PERCHLORIC ACID AND ITS COMPOUNDS IN ORGANIC SYNTHESIS

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PERCHLORIC ACID AND ITS COMPOUNDS IN ORGANIC SYNTHESIS

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CONTENTS

I. INTRODUCTION

In recent years acid catalysts, among which perchloric acid and its compounds occupy an important place, have been attracting increasing attention. During the past 10–15 years more than 300 papers and patents have appeared, dealing with the use of $HClO_4$ and its compounds in organic chemistry.

Perchloric acid is the strongest mineral acid but at ordinary temperatures its oxidising power is less than that of the other oxygen acids of chlorine, bromine, and iodine[1]. In many organic solvents perchloric acid is readily solvated and this changes the polarity of the bond between the hydrogen atom and the ClO_4 residue. In polar organic solvents (acetic acid[2-4], nitromethane[5], nitrobenzene[6], etc.) perchloric acid is ionised to a greater degree than other acids. Comparison of the ionisation constants of mineral acids in anhydrous acetic acid confirms that perchloric acid ($K = 1.6 \times 10^{-4}$) is tens or hundreds of times stronger than hydrobromic ($K = 4 \times 10^{-5}$), sulphuric ($K = 6 \times 10^{-7}$), hydrochloric ($K = 1.4 \times 10^{-7}$), nitric ($K = 4.2 \times 10^{-8}$), and trichloracetic ($K = 2.3 \times 10^{-10}$) acids.

For many years the wide use of perchloric acid in organic synthesis has been hindered by greatly exaggerated ideas about the danger of explosions. However, although work with the anhydrous acid is in fact not without danger, the use of an aqueous solution (30, 60, and 72%) involves practically no risk. Solutions of the anhydrous acid in acetic acid or acetic anhydride containing less than 55% of $HClO_4$ by volume, which are frequently used, are also quite safe[8].

Much experimental data on the use of perchloric acid and its compounds in various fields of organic chemistry has accumulated. This work requires to be correlated and systematised since the published reviews dealing with only parts of the problem are already out of date[8-10].

II. PERCHLORATES OF ORGANIC COMPOUNDS

The study of organic perchlorates started in the 19th century when crystalline perchlorates of alkaloids were obtained[11]. Later it was found that perchloric acid readily forms perchlorates with ethers, ketones, weakly basic compounds containing nitrogen, and pyridine; this property is used successfully in the purification and identification of many basic organic compounds[12-15]. Organic perchlorates are usually obtained by treating solutions of organic compounds in polar or non-polar solvents (water, alcohols, ether, nitromethane, etc.) with perchloric acid in the cold[16-18].

In their structure the esters of perchloric acid are superficially similar to salts, the metal being replaced by a hydrocarbon radical. The bond between the perchlorate ion and the hydrocarbon radical is covalent or nearly ionic, depending on the degree of polarisation. Nearly all these compounds are unstable and only some of them can be obtained in the pure state. Among the various methods of synthesising perchloric esters the most widely applicable method is based on the reaction of alkyl halides with silver perchlorate[19-22]:

$$RX + AgClO_4 \rightarrow RClO_4 + AgX.$$

The esters may also be obtained by the interaction of the alcohol with chlorine heptoxide or by the action of diazomethane on aqueous $HClO_4$:[23]

$$ROH + Cl_2O_7 \rightarrow RClO_4 + HClO_4,$$
$$CH_2N_2 + HClO_4 \rightarrow CH_3ClO_4 + N_2.$$

The esters of perchloric acid are widely used as alkylating agents. They are colourless low-boiling oils, miscible with alcohol and insoluble in water, which slowly hydrolyses them[24].

The introduction of aryl residues into the perchlorate molecule has a considerable polarising effect on the C–O ester bond. As the number of aryl groups in an aralkyl perchlorate molecule increases, the C–O bond approaches the ionic type. Aralkyl perchlorates are obtained by the methods used for the preparation of esters.

However, when 72% perchloric acid acts on diphenylmethylmethanol in nitromethane, a mixture of diphenylmethyl ether, diphenylmethane, and benzophenone is obtained instead of the expected diphenylmethyl perchlorate[25].

In the reaction of diphenylmethyl chloride with silver perchlorate in benzene solution diphenylmethyl perchlorate, which has considerable alkylating power, was obtained[26].

Benzyl perchlorate is also highly reactive but this could not be obtained pure, because it rapidly polymerised at the moment of formation[27-30].

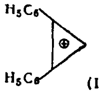
The most interesting of the aralkyl perchlorates are the triarylmethyl perchlorates, as these can be used in hydride displacement reactions.

Experimental data on electrical conductivity[31-33] and absorption spectra[34,35] indicate that the triarylmethyl perchlorates are typical carbonium salts. They are conveniently obtained by the addition of 70% $HClO_4$ to a solution of triarylmethanol in acetic anhydride at room temperature or by the exchange reaction of triarylalkyl chlorides with $AgClO_4$ in a polar solvent[36,37].

Interesting organosilicon perchlorates have been recently obtained by slowly mixing benzene solutions of trialkyl- or triaryl-silicon chloride and silver perchlorate in a stream of dry nitrogen[38,39]. The trialkylsilicon perchlorates (Alk_3SiClO_4) were isolated as colourless liquids fuming in air and exploding at 180–200°; they can be distilled under vacuum without decomposition. The triarylsilicon perchlorates are crystalline compounds insoluble in benzene; they evidently have an ionic structure, which was confirmed by a study of their infrared spectra and chemical properties. Recently the synthesis of new hetero-organic perchlorates, $Alk_3\overset{+}{S}ClO_4^-$ and $(CH_3)_3\overset{+}{Sn}ClO_4^-$, has been reported; they were obtained in the crystalline state[40,41]. Compounds of the first type are easily obtained by the action of perchloric acid on a mixture of thioether and the corresponding alcohol.

Among diverse carbonium salts[42,43] a special place is occupied by aromatic cations, of which the cyclopropenyl cation is the simplest representative; this cation has the properties of an aromatic system. However, salts of the unsubstituted cyclopropenyl cation are still unknown.

In the reaction of 1,2-diphenylcyclopropene-3-carboxylic acid with 10% $HClO_4$ in acetic anhydride a 70% yield of diphenylcyclopropenyl perchlorate (I) was obtained[44]: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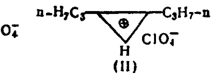
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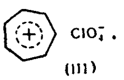
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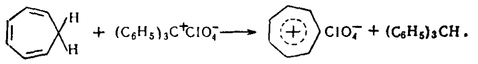
The entirely stable dipropylcyclopropenyl cation (II) has been obtained by this method, acetyl perchlorate in acetic anhydride acting on dipropylcyclopropenecarboxylic acid[45]; this shows that the hypothesis that phenyl groups are required to stabilise the cyclopropenyl cation is untenable.

The properties of cyclopropenyl perchlorates are in many ways similar to the properties of tropylium salts (III). Tropylium perchlorate is easily obtained by the action of triphenylmethyl perchlorate, which is an effective hydride ion acceptor, on cycloheptatriene[46]:



The same method has been used to synthesise some homologues of tropylium salts and vinyltropylium perchlorate[47,48].

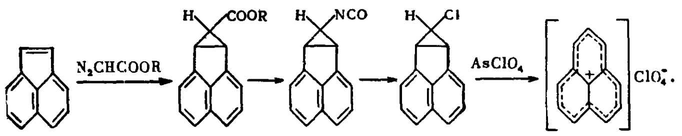
Tropylium perchlorate is also obtained in high yield from cycloheptatriene, phosphorus pentachloride, and 50% perchloric acid in dry carbon tetrachloride solution by the method of Kursanov and Vol'pin[49,50].

A British patent indicates the possibility of preparing tropylium perchlorate by the acid oxidation with perchloric acid of cycloheptatriene with no more than one substituent at the methylene group[51].

A report on the preparation of tropylium perchlorate by the autoxidation of cycloheptatriene in acetic acid solution in the presence of perchloric acid is noteworthy[52].

The reaction in which fundamental groups R are eliminated from 1-substituted cyclohepta-2,4,6-trienes C_7H_7R (R = COOH, COCl, CN) has been studied with the object of preparing tropylium salts[53]. Tropylium perchlorate was obtained by the action on the latter of silver perchlorate in nitromethane.

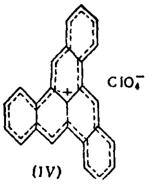
Among the various polycyclic systems the perinaphthenyl system has attracted attention; this can exist as a cation, anion, or free radical. The perinaphthenyl cation was obtained[54,55] as the perchlorate from acenaphthylene and diazoacetic ester by the method developed for the synthesis of tropylium salts[53]:



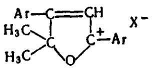
Theoretically it is possible to obtain perinaphthenyl perchlorate by the reaction of silver perchlorate with the perinaphthenyl radical[56]:

$$C_{13}H_9^{\cdot} + AgClO_4 \rightarrow C_{13}H_9^+ClO_4^- + Ag.$$

The perinaphthenyl cation is more stable than the triarylmethyl cation but less stable than the tropylium cation. Perinaphthenyl perchlorate is insoluble in non-polar solvents but soluble in strong acids; it is readily hydrolysed and is unstable in air. Tribenzoperinaphthenyl perchlorate (IV) has similar properties[57]:



(IV)



(V)

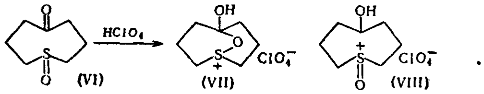
A very interesting synthesis is that of 4,6,8-trimethyllazulenium perchlorate, obtained by boiling 4,6,8-trimethyllazulene with an excess of 70% $HClO_4$ in acetic acid for a short time[58]. The crystalline perchlorate melts with decomposition at 168–171°; it is stable in air but is decomposed by water.

Kirby and Reid have shown that substituents in positions 4 and 8 are necessary for the formation of azulenium perchlorate.

Dihydrofurylium perchlorate is obtained in almost quantitative yield by the action of an ethereal solution of $HClO_4$ on hydroxydihydrofuran[59]. The product (V) is a yellow compound, insoluble in ether and benzene and slightly soluble in alcohol. A resemblance between dihydrofurylium salts and salts of benzopyrylium, xanthylium, and chromylium has been noted.

