95. A. L. Mndzhoyan, E. A. Markaryan, N. E. Akopyan, and L. P. Solomina, Izv. Akad. Nauk Arm. SSR, Ser. Khim., 18, 397 (1965).
96. M. Valenta and M. Janda, Coll. Czech. Chem. Comm., 29, 1577 (1964).
97. M. Janda and P. Novak, Coll. Czech. Chem. Comm., 29, 1731 (1964); Chem. Abs., 61, 6977c (1964).
98. K. Yu. Novitskii, Yu. K. Ur'ev, V. N. Zhingareva, and Kh. Gresl', Zhur. Obshch. Khim., 34, 2568 (1964).
99. K. Yu. Novitskii, G. T. Khachaturova, M. A. Gal'-bershtam, I. I. Kandror, and Yu. K. Ur'ev, Vestnik Moskov. Gos. Univ., Ser. II, Khim., No. 6, 63 (1964).
100. J. G. Michels, G. Gever, and P. H. L. Wei, J. Med. Pharm. Chem., 5, 1042 (1962).
101. N. I. Shuikin and I. F. Bel'skii, USSR P. 157977 (1963); Byull. Izobret., No. 20, 13 (1963).
102. K. Thewalt, Chem. Ber., 98, 3092 (1965).
103. R. C. Fuson, H. S. Killam, and W. S. Smith, J. Org. Chem., 27, 3355 (1962).
104. Ya. L. Gol'dfarb, M. A. Kalik, and M. L. Kirmalova, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 701 (1962).
105. Ya. L. Gol'dfarb and Ya. L. Danyushevskii, Izv. Akad. Nauk SSSR, Ser. Khim., 1345 (1964).
106. L. D. Tarasova and Ya. L. Gol'dfarb, Izv. Akad. Nauk SSSR, Ser. Khim., 2013 (1965).

107. A. P. Dunlop and F. N. Peters, "The Furans", New York, 163 (1953).
108. S. A. Giller and A. E. Berzin', Izv. Akad. Nauk Latv. SSR, Ser. Khim., 103 (1962).
109. N. I. Shuikin, B. L. Lebedev, et al., Izv. Akad. Nauk SSSR, Ser. Khim., 1618 (1967).
110. H. Rogerson, J. Chem. Soc., **101**, 1044 (1912).
111. F. B. Powers and A. H. Salway, Pharm. J., [4], **36**, 550 (1913).
112. R. Goto, J. Pharm. Soc. Japan, **57**, 77 (1937); Chem. Abs., **31**, 4056 (1937).
113. V. Sebe, J. Chem. Soc. Japan, **64**, 1130 (1943); Chem. Abs., **41**, 3785 (1947).
114. H. Kondo and H. Susuki, Ber., **69**, 2459 (1936).
115. R. L. N. Rao, J. Sci. Ind. Res. (India), **7** (B), 11 (1948); Chem. Abs., **42**, 5900b (1948).
116. T. Kubota and K. Naya, Chem. Ind., 1427 (1954).
117. T. Kubota, T. Matsuura, and N. Ichikawa, Chem. Ind., 902 (1954).
118. T. Kubota and T. Matsuura, Bull. Chem. Soc. Japan, **31**, 491 (1958); Chem. Abs., **53**, 8102f (1959).
119. T. Ueda and Y. Fujita, Chem. Ind., 1618 (1962).
120. W. Cocker, B. E. Cross, S. R. Duff, J. T. Edward, and T. F. Holley, J. Chem. Soc., 2540 (1953).
121. W. Cocker and P. H. Boyle, J. Chem. Soc., 972 (1964).
122. Z. Valenta and A. Khaleque, Tetrahedron Letters, No. 12, 1 (1959).
123. C. R. Narayanan and R. V. Pachapurkar, Tetrahedron Letters, 553 (1966).
124. J. D. Connolly, R. McCrindle, and K. H. Overton, Chem. Comm., 8, 162 (1965).
125. P. Karrer, "Lehrbuch der organischen Chemie" (Translated into Russian), Goskhimizdat, Moscow, 1966, p. 326.
126. F. Korte, R. Heinz, and D. Scharf, Ber., **94**, 825 (1961).
127. J. W. Cornforth, J. Chem. Soc., 1310 (1958).
128. H. Wynberg, J. Amer. Chem. Soc., **80**, 364 (1958).
129. Yu. K. Yur'ev, E. M. Lukina, and I. K. Korobitsyna, Zhur. Obshch. Khim., **24**, 1238 (1954).
130. Yu. K. Yur'ev, I. K. Korobitsyna, and L. A. Savina, Dokl. Akad. Nauk SSSR, **86**, 91 (1952).
131. "Organic Syntheses", NewYork, 1950, Vol. 39, p. 46.
