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New Reactions of *N*-Methylated Oxopurines

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The reactions of *N*-methylated oxopurines with phosphorus chlorides, resulting in the formation of highly reactive amidochloride compounds (amidochlorides or adducts), are described. Two isomeric series of $C_{(2)}$- or $C_{(6)}$-substituted oxopurine derivatives as well as $C_{(6)}$- or $C_{(2)}$-iminopurines can be obtained from such compounds.
The properties and characteristics of the compounds, their structures, and the demethylation reactions of the amidochlorides and the adducts, accompanied by the elimination of methyl chloride, are discussed.
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I. INTRODUCTION

The synthesis of various derivatives of *N*-methylated xanthines (2,6-dioxopurines) from natural purine alkaloids (theobromine, theophylline, and caffeine) has been for a long time one of the popular ways of seeking new medicinal preparations, mainly with cardiovascular activity, in the purine series.

Hitherto, the protons at the $N_{(1)}$ or $N_{(7)}$ atoms in 3,7-dimethyl-or 1,3-dimethyl-xanthines (theobromine or theophylline)[1] as well as the hydrogen linked to the $C_{(8)}$ carbon atom of the imidazole ring in all three purine alkaloids[2] were usually substituted by various groups for this purpose.

The substitution at ring nitrogen and carbon atoms does not entail a change in the xanthine structure. Therefore new sometimes extremely valuable properties, appearing as a result of the introduction of additional substituents, are always manifested against the background of the manifold pharmacological activity characteristic of the initial purine alkaloids, although individual aspects of this activity may vary within fairly wide limits.

Such studies were begun as early as 60—70 years ago. Nevertheless, they cannot be regarded as exhausted: the literature of the last decade contains numerous examples of the synthesis of previously unknown theobromine, theophylline, and caffeine derivatives as well as certain monomethylxanthines, which, although not fundamentally different from those described earlier, contain substituents with a more complex structure, frequently simultaneously in the 1-, 7-, and 8-positions.

Reactions of *N*-methylated xanthines which lead to the loss of the xanthine structure and hence of the set of pharmacological properties characteristic of this structure have also been known for a long time. One of the clearest examples of this is provided by the interaction of theobromine with phosphoryl chloride in a closed system at a high temperature, described for the first time by Fischer as early as the end of the last century, which leads to the elimination of the methyl in the 3-position and to the formation of 2,6-dichloro-7-methylpurine, from which it is subsequently easy to obtain various derivatives of 7-methylpoxanthine and oxygen-free purine, as well as paraxanthine, its derivatives, and many other compounds[1,3,4].

Although the mechanism of this reaction has been little investigated and has remained obscure until recently, the principles underlying it subsequently acquired considerable preparative value, since the synthetic possibilities in the purine series were greatly extended with the aid of similar reactions[5].

Studies dealing with the reactions of theobromine with phosphorus chlorides under milder conditions than those described by Fischer have been published since 1962. Such reactions lead to the formation of various derivatives of 6- or 2-oxodihydropurines retaining both methyl groups in the 3- and 7-positions—compounds which differ significantly in their structure and in their chemical and physical properties not only from methylated xanthines but also from all other purine derivatives described previously. These extremely reactive compounds can be of considerable interest as a new potential source of biologically active compounds.

The present review deals with problems of their synthesis and structure and also with certain aspects of the mechanism of their formation.

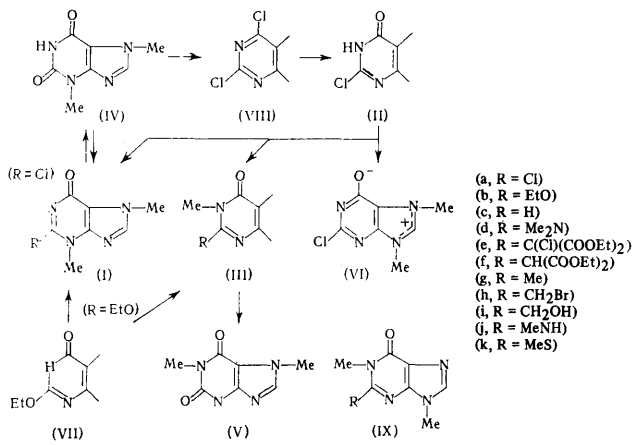
II. DERIVATIVES OF DIHYDRO-3,7-DIMETHYLMONOXOPURINES

1. Synthesis of $C_{(2)}$-Substituted Derivatives of 3,7-Dimethylhypoxanthine (3,6-Dihydro-3,7-dimethyl-6-oxopurine)

The first representative of the 3,7-dimethylhypoxanthine (I) series, namely 2-chloro-3,7-dimethylhypoxanthine (Ia), was recently isolated[6] as one of the side products in the methylation of 2-chloro-7-methylhypoxanthine (II) to form 2-chloro-1,7-dimethylhypoxanthine (IIIa), which, like (II), is an intermediate in the conversion of theobromine (IV) into paraxanthine (1,7-dimethylxanthine) (V).[3,4] This reaction has been known for a long time. 2-Chloro-6-oxo-7,9-dimethylpurinium betaine (VI), which is stable on heating with inorganic acids, is yet another side product in the methylation of (II) by dimethyl sulphate (DMS) in an aqueous alkaline medium[7]. It is formed as the main product when the reaction is carried out in dimethylformamide (DMF).[8]

2-Chloro-3,7-dimethylhypoxanthine (Ia), which is readily hydrolysed to theobromine, is converted on treatment with sodium ethoxide into the 2-ethoxy-derivative (Ib), identical with the side product isolated in a small amount in the analogous methylation of 2-ethoxy-7-methylhypoxanthine (VII).[9]

A single-stage preparative method for the synthesis of the key chloride (Ia) directly from theobromine was discovered somewhat later. A 1:10 mixture of theobromine and $POCl_3$ is heated until the former dissolves, the excess $POCl_3$ is distilled off, and the residue is treated with ice in the presence of $NaHCO_3$. Apart from the chloro-derivative (Ia), about 10% of 2,6-dichloro-7-methylpurine (VIII) can be isolated in this reaction[5]. If the treatment with ice is carried out in the absence of $NaHCO_3$, i.e. at a low pH, the entire chloro-derivative formed hydrolyses and the initial theobromine (IV) is regenerated (see below).

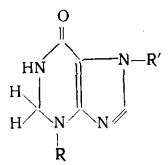


The above easy method of synthesising the chloro-derivative (Ia) and the high mobility of its chlorine atoms made it possible to synthesise many derivatives of 3,7-dimethylhypoxanthine substituted in the 2-positions by various groups [for example compounds (Ib)—(Ik) and many others][10,11], in which the presence of the methyl group in the 3-position fixes one of the double bonds of the pyrimidine ring in the 1,2-positions. Owing to the *p*-quinonoid structure of the ring due to the distribution of the substituents, the entire series of compounds (I), probably differs fairly significantly in its properties from compounds of the 2-R-1,9-dimethylhypoxanthine series (IX) and (III) with the same substituents R,[12-14] i.e. from the isomeric 2-substituted derivatives of *NN*-dimethylhypoxanthines with a "normal" bond distribution.