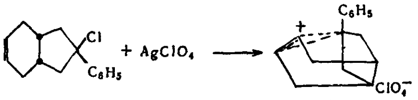
The stable 4,5,5-trimethyl-2-phenyldihydrofurylium perchlorate has been prepared[60]; 2,2,3,5-tetramethyl-5-phenyl-2,5-dihydrofuran is obtained by the action of methylmagnesium iodide on this perchlorate. The reactivity of 4-methyldihydrofurylium salts has been studied[61].

The perchlorate of 1-oxo-1-thiacyclooctan-5-one (VI) has been prepared[62,63]; this may have structure (VII) or (VIII).

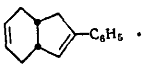


(VI) (VII) (VIII)

Leal and Pettit obtained a characteristic stable non-classical carbonium ion by the following reaction[64]:



(IX)



(X)

Compound (IX) is a yellow saltlike product, insoluble in hexane, chloroform, carbon tetrachloride, and benzene. With water or alcohol it forms the diene (X).

III. ELECTROPHILIC SUBSTITUTION REACTIONS

1. Perchlorylation of Organic Compounds

The electrophilic substitution reaction, which is widely used in organic chemistry, proceeds readily when halogens or mineral acids act on compounds of the aromatic series. However, the introduction of the ClO_3 residue into organic compounds by the action of perchloric acid on aromatic compounds is not possible. A direct method of perchlorylation of organic compounds was not developed until 1958.[65,66] Perchloryl compounds of the aromatic series are easily formed by the action of $FClO_3$ in the presence of $AlCl_3$ or $AlBr_3$ on benzene and other aromatic hydrocarbons containing no electron-acceptor groups:

$$ArH + FClO_3 \xrightarrow{AlCl_3} ArClO_3 + HF .$$

The spectra[65] and chemical properties of the perchloryl compounds confirm that they have the $ArClO_3$ and not the ester structure $ArOClO_2$.[65–68].

Perchlorylation in the *para*-position also proceeds smoothly with anisole[65] and with fluoro-,[65] chloro-,[67] and bromo-benzene[67]. The perchlorylarenes are stable liquids or solid compounds; some of them can be distilled without decomposition. They are entirely stable in neutral and acid media, but are hydrolysed to phenols by concentrated alkali solutions. The perchloryl compounds are detonated by a sharp blow or when the temperature is raised; they decompose explosively. When perchlorylbenzene is hydrogenated by hydrogen in alcoholic solution, the perchloryl group is smoothly eliminated and benzene is formed[68]. Perchlorylbenzene is nitrated in the *meta*-position and its nitro-compound can be reduced to the amine[65]. It is also possible to reduce *m*-nitroperchlorylbenzene completely; the reaction proceeds with the absorption of 7 moles of hydrogen and the elimination of the perchloryl group[68].

The action of nucleophilic reagents on perchloryl compounds has been studied and it has been shown that although perchlorylbenzene does not react with metallic lithium or magnesium, it does react vigorously even at -33° with $NaNH_2$ and $ArNH_2$ in liquid ammonia with the formation of triphenylamine[67]. The formation of dehydrobenzene from perchlorylarenes is confirmed by study of the elimination of the perchloryl group which proceeds readily to the extent of 87% under the action of the NH_2^- anion in liquid ammonia.

Measurement of the dipole moment of $FClO_3$ has shown that, although the molecule is electrically neutral, the ClO_3 group is the electropositive end of a dipole and the fluorine atom is the electronegative end[69]. Therefore, in the presence of Brønsted or Lewis acids (as occurs in the perchlorylation reaction) the organic compound will be attacked by the electrophilic cation ClO_3^+. In contrast, in an alkaline medium, because of an inductomeric shift, $FClO_3$ may act as an effective fluorinating agent with electropositive fluorine. Thus, when $FClO_3$ acts on 1-ethoxycyclohexene in pyridine at 0°, 2-fluorocyclohexanol is formed. Compounds with an active methylene group (acetylacetone, diethyl malonate, etc.) are smoothly fluorinated by perchloryl fluoride[70,71].

Perchloric acid and its derivatives may be used in the halogenation[72–76], nitration[77–79], nitrosation[80,81], and diazotization[82–85] of organic compounds.

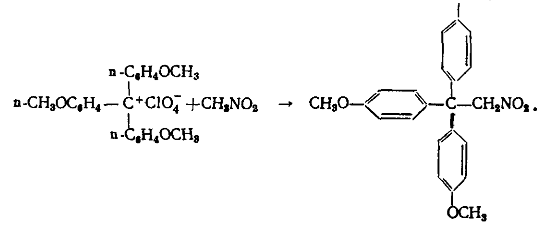
2. Alkylation

Alkyl perchlorates may be used as alkylating agents. Thus, methyl perchlorate, obtained from methyl iodide and silver perchlorate, slowly reacts with anisole at ordinary temperatures to give *p*-methylanisole[86,87]. Methyl perchlorate reacts much less rapidly with benzene. Ethyl, propyl, and n-butyl perchlorates have similar properties.

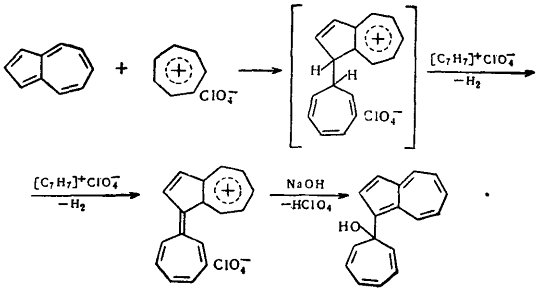
It is interesting that isobutyl perchlorate isomerises to t-butyl perchlorate, and when anisole and benzene are alkylated with isobutyl iodide and $AgClO_4$, t-butylanisole

(76%) and t-butylbenzene are obtained. There are data on the alkylation of toluene by cyclohexyl perchlorate[88,89].

Aralkyl perchlorates are very reactive. Benzyl perchlorate, prepared in solution of the compound to be alkylated, smoothly reacts with benzene and toluene forming diphenylmethane and *p*-methyldiphenylmethane in good yield[86]. Diphenylmethyl perchlorate readily combines with benzene to give triphenylmethane (65%) in two hours at room temperature[26]. When trityl perchlorate ($Tr^+ClO_4^-$) acts on a mixture of phenol and aniline, *p*-aminotetraphenylmethane is obtained in 78–84% yield[90]. At room temperature $Tr^+ClO_4^-$ converts anisole into *p*-methoxytetraphenylmethane in 63% yield; the same product is obtained from anisole and triphenylmethanol in the presence of 72% $HClO_4$ in nitromethane. Hydroxytetraphenylmethane was obtained from $Tr^+ClO_4^-$ and phenol in nitromethane at room temperature in yields of 23% (8 hours) and 68% (7 days). It is interesting that, when heated with 72% $HClO_4$ in nitromethane for 7 days, tri-*p*-methoxyphenylmethanol forms 1,1,1-tri-*p*-methoxyphenylnitroethane in good yield[26]:



Azulene and triphenylmethyl perchlorate in boiling acetic acid form a mixture of 1-triphenylmethyl- and 1,3-bis(triphenylmethyl)-azulene[91]. The reaction of azulene and its methyl homologues with tropylium perchlorate in dimethylformamide has been studied[81]; it proceeds according to the following scheme:



When unsubstituted azulene is alkylated under the conditions mentioned, a 1,3-dicycloheptatrienyl derivative of azulene is formed.

When an attempt was made to alkylate benzene and anisole with allyl perchlorate, obtained from allyl chloride and silver perchlorate, only resinous products were obtained[29].

Perchloric acid can be used for the alkylation of phenol by different alcohols[25,92-94]. When phenol is alkylated with t-butyl alcohol in 50% perchloric acid, 4-t-butylphenol and 2,4-di-t-butylphenol are formed[92].

Diphenylmethanol, phenol, and 72% $HClO_4$ give 63% of *p*-hydroxytriphenylmethane or 86% of 2,4,6-tris(diphenylmethyl)phenol, depending on the molecular proportions employed[25,26]. Similarly anisole forms *p*-methoxytriphenylmethane (89%), which is further converted to 2,4-bis-(diphenylmethyl)anisole (93%). Trisubstituted anisole could not be isolated. In the presence of perchloric acid hydroxymethyldimethylamine reacts with azulene to form mono- and bis-(dimethylaminomethyl) derivatives[95].

The patent literature contains references to the use of perchloric acid[96] and its salts[97,98] in the alkylation of phenols by olefins. In the presence of crystalline aluminium or iron perchlorate or aqueous lead perchlorate, *o*-cresol reacts with dodecene to give 4-s-dodecyl-*o*-cresol in excellent yield; similarly octene and aluminium perchlorate gives 4-s-octyl-*o*-cresol[98]. Phenylethylphenols (*o*- and *p*-) have been obtained by allowing styrene and perchloric acid in acetic acid to react with phenol[99].

The interaction of β-acetoxyethylmercury acetate with anisole to form β-(*p*-anisyl)ethylmercury acetate is an interesting case of alkylation[100].

Recently a method of alkylating phenols with ketones using small amounts of perchloric acid has been developed[101,102], and it has been shown that when benzyl phenyl ethers are treated with acetic anhydride and perchloric acid they are smoothly debenzylated[29,103].

3. *C*-Acylation

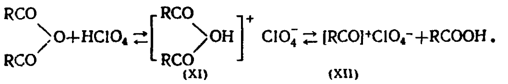
There are a number of serious disadvantages in the use of the usual catalysts such as $AlCl_3$, $ZnCl_2$, HF, etc. in acylation. It is sufficient to mention that the acylation of many organic compounds in the presence of these catalysts is associated with great difficulties arising from resinification of the starting materials, their isomerisation, degradation, and polymerisation. Extremely large amounts of catalyst are required. There are also difficulties in separating the products from the catalysts. Some of these difficulties can be overcome by the use of perchloric acid and its compounds as catalysts.

In 1927 Diels and Alder published the first account of the use of perchloric acid in the acylation of toluene and *o*-xylene by hot acetic anhydride[104].