132. T. Reichstein and H. Zschokke, Helv. Chim. Acta, **15**, 268 (1932).
133. T. Reichstein, A. Grüssner, K. Schindler, and E. Harndmeier, Helv. Chim. Acta, **16**, 276 (1933).
134. H. Gilman and R. R. Burtner, J. Amer. Chem. Soc., 55, 2903 (1933).
135. E. C. Kornfeld and R. G. Jones, J. Org. Chem., **19**, 1671 (1954).
136. K. Galuszko and J. T. Wrobel, Roczniki Chem., **38**, 511 (1964); Ref. Zhur. Khim., 2Zh258 (1965).
137. V. Asahina et al., Acta phytochim., **2**, 1(1924): Chem. Abs., **19**, 1139 (1925).
138. D. M. Burness, J. Org. Chem., **21**, 102 (1956).
139. R. O'Cinneide, Nature, **160**, 260 (1947): Chem. Abs., 42, 165e (1948).
140. H. B. Hill and A. W. Palmer, Amer. Chem. J., **10**, 413 (1888).
141. H. B. Hill and I. P. Sylvester, Amer. Chem. J., **32**, 185 (1904).
142. R. Ciusa and G. Grilla, Gazzetta., **57**, 323 (1927); Chem. Zentr., 931 (1927).
143. A. F. Shepard, N. R. Winslow, and J. R. Johnson, J. Amer. Chem. Soc., **52**, 2083 (1930).
144. S. Gronowitz, Arkiv Kemi, **12**, 533 (1958).
145. W. W. Lewis, U. S. P. 2 773 882 (1956); Chem. Abs., **51**, 8803i (1957).
146. H. Gilman, B. L. Wooley, and G. F. Wright, J. Amer. Chem. Soc., **55**, 2609 (1933).
147. S. Gronowitz and G. Sorlin, Arkiv Kemi, **19**, 515 (1962).
148. T. Kubota and K. Naya, J. Chem. Soc. Japan, **77**, 86 (1956); Chem. Abs., **52**, 347 (1958).
149. G. A. Reynolds and C. R. Hauser, Org. Synthes., **30**, 70 (1950).
150. P. Grunanger and A. Mantegani, Gazzetta, **89**, 913 (1959).
151. C. Tegner, Acta Chem. Scand., **6**, 782 (1952); Chem. Abs., **47**, 8013g (1953).
152. L. Capuano, Ber., **94**, 302 (1961).
153. R. R. Burtner, J. Amer. Chem. Soc., **56**, 666 (1934).
154. R. Kuhn and G. Krüger, Ber., **90**, 264 (1957).
155. R. Kuhn and G. Krüger, Ber., 1475 (1956).
156. C. Naegeli and G. Stefanovitsch, Helv. Chim. Acta, **11**, 609 (1928).
157. N. S. Wul'fson and V. E. Kolchin, Zhur. Obshch. Khim., **29**, 3760 (1960).
158. R. A. Massy-Westropp and G. D. Reynolds, Austral. J. Chem., **19**, 891 (1966); Chem. Abs., **65**, 2193c (1966).
159. L. Pesci, Atti R. Accad. Lincei Roma, [5], **10**, 1, 362 (1901); Chem. Zentr., II, 108 (1901).
160. S. Gronowitz and G. Sorlin, Acta Chem. Scand., **15**, 1419 (1961).
161. B. Bak, L. Hansen, and A. Rastrup, Discuss. Faraday Soc., **19**, 30 (1955).
162. D. G. Manly and E. D. Amstutz, J. Org. Chem., **21**, 516 (1956).
163. A. Hofmann, W. V. Philipsborn, and C. H. Eugster, Helv. Chim. Acta, **48**, 1322 (1965).
164. H. Gilman and N. O. Calloway, J. Amer. Chem. Soc., **55**, 4197 (1933).
165. H. Gilman, M. McCornle, and N. O. Calloway, J. Amer. Chem. Soc., **56**, 745 (1934):
166. H. Pechman, Annalen, **264**, 261 (1891).
167. F. Feist, Ber., **34**, 1992 (1901).
168. R. C. Fuson, C. L. Fleming, and R. Johnson, J. Amer. Chem. Soc., **60**, 1994 (1938).