The characteristics of compounds (I), due to the high electrophilicity of the second ring carbon atom, have been noted in many reactions. They are shown by the enhanced reactivity of the substituents at this carbon atom, which is particularly evident in certain reactions of the chloro-derivative (Ia): it is not only exceptionally readily hydrolysed with elimination of chlorine at low pH, but it also undergoes nucleophilic substitution reactions when treated with alkoxides, ammonia, primary and secondary amines, and other nucleophilic agents, much more vigorously than the isomeric 2-chloro-1,9- and 2-chloro-1,7-dimethylhypoxanthines (IXa) and (IIIa). Such reactions of compound (Ia) usually do not require heating and actually occur with evolution of heat.

The system of compounds (I) as a whole exhibits an enhanced reactivity. This is shown, in particular, by the fact that the catalytic dehalogenation of (Ia) in the presence of Pd/C or Raney nickel results in the formation of a mixture of the expected compound (Ic) and its dihydro-derivative—1,2,3,6-tetrahydro-3,7-dimethyl-6-oxopurine (X).[10]

The catalytic debenzylation of 3-benzyl-7-β-D-ribofuranosylhypoxanthine, i.e. a compound which does not differ from (Ic) in the distribution of the double bonds in the pyrimidine ring, resulted in a mixture of 7-β-D-ribofuranosylhypoxanthine and a dihydro-derivative of the initial compound, which should be regarded as 3-benzyl-1,2,3,6-tetrahydro-6-oxo-β-D-ribofuranosylpurine (XI) on the basis of the results of a study of the ^1H NMR spectra[15].



(X, R+R′=Me)

(XI, R = $PhCH_2$, R′ = β-D-ribofuranosyl

Comparison of the abilities of 2-ethoxy-derivatives of three *NN*-dimethylhypoxanthines (the 3,7-, 1,7-, and 1,9-dimethyl derivatives) to function as ethylating agents with respect to malonic ester by splitting off their ethoxy-group (which is described in greater detail in another review[2]) demonstrates yet again that the isomer (Ib), containing *N*-methyl groups in the 3- and 7-positions, is the most reactive and forms ethylmalonic ester in a high yield. Data obtained by quantum-chemical calculations for the electronic structures of (Ib), the isomeric compounds (IIIb) and (IXb), their 8-chloro-derivatives, and three dimethylmonoxopurines unsubstituted at $C_{(2)}$ and $C_{(8)}$ [compounds (Ic), (IIIc), and (IXc)] confirmed that the electron density and the free valence index at $C_{(2)}$ in 3,7-dimethyl-6-oxopurines are appreciably reduced and therefore compound (Ib) and its 8-chloro-derivative should indeed exhibit the maximum alkylating capacity[16]. It has also been noted that the dialkylamino-group in the 2-position in compounds of type (Id) is readily hydrolysed in the presence of inorganic acids with regeneration of theobromine[2,17].

The replacement of chlorine in compound (Ia) by a dialkylamino-group and its subsequent hydrolytic elimination in the last stage can be used in the synthesis of $C_{(8)}$—C derivatives of theobromine as a method of protecting the proton at the first nitrogen atom[18].

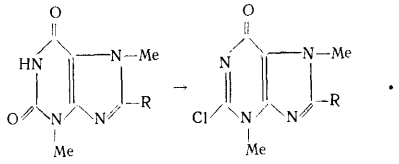
Not only the Cl—$C_{(2)}$ and N—$C_{(2)}$ bonds but also the C—$C_{(2)}$ bond can readily undergo hydrolytic cleavage in compounds (I). An example of this reaction is provided by the formation of theobromine as a result of heating 2-chloromalonate (Ia) with inorganic acids[19].

It is interesting that the $C_{(2)}$—C bond in 1,7- and 1,9-dimethylhypoxanthines with chloromalonic acid groups [compounds (IIIe) and (IXe)] does not undergo cleavage and the main reaction products are the corresponding 2-hydroxymethyldimethylhypoxanthine (IIIi) or 2-chloromethyldimethylhypoxanthine (IXi).[13,14]

In derivatives of compounds (I) the $C_{(2)}$—C bond is not cleaved when the malonic acid residue does not contain chlorine: in compound (If) only the ester groups are hydrolysed with decarboxylation. 2,3,7-Trimethylhypoxanthine (Ig) was obtained in this way and was subsequently converted by treatment with dibromodioxan into the monobromo-derivative (Ih). A wide variety of compounds can be obtained from the latter on replacing the bromine by various substituents (including groups with a complex structure). When the purinylmalonate (If) is treated with ethanol in the presence of catalytic amounts of hydrogen

chloride, only one ethoxycarbonyl group is split off. The resulting ethyl ester of 3,7-dimethylhypoxanthine-2-acetic acid was converted into its amides by treatment with ammonia and amines[19].

The series of compounds with structure (I), whose synthesis is based on the reaction of theobromine with $POCl_3$, can be greatly extended by introducing a second substituent at the $C_{(8)}$ atom of the imidazole ring. For this purpose, instead of theobromine one may treat with $POCl_3$ its 8-substituted derivatives—8-chlorotheobromine (XII) or 8-methyltheobromine (XIII)—which are thereby converted into the dichloro-derivative (XIV) or into 2-chloro-3,7,8-trimethylhypoxanthine (XV).[20-22] The use of the former leads to the greatest possibilities: by successive substitution of the chlorine atoms, initially at $C_{(2)}$ and then at $C_{(8)}$, it is possible to vary the nature of the substituents at the ring carbon atoms in both rings of the purine molecule.



(XII, R=Cl) (XIV, R=Cl)
(XIII, R=Me) (XV, R=Me)

The above reactions of 8-chlorotheobromine and the synthesis from it of 2,8-disubstituted derivatives of 3,7-dimethylhypoxanthine result in relative freedom from restrictions on the structure of the substituents at $C_{(8)}$, while that of the substituents at $C_{(2)}$ may sometimes be subject to limitations due to the characteristics of the system, mentioned above, probably due to its *p*-quinonoid structure.

On the other hand, syntheses from 8-methyltheobromine provide a considerable scope for the preparation of 3,7,8-trimethylhypoxanthines with a wide variety of substituents in the 2-position. However, the attempts to modify subsequently the substituent at $C_{(8)}$ by replacing one of the hydrogen atoms of the methyl group by a halogen[2] were unsuccessful. Nor is it always possible to employ as starting materials 8-substituted theobromine derivatives with a specified structure of the substituent at $C_{(8)}$ joined to the ring via a C—C bond; such compounds char appreciably on heating with $POCl_3$.[17,22]

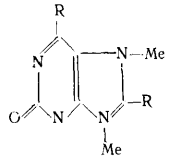
Derivatives of 3,7-dimethylhypoxanthine differ from the isomeric 1,7- and 1,9-dimethylhypoxanthines not only in their chemical properties but also in their physical properties[10]. For example, the ultraviolet spectrum of (Ia) exhibits an 8 nm bathochromic shift of the long-wavelength maximum accompanied by an increase of ϵ relative to the ultraviolet spectrum of the chloro-derivative (IIIa); a similar shift is characteristic of the majority of compounds (I) obtained from the chloro-derivative (Ia) as a result of the replacement of its chlorine atom by other substituents. Comparison of the infrared spectra of the isomeric 3,7- and 1,7-dimethylhypoxanthines shows clearly in the latter a shift of the characteristic bands of the amide carbonyl towards longer wavelengths, in full agreement with data[23] indicating a decrease of the C—O vibration frequency in purines having the *p*-quinonoid structure relative to other purine derivatives.