In 1944 Berlin, who was studying the *N*-acylation of amines difficult to acylate, found that, when pyrrole is heated with acetic anhydride in the presence of catalytic quantities of 30% perchloric acid, a mixture of 1- and 2-acetylpyrroles is formed; he suggested that 2-acetylpyrrole (yield 33%) is a product of the thermal isomerisation of 1-acetylpyrrole[105].

In 1950 Burton and Praill commenced extensive studies of the catalytic properties of 72% perchloric acid, and showed that reactive aromatic compounds (*m*-xylene and anisole) could by acylated by carboxylic acid anhydrides in the presence of half-molar quantities of this catalyst[106-109]. In the same year Foster obtained a patent for the catalytic acylation of aromatic compounds in the presence of perchloric acid[110]. Aqueous (usually 60–72%) perchloric acid is generally employed in acylation.

Perchloric acid reacts with acid anhydrides evidently forming an oxonium ion (XI) which dissociates in solution to form an electrophilic acylium carbonium ion (XII) and a carboxylic acid[106]:

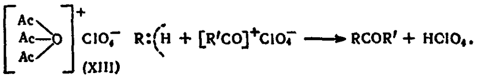


$$\begin{matrix}RCO\\ \quad\rangle O\\ RCO\end{matrix} + HClO_4 \rightleftarrows \left[\begin{matrix}RCO\\ \quad\rangle OH\\ RCO\end{matrix}\right]^+ ClO_4^- \rightleftarrows [RCO]^+ClO_4^- + RCOOH.$$

(XI) (XII)

The existence of the triacetyloxonium cation (XIII), obtained from acetyl perchlorate and acetic anhydride, has also been suggested[111]. The possibility that these ions exist has been confirmed by electrical conductivity measurements of solutions of perchloric acid in acetic anhydride[111,112] and also by kinetic studies[112-114].

Acylium carbonium ions (XII) are effective acylating agents and are therefore used for the acylation of reactive compounds of aromatic character[106-109,115,116].



(XIII)

Acyl perchlorates of various structures are also easily obtained by the reaction of equimolar quantities of acid chlorides with silver perchlorate in solution in nitromethane, absolute ether, or acetonitrile[107-109]:

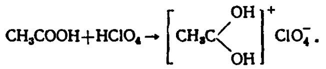
$$RCOCl+AgClO_4 \rightarrow [RCO]^+ClO_4^- + AgCl.$$

"Pure" acyl perchlorates obtained in this way are more effective acylating agents than those formed from acid anhydrides and perchloric acid[107], since in the latter case the acylating reagent consists of a mixture of carbonium (XII) and oxonium (XI) ions.

When a solution of perchloric acid in acetic anhydride is allowed to stand for a long time, or when freshly prepared acetyl perchlorate is added to acetic anhydride even at 20°, self-acylation occurs, probably in the following way[13]:

$$(CH_3CO)_2O+CH_3CO^+ \rightarrow CH_3COCH_2CO^+ + CH_3COOH.$$

At room temperature perchloric acid reacts with acetic acid to form an acidium complex (XIV) with no *C*-acylating properties[106,116]. This explains the negative results obtained in attempts to acylate a number of aromatic compounds by carboxylic acids in the presence of perchloric acid[116]. However, when a dehydrating agent is added to the complex, it is converted to the acylium cation (XII)[107]:



$$CH_3COOH+HClO_4 \rightarrow \left[CH_3C\begin{matrix}OH\\ \\OH\end{matrix}\right]^+ClO_4^-.$$

(XIV)

Since perchloric acid is eliminated in the acylation of organic compounds by acyl perchlorates, the reaction is advantageously carried out with a slight excess of the acid anhydride and very small catalytic quantities of $HClO_4$.[115,116]

Dorofeenko and coworkers made a detailed study of the acylation of a series of reactive aromatic and heterocyclic compounds with carboxylic acid anhydrides in the presence of catalytic quantities of perchloric acid (0.001–0.05 mole of catalyst per mole of compound) and they substantially extended the field of application of this catalyst in the acylation of various organic compounds[115,116,117-127].

When aromatic hydrocarbons are acylated with pure acetyl perchlorate[109,128,129], or with acetic anhydride in the presence of perchloric acid[116,117], the corresponding aliphatic-aromatic ketones are obtained in low yield. Benzene forms only traces of acetophenone[109,116,129], but the yield of substituted alkyl aryl ketones increases considerably as the number of alkyl groups in the benzene nucleus increases[117]. Thus, for example, in the acylation of toluene *p*-methylacetophenone is formed in 5–6% yield[109,116,129], while under the same conditions the yield of ketone from *m*-xylene reaches 22–30%[109,119,128] and the yield of the ketone from mesitylene reaches 45%.[17,119] Naphthalene is also acylated by acetic anhydride, but the yield of α-acetylnaphthalene does not exceed 10–15%.[119]

A slight increase in the nucleophilic properties of the aromatic compounds materially increases the yield of ketone. Good results have been obtained in the acylation of acenaphthene with acid anhydrides in the presence of catalytic quantities of perchloric acid or Anhydrone; the yield of 5-substituted acylacenaphthenes was 50–81%.[119-121] It is interesting that acylation by this method gives mainly ketones substituted in the 5-position; acylation in the presence of aluminium chloride[130] or hydrogen fluoride[131] leads to the formation of a mixture of isomeric ketones.

Cauquil and coworkers found that silver perchlorate is also a good catalyst in the acetylation or aromatic hydrocarbons by acetic anhydride[132,133]. However, this expensive and very light-sensitive compound has no advantages over perchloric acid.

Magnesium perchlorate (Anhydrone)[134,135] and other aprotic or proton-containing derivatives of perchloric acid of the type of inorganic and organic salts, and also aralkyl perchlorates[119], were found to be good catalysts in the acylation of reactive aromatic and heterocyclic compounds by acid anhydrides. In this series of compounds the greatest catalytic activity was shown by magnesium perchlorate, benzyl perchlorate, and triphenylmethyl perchlorate[119].

Magnesium perchlorate has a milder catalytic action than perchloric acid and for this reason its use is preferred in the acylation of acid-labile compounds[134,135]. It may be supposed that the acylating agents in this reaction are acyl perchlorates (XII), i.e. this process proceeds in principle in the same way as the reaction catalysed by perchloric acid.

Detailed studies of the acetylation of anisole by acetic anhydride in the presence of perchloric acid enabled a convenient preparative method to be worked out for the preparation of *p*-methoxyacetophenone in 60–72% yield[106,107,116]. The use of pure acetyl perchlorate in this case has no advantages over the procedure described above[107].

The acetylation of anisole and phenetole in the presence of catalytic quantities of Anydrone gives the same yield (60–66%) as when perchloric acid is employed, but purer ketones are formed[134-136].

Kuhn and Daxner, using the method of Burton and Praill for the acylation of phenyl ethers with the anhydrides of acetic, propionic, and n-butyric acids in solution in the corresponding acid, obtained alkoxyacetophenones in good yield[137].

When anisole and phenetole are acylated with carboxylic acid anhydrides (propionic, n- and iso-butyric, n- and iso-pentanoic, and hexanoic) in the presence of small quantities of perchloric acid, the corresponding *p*-alkoxyphenyl alkyl ketones are obtained in 70–90% yield[138].

Aromatic hydrocarbons (*m*-xylene, mesitylene), phenol ethers (anisole and phenetole), and some heterocyclic compounds (thiophen) may be successfully acylated by carboxylic acid chlorides in the presence of small quantities of perchloric acid or Anhydrone[118,122,125]. However in acylation with aliphatic acid chlorides (from acetic to hexanoic) the yield of the corresponding ketones is as a rule much lower (20–55%) than when acid anhydrides are used. Good results were also obtained with other acylating agents; mixed anhydrides, silicon anhydrides† and boron anhydrides† of the acids were used[119].

Investigation of the benzoylation of a series of aromatic hydrocarbons and phenol ethers with benzoyl chloride in the presence of small quantities of perchloric acid or Anhydrone enabled a convenient preparative procedure to be developed for the synthesis of *p*-alkyl- and *p*-alkoxy-substituted benzophenones[125,127].

Good results have been obtained in the benzoylation of anisole and thiophen with benzoic anhydride in the presence of catalytic quantities of perchloric acid[139].

The benzoylation of anisole with aromatic acid chlorides (benzoyl, 2,4,6-trimethylbenzoyl, *p*-nitrobenzoyl, and anisoyl) in the presence of equimolar amounts of silver perchlorate in nitromethane solution has been studied; *p*-methoxybenzophenone and its derivatives were obtained in 50–84% yield[108]. Benzoylation of anisole with benzoic anhydride in nitromethane solution gives a lower (27%) yield.

When toluene and anisole are acylated with aralkylcarboxylic acid perchlorates of the type $[C_6H_5(CH_2)_nCO]^+ClO_4^-$ (n = 1–4) [obtained from $C_6H_5(CH_2)_nCOCl$ and $AgClO_4$ in nitromethane solution], ketones of the general formula $C_6H_5(CH_2)_nCOC_6H_4R$ are obtained in good yield[140]. *p*-Allyloxyacetophenone was obtained in 32% yield from allyl phenyl ether[29].

When ethers of mono- and poly-hydric phenols are acylated with a complex acylating agent consisting of molar quantities of acetyl chloride, acetic anhydride, and sodium perchlorate in glacial acetic acid, the corresponding alkoxy-substituted ketones are obtained in 30–50% yield[141]. However, these and other similar ketones are obtained in a higher yield (40–65%) in the acylation of phenol ethers with acetic anhydride in the presence of catalytic quantities of 60% perchloric acid[117].

Acylation of anisole and xylenes with tosyl perchlorate (from p-$CH_3C_6H_4SO_2Cl$ and $AgClO_4$ in nitromethane) led to the formation of substituted *p*-tolylphenylsulphones[142].

As already mentioned, in the acylation of phenols *O*-acyl derivatives are obtained in good yield, but hydroxyketones are not formed[106,116,135]. Under the same conditions aromatic amines undergo *N*-acylation[106]; acetylation of dimethylaniline in the presence of Anhydrone gave *p*-dimethylaminoacetophenone[135].

The acylation of azulene and its derivatives with acid anhydrides in the presence of perchloric acid has recently been studied[143].

