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THE CHEMISTRY OF β-KETOACETALS

N. K. Kochetkov and E. E. Nifant'ev

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I. INTRODUCTION

The study of β-dicarbonyl compounds has furthered the

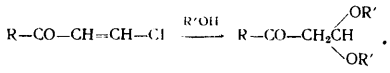
development of theoretical organic chemistry, and they and their derivatives are also versatile synthetic agents. While β-ketoesters, β-diketones, and similar compounds are readily accessible, syntheses and synthetic uses of β-ketoaldehydes have received relatively little attention for three reasons. Firstly, few β-ketoaldehydes of established structure are available. Until recently the main synthesis was the Claisen formylation[1-3], which gives unambiguous results only with symmetrical alkyl, alkyl aryl, and some other ketones. Most other ketones undergo side reactions[3-5] which make the isolation of the β-ketoaldehyde difficult or impossible. A number of hitherto inaccessible β-ketoaldehydes have been made by alkylation of β-aminovinyl ketones, a route which was recently proposed by Kochetkov, Ivanova, and Nesmeyanov[6]. Secondly, β-ketoaldehydes are very labile, except for formyl derivation of aryl methyl ketones and for those α-substituted by alkyl, nitro, or halogeno groups[3,7-14]; others exist only as the metal derivatives of the enols. Thirdly, β-ketoaldehydes often react simultaneously in different ways; syntheses of pyrazoles, isoxazoles, etc., nearly always give mixtures of isomers[15], which reduces their preparative value.

The β-ketoacetals are important as stable and accessible derivatives of β-ketoaldehydes, still retaining the high and diverse reactivity of those compounds.

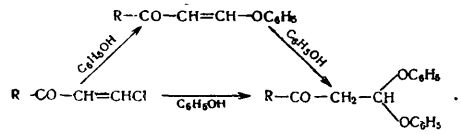
II. SYNTHESIS OF β-KETOACETALS

1. Synthesis from β-Chlorovinyl Ketones

This is the most important synthetic method, used in 1937 by Nells[16,17] and a group of German chemists[18] to obtain the first simple β-ketoacetals. Alcohols react with β-chlorovinyl ketones in the presence of bases such as alkali-metal hydroxides and carbonates, or tertiary amines:



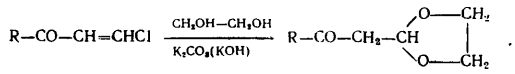
Since this synthesis was described only in patents, with little detail, β-ketoacetals attracted little attention at first*. In 1950 Nesmeyanov, Kochetkov, and Rybinskaya[19] and Price and Pappalardo[20] studied this method independently and simultaneously, and recommended it for the preparation of dialkylacetals of β-ketoaldehydes in 50–90% yield**. It has been suggested that an alkyl β-alkoxyvinyl ketone, R–CO–CH=CH–OR, is an intermediate[1], which reacts with a second alcohol molecule, in the presence of a base, to give a β-ketoacetal. This is a general reaction of α,β-unsaturated ketones. The suggestion is supported by the reaction between β-chlorovinyl ketones and phenol to give β-phenoxyvinyl ketones, which under suitable conditions can react with more phenol to give diphenylacetals[19]:



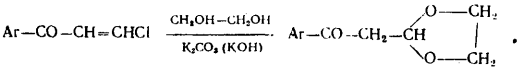
* The use of β-ketoacetals was impeded by lack of a suitable synthesis of β-chlorovinyl ketones. The latter are now well known and accessible[21].

** The reaction between β-chlorovinyl ketones and alcoholic hydrogen chloride also gives β-ketoacetals but in small yield[19].

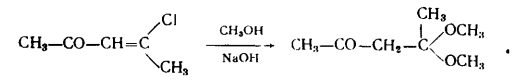
By recent modifications of the dialkylacetal synthesis, higher β-ketoacetals[22-24] and β-ketoacetals with a functional group in the alkyl radical[25] have been prepared. In 1957 Kochetkov, Nifant'ev, and Nesmeyanov[26] synthesised cyclic ethyleneacetals by the reaction between β-chlorovinyl ketones and ethylene glycol in alkaline media:



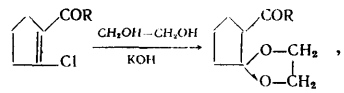
These products are widely applicable synthetic agents, being very stable relative to the dialkylacetals. While syntheses of dialkylacetals of aromatic β-ketoaldehydes have been limited to the unstable dimethylacetal of benzoylacetaldehyde[28], the analogous cyclic derivatives are readily made[27]:



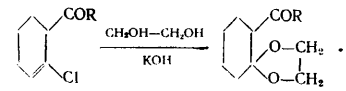
Recently acetals of heterocyclic aldehydes, such as α-furoylacetaldehyde and its sulphur and selenium analogues[29], have been made. Alcohols and α-glycols also react with β-alkyl-β-chlorovinyl ketones in the presence of alkali to give the monoketals of β-diketones[30-33]:



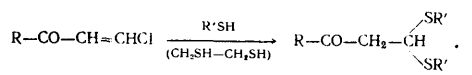
Ethylene glycol reacts in this way with 1-chloro-2-acylcyclopent-1-enes to give ethyleneketals of 2-acylcyclopentanones[31]:



and with 2-chloro-3-acylcyclohexenes[32-33]:



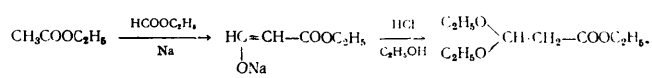
Very recently, mercaptans have been converted in this way to the hitherto almost unknown β-ketomercaptals[34]:



Ethanedithiol, giving cyclic ethylenemercaptals, was more effective than simpler mercaptans.

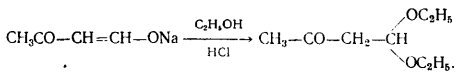
2. Synthesis from β-Ketoaldehydes and Their Sodium Derivatives

In 1927 Sugasawa[35] first converted the enol form of a β-dicarbonyl compound to an acetal, using the sodium derivative of malonic monoaldehyde ethyl ester:

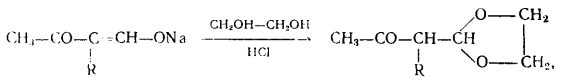


This was later developed into a general synthesis of acetals from derivatives of that ester[36,37].

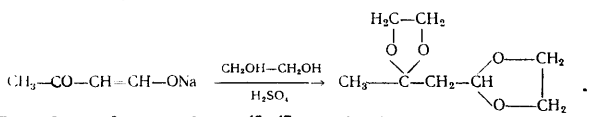
In the 1950's Sugasawa, Yamada, and other Japanese chemists described syntheses of acetals from acetoacetaldehyde; Sugasawa[38] converted the sodium derivative to the diethylacetal:



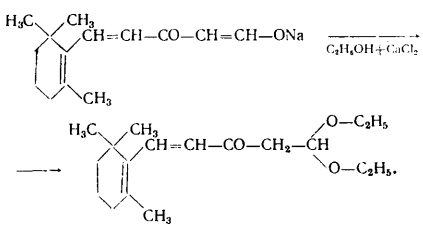
The dimethylacetal was obtained in the same way in 45% yield[39]. Chlorosulphonic acid, phosphorus trichloride, thionyl chloride, and hydrogen chloride, were later shown to catalyse this reaction[40]. Later, Richmond[41] studied these reactions and improved the conditions and the yield in the synthesis of acetoacetaldehyde diethylacetal. The same synthesis was applied to the ethyleneacetals of acetoacetaldehyde and α-methylacetoacetaldehyde[42,43]:



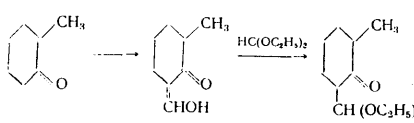
where R = H or CH_3. Yields of the latter were usually small; in the former case, some of the bisethylene acetal-ketal was also formed, which Sugasawa et al.[44] obtained pure in 1950 by using sulphuric acid as catalyst:



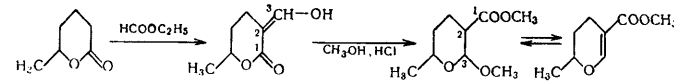
Royals and coworkers[45-47] studied the formylation of ketones, and showed that the reaction between sodium derivatives thus formed of β-ketoaldehydes and alcoholic hydrogen chloride give β-ketoacetals or, more often, β-alkoxyvinyl ketones, depending on the initial compound. Cyclohexanone-2-aldehyde and benzoylacetaldehyde give only vinyl ethers, other compounds give mixed products, and only some of the simplest β-ketoaldehydes give β-ketoacetals alone. Schanz[48] obtained an acetal from the sodium derivative of ω-formyl-β-ionone and ethanolic calcium chloride:



Ružicka and coworkers[49] synthesised β-ketoacetals of the cyclohexane and cycloheptane series from the free parent enol and orthoformic ester:



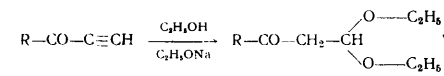
Cyclohexanone-2-aldehyde has recently been shown to form a β-ethoxyvinyl ketone, not a β-ketoacetal, under similar conditions[50]. Korte[51-53] recently discovered a related conversion of lactones and thiolactones to acids of the dihydropyran, dihydrofuran, and dihydrothiophene series, e.g.:



It is therefore clear that β-ketoaldehydes cannot always be converted to β-ketoacetals, on account of the diversity of the products and the subsequent difficulty of isolation.

3. Other Methods

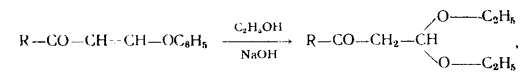
Bowden, Braude, and Jones[54] reported the addition of ethanol across the triple bond of benzoyl and n-butyryl acetylene in the presence of sodium ethoxide:



where R = C_6H_5 or C_3H_7.

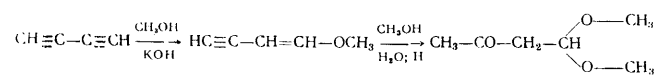
The oxidation of β-hydroxyacetals[55] is not a widely applicable synthesis, since these compounds are not readily available; since they are useful synthetic agents, they are in fact made by reducing β-ketoacetals, as is shown below.

The preparation of β-ketoacetals from β-phenoxyvinyl ketones[56],

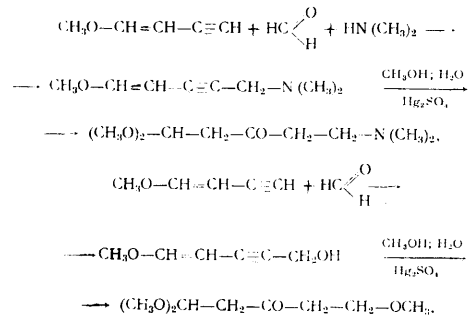


is of theoretical interest only, as are the other two syntheses described above.

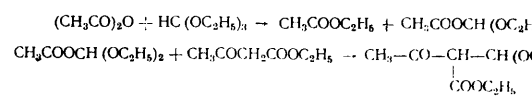
In 1953 Franke, Kraft, Teitejen, and Weber[57] developed an industrial synthesis of acetoacetaldehyde dimethylacetal from butadiyne,



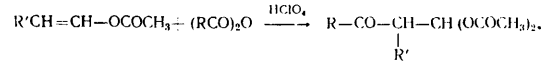
based on earlier detailed studies of the reactions of butadiyne and its derivatives[58-62]. This synthesis has not been applied generally, but some β-ketoacetals bearing other functional groups have been prepared[63,64]:



α-Ethoxycarbonyl-β-ketoacetals[65], such as α-ethoxycarbonylacetoacetaldehyde acetal,



are compounds of great interest, but no general synthesis has been suggested for them. A related reaction was recently described giving the hitherto unknown β-keto-aldehyde diacetates[66]:

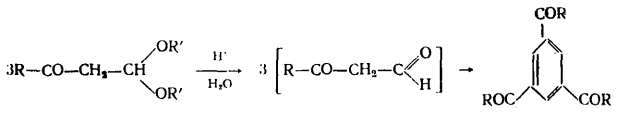


III. PROPERTIES OF β-KETOACETALS

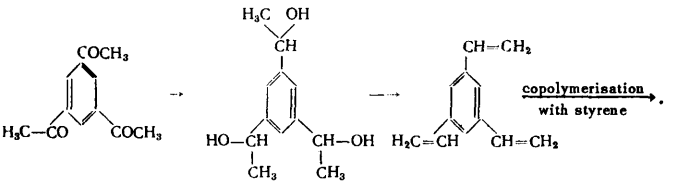
β-Ketoacetals contain two functional groups, show many of the reactions of β-dicarbonyl compounds, and possess a reactive methylene grouping. Their reactions are conveniently classified in this way.