Certain characteristics of compounds of type (I) arising from their structure are not typical for this series alone (cf. Refs. 24—26). They are typical to some extent for many purines, including those substituted at the nitrogen atoms of the pyrimidine ring, but not for 6- or 2-aminopurines unsubstituted in the imidazole ring. Such aminopurines have been obtained in different ways, for example by direct alkylation or glucosidation of adenine[27-31], *N*-benzoyladenine, or 6-dimethylaminopurine[32], by synthesis from the corresponding 4,5-diaminopyrimidines[33-35], or from 3-methylguanine by the reaction of the latter with P_2S_5 and subsequent alkylation of the resulting 2-amino-6-mercapto-3-methyl-3,6-dihydropurine and substitution of the alkylthio-group in the 6-position by various groups[26,32].

It has been shown convincingly by ultraviolet spectroscopy and ^1H NMR that these compounds exist in the amino- and not in the imino-form and that consequently substitution at $N_{(1)}$ or $N_{(3)}$ should be accompanied by the transfer of a proton from the imidazole ring of the aminopurines to the pyrimidine ring and migration of double bonds, which results in an *o*- or *p*-quinonoid structure of the purine stabilised by the substituent at the ring nitrogen atom. These and many other purine compounds with an unusual fixed distribution of double bonds differ from purine derivatives having the "classical" structure by their chemical behaviour and spectroscopic characteristics. These differences are shown particularly clearly when there is a substituent at the $N_{(3)}$ atom and in most cases they are very similar to the differences characteristic of compounds of series (I), which were mentioned above. It is self-evident that substitution at the nitrogen atom of the imidazole ring of aminopurines is not reflected in the state of the system, since it involves merely a simple replacement of the proton and does not entail changes in the distribution of double bonds[36].

2. Synthesis of $C_{(6)}$-Substituted Derivatives of 2,3-Dihydro-3,7-dimethyl-2-oxopurine

The applications of the reaction of theobromine with phosphoryl chloride are not limited to the synthesis of compounds of series (I). This reaction is also used to synthesise certain isomeric derivatives of the 6-R-2,3-dihydro-3,7-dimethyl-2-oxopurine series (XVI). 8-Chloro- and 8-methyl-derivatives of (XVI) [compounds (XVII) and (XVIII)] can be obtained similarly from the 8-chloro- and 8-methyl derivatives of theobromine [(XII) and (XIII)].



(a, R = MeO)
(b, R = EtO)
(c, R = PrO)
(d, R = BuO)
(e, R = MeS)
(f, R = NH_2)
(g, R = MeNH)
(h, R = Me_2N)
(i, R = Cl)

(XVI; R=H); (XVII; R=Cl);
(XVIII; R=Me)

6-Alkoxypurines (XVI, a—d) have been obtained by treating with the corresponding alcohols the product of the reaction of theobromine with $POCl_3$ and subsequent hydrolysis with $NaHCO_3$ solution[37].

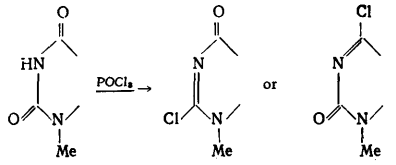
The structures of these compounds have been confirmed by many reactions and that of compound (XVIb) has been demonstrated unambiguously by its identification with the compound obtained by allowing sodium ethoxide to react with 1,2-dihydro-3,7-dimethyl-6-methylthio-2-oxopurine (XVIe) known previously under the trivial name "6-methylthiotheobromine"[38,39]. When compound (XVIb) was heated with ammonia, methylamine, and dimethylamine, the corresponding 6-amino-derivatives (XVIf), (XVIg), and

(XVIh) were obtained, the last two being identical with the compounds synthesised by allowing the same amine to react with compound (XVIe).[40]

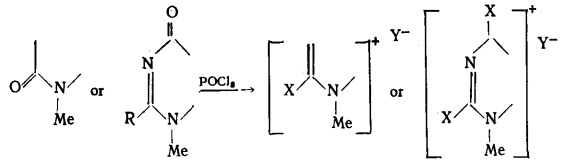
It is noteworthy that the properties of compound (XVIa) agree fully with those described for dihydromethoxy-3,7-dimethyloxopurine obtained by the methanolysis of the tetra-acetate of theobromine β-D-glucoside[41].

The above syntheses are not merely of preparative value. They throw light on the essential features of the reactions, occurring when *N*-methyloxopurines are heated with $POCl_3$ and also on certain problems concerning the structures of the primary products of these reactions (this is discussed in greater detail in Section III).

Depending on the method of treatment of the residue obtained after distilling off the excess $POCl_3$ from the reaction mass (treatment with $NaHCO_3$ solution or with alcohol first and only then with aqueous $NaHCO_3$), it is possible to obtain from compound (IV) either the chloro-derivative (Ia) [10] or one of the compounds of type (XVI, a–d),[40] each in a yield exceeding 50%. This undoubtedly shows that the members of both isomeric series, (I) and (XVI), have a common precursor, which is formed by the reaction of both carbonyl groups with $POCl_3$. One of them (probably either one) should react with $POCl_3$, by virtue of the presence of a proton at the neighbouring ring nitrogen atom, via the general mechanism of the conversion into the corresponding chloro-derivative of 2- and 4-oxo-(hydroxy)pyrimidines[42], α-oxo(hydroxy)purines[1], and also oxo(hydroxy)-derivatives of other nitrogen heterocycles:

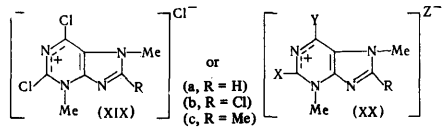


The second carbonyl probably reacts with $POCl_3$ as an *N*-substituted cyclic amide, which may result in the formation of a fairly stable compound containing the amido-chloride group[43]:



(where X and Y are both Cl or Cl and $OPOCl_2$)

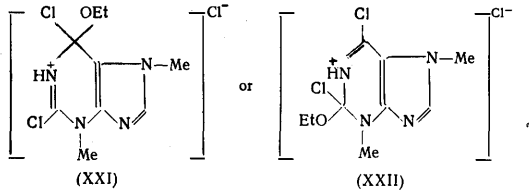
Since each carbonyl group of theobromine or its derivatives (XII) and (XIII) is probably capable of reacting in either way, the primary products of their interaction with $POCl_3$ are compounds (XIX) or (XX):



(X, Y and Z = Cl or Cl and $OPOCl_2$)

The presence of amidochloride groups in these compounds has been confirmed by numerous reactions[43], primarily by their ability to combine with an alcohol molecule to form the hydrochlorides of amidoester chlorides.