Good results have been obtained by the acylation of various heterocylic compounds by this method[115,116,122,124,126,134-136,139]. Magnesium perchlorate is more convenient than perchloric acid as a catalyst in the acylation of heterocyclic compounds, because it does not destroy heterocyclic compounds and for this reason only quite small amounts of resinous products and by-products are obtained. Furan and α-methylfuran are easily acylated in the presence of traces of perchloric acid or Anhydrone to form 2-acetylfuran, 5-acetyl-2-methyl furan, and other furyl α-alkyl ketones in yields of 68–75%.[116,121,126,135,139]. When 2-halogenofurans were acetylated by this method, 5-acetyl-2-halogenofurans were obtained in 85–90% yield[144]. Acylation of thiophen with acid anhydrides proceeds with the same high yield (92–95%) as in the presence of stannic chloride[145], but the method of preparing ketones with perchloric acid is simpler and more convenient[116,126,135,138]. Thiophen is also easily acylated by aliphatic acid chlorides in the presence of Anhydrone to give thienyl α-alkyl ketones in 55–65% yield[125].

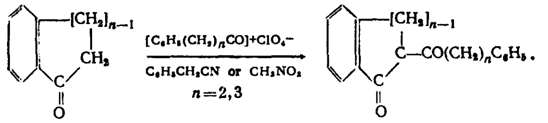
In the acylation of pyrrole by carboxylic acid anhydrides (from acetic to hexanoic) in the presence of small quantities of $HClO_4$ or $Mg(ClO_4)_2$ alkyl 2-pyrrolyl ketones are formed in 35–55% yield[124]. Even when pyrrole is acylated in the cold, 2-acylpyrrole, which is easily separated after neutralisation of the reaction mixture, is the main product; in the majority of experiments, 1-acylpyrroles have not been found in significant quantities. These results indicate that the conclusion of Berlin on the primary *N*-acylation of pyrrole is erroneous[105].

In the same way, in the acetylation or propionylation of pyrrole derivatives (1-methylpyrrole, 1-phenylpyrrole, and 2,4-dimethylpyrrole) substituted 2-acylpyrroles are obtained in high yield (50–72%)[124]. Indole is also easily acetylated in the presence of perchloric acid[116] or Anhydrone[134] to give 3-acetylindole in 32–50% yield together with some 1-acetylindole.

Alkyl aryl ketones (acetophenone and methylacetophenone) are acetylated by acetyl perchlorate on the methyl group to give the corresponding β-diketones in up to 20% yield[109].

$$ArCOCH_3 \xrightarrow[CH_3NO_2]{CH_3COCl+AgClO_4} ArCOCH_2COCH_3 .$$

Burton and Munday[146] extended this reaction to cyclic ketones (cyclopentanone, cyclohexanone, 1-indanone, and 1-tetralone); acylating with acetyl perchlorate and phenylalkanoyl perchlorates, they obtained cyclic β-diketones in low yield:



Recently it was shown that it was in principle possible to obtain αβ-unsaturated ketones by acylating olefins by Kondakov's method with acid anhydrides in the presence of perchloric acid and its compounds. Acylation of cyclohexene with acetic anhydride in the presence of perchloric acid[147] or with acetyl chloride and silver perchlorate in nitromethane[128,147] leads to the formation of 2-acetylcyclohex-1-ene in yields of 32 and 42% respectively. Hex-1-ene and triisobutylene are also acetylated by acetic anhydride in the presence of catalytic quantities of perchloric acid, unsaturated ketones being formed in 15–20% yield[119]. In the acylation of vinylaromatic compounds (styrene and vinyltoluene) under similar conditions unsaturated ketones were obtained in 15–20% yield, but the formation of considerable amounts of polymeric compounds was also noted[119,128]. Other arylethylenes (acenaphthylene and indene) alone or mixed with styrene only form polymers and copolymers in quantitative yield under the acylation conditions[148]. As shown by Plesh and coworkers the polymerisation of unsaturated compounds is initiated by acetyl perchlorate and proceeds by the usual cationic polymerisation mechanism[149].

Perchloric acid has also proved an effective catalyst in the acylation of a number of high-molecular-weight compounds containing reactive linkages in the polymer chain[123,148].

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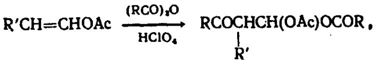
† Mixed anhydrides with silicic and boric acids ? (Ed. of Translation).

In particular, the C-acylation of polyacenaphthylene and of the copolymer of acenaphthylene with styrene have been carried out by this method[148].

The addition of anhydrides of carboxylic acids to vinyl acetate in the presence of catalytic quantities of perchloric acid or silver perchlorate leads to the formation of acylals of β-ketoaldehydes (10–60% yield), which are widely used in organic synthesis for the preparation of heterocyclic compounds[150,151]:



$$R'CH{=}CHOAc \xrightarrow[HClO_4]{(RCO)_2O} RCO\underset{\displaystyle R'}{\underset{|}{C}}HCH(OAc)OCOR,$$

where R = CH_3, C_2H_5, C_3H_7; R′ = H, CH_3.

Of other cases in which perchloric acid is used in an acylation reaction, the cyclisation of benzoylbenzoic acid to anthraquinone should be mentioned; the components are boiled in acetic acid solution[152].

IV. ACYLATION AND ALKYLATION OF THE HYDROXY-GROUP

Perchloric acid and its salts are widely used for the catalytic acylation of alcohols, phenols, and other hydroxy-compounds, and also for the analytical determination of the hydroxy-group[153]. Alcohols[154] and phenols[106,116] are acylated by acid anhydrides in the presence of traces of perchloric acid or Anhydrone[106,155]. In this way even compounds such as arylnitroalcohols[156] and tertiary alcohols[157], which are sensitive to mineral acids, have been successfully acylated. The acetylation of phenol[116], guaiacol[137], resorcinol[116], hydroquinone[106], and naphthols[114] gives aryl acetates in high yield. Information on the mechanism and kinetics of the O-acylation of phenols is given in a paper by Satchell[114].

The catalytic decomposition of 1,3,5-trioxan in acetic anhydride has been described; a mixture of mono-, di-, and (at low temperatures) even tri-oxymethylenediacetates is formed[158].

When $(CH_3CO)_2O$ and $HClO_4$ act on derivatives of 2-phenylcoumarin and tetrahydrofuran, the opening of the heterocyclic ring is accompanied by the formation of O-acyl compounds[159].

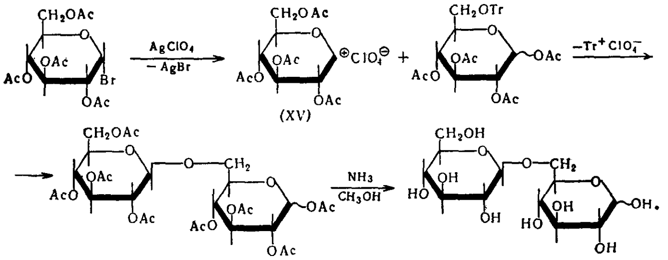
The use of perchloric acid in the acylation of polyhydric alcohols[160], monosaccharides[160,161], and cellulose[162-164] gives particularly good results. Glucose is acetylated rapidly and easily at ordinary temperatures to the α-pentaacetate[161]. Partial acetylation of cotton cellulose, in a continuous-process apparatus, is effected in a heterogeneous medium by a mixture of 85% CH_3COOH + 15% $(CH_3.CO)_2O$ and 0.1–0.2% $HClO_4$, or by 50% $(CH_3CO)_2O$, 50% pentyl acetate, and 0.2% $HClO_4$.[165] When acetylated D-glucosides are heated with acetic anhydride and perchloric acid, D-glucoseheptaacetate is obtained[166].

Heating glucose β-pentaacetate with perchloric acid in a solution of $(CH_3CO)_2O$ and CH_3COOH leads to its isomerisation to an equilibrium mixture containing 90% of the α-anomer[113,167].

A convenient preparative method has been developed for acetylating polyhydric alcohols, cyclitols, and some monosaccharides and O- and C-glycosides in the presence of small amounts of magnesium perchlorate, which is more convenient in this reaction than perchloric acid[154,155,168]. For example, with this method polyhydric alcohol polyacetates are obtained in 85–90% yield, and pure D-glucose α-pentaacetate is obtained in 80% yield.

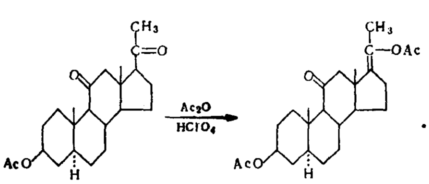
A simple and convenient method has been proposed for deacetylating polyhydric alcohol polyacetates and C-glycosides by heating the acetates with small quantities of perchloric acid in methanol solution[168,169]. Hydrolysis of O-glycosides with aqueous perchloric acid proceeds through the intermediate glucopyranosylcarbonium cation ("sucronium" cation)[170].

Recently a new method of synthesising oligosaccharides has been proposed[171]. Essentially this method consists in the reaction of acetohalogenose and silver perchlorate in nitromethane to give the sucronium perchlorate, which then reacts with acyl derivatives of 6-tritylmonose. In this way di- and tri-saccharides with 1,1- and 1,6-O-glycosidic bonds have been synthesised[172,173] and branching has been introduced into polysaccharide molecules[174]. The synthesis of the disaccharide gentiobiose in 59% yield has been effected according to the following scheme[173,175]:

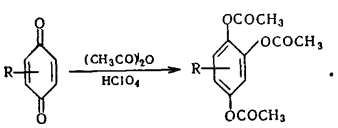


By a similar reaction of (XV) with the trityl derivative of Δ^5-3β-hydroxypregnen-20-one the O-glycoside of this steroid has been synthesised[175]. A series of acetylated O-glycosides has been synthesised by the interaction of sucronium perchlorates (XV), obtained as unstable colourless syrups from 1-chloro-2,3,4,6-tetra-O-acetyl-D-glucose, D-galactose, and D-xylose and $AgClO_4$, with aliphatic and alicyclic alcohols[176].