169. T. Morell and P. E. Verkade, Rec. Trav. chim., **67**, 539 (1948).
170. R. G. Jones, J. Amer. Chem. Soc., 4069 (1955).
171. H. Gilman, R. R. Burtner, and E. W. Smith, J. Amer. Chem. Soc., **55**, 403 (1933).
172. C. Naegeli and A. Tyabji, Helv. Chim. Acta, **16**, 349 (1933).
173. P. A. Finan and G. A. Fothergill, J. Chem. Soc., 2723 (1963).
174. Ya. L. Gol'dfarb, Ya. L. Danyushevskii, and N. A. Marakatkina, Izv. Akad. Nauk SSSR, Ser. Khim., 2532 (1968).
175. Ya. L. Gol'dfarb and L. D. Tarasova, Dokl. Akad. Nauk SSSR, **142**, 358 (1962).
176. Ya. L. Gol'dfarb and L. D. Tarasova, Dokl. Akad. Nauk SSSR, **163**, 1393 (1965).
177. "Organic Syntheses" (Translated into Russian), Inostr. Lit., Moscow, 1948, Vol. I, p. 204.
178. R. E. Lutz and R. I. Rowlett, J. Amer. Chem. Soc., **70**, 1359 (1948).
179. I. Levisalles, Perfumery Essent. Oil Record, **46**, 627 (1958); Chem. Abs., **53**, 7514h (1959).
180. V. Asahina and V. Murayama, Arch. Pharm., **252**, 435 (1914); Chem. Zentr., II, 1196 (1914).
181. V. Fujita, J. Chem. Soc. Japan, **79**, 1067 (1958): Chem. Abs., **54**, 25 596a (1960).

182. V. R. Naves and P. Ochsner, Helv. Chim. Acta, 43, 406 (1960).
183. T. Kubota and T. Matsuura, J. Chem. Soc., 3667 (1958).
184. M. Romanuk, V. Herout, F. Sorm et al., Coll. Czech. Chem. Comm., 29, 1048 (1964); Chem. Abs., 60, 14 547d (1964).
185. A. Back, Compt. rend., 150, 540 (1910); Chem. Zentr., II, 738 (1910).
186. J. E. Hodge and E. C. Helson, Cereal Chem., 38, 207 (1961); Chem. Abs., 56, 60 631 (1962).
187. B. F. Fischer and J. E. Hodge, J. Org. Chem., 29, 774 (1964).
188. F. Wessely and E. Nadler, Monatsh. Chem., 60, 141 (1932); Chem. Zentr., II, 2196 (1932).
189. G. Plancher and S. Albini, Atti R. Accad. Lincei Roma, [5], 13, 1, 39 (1904); Chem. Zentr., I, 955 (1904).
190. A. Wool, Ber., 39, 1952 (1906).
191. P. A. Finan and G. A. Fothergill, J. Chem. Soc., 2728 (1963).
192. I. Arata and K. Achiwa, Kanazawa Daigaku Yakugakubu Kenkyu Nempo, 8, 29 (1958); Chem. Abs., 53, 5228 (1959).
193. H. G. Walker and C. R. Hauser, J. Amer. Chem. Soc., 68, 1386 (1946).
194. W. H. Puterbaugh, F. W. Swamer, and C. R. Hauser, J. Amer. Chem. Soc., 74, 3438 (1952).
195. P. A. Finan and G. A. Fothergill, J. Chem. Soc., 2262 (1962).
196. H. Leditschke, Arch. Pharm., 323 (1962).
197. J. D. Prugh, A. C. Huitric, and W. C. McCarthy, J. Org. Chem., 29, 1991 (1964).
198. H. Gilman, V. Wal, R. Franz, and E. V. Brown, J. Amer. Chem. Soc., 57, 1146 (1935).
199. V. Wal, Iowa State Coll. J. Sci., 11, 128 (1936).
200. E. Votocek and S. Malachta, Coll. Czech, Chem. Comm., 4, 87 (1932); Chem. Abs., 26, 3234 (1932).
201. H. Gilman and R. Burtner, J. Amer. Chem. Soc., 55, 859 (1933).
202. E. Sherman and E. D. Amstultz, J. Amer. Chem. Soc., 72, 2195 (1950).

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