In the present instance the crystalline substances formed when alcohols are allowed to react with the products of the reaction of (IV), (XII), or (XIII) with $POCl_3$ are of this kind. The overall formula $C_9H_{13}N_4Cl_3O$ of the crystalline compound obtained from (IV) after treatment with ethanol makes it possible to attribute to it the structure of the hydrochloride of 2,6-dichloro-6(or 2)ethoxy-3,6(or 2,3)-dihydropurine [(XXI) or (XXII)]:



Many reactions of this compound—hydrolytic cleavage at low pH, aminolysis, interaction with thiourea, etc.—are consistent with both structure (XXI) and (XXII) and there are no grounds for making a choice between them, since in either case the same products should be obtained: theobromine, the hydrochloride of 6(2)-amino-3,6(3,2)-dihydro-2(6)-imino-3,7-dimethylpurine and 2,6-dithio-theobromine[44]. On the other hand, the formation from it of 6-ethoxy-2,3-dihydro-3,7-dimethyl-2-oxopurine (XVIb) on hydrolysis in a neutral medium undoubtedly indicates that the ethoxy-group is at $C_{(6)}$, i.e. there is evidence that the compound has the structure (XXI). This is also shown by another reaction characteristic of amidoester chlorides, namely the thermal cleavage of the ester chloride group accompanied by the evolution of an alkyl chloride and the regeneration of the initial amide[43].

When the above amidoester chloride is heated, ethyl chloride is liberated and the chloro-derivative (Ia) is formed in a high yield. Since the fragment C(Cl)(OEt) must be the precursor of the carbonyl group, the formation of the chloro-derivative (Ia) as a result of the thermal cleavage constitutes yet another confirmation of the presence of the ethoxy-group in the amidoester chloride at $C_{(6)}$ and not at $C_{(2)}$, i.e. of structure (XXI) rather than (XXII).

On the other hand, the formation of the amidoester chloride (XXI) from the amidochloride compound (XIXa) or (XXa) suggests that the ring carbon atom $C_{(6)}$ in the latter is more electrophilic than $C_{(2)}$ and that consequently the substituents in the 6-position in (XIX) and (XX) should undergo hydrolytic cleavage first, with regeneration of the carbonyl group. Therefore it is quite reasonable that hydrolysis at pH 7 of the intermediates obtained from theobromine on heating the latter with $POCl_3$ results in the formation of the monochloromonoxopurine (Ia) as the main product, both substituents (at $C_{(6)}$ and $C_{(2)}$ atoms) undergoing hydrolytic cleavage only under more severe conditions (pH 2–3).

This sequence in the hydrolytic cleavage of the intermediate does not, however, rule out the probability of the simultaneous formation in the hydrolysis also of a certain amount of another monoxopurine, namely the isomeric 6-chloro-2,3-dihydro-3,7-dimethyl-2-oxopurine (XVIi). In practice it proved impossible to isolate this compound from the reaction mass (see below), but the study of similar reactions with 8-substituted theobromine derivatives, (XII) and (XIII), showed that 2-chloro-6-oxopurines (XIV) and (XV) are not the only products of hydrolytic cleavage at pH ~7 of the intermediates (XIX, b and c) or (XX, b and c) and that the formation of small amounts of the isomeric 6-chloro-2-oxo-derivatives (XVIIi) and (XVIIIi) does indeed occur[20,22].

It was also impossible to isolate 6,8-dichloro-2-oxopurine (XVIIi) in a pure state after hydrolysis, but its presence in the unpurified dichloro-derivatives (XIV) was demonstrated chromatographically and confirmed by the

formation of the 6-ethoxy-derivatives (XVIIb) in the reaction with sodium ethoxide. It was identified with specimens of the compound (XVIIb) obtained in two ways: by treating (XVIb) with sulphuryl chloride[45] and by the hydrolysis of the 8-chloro-derivative of the amidoester chloride (XXI).[20] Both isomeric monochloro-oxo-3,7-dimethylpurines ($C_8H_8ClN_4O$) were comparatively readily isolated in 43 and 9% yields only in the reaction of 8-methyltheobromine (XIII) with $POCl_3$. The former was characterised as the 2-chloro-6-oxo-derivative (XV) and the latter proved to be 6-chloro-2-oxopurine (XVIIIk). As a result of the substitution of chlorine by other groups, they gave rise to two series of compounds—8-methyl derivatives of (I) and (XVIII).

The ultraviolet spectra of compounds (I) and their 8-methyl derivatives with the same substituent R proved to be very similar, just as the ultraviolet spectra of (XVI) and (XVIII) are similar, differing from the former pair by the bathochromic shift of the long-wavelength maximum. Possibly this can be accounted for by the presence in these compounds of the straight conjugation chain $O{=}C_{(2)}{-}N{=}C_{(6)}R{-}C_{(5)}{=}C_{(4)}{-}N{=}C_{(8)}$.[20] The study of the ultraviolet spectrum of unpurified (Ia), isolated directly in the hydrolytic reaction at pH 7 of the product of the interaction of theobromine with $POCl_3$, suggests that in this case a small amount of a second isomer, i.e. (XVIi), can nevertheless be formed in the course of the hydrolysis. The isomer (XVIi) probably cannot be isolated from the reaction mixture because it is formed in comparatively small amounts and, by virtue of its high reactivity, is completely hydrolysed to theobromine[46].

III. AMIDOCHLORIDE DERIVATIVES OF THE PURINE SERIES

1. Phosphorodichloridates and Their Structure

The ability of theobromine and its 8-substituted derivatives to be converted on heating with $POCl_3$ into compounds of the amidochloride type† is not a distinctive feature of 3,7-dimethyldioxopurines. It is characteristic also of other oxopurines methylated at $N_{(1)}$ or $N_{(3)}$, which react with phosphorus chlorides in the form of cyclic *N*-methylamides[47-49].

The properties of amidochlorides and adducts of the amidochloride type have been investigated in comparative detail only recently. The initial objects of these investigations were DMF and other aliphatic acid amides[50,51] and then cyclic *N*-substituted lactams—1-methylpyridone, 1-methylquinolone, etc.[52] In 1966 an adduct obtained from 4-dimethylamino-1,3-dimethyluracil was described[53]. The hypothesis of the formation of cyclic amidochlorides or adducts as a result of the reaction of $POCl_3$ with *N*-methyloxopurines was put forward somewhat earlier[47] and the first experimental data confirming it were published.