A method of O-acylation previously developed has been applied to the synthesis of fats[171,177]. When mono- and di-trityl ethers of various glycerides react with aliphatic acid chlorides and $AgClO_4$ in nitromethane, homogeneous triglycerides are formed in good yield[177]. There are also reports of the use of perchloric acid in O-acylation reactions of some steroids[178,179] and alkaloids[180,181]. Thus when 3-β-acetoxyallopregnane-11,20-dione was treated with acetic anhydride containing traces of perchloric acid in CCl_4 solution, the monoenol acetate was obtained in good yield[180]:



Perchloric acid is the most effective catalyst in the acylation of quinones by Thiele's method, since the triacetates of 1,2,4-trihydroxybenzene and its derivatives can be obtained in yields of 90% and more[112,182]:



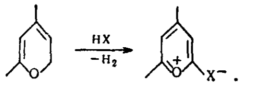
When treated with acetic anhydride and perchloric acid, 1,4-naphthoquinone forms 1,2,4-triacetoxynaphthalene in quantitative yield[183].

V. SYNTHESIS OF HETEROCYCLIC COMPOUNDS

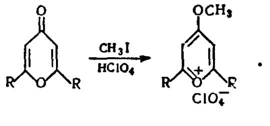
The systematic use of perchloric acid in the synthesis of heterocyclic compounds only began in recent years.

Perchloric acid is an effective catalyst and condensing agent in the synthesis of pyrylium salts, which are easily separated and purified as stable perchlorates. Methods of preparing pyrylium salts associated with the use of the acid may be classified according to three general synthetic routes: (a) synthesis from compounds containing the pyran ring; (b) the alkylation of olefins and other unsaturated compounds; (c) condensation reactions of carbonyl compounds. However, even in the latest reviews and monographs dealing with the chemistry of heterocyclic compounds the methods of synthesis and the properties of pyrylium salts are considered very superficially[184-188].

Under the action of strong mineral acids pyran derivatives eliminate a hydride ion and form pyrylium salts[189]:

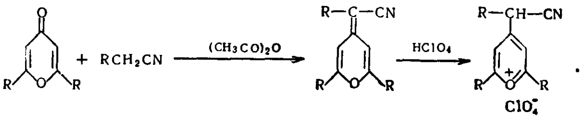


On alkylation with methyl iodide or dimethyl sulphate and subsequent treatment with perchloric acid, the readily accessible 2,6-dimethyl-4-pyrone, 2,6-diphenyl-4-pyrone, and 2,4-dimethyl-2-pyrone form 4(2)-alkoxypyrylium perchlorates[184,185].



2,4,6-Trisubstituted pyrylium salts with different substituents in position 4 of the pyrylium ring may be synthesised by the successive action of organomagnesium compounds and perchloric acid on 2,6-disubstituted 4-pyrones[190,191].

Similarly, in the presence of acetic anhydride or other dehydrating agents disubstituted 4-pyrones react with various nucleophilic compounds (dimethylaniline[192], malonic acid dinitrile, cyanacetic ester[193], etc.) to form substituted pyrylium salts:

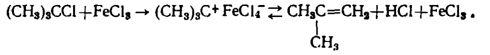


Some information on the conversion of pyrones to pyrylium salts is given in a recent review by Dimroth[193].

Data on the second of the aforementioned methods of preparing pyrylium salts, which was discovered almost simultaneously in 1959 by Balaban and Nenitzescu[194,195] and also by Praill and Whitear[157,196], are systematised in a detailed review by the Rumanian workers[197].

When olefins are acylated by Kondakov's reaction in the presence of the usual catalysts ($AlCl_3$, $SnCl_4$, $ZnCl_2$, $HClO_4$, BF_3 complexes, etc.), $\alpha\beta$-unsaturated ketones are formed[198]. However, as has been shown in recent work, pyrylium salts are formed in this reaction in addition to $\alpha\beta$-unsaturated ketones; because of their solubility in water, the pyrylium salts remained unnoticed for a long time[195,199-201].

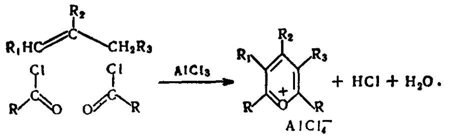
In their study of the carbonylation of t-butyl chloride by carbon monoxide in the presence of ferric chloride, Balaban and Nenitzescu observed a small quantity of crystalline product (~3%) in addition to trimethylacetic acid and t-butyl isobutenyl ketone; this turned out to be 2,6-di-t-butyl-4-methylpyrylium tetrachloroferrate[194]. From this the correct conclusion was drawn that the pyrylium salt is formed from isobutene produced by the decomposition of t-butyl tetrachloroferrate:



$$(CH_3)_3CCl + FeCl_3 \rightarrow (CH_3)_3C^+ FeCl_4^- \rightleftarrows \underset{\displaystyle CH_3}{\underset{|}{CH_3C}}{=}CH_2 + HCl + FeCl_3 .$$

On bisacylation of an olefin with trimethylacetyl chloride and subsequent cyclisation of the 1,5-diketone formed in the reaction, a pyrylium salt is obtained.

A detailed investigation of the acylation of a series of olefins (isobutene, α-methylstyrene, 1,2-diphenylpropene, etc.) with an excess of acid chlorides in the presence of aluminium led to a simple and original method of preparing substituted pyrylium salts in 20–40% yield[195]:



The pyrylium salts formed in the reaction are separated from aqueous solution as slightly soluble perchlorates, chloroplatinates, or derivatives of Reinecke's salt, or they are converted by ammonia to the corresponding pyridine bases.

Tri- and tetra-substituted pyrylium salts may be obtained in 25–50% yield by the acylation of olefins (isobutene, 2-methyl-1-butene, pent-1-ene, α-methylstyrene, etc.) with a large excess of acetic or propionic anhydride in the presence of molar quantities of 72% perchloric acid[196]. The structure of the pyrylium salts was established by their conversion into the corresponding pyridine derivatives, which is easily effected by treating the salts with aqueous ammonia or with ammonium acetate in acetic acid solution.

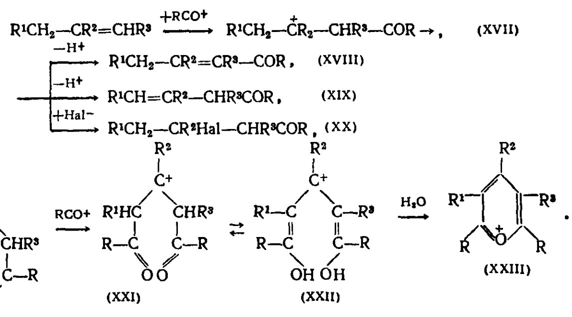
The reaction is obviously a general method of synthesising pyrylium salts from unsaturated compounds, containing the propenyl group, of the general formula (XVI):

$$R_1CH_2{-}CR_2{=}CHR_3$$

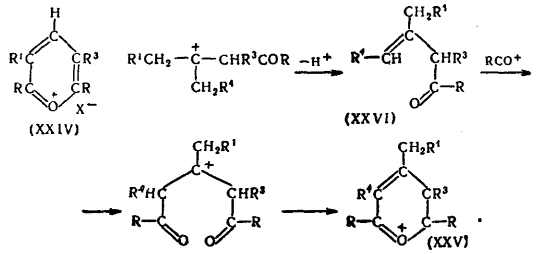
(XVI)

(where R_1, R_2, and R_3 = H, Alk, or Ar).

The mechanism of bisacylation of olefins is discussed in a series of papers on the synthesis of pyrylium salts and may be represented by the following scheme[197,201,202]:



The first stage of the reaction consists in the addition of an acylium cation to the unsaturated compound (XVI) to form a carbonium ion (XVII), which is stabilised by elimination of a proton, being converted into $\alpha\beta$-(XVIII) or a $\beta\gamma$-unsaturated ketone (XIX), or in the addition of a halide ion to form in the latter case a β-halogeno-substituted ketone (XX) (if the acylation is carried out by an acid halide). Since the double bond in the $\beta\gamma$-unsaturated ketone (XIX) formed in the reaction is not conjugated with the carbonyl group, it readily reacts with a second molecule of acylium cation to form the dicarbonyl compound (XXI), which is converted into the pyrylium cation (XXIII) by elimination of a molecule of water from the enol form (XXII). The proposed mechanism was further confirmed in work on the bisacetylation of olefins with $CH_3{}^{14}CO^+$.[203] When $R^2 = H$, only one pyrylium salt isomer (XXIV) is formed. When $R^2 = CH_2R^4$, two isomers can be obtained, the pyrylium cation (XXIII) obtained as described above and the isomeric cation (XXV) formed by the following reaction:

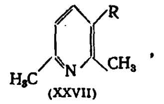


The formation and yield of the isomers (XXIII) and (XXV) is obviously determined by the quantitative ratio of the unsaturated cations (XIX) and (XXVI) and also by thermodynamic and kinetic factors.

As is to be expected, in the acetylation, propionylation and benzoylation of unsubstituted propene (the simplest compound which can be converted into a pyrylium salt by bisacylation), 2,6-disubstituted pyrylium salts are formed in low yield (0.5–5.7%)[204].

Praill and Whitear have made a detailed study of the acylation of a number of olefins (pent-1-ene, pent-2-ene, 3-ethylpent-2-ene, etc.) and other unsaturated compounds by acetic anhydride in the presence of perchloric acid[201].

Dulenko and Dorofeenko studied the bisacylation of higher olefins (the hex-1-ene, hept-1-ene, non-1-ene, and dec-1-ene) but in this case they did not succeed in separating pyrylium salts as perchlorates; these are difficult to crystallise and very soluble in water[205]. However, treatment of the reaction mixture with ammonia gave the corresponding 2,6-dimethyl-3-alkylpyridines (XXVII) (yield 23–42%), which are difficult to obtain

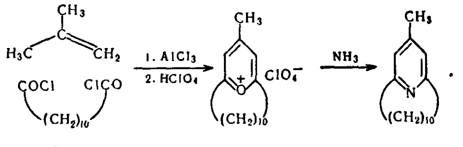

(XXVII)

where R = C_3H_7, C_4H_9, C_6H_{13}, and C_7H_{15}.