1. Reactions of the Acetal Group

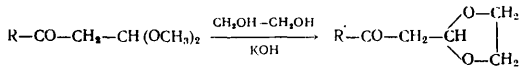
Almost all the reactions typical of acetals are undergone by β-ketoacetals. They are hydrolysed by traces of mineral acid or by acetic acid, the resultant β-ketoaldehydes polymerising spontaneously to *sym*-triacylbenzenes[19]:



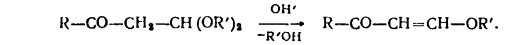
1,3,5-triacetylbenzene has recently been converted to trivinylbenzene on an industrial scale, and hence to synthetic resins[67]:



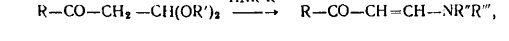
Dialkyl-β-ketoacetals undergo the usual transacetalisation with ethylene glycol[26]:



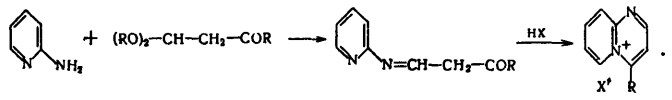
where R = n-C_3H_7 or C_6H_5. A molecule of alcohol is lost in the presence of alkaline catalysts to give β-alkoxyvinyl ketones[47]:



Aromatic β-ketoacetals undergo this reaction readily, but aliphatic analogues only with difficulty. Reaction with ammonia and primary and secondary amines is exceptionally ready[68]:



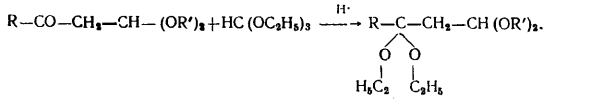
where R'', R''' = H or an alkyl group. The resultant β-aminovinyl ketones are usually more conveniently obtained, however, direct from β-chlorovinyl ketones[69-71]. Nesmeyanov, Rybinskaya, and Kel'skii[72] recently obtained 4-alkylpyrido[1,2-e]pyrimidinium salts from β-ketoacetals and 2-aminopyridine, and also isolated the intermediate aminovinyl ketones:



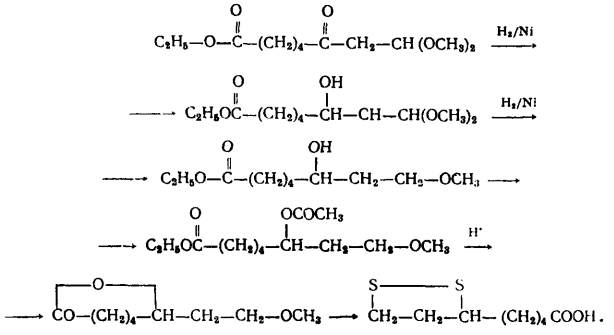
Later, the improved synthesis was carried out in one stage[73].

2. Reactions of the Carbonyl Group

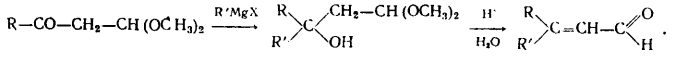
Orthoformic ester reacts with β-ketoacetals in the presence of acidic catalysts to give acetal-ketals in high yield[74]:



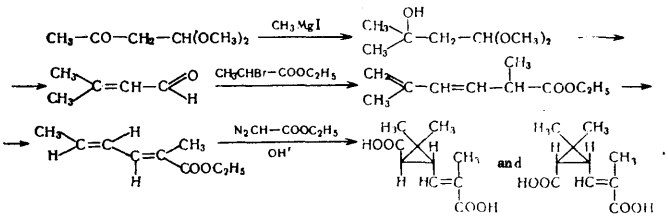
The carbonyl group is readily reduced by lithium aluminium hydride[4,42], aluminium isopropoxide[23], and sodium and ethanol[49]. The resulting secondary alcohols are readily dehydrated and hydrolysed to α,β-unsaturated aldehydes. A recent synthesis of α-lipoic acid has as its first stage the catalytic reduction of ω-ethoxycarbonylpentanoyl-acetaldehyde dimethylacetal[25]:



Grignard reagents react smoothly with β-ketoacetals; Price and Pappalardo[20] synthesised a series of α,β-unsaturated aldehydes related to the terpenes:

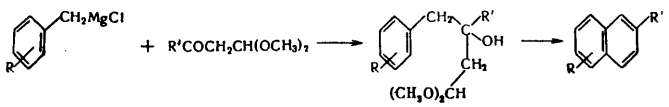


Crombie[75] used similar aldehydes to prepare naturally occurring acids derived from cyclopropane:

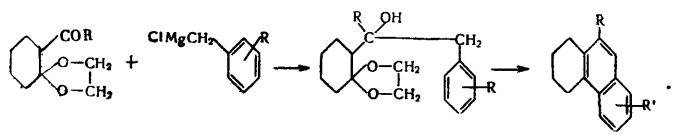


The tertiary alcohols obtained from β-ketoacetals and Grignard reagents have recently been cyclised to aromatic

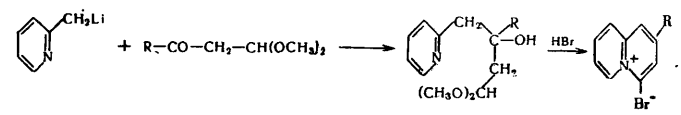
and heterocyclic compounds. Kochetkov, Nifant'ev, and Nesmeyanov[26,76] readily obtained alkylnaphthalenes from derivatives of benzylmagnesium chloride:



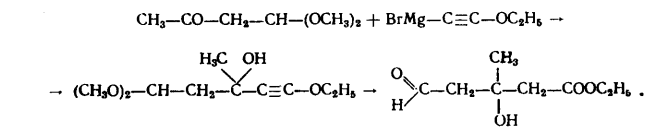
A general synthesis of alkyltetrahydrophenanthrenes from cyclohexane β-ketoacetals afforded hitherto unknown compounds[32,33]:



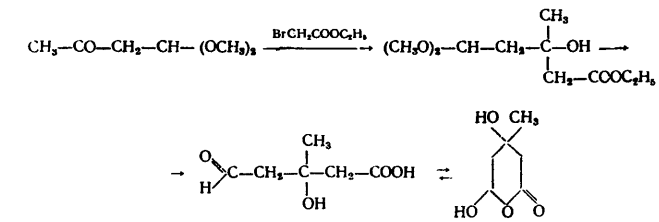
Palladium dehydrogenation readily converted these into alkylphenanthrenes in almost quantitative yields. Nesmeyanov and Rybinskaya[77] and Richards and Stevens[78] obtained 2-alkyldehydroquinolizinium salts from β-ketoacetals and α-picolyllithium:



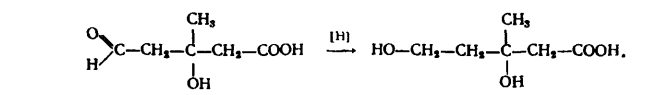
Compounds have been synthesised related to β,δ-dihydroxy-β-methylvaleric (mevalonic) acid, a growth factor for microorganisms such as *Lactobacillus acidophilus*. In 1957 Birch, Pride, and Smith[79] synthesised a related aldehydo-ester from acetoacetaldehyde dimethylacetal and ethoxyethynylmagnesium bromide:



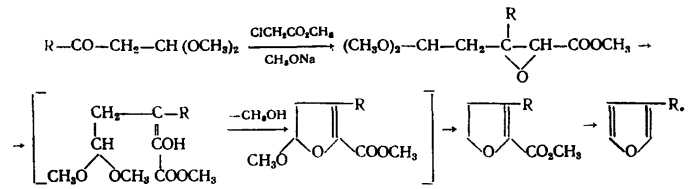
Almost simultaneously Folkers and coworkers[80] synthesised (±)-β-hydroxy-β-methylglutaric monoaldehyde by the Reformatsky reaction:



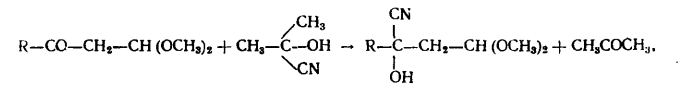
Sodium borohydride or platinum and hydrogen reduced the product to mevalonic acid[80]:



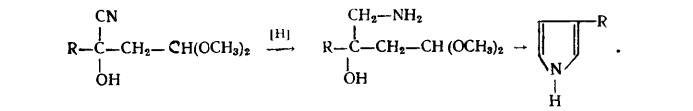
In 1956 Burness first applied the Darzens condensation to β-ketoacetals, and cyclised the glycidic esters produced to furan derivatives[81]:



Although of great potential value, this reaction has not been investigated further. Acetone cyanhydrin converts β-ketoacetals to cyanhydrins[82]:

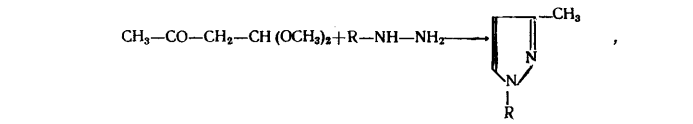


From these, 3-alkylpyrroles may be made[82]:

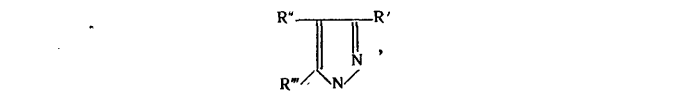


3. Reactions Typical of β-Dicarbonyl Compounds

Like other β-dicarbonyl compounds, β-ketoacetals may be used to synthesise heterocyclic compounds. In 1951 Nesmeyanov, Kochetkov, and Rybinskaya[19] obtained *N*-substituted 3-methylpyrazoles from acetoacetaldehyde dimethylacetal:

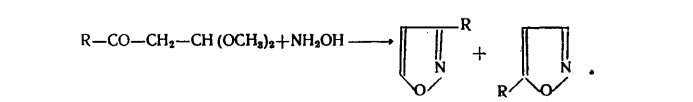


where R = C_6H_5 or *p*-$C_6H_4NO_2$. In this way, other authors[22,64,83,84] obtained 50–85% yields of pyrazoles of general formula

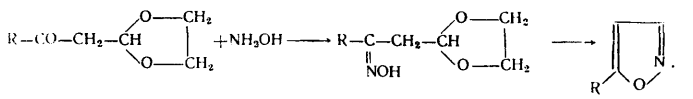


where R = H, alkyl, C_6H_5, *p*-$C_6H_4NO_2$, 2,4-$C_6H_3(NO_2)_2$, $CONH_2$, or $CSNH_2$; R′, R″, and R‴ = H or alkyl. The expected hydrazone is clearly an intermediate, and was isolated in some cases.

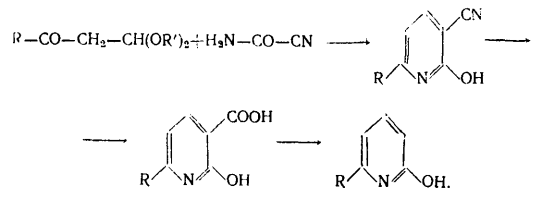
Dimethylacetals may be converted into mixtures of 3- and 5-alkylisoxazoles[83]:



The stabler ethyleneacetals yield only 5-derivatives[85]; an intermediate oxime can be isolated:

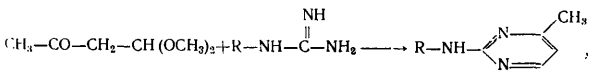


In 1952 Kochetkov[86] published a general synthesis of 6-alkyl-3-cyano-2-hydroxypyridines, which he used to prepare the relatively inaccessible 6-alkyl-2-hydroxypyridines:

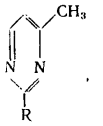


Franke and Kraft[83] recently prepared highly substituted pyridine derivatives by this method.