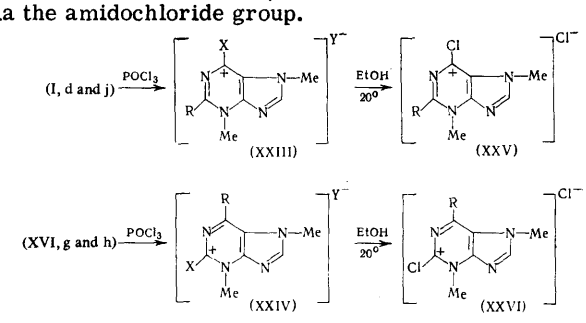
† In this review the name amidochlorides is given only to the true amidochlorides having the general structure [N—C(Cl)—]$^+$Cl$^-$, for example compound (XIX), while all the amidochloride products obtained by the addition of acid chlorides to *N*-methyloxopurines will be referred to by the general term adducts. These therefore include the phosphorodichloridates [N—C(X)—]$^+$Y$^-$ (X and L = Cl and $OPOCl_2$) formed as a result of the addition of $POCl_3$ to *N*-methyloxopurines for example (XX).[43]

Depending on the nature of the initial *N*-methylated oxopurine, the products of the reactions with $POCl_3$, isolated from the reaction mass on cooling the latter or after partial distillation of $POCl_3$, may be amidochlorides or, as happens in most cases, the phosphorodichloridates [—N(Me)—C(X)—]$^+$Y$^-$ or [—N(Me)—CR=N—C(X)—]$^+$Y$^-$ (X and Y = Cl and $OPOCl_2$). The reaction product is sometimes a mixture of the amidochloride and the phosphorodichloridate[48,49,54].

The conversion of 1,9- and 3,7-dimethylxanthines (2,6-dioxopurines), their 8-substituted derivatives, and 2-chloro-derivatives of 1,9- and 3,7-dimethylhypoxanthines (IX, R = Cl) and (Ia) into phosphorodichloridates requires fairly prolonged refluxing with $POCl_3$. For other monooxopurines, for example, 6-R-2,3-dihydro-3,7-dimethyl-2-oxopurines (XVI), heating at 50—60°C for 5—30 min is sufficient, while the majority of the isomeric 2-R-3,7-dimethylhypoxanthines (I), with the exception of the chloro-derivative (Ia), react vigorously with $POCl_3$ at 20°C, the reactions in many instances occurring with spontaneous evolution of heat[54].

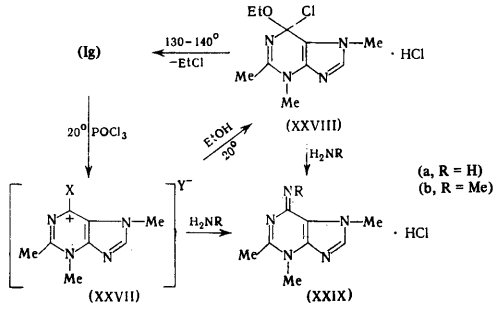
Purine phosphorodichloridates and amidochlorides are crystalline substances, almost insoluble in non-polar solvents and usually fairly and sometimes very soluble in $POCl_3$. Therefore the isolation of the phosphorodichloridates from the reaction solutions obtained as a result of the reflexing of *N*-methyloxopurines with $POCl_3$ sometimes involves appreciable difficulties. In particular, the phosphorodichloridate (XXa), formed when theobromine is refluxed with $POCl_3$, cannot be isolated from the reaction solution. It has to be converted, by being passed through a solution of hydrogen chloride, into the less soluble amidochloride (XIXc), which crystallises from the solution. To obtain the phosphorodichloridate (XXa) in a pure state and to characterise it, the purified chloro-derivative (Ia) was made to react briefly with a small amount of $POCl_3$ at a moderate temperature (60—80°C).[46] The crystalline adduct (XXa) formed is hydrolysed at pH ~7 to the initial chloro-derivative (Ia), exactly like the overall product of the reaction of compound (IV) with $POCl_3$, obtained after the distillation of the latter from the reaction solution.

Like other adducts of the purine series, the phosphorodichloridates have the properties of the amidochlorides. One of these, the ability to combine with an alcohol molecule and be converted thereby into the hydrochlorides of amidoester chlorides, does not, however, extend to all purine phosphorodichloridates. For example, those which have been obtained from the isomeric 2- and 6-methylamino-derivatives of 3,7-dimethyloxopurines [I, d and j) or (XVI, g and h)], i.e. the phosphorodichloridates (XXIII) and (XXIV), react slowly with alcohols at room temperature and are converted into the corresponding amidochloride (XXV) or (XXVI), but do not combine with alcohol via the amidochloride group.

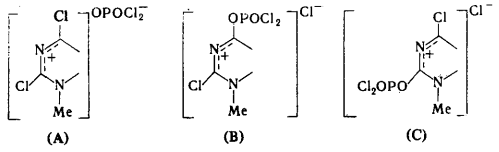


(R = MeNH or Me_2N; X and Y = Cl or $OPOCl_2$

In contrast to these, the phosphorodichloridate (XXVII), obtained from the 2-methyl derivative (Ig) is readily converted on treatment with alcohol into the hydrochloride of the amidoester chloride (XXVIII), which was found to undergo all the reactions characteristic of compounds belonging to this class. Thus, on treatment with ammonia or monoalkylamines, it is converted into the hydrochlorides of 6-amino(or alkylimino)-2,6-dihydro-2,3,7-trimethylpurine (XXIX, a and b) and its ester chloride group is cleaved on heating with evolution of ethyl chloride and the formation of the hydrochloride of the initial oxopurine (Ig).[54]



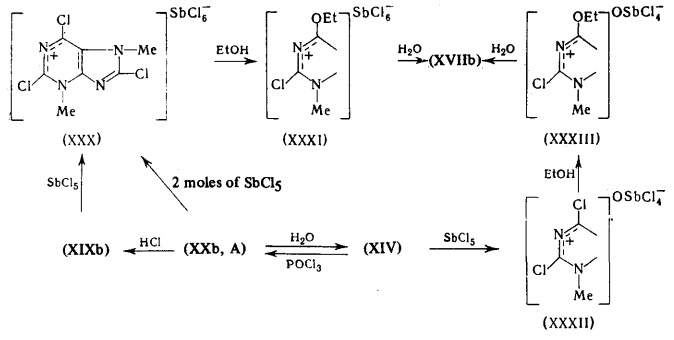
In order to make a choice between the three possible structures of the phosphorodichloridates (XX)—(A), (B), and (C)—a study was made of the interaction of (XXb) with antimony pentachloride[55].



The reaction with two moles of antimony pentachloride led to an almost quantitative yield of the hexachloroantimonate (XXX), i.e. to the replacement of the $\overset{\oplus}{O}POCl_2$ residue by the $SbCl_6$ residue. When the adduct (XXX) was treated with alcohol, one of the chlorine atoms was exchanged for the ethoxy-group and the resulting hexachloroantimonate of the ethoxy-derivative, i.e. the adduct (XXXI), was converted as a result of hydrolysis in a neutral medium into the known compound (XVIIb). These last two reactions also take place with high yields.