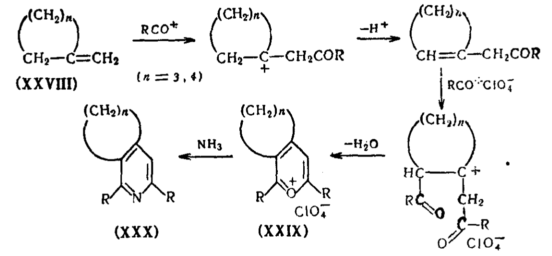
Crystalline pyrylium salts were not obtained when allylbenzene was acetylated in the presence of perchloric acid, but when the final product was treated with ammonia 2,6-dimethyl-3-phenylpyridine and 3-p-acetylphenyl-2,6-dimethylpyridine were obtained[206].

Acetylation of 2-methylpropenylbenzene ($CH_3COCl + AlCl_3$) gave a small amount of 2,6-dimethyl-4-benzylpyridine after the usual treatment[207]. The structure of the olefin materially effects the bisacylation reaction and the yield of pyrylium salts. The best results are obtained in the acylation of di- and tri-alkyl-substituted propenes, and also the "middle" members of the α-olefin series containing an activated double bond. When one or two aryl residues are introduced into the propene molecule, the yield of pyrylium salts is appreciably reduced. Attempts to synthesise pyrylium salts from olefins with a deactivated double bond (1,2,3-triphenylpropene and methyl methacrylate) have proved unsuccessful[197]. Attempts to synthesise pyrylium salts by acetylation of allyl halides and isoprene, which immediately polymerise under the reaction conditions, were also unsuccessful[208].

An interesting case of intramolecular bisacylation was observed in the action of decane-1,10-dicarboxylic acid chloride and $AlCl_3$ in nitromethane on isobutene[209]: the bicyclic 4-methyl-2,6-decamethylenepyrylium salt was obtained as perchlorate and this was converted into the corresponding pyridine, as isomer of the natural muskopyridine:

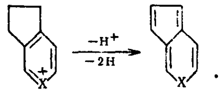


Balaban and Nenitzescu have done interesting work on the bisacylation of methylenecycloalkanes (XXVIII)[200]. Here, too, the pyrylium salts (XXIX) formed in the reaction could not be separated, but when the mixture was treated with ammonia 2,6-disubstituted pyridine, condensed with cycloalkene rings (XXX) were obtained in 18–25% yield



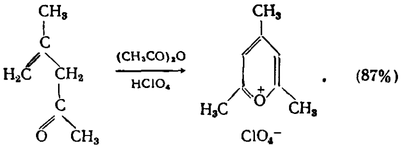
1,3-Dimethyl-5,6,7,8-tetrahydroisochromylium (n = 4) perchlorate was obtained in 30% yield by the acetylation of 1-methylcyclohexene, an isomer of (XXVIII) (n = 4).[201]

The pyrylium salts condensed with a cyclopentane ring (X = O) are of considerable interest, because they themselves and the quaternary pyridinium (X = NR) salts obtained from them can be used as starting materials in the synthesis of pseudoazulenes:



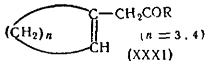
where X = O or NR.

As is to be expected, βγ-unsaturated ketones (for example 4-methylpent-4-en-2-one), which are intermediates in the bisacylation of olefins, form pyrylium salts in excellent yield under the conditions mentioned[201]



The acylation of products of the crotonic condensation of cyclic ketones (cyclopentanone, cyclohexanone, etc.) with aliphatic and alkyl aryl ketones, in one of the isomers of which (n = 4) the double bond is in the βγ-position to the carbonyl group, has been studied with the object of obtaining 5,6,7,8-tetrahydroisochromylium salts[208,211].

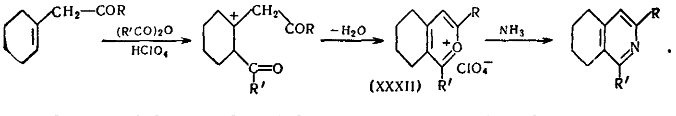
βγ-Unsaturated ketones (XXXI) (for example cyclohexenylacetone, cyclohexenylacetophenone, etc.) are acylated very rapidly by anhydrides of carboxylic acids in the presence of perchloric acid, the reaction mixtures becoming hot, and crystalline 5,6,7,8-tetrahydroisochromylium perchlorates (XXXII) can be isolated in good yield (70–90%):



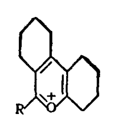
(n = 3, 4)

(XXXI)

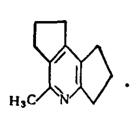
where $R = CH_3, C(CH_3)_3, C_6H_5$, etc.; $R' = CH_3, C_2H_5, C_3H_7, C_6H_5$, etc.



When cyclohexenylcyclohexanone was acylated in the manner described, 2-alkyloctahydrodibenzopyrylium (XXXIII) perchlorates were obtained in high yield (up to 80%)[208]. Attempts to acetylate the product of the autocondensation of cyclopentanone were also successful[208]. Although in this case the crystalline perchlorate was not isolated, treatment of the mixture with ammonia gave 2-methyl-3,4:5,6-biscyclopentadienopyridine (XXXIV) in 30% yield:



(XXXIII)



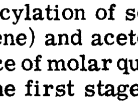
(XXXIV)

These results show that a variety of 1,3-disubstituted salts of 5,6,7,8-tetrahydroisochromylium can be easily synthesised by this method, and the salts may be used for the preparation of a number of isoquinolines, analogues of isoquinoline alkaloids, and other aromatic compounds difficult to obtain[208,211].

When t-butyl alcohol is acetylated in the presence of molar quantities of perchloric acid[157,199,201,212] or other acid catalysts[199], the final reaction product, obtained in the high yield (55–75%), is 2,4,6-trimethylpyrylium perchlorate. The same product is obtained in 72% yield by acetylating diacetone alcohol, which is evidently converted into a βγ-unsaturated ketone that readily forms a pyrylium salt[201].

Under the same conditions t-pentyl alcohol forms a mixture of pyrylium salts (yield 60%) consisting of 2,3,4,6-tetramethylpyrylium perchlorate (79%) and 2,6-dimethyl-4-ethylpyrylium perchlorate (21%).[157,158,201] Bisacylation of dimethylbenzylmethanol leads to the formation of 2,4,6-trimethyl-3-phenylpyrylium perchlorate[207], and 2,6-dimethyl-4-phenylpyrylium perchlorate is obtained from dimethylphenylmethanol[208]. Studies on the acylation of secondary alcohols in the presence of perchloric acid have shown that the process is accompanied by slow dehydration of the alcohols to the corresponding olefins, which are then diacylated with the formation of pyrylium salts, convertible by ammonia into the corresponding pyridines[208,213]. By this method 2,6-lutidine (11%) has been obtained from isopropanol, and 2,3,6-collidine (15%) has been obtained from butan-2-ol.

Other secondary alcohols (pentan-2-ol, hexan-2-ol, and octan-2-ol) form 2,3,4,6-tetrasubstituted pyridines (XXXV), which are difficult to obtain, in 27–30% yield:

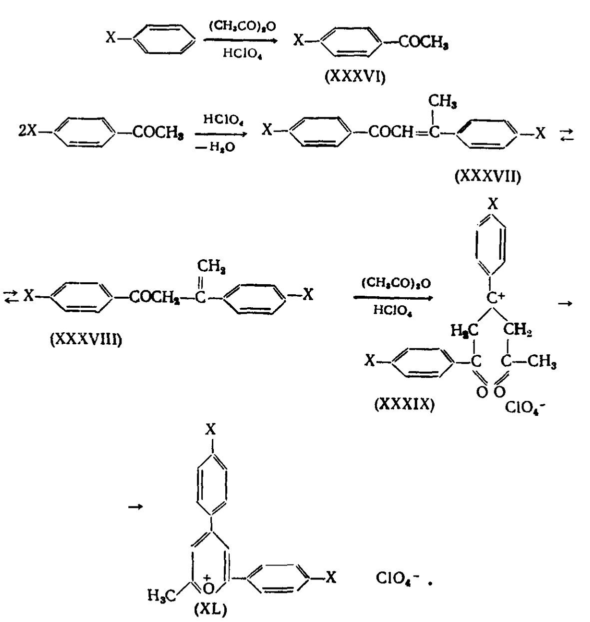


(XXXV)

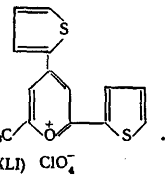
where R = CH_3, C_2H_5, C_4H_9.

However, attempts to extent this reaction to primary alcohols have not been successful[208].

In 1927 Diels and Alder reported on the preparation of pyrylium salts by the acylation of some aromatic compounds (toluene, o-xylene) and acetophenone with acetic anhydride in the presence of molar quantities of perchloric acid[104]. Obviously, the first stage in this reaction consists in the acetylation of the aromatic compound to an alkyl aryl ketone (XXXVI). The ketone obtained in this way, or introduced directly, forms a crotonic condensation product (XXXVII). The latter isomerises with a shift of the double bond to form a βγ-unsaturated ketone (XXXVIII), which is acylated again at the double bond with subsequent cyclisation of the diketone (XXXIX) to the pyrylium salt (XL):



2-Methyl-4,6-di(*p*-alkoxyphenyl)pyrylium salts (and from them substituted pyridines) are formed in good yield by acetylating phenol ethers (anisole and phenetole) or the corresponding *p*-alkoxyacetophenones in the presence of perchloric acid[208,214]. When thiophen or methyl-2-thienyl ketone is acetylated in this way, a pyrylium salt with heterocyclic radicals in the ring (XLI) is obtained in good yield (45%).

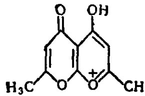


(XLI) ClO_4^-

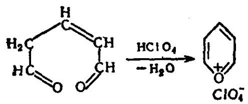
It is interesting that, when dibenzyl ketone is bisacetylated under similar conditions, it forms 2,6-dimethyl-3,5-diphenyl-4-pyrone in low yield, because of the high mobility of its methylene group hydrogen atoms[215].

The schemes given for the formation of pyrylium salts from olefins and ketones are confirmed by the fact that αβ-unsaturated ketones of suitable structure also form pyrylium salts[105,195,201,216]. For example, when mesityl oxide is treated with acetyl perchlorate, it forms 2,4,6-trimethylpyrylium perchlorate in 46% yield[105,201]. Acetylation of acetone in the presence of perchloric acid, which catalyses the crotonic condensation reaction as with mesityl oxide, readily gives a good yield (45–50%) of 2,4,6-trimethylpyrylium[214].