One of the most important pyrimidine sulphonamides, sulphamerazine or 2-sulphanilamido-4-methylpyrimidine, and its *N*-substituted derivatives were made by Japanese chemists[39,42,43,87] from acetoacetaldehyde dimethylacetal or methyl β-methoxyvinyl ketone, in 70–80% yield:

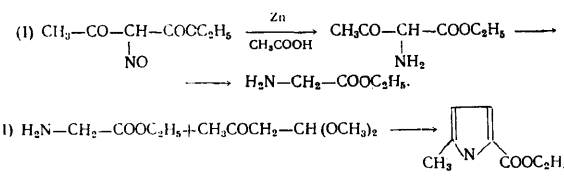


where R = H, *p*-$NH_2C_6H_4SO_2$, *p*-$CH_3CONHC_6H_4SO_2$, or *p*-$(CH_3)_2NC_6H_4SO_2$. The same authors, as well as Franke and Kraft[83], synthesised other 2-derivatives of 4-methylpyrimidine, of general structure



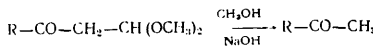
where R = OH, SH, Cl, NH_2, NH–CN, or C_6H_5. An 85% yield of the important pharmaceutical 2-amino-4-methylpyrimidine was obtained.

Fischer and Fink[88] used acetoacetaldehyde dimethylacetal in the Knorr pyrrole synthesis, but obtained 2-methyl-5-ethoxycarbonylpyrrole and not the expected 2,4-dimethyl-5-ethoxycarbonylpyrrole-3-aldehyde. This they explained by the elimination of acetic acid from α-aminoacetoacetic ester, formed by reduction of the corresponding isonitroso compound; the resultant glycine ester reacts with the β-ketoacetal:



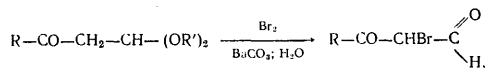
The formation of the same product from isonitroso-n-butyroacetic acid lends support to the above mechanism. The reaction has been recently re-examined[89].

The ready ketonic hydrolysis of other β-dicarbonyl compounds applies to β-ketoacetals[90,91], and has been used by Wakayama and Maekana[92] as a source of methyl ketones:

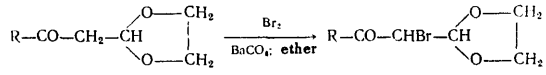


4. Reactions of the α-Methylene Group

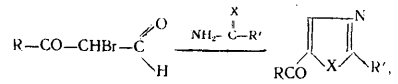
Substitution in this group was discovered only recently when bromination of β-ketoacetals with *N*-bromosuccinimide, dioxan dibromide, and bromine itself, was carefully examined[93,94]. Bromination is most effective when bromine is used together with hydrogen bromide acceptors; the solvent also influences the reaction. Aqueous bromine and barium carbonate cause monosubstitution in the α-CH_2 group and hydrolysis of ethylene- or dialkyl-acetal groups, giving α-bromo-β-ketoaldehydes:



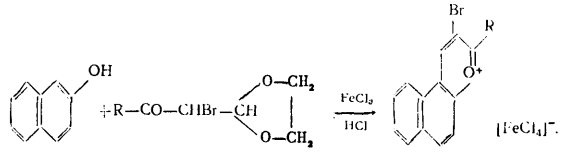
where R = CH_3, C_2H_5, or n-C_3H_7; R′ = CH_3; R′–R′ = = CH_2–CH_2. Ethyleneacetals alone withstand hydrolysis when dry ether is the solvent:



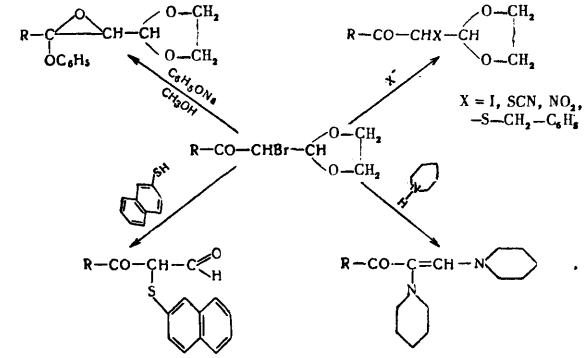
where R is an alkyl or aryl group. Mild treatment of the product with acid effects hydrolysis. The exclusive bromination of the α-methylene group indicates activation by the acetal group. The products are useful synthetic agents; α-bromo-β-ketoaldehydes react readily with urea, thiourea, and thioamides to give the hitherto inaccessible oxazole and thiazole ketones[94]:



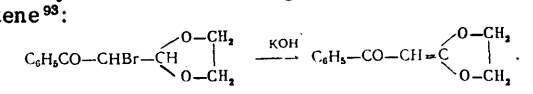
where R = an alkyl group; R′ = NH_2, H, or C_6H_5; X = O or S. Corresponding acetals will also yield heterocyclic compounds, such as brominated pyrylium derivatives[94]:



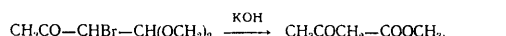
Other syntheses depend on the ready replacement of the bromine atom[95]:



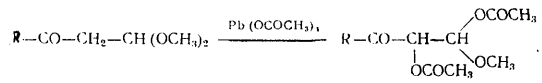
Dehydrobromination of α-bromo-β-acetals with powdered potassium hydroxide in benzene gives the acetal of an acylketene[93]:



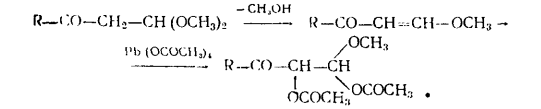
Excess of alcoholic alkali gives a β-ketoester[93]:



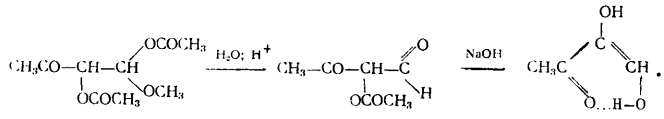
The action of lead tetraacetate on β-ketoacetals was shown by two groups of chemists[93,95,97] to give the acylals of α-acetoxy-β-ketoaldehydes:



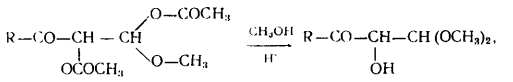
where R = CH_3, C_2H_5, n-C_3H_7, or C_6H_5. The double bond of the β-methoxyvinyl ketone, formed by β-elimination of alcohol[98], is attacked as in other vinyl ethers[99]:



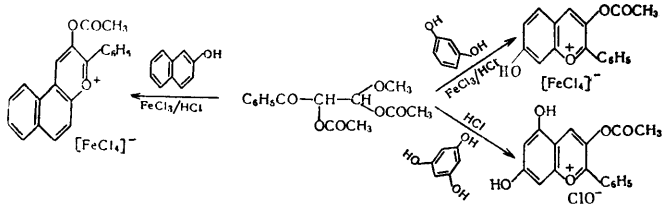
Stepwise hydrolysis of the simplest product gave a high yield of methylreductone[100]:



Other alkylreductones may be made similarly. Alcoholic hydrogen chloride yields acetals of α-hydroxy-β-ketoaldehydes[97,98]:



where R = CH_3, C_2H_5, n-C_3H_7, or C_6H_5. Acylals of α-acetoxy-β-ketoaldehydes react with phenols to give acetoxy-substituted pyrylium derivatives[98]. Ferric chloride catalyses the condensation with β-naphthol and resorcinol, but is unnecessary with phloroglucinol:



The flavilium salts produced are monoacetyl derivatives of anthocyanins.

The β-ketoacetals are readily available, versatile synthetic reagents, from which natural and pharmacologically active products have been made, as well as others difficult or impossible to obtain earlier. Much doubtless remains to be discovered about the uses of these recently developed compounds.

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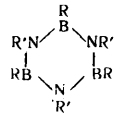
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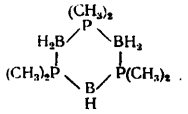
POLYMERIC COMPOUNDS OF BORON

V. A. Zamyatina and N. I. Bekasova

Little information is available in the scientific and patent literature about polymers of boron, although it is known[1] that they are of great importance because of their resistance to heat and the action of hydrocarbons. Of special interest are polymers containing in the main chain atoms of boron and nitrogen, –B–N–B–N–, or boron and phosphorus, –B–P–B–P–[2], although up to the present the only systematic descriptions of such compounds which have been published are of cyclic representatives with low molecular weights, namely the borazoles,



(where R and R′ can be H, alkyl, or aryl), and the phosphinoborines,



Very little is as yet known about linear polymers whose molecular chains consist of atoms of boron and nitrogen or of boron and phosphorus. In most cases the properties of polymeric compounds of boron have been inadequately described, and often no information is given on their molecular weight, melting points, solubility, or resistance to oxidation and hydrolysis. In addition to work on the preparation of polymeric compounds containing boron, the following review covers also investigations concerned with