Analysis of the quantitative aspects of the above reactions—the theoretical yield of the hexachloroantimonate (XXX) and the high yields of compounds (XXXI) and (XVIIb) obtained from it—permitted the conclusion that the initial phosphorodichloridate (XXb) is a pure compound and not a mixture of the isomers (A), (B), and (C) and that the $SbCl_6$ residue in compound (XXX) and hence the $OPOCl_2$ residue in the initial phosphorodichloridate (XXb) constitute the anionic part of the molecules of these adducts and not a fragment of their cationic component. On the basis of these findings, it is suggested that the phosphorodichloridate (XXb) most probably has the structure (A), which is in full agreement with current ideas about the structure of the adduct obtained when $POCl_3$ is allowed to react with DMF: $[-HC(Cl)NMe_2]_2OPOCl_2^-$.[56]

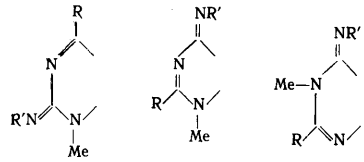
The adduct (XXX) is also formed as a result of the addition of one mole of antimony pentachloride to the amidochloride (XIXb), which in turn is obtained by the reaction of hydrogen chloride with a solution of the phosphorodichloridate (XXb) in $POCl_3$.[55] Yet another antimony-containing purine adduct (XXXII) with the $OSbCl_4$ residue is formed when 2,8-dichloromonoxopurine (XIV) reacts with antimony pentachloride, by analogy with the method of the synthesis from it of the phosphorodichloridate (XXb) by reaction with $POCl_3$.[46] Like the adduct (XXX), it reacts with alcohol, whereby it is converted into the ethoxy-derivative (XXXIII), in which the position of the ethoxy-group at $C_{(6)}$ was confirmed by the formation of (XVIIb) from it. The entire series of the above reactions fits the scheme illustrated below[55,57]:



Phosphorodichloridates, other purine adducts, amidochlorides, and also amidoester chlorides are comparatively stable in the absence of moisture, but are rapidly hydrolysed by water with regeneration of the initial oxopurines. They are particularly reactive in reactions with nucleophilic agents—ammonia, amines, alkoxides, etc.[2]

2. *C*-Iminopurines

Amidochloride compounds of different classes—aliphatic, aromatic, and heteroaromatic—are known to react with ammonia and primary amines to form amidines[50,52,58,59]. In the amidines obtained from purine amidochlorides, adducts, and amidoester chlorides[54] one of the nitrogen atoms forms part of the pyrimidine ring in the purine system.

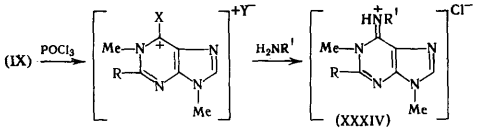


Consequently these amidines are $C_{(2)}$ or $C_{(6)}$-iminopurines, which differ from *C*-aminopurines by their high basicity (pK_a = 10—12, instead of 3—4).

The first iminopurines alkylated at the nitrogen atoms of both rings of the purine system, namely $N_{(1)}$-alkyl-6-iminopurines, were described about 30 years ago. They were obtained from 4-amino-5-cyano-1-methylimidazole[60] or by the alkylation of adenosine, adenylic acid, and other adenine derivatives substituted at the nitrogen atom of the imidazole ring[61–66].

The method of preparation of *C*-iminopurines from *NN*-dimethyloxopurines, based on the intermediate formation of amidochloride compounds and treatment of the latter with ammonia or monoalkylamines[67], has led to new possibilities in the synthesis of this unusual group of purine derivatives. It permits the variation of the structure of the substituents at the exocyclic nitrogen atom by employing a wide variety of primary amines and also the introduction of additional groups at the second ring carbon atom of the pyrimidine part of the molecule.

The first series of iminopurines obtained in this way—the hydrochlorides of 2-R-1,6-dihydro-6-imino-1,9-dimethylpurines (XXXIV)—were synthesised from compounds (IX) in accordance with the following scheme[48,49]:



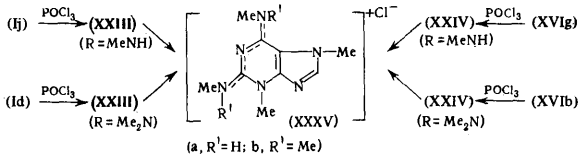
(X and Y = Cl or $OPOCl_2$; R' = H or Me)

The hydrochlorides of $C_{(6)}$- and $C_{(2)}$-imino(or alkylimino)-3,6(or 2,3)-dihydro-3,7-dimethylpurines, including 6-imino-2,3,7-trimethylpurines (XXIX, a and b) mentioned above, were synthesised similarly from 2-R(or 6-R)-3,7-dimethyloxopurines (I) and (XVI).[54]

If the substituent R in (XXIII) and (XXIV) is an amino- or monoalkylamino-group, it is possible to obtain the same aminoiminopurine from the corresponding representatives of two different series—(I) and (XVI). For example, the hydrochloride of 2,6-di(methylamino)-3,7-dimethylpurine (XXXVa) was obtained from (Ij) and (XVIg) by treatment with methylamine[67].

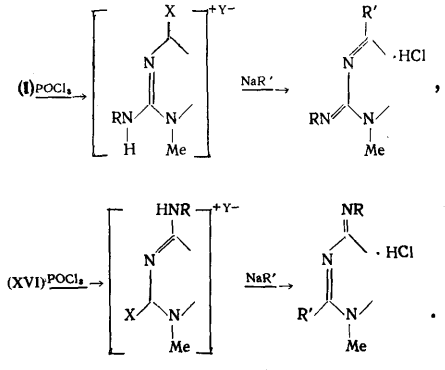
The problem of which exocylic nitrogen atom (at $C_{(2)}$ or at $C_{(6)}$) undergoes protonation in this case remains open.

Under similar conditions, the two isomeric phosphorodichloridates obtained from (Id) and (XVIh) react with dimethylamine to form 2,6-bis(dimethylamino)-3,7-dimethylpurinium chloride (XXXVb).



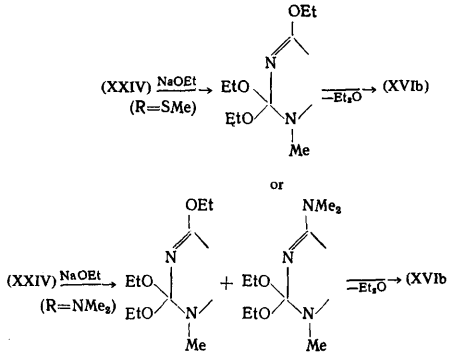
(a, R'=H; b, R'=Me)

This method of synthesis of *C*-iminopurines can be usefully employed to obtain compounds substituted at the second ring carbon atom ($C_{(2)}$ or $C_{(6)}$) by alkoxy-groups or other substituents capable of reacting with $POCl_3$ or of being substituted by amines. The *C*-methyl group also interferes with the reaction, since its presence entails charring of the reaction mass on heating with $POCl_3$. In such cases the synthesis can be carried out in accordance with another, more universal scheme based on the use of *C*-amino- or monoalkylamino-oxopurines as starting materials. The amino-group in the phosphorodichloridates or amidochlorides formed from them plays the role of a potential imino-group, while the labile substituent is introduced into the latter by treatment with nucleophilic agents such as alkoxides, sodiomalonic ester, sulphides, etc.