The Diels–Alder method of preparing pyrylium salts is a special case of a general method of synthesising compounds of this class by the bisacylation of olefins and other unsaturated compounds. However, the Diels–Alder method, the synthetic possibilities of which have not been fully elucidated, is very promising since it permits the preparation from readily accessible materials of pyrylium salts that are otherwise difficult to obtain. When a mixture of equimolecular quantities of acetic anhydride and perchloric acid is heated, self-acylation of the anhydride occurs and the acetoacetic acid is subsequently cyclised to the perchlorate of a base to which structure (XLII) has been ascribed[217]; the same compound is obtained when dehydroacetic acid is acetylated:



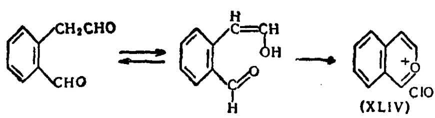
(XLII)



(XLIII)

A third route to the synthesis of pyrylium salts is associated with the condensation of carbonyl compounds and the cyclisation of dicarbonyl compounds in the presence of perchloric acid.

Thus, the unsubstituted pyrylium salt (XLIII) is formed in good yield by the action of perchloric acid on glutaconic dialdehyde[218]. Under the action of dehydrating complexes ($FeCl_3$, $SbCl_5$)[219,220] or trityl perchlorate[221] 1,5-diketones are smoothly converted into 2,4,6-trisubstituted pyrylium salts in 50% yield. Robinson and coworkers obtained salts of the isochromylium cation (XLIV) by treating homophthalic aldehyde with perchloric acid or ferric chloride, which results in the reaction[222,223]:



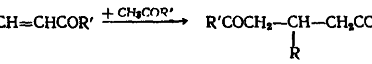
(XLIV)

The salts formed (XLIV) readily react with ammonia or primary amines to form isoquinoline and various *N*-substituted quaternary isoquinolinium salts.

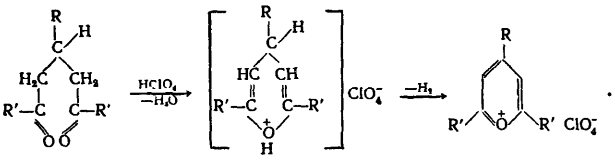
A simple method of preparing 2,4,6-triarylsubstituted pyrylium salts has been developed; these are obtained by the interaction of αβ-unsaturated ketones (chalkones) with alkyl aryl ketones[224–226] or by the direct condensation of aromatic aldehydes with ketones[220,227] in acetic anhydride in the presence of ferric chloride.

Dorofeenko and Krivun, who studied the condensation of aromatic aldehydes with alkyl aryl ketones in the presence of 70% perchloric acid, have proposed a simple and convenient method for the preparation of pyrylium salts with aryl substituents[228,229]. The synthesis of pyrylium salts appears to proceed through intermediate 1,5-diketones according to the scheme

$$RCHO + CH_3COR' \xrightarrow{HClO_4} RCH{=}CHCOR' + H_2O,$$



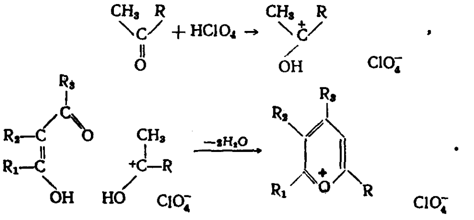
$$RCH{=}CHCOR' \xrightarrow{+CH_3COR'} R'COCH_2{-}\underset{R}{CH}{-}CH_2COR',$$



Pyrylium salts are readily formed by brief heating (1–2 hours) or an aromatic aldehyde and ketone (molar ratio 1 : 2) at 100–110° with or without an inert solvent. In this way 2,4,6-triphenylpyrylium perchlorate (50–60%), 2,6-diphenyl-4-*p*-nitrophenylpyrylium perchlorate (30%), 2,6-diphenyl-4-*p*-dimethylaminophenylpyrylium perchlorate (33–35%), and a number of other pyrylium salts have been obtained[228,229].

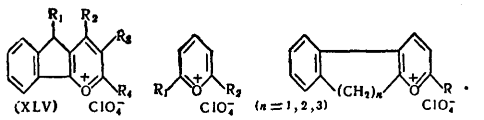
The recently described condensation of benzylideneacetophenone and phenacyl acetate to 3-acetoxy-2,4,6-triphenylpyrylium perchlorate is effected in a similar way[230]. When chalkones are condensed with cyclohexanone in the presence of perchloric acid, 2,4-diaryl-5,6,7,8-tetrahydrochromylium perchlorates are formed[231,232].

A method has been developed for preparing pyrylium salts in which β-dicarbonyl compounds are condensed with ketones in the presence of perchloric acid[208,233]:

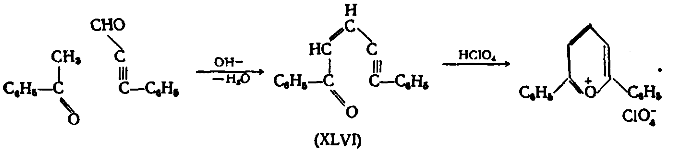


Although the pyrylium salts are obtained in low yield (15–30%) by this method, it appears to have wide possibilities, since it permits the synthesis of pyrylium salts that have not been obtained by other methods.

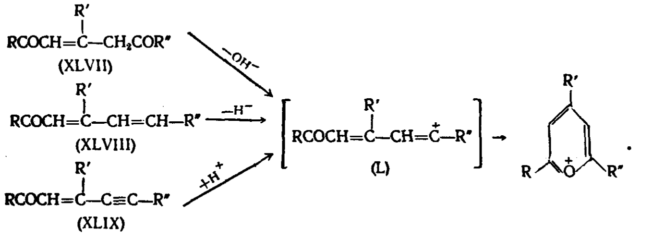
When 2-indanone and its derivatives are condensed with β-diketones, indeno[2,3*h*]pyrylium perchlorates (XLV) are obtained[234]; these form dyes when treated with sodium acetate[235]. Condensation of β-chlorovinyl ketones with ketones[236] or enamines[237] also leads to pyrylium salts of the following structure:


(XLV)

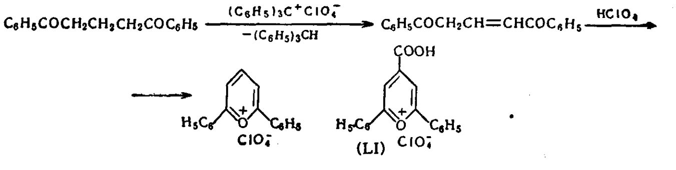
When acetophenone is condensed with phenylpropiolic aldehyde, the chalkone (XLVI) is formed; in the presence of perchloric acid this cyclises to a 2,6-diphenylpyrylium salt in 60% yield[238]:


(XLVI)

In a paper by Siemiatycki and Fugnitto a general mechanism is proposed for the formation of pyrylium salts from unsaturated δ-diketones (XLVII) and unsaturated ketones (XLVIII) and (XLIX) containing two double bonds, or a double and a triple bond, conjugated with a carbonyl group[221]. According to this interpretation, the formation of a pyrylium ring from ketones of the structure mentioned proceeds through the same carbonium ion (L), which is converted into a pyrylium cation:



This mechanism is confirmed by results in the paper quoted above[238] and by the studies of Siemiatycki and Fugnitto[221], who, showed that when 1,5-diphenylpenta-2,4-dien-1-one reacts with triphenylmethyl perchlorate, which has considerable dehydrating properties, 2,6-diphenylpyrylium perchlorate is formed (23%).[239,240] The same salt is obtained in good yield (88%) by the dehydration of 1,3-dibenzoylpropane with trityl perchlorate:

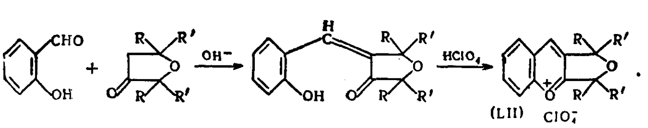

(LI)

In a similar way diphenacylacetic acid is dehydrated to form 2,6-diphenyl-4-carboxypyrylium perchlorate (LI) in good yield (85%)[221]; this compound has not been otherwise synthesised.

Perchloric acid is frequently used as a condensing agent in the synthesis of benzopyrylium salts[241]. A new method has been proposed for the synthesis of benzopyrylium salts by condensation of various β-chlorovinyl ketones with phenols and naphthols in the presence of ferric chloride or perchloric acid[242-246].

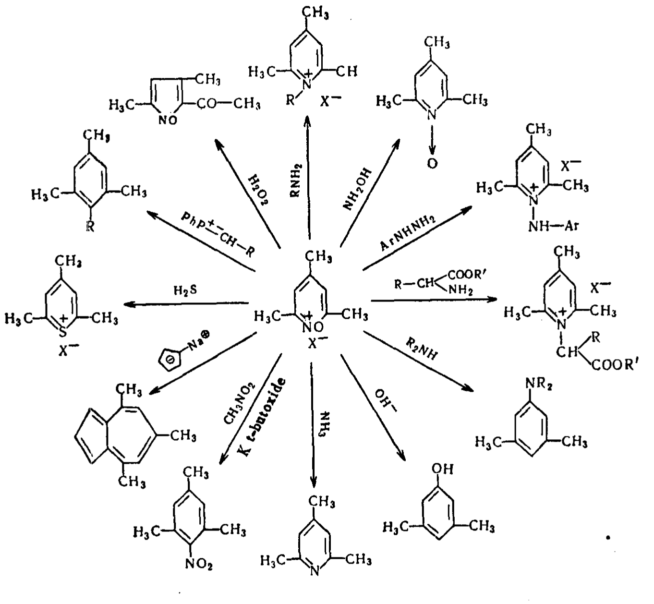
When xanthydrol or its derivatives is treated with perchloric acid in acetic anhydride, xanthylium salts are formed in good yield[247,248]. In this way 9-phenylethynylxanthylium perchlorate was obtained from 9-phenylethynylxanthydrol[249].

Recently it was shown that benzopyrylium perchlorates could be prepared by treating 2-acylcoumarins with perchloric acid in acetic acid[250]. Perchloric acid has also been used as a condensing agent in the Robinson–Kostanetskii reaction for the synthesis of furanidinobenzopyrylium perchlorates (LII), obtained in 30–65% yield[251].


(LII)

In recent years pyrylium salts have become of very great importance in organic chemistry because they are easily converted in high yield into alkyl- and aryl-pyridines[191,205], which are difficult to prepare; they also form *N*-alkyl(aryl)pyridinium salts[190,191], thiopyrylium salts[252], pyran derivatives[253-255], azulene derivatives[256,257], aromatic hydrocarbons[258,259], nitro-compounds[260], amines[104], phenols[190], and other aromatic compounds[258,261] that are frequently difficult to synthesise by other methods. Recently a new reaction of pyrylium salts was discovered that permits them to be readily converted into substituted alkyl α-furyl ketones[262] by the action of hydrogen peroxide, catalytic hydrogenation of which gives *sym*-trialkyltetrahydropyrans[212].

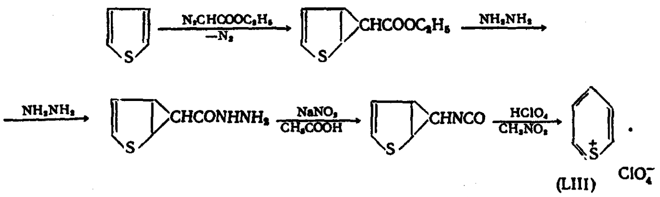
An interesting conversion of pyrylium salts into benzene derivatives by interaction with alkylidenetriphenylphosphoranes was recently discovered by Mark[263]. When pyrylium salts react with esters of α-amino-acids or diamino-acids, quaternary pyridinium salts are formed[264]:



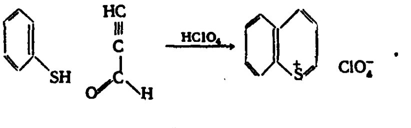
Detailed information on the chemical properties of pyrylium salts and their various reactions is given in an excellent review by Dimroth[193].

The use of perchloric acid and its compounds in the synthesis of sulphur- and nitrogen-containing heterocycles has also been described.

The preparation of thiopyrylium salts (LIII) by a new and interesting method has recently been described[265]:

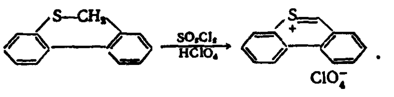

(LIII)

Engelhard and Kolb have proposed a simple single-step synthesis of thionaphththalenium salts; thiophenol or its derivatives is condensed with propargyl aldehyde in the presence of 70% perchloric acid[266].

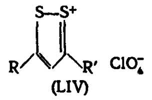


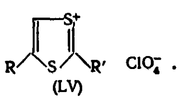
When thioxanthene is dehydrated with trityl perchlorate in acetic acid, thioxanthylium perchlorate is formed in good yield; with the same reagent 1-thiochromanone forms 1-thiochromone, also in good yield[267].

9-Thio-9,10-dihydrophenanthrene is smoothly converted into 9-thiophenanthrenium perchlorate by the action of sulphuryl chloride and perchloric acid in ether solution[268].



Perchlorates of 1,2-dithiolium derivatives (LIV) were obtained in good yield by the interaction of β-diketones with hydrogen sulphide in ether solution saturated with hydrogen chloride, and subsequent treatment with perchloric acid[269].

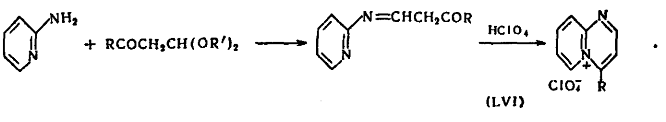

(LIV)


(LV)

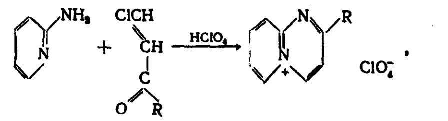
Similarly, when phenacyl- or acetonyl-carbodithionates were condensed with H_2S in ether solution saturated with HCl, salts of the 1,3-dithiolium cation (LV) were obtained.

There are reports on the use of perchloric acid in Fischer's indole synthesis. When acetophenone phenylhydrazone was heated to boiling in bromobenzene solution with perchloric acid, 2-phenylindole was obtained[270]. Perchloric acid has been used as a condensing agent in the synthesis of *N-p*-tolyl-4,6-dimethylquinolinium perchlorate obtained by Bayer's method by the reaction of *pp*-ditolylamine with acetone and formaldehyde in nitromethane solution[271].

A new method of synthesising salts of 4-alkyl-1-azadehydroquinolizinium cation (LVI) has been developed; this is based on the condensation of α-aminopyridine with acetals of acylacetaldehydes, followed by cyclisation of the condensation products with concentrated acids ($HClO_4$, HBr)[272, 273]:

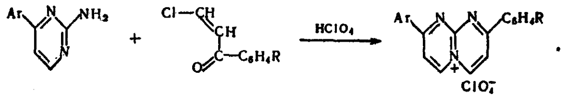

(LVI)

Compounds of this type are obtained easily and in good yield by the reaction of α-aminopyridine with β-chlorovinyl ketones in the presence of 70% perchloric acid[274]:



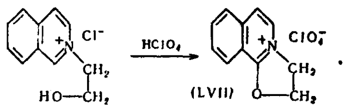
where R = CH_3, C_3H_7, C_6H_5.

2,8-Diaryl-1,9-diazadehydroquinolizinium{pyrimidino-[1,2-*a*]pyrimidinium} perchlorates (LVII), derivatives of a new heterocyclic system, were synthesised by condensing 4-aryl-2-aminopyrimidines with aryl β-chlorovinyl ketones in the presence of perchloric acid[275]:

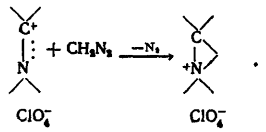

(LVII)

where R = H, *o*-Br, *p*-Br, *p*-NO_2.

N-(Hydroxy)isoquinolinium chloride is almost quantitatively cyclised to 4,9,5,6,7-hexadehydro-1-oxa-7,8-benzoindolizinium perchlorate (LVII) by boiling with 70% $HClO_4$ in alcoholic solution[276]:



When immonium perchlorates react with diazomethane, aziridinium salts, easily isolated in the crystalline state, are formed in good yield[277]:



We have described the most promising and most developed ways of using perchloric acid and its derivatives in organic synthesis. The scope of this review does not allow us to deal with its use in hydrolysis and solvolysis reactions, addition of carboxylic acids to olefins, polymerisation, dehydration with trityl perchlorate and quinone perchlorates, oxidation, isomerisation, and rearrangements, and also in various condensation reactions.

Although perchloric acid and its compounds began to be used only comparatively recently in organic chemistry, the data presented show that it undoubtedly has a wide and promising range of uses.

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ION-EXCHANGE CELLULOSES AND THEIR USE IN CHROMATOGRAPHY

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CONTENTS

I. INTRODUCTION

The successful development of sorption technique and chromatography is to a considerable extent dependent on the discovery and utilisation of new types of synthetic sorbents. The production and introduction into sorption technology, particularly chromatography, of a new type of ion-exchange sorbent, the ion-exchange celluloses, is an outstanding achievement of modern chemistry and biochemistry.

The number of papers dealing with the chromatographic use of ion-exchange celluloses has been rapidly growing in recent years, and about 500 have already been published. The use of ion-exchange celluloses in chromatography and other varieties of sorption technology has enabled considerable progress to be made in the resolution of some of the most difficult problems in biochemistry — the separation of proteins, enzymes, nucleic acids, and other high- and low-molecular-weight substances found in living matter.

It is to be expected that ion-exchange celluloses will rapidly find wider application in ever increasing numbers of chemical fields.

The object of this review is to provide an account of current knowledge of the properties and uses of ion-exchange celluloses.

II. PREPARATION OF ION-EXCHANGE CELLULOSES

We shall not concern ourselves here with the ion-exchange properties of natural and commercial (including chromatographic) celluloses, which may be found in a number of monographs, e.g. those of Rogovin[1] and Hais and Macek[2]. We note only that both natural and the various types of commercial cellulose possess ion-exchange properties mainly because of the presence of carboxyl groups, but their absorption capacity is negligibly small, being only ~ 0.05 mg-equiv. g^{-1}, which corresponds to about one carboxyl group for 90–130 glucose structural units[3,4].

The use of ion-exchange forms of cellulose for chromatographic purposes already has a history of more than 50 years. Goppelsröder[5] mentioned oxycellulose (a weakly acidic carboxyl-type cation exchanger) as a suitable material for capillary analysis. Oxycellulose is obtained by saponifying the esters present in the initial cellulose and oxidising the primary alcoholic groups present in the 6-position of the glucose structural units[1,2]. Even in this process definite limitations are found in the content of carboxyl groups: there exists a certain critical level for the introduction of these ionogenic groups into cellulose; above this level the cellulose loses the character of an insoluble sorbent. For oxycellulose it was found that the content of carboxyl groups could not exceed 1–4%; with more than 5% (every fifth glucose structural unit then being oxidised in the 6-position) the oxycellulose becomes soluble in water at pH above 9.[2]

The "pioneering" work on the production of different types of ion-exchange cellulose includes that of Lautsch and coworkers[6], Micheel and Albers[7], Sober and Peterson[8,9], and Porath[11]. Lautsch and coworkers obtained a number of ion-exchange cellulose ion exchangers: a carboxyl-type cation exchanger, the ether of glycolic acid containing the $-CH_2OCH_2COOH$ group, by the action of chloroacetic acid in alkaline solution; a strongly acidic cation exchanger containing the $-CH_2OCH_2CH_2CH(SO_3H)CH_3$ group by the action of butane sulphone; and an anion exchange containing $-CH_2\overset{+}{N}R_3X^-$ groups by esterification with *p*-toluenesulphonyl chloride and reaction of the ester with tertiary amines. In each case one ionogenic group could be introduced for each 20–30 glucose structural units; this was the limit of ion-exchange capacity for these ion exchangers, since with more ionogenic groups the cellulose decomposed.

Micheel and Albers[7] obtained a carboxyl-type cation-exchange cellulose in the form of the phthalic acid mono-