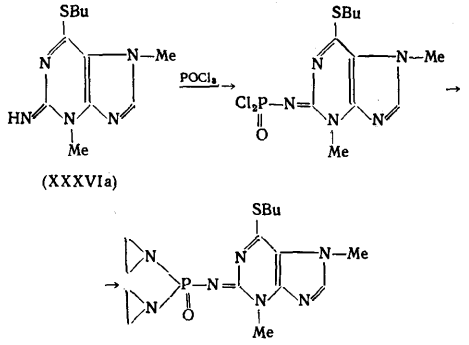


(X, Y=Cl, $OPOCl_2$)

When purine amidochloride or phosphorodichloridate, in which the substituent R is an alkylthio-, dialkylamino-, or other group without a hydrogen atom capable of migrating to form a tautomer, is acted upon by an alkoxide, the final reaction product is the initial oxopurine. Its formation from the amidochloride compound is accompanied by the formation of a dialkyl ether, probably as the result of the cleavage of an unstable intermediate acetal[68]. In such reactions there is a possibility also of a simultaneous replacement of the residue R, linked to $C_{(6)}$, by an alkoxy-group, for example:

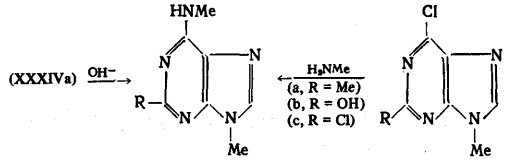


As was to be expected, the *C*-iminopurines, whose basicity is close to that of aliphatic amines, are much more vigorously acylated and, in particular, react much more vigorously with $POCl_3$ than *C*-aminopurine, which are much less basic. Whereas the formation of acid dichlorides of 7(or 9)-methyl-6-phosphoramidopurines requires prolonged heating of the initial $C_{(6)}$-aminopurines with an excess of $POCl_3$,[69] the iminopurine bases, for example (XXIX), (XXXIVa, R = Me), the two isomeric $C_{(6)}$- and $C_{(2)}$-butylthio-2-imino-3,7-dimethylpurines (XXXVIa), and the corresponding 6-imino-derivatives (XXXVIb) react with a calculated amount of $POCl_3$ in methylene chloride at a temperature as low as 15—20°C. A number of diaziridides of *NN*-dimethylpurinylphosphoramidic acids were synthesised in this way for biological tests from the acid dichlorides of *NN*-dimethylpurinylphosphoramidic acids by reaction of the latter with aziridine in the presence of hydrogen chloride acceptors[70]. These reactions are illustrated schematically below using compound (XXXVIa) as an example:



When 6-imino-1,9-dimethylpurines (XXXIV) are heated with a solution of alkali, various reactions take place, which are greatly influenced by the substituent R in the 2-position. Compound (XXXIVa) undergoes the Dimroth rearrangement in an alkaline medium, i.e. is converted into 2,9-dimethyl-6-methylaminopurine (XXXVIIa), which

is identical with the compound obtained from 6-chloro-2,9-dimethylpurine (XXXVIII) and monomethylamine:



(R'=Me) (XXXVII) (XXXVIII)

When monoalkylamino-derivatives (XXXIV, R = NHMe) are acted upon by alkali, there is partial hydrolytic cleavage of the 6-imino-group and the final reaction product consists of a mixture of the initial iminopurines and 2-monoalkylamino-1,9-dimethylhypoxanthines.

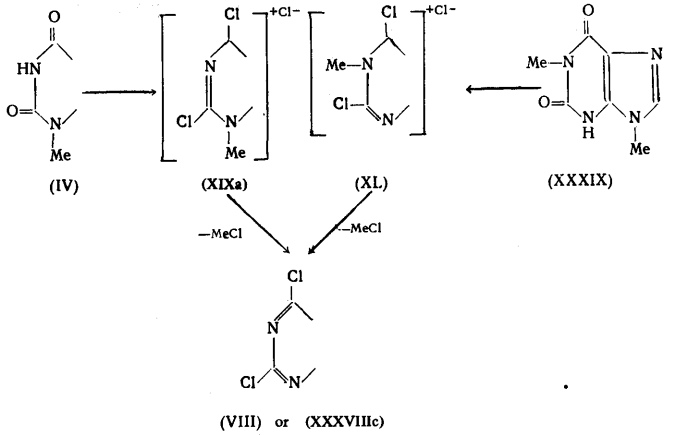
On the other hand, when the dimethylamino-group is present in the 2-position, the reaction product is 2-hydroxy-6-monomethylamino-9-methylpurine (XXXVIIb), since in this case two processes probably take place: the Dimroth rearrangement and hydrolytic elimination of the dimethylamino-group[49].

3. The Cleavage of Purine Adducts and Amidochlorides

Another feature of *NN*-dialkylamidochlorides, which is of considerable preparative importance together with nucleophilic substitution reactions, is their capacity to undergo cleavage with liberation of an alkyl chloride and to be converted thereby into imidochlorides:

$$Alk_2N{-}CO{-} \rightarrow [Alk_2N{-}C(Cl){-}]^+Cl^- \xrightarrow{-AlkCl} AlkN{=}C(Cl){-},$$

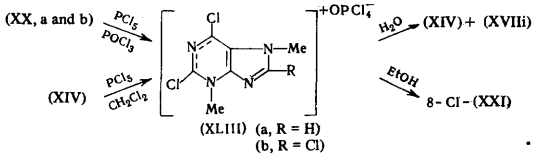
i.e. to undergo the reaction on which a method of dealkylation of dialkylamines, known for a long time, is based[71]. Accordingly, the conversion of theobromine into 2,6-dichloro-7-methylpurine (VIII) and also the analogous conversion of the isomeric 1,9-dimethylxanthine (XXXIX) into 2,6-dichloro-9-methylpurine (XXXVIIIc) [11] can be represented as the demethylation of cyclic *N*-methylamides, which leads to the formation of cyclic iminodchlorides and proceeds with formation of the intermediate amidochlorides (XIXa) and (XL).



(IV) (XIXa) (XL) (XXXIX)

(VIII) or (XXXVIIIc)

The amidochlorides (XIX, a and b) are readily cleaved on heating with $POCl_3$, liberating methyl chloride[57], and are converted at the same time into 2,6-dichloro-7-methylpurines (VIII) and its 8-chloro-derivative (XLI) in high yields. In contrast to these, the phosphorodichloridates (XX, a and b) undergo such cleavage only to a slight extent even on prolonged refluxing with $POCl_3$.

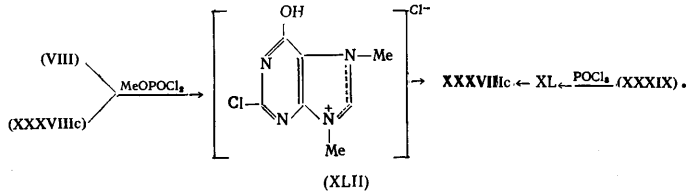


The reason for this difference may be that, on being cleaved, the phosphorodichloridates split off not only the volatile methyl chloride but also the high-boiling methyl phosphorodichloridate ($MeOPOCl_2$), which remains in the reaction sphere and alkylates the imidochlorides formed as a result of the cleavage.

The hypothesis that this ester can alkylate (cf. Lugovkin and Arbuzov[72]) 2,6-dichloropurines was confirmed by the preparation of 8-chlorotheobromine (XII) by heating the trichloride (XLI) with $MeOPOCl_2$ in $POCl_3$ and by the hydrolysis of the product:

$$(XLI) + MeOPOCl_2 \rightarrow (XXb) \xrightarrow{H_2O} (XII).$$

The ring nitrogen of not only the pyrimidine component but also of the imidazole component of the molecule can be methylated under these conditions: when $MeOPOCl_2$ was allowed to react with the two isomeric $N_{(7)}$- and $N_{(9)}$-methyl derivatives of 2,6-dichloropurine [(VIII) and (XXXVIIIc)], the same compound was isolated after treating the products with water—2-chloro-7,9-dimethylhypoxanthinium chloride (XLII):



(XLII)

The same chloro-derivative (XLII) was detected in the reaction product after heating 1,9-dimethylxanthine (XXXIX) with $POCl_3$ (cf. Pfleiderer[73] and Gutorov[74]).

The formation of 2,6-dichloro-7-methylpurines from the phosphorodichloridates (XX) can also be facilitated by agents other than hydrogen chloride, the purines being converted into the readily cleaved amidochlorides (XIX). Tertiary amines have also come to be used in reactions of this kind. For example, on heating with $POCl_3$ in the presence of *NN*-dimethylaniline[75], theobromine is known to be converted into the dichloro-derivative (VIII) in 25% yield instead of 10—15%.[3] It has been suggested that in this reaction tertiary amines can partly promote the processes occurring because they prevent the elimination from the reaction sphere of the hydrogen chloride which promotes the conversion of the phosphorodichloridate (XXa) into the readily cleaved amidochloride (XIXa). Indeed, the use of dimethylanilinium hydrochloride instead of the base increased the yield of (VIII) to 35—40%. Nevertheless the yields in this reaction or in the analogous syntheses of (XLI) or (XXXVIIIc) continued to be fairly low, evidently due to side processes involving the *para*-condensation of the intermediate amidochloride and the adduct with dimethylaniline[2,76].

In order to rule out the possibility of the *para*-condensation side reaction, dimethylanilinium hydrochloride was replaced by triethylammonium hydrochloride (the hydrochloride of a tertiary amine), which cannot block the

intermediate phosphorodichloridates. This replacement immediately led to an appreciable enhancement of the yields: 2,6-dichloro-7-methylpurine (VIII) and its 8-chloro-derivative (XLIII) were obtained in 90—95% yield and the yield of 2,6-dichloro-9-methylpurine from 1,9-dimethylxanthine (XXXIX) was 75%.[76]

The most effective method for synthesising 2,6-dichloro-7-methyl- or 2,6-dichloro-9-methyl-purines [(VIII), (XLI) and (XXXVIIIc)] from the corresponding $N_{(3)}$- or $N_{(1)}$-methyloxopurines involves the conversion of the intermediate phosphorodichloridates into more readily cleaved phosphorus-containing adducts, which differ from the phosphorodichloridates by the fact that their anion is $OPCl_4^-$ instead of $OPOCl_2^-$.[57]

The formation of these new adducts, which for brevity may be called phosphorotetrachloridates, is achieved by treating solutions of phosphorodichloridates in $POCl_3$ with phosphorus pentachloride. Being much less soluble in this solvent than the initial phosphorodichloridates, the phosphorotetrachloridates can be crystallised comparatively rapidly. The phosphorotetrachloridates (XLIII, a and b)‡ were obtained in this way from the phosphorodichloridates (XX, a and b) and the phosphorotetrachloridate (XLIIIb) was obtained in addition by treating 2,8-dichloro-6-oxopurine (XIV) in methylene chloride with phosphorus pentachloride.

The ability to be readily cleaved with formation of 2,6-dichloropurines constitutes the most significant difference between phosphorotetrachloridates and phosphorodichloridichloridates. Their cleavage is accompanied by the liberation of $POCl_3$ and methyl chloride. It takes place comparatively rapidly on heating not only in $POCl_3$ but also in chlorobenzene, as well as in the absence of a solvent at the melting point and leads to the formation of 2,6-dichloropurines in high yields[57]. An example of the employment of the principle of the conversion of phosphorodichloridates into phosphorotetrachloridates is provided by the preparative syntheses of 2,6-dichloro-7-methylpurines (VIII) and (XLI) from theobromine[5,20,21].

The remaining properties of the phosphorotetrachloridates are very similar to those of the phosphorodichloridates and they exhibit all the features typical for purine adducts and amidochlorides. For example, the hydrolysis of the phosphorotetrachloridate (XLIIIb) in a neutral medium leads to the formation of a mixture of 2,8- and 6,8-dichloro-3,7-dimethylmonoxopurines (XIV) and (XVIIj), while in the reaction with ethyl alcohol it is converted into the amidoester chloride [the 8-chloro-derivative of (XXI)][57].

Presumably the phosphorotetrachloridates are not the last link in the long chain of reactions undergone by dimethylxanthines on treatment with $POCl_3$ compounds which are completed by the elimination of $N_{(3)}$- or $N_{(1)}$-methyl groups and the formation of 2,6-dichloropurines (VIII), (XLI), or (XXXVIIIc). It appears most likely that the cleavage of the phosphorotetrachloridates is a two-stage consecutive process and that the true precursors of 2,6-dichloro-7-methyl- or 2,6-dichloro-9-methyl-purines are the thermally unstable amidochlorides formed as a result of the elimination of $POCl_3$ from the phosphorotetrachloridates.

The principal stages of the process, illustrated by the schemes quoted in this review, can be followed experimentally for 3,7-dimethylxanthines. Nevertheless one cannot claim that this represents all the features of the complex conversion of *NN*-dimethylxanthines into the corresponding 2,6-dichloromonomethylpurines. It is quite probable that this process includes also additional hitherto undetected stages, which should be investigated further.

‡ The conversion of phosphorodichloridates into phosphorotetrachloridates is probably a result of the chlorination of the $OPOCl_2^-$ anion by phosphorus pentachloride and not of the exchange of its phosphorus-containing component $POCl_2$ for the PCl_4 residue. This hypothesis followed from the experimental preparation of the phosphorotetrachloridate (XLIIIb) by treating the phosphorodichloridate (XXb) with $^{32}PCl_5$ at 20°C in $POCl_3$: the yield of the resulting phosphorotetrachloridate was 92—94% and its molar radioactivity hardly reached 5% of the value for the initial $^{32}PCl_5$.

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