U.D.C. 547.307

Advances in the Synthesis of Purine Derivatives from Uric Acid

E.S.Golovchinskaya

The review deals mainly with the discussion of the synthesis of purine derivatives based on the interaction between uric acid and acetic anhydride. Problems of the structure, intermediates in the reaction, *N*-methylated derivatives of the compounds, and their conversion into 8-methylxanthines are discussed. Much attention has been devoted to the synthesis of 9-methylpurine derivatives from uric acid using 1,3,8,9-tetramethylxanthine as an intermediate. Various methods of synthesising *N*-methylated purines substituted in the 8-position have been described.
The bibliography includes 157 references.

CONTENTS

I. Introduction 413
II. Reactions of uric acid 413
III. Syntheses based on *N*-methylated 8-methylxanthines 417

I. INTRODUCTION

In the course of the last two decades, synthetic studies on purines have developed on an enormous scale throughout the world. The great interest in purine derivatives, which re-emerged in the 1950's after a fairly long slack period, has been to a great extent the result of the outstanding advances achieved in the study of various enzymes systems, cell biochemistry, and principally the structure and role of nucleic acids. This renewed interest is associated with one of the most urgent problems in modern medicine—the search for effective therapeutic agents for the treatment of diseases involving various types of impairment of nucleic acid metabolism, including those used in the fight against malignant diseases. Numerous studies in this field ultimately led to the synthesis of many hundreds of new derivatives of purine and its analogues, the aim being to investigate their biological activity.

All the syntheses in the purine series described in the literature may be divided into two groups. The first and largest group includes methods based on successive or simultaneous synthesis of the pyrimidine and imidazole rings of the purine molecule[1-3]. A fairly exhaustive systematic account of these methods has been given in a number of reviews (including Robins's detailed review[4]) and they will not be considered in this paper.

The syntheses of the second group, based on the so called semisynthetic methods, i.e. on the employment and reactions of natural compounds already containing a purine skeleton, have been much less satisfactorily described in the review literature.

More than 30 natural purines from various sources of plant and animal origin are known. These are primarily the aglucones of nucleosides constituting the structural elements of nucleic acids, the purine components of antibiotics (puromycin, nebularine, etc.), and also the normal metabolic products of the organisms of higher animals. Despite the comparatively great variety of the purine glucosides known at present, the fairly constant structure of their purine moiety is striking—with rare exceptions this is adenine and its derivatives substituted at the amino-group or at $C_{(2)}$ and also guanine and its derivatives methylated at the exocyclic nitrogen atom or at the $N_{(1)}$ atom.[5]

Recently a substance called herbipoline, characterised as a new type of purine derivatives, mainly purinium betaines with a zwitter-ionic structure hitherto unknown for purine, was recently isolated from the organisms of lower animals, in particular from the stroma of the sponge *Geodia gigas*[6,7]. Natural 1-methyladenine, identified by comparison with the synthetic specimen and called by the author spongopurine, was obtained from the same source[8].

With the exception of the main examples of aglucones mentioned above—adenine and guanine—almost inexhaustible amounts of which are available in living organisms, the remaining aminopurines are present in the organs and tissues of animals in very small amounts and their isolation and characterisation constitute refined and laborious operations. From this standpoint, the most promising natural purines are uric acid and two purine alkaloids from the group of methylated xanthines—caffeine and theobromine. The amounts of these purine derivatives in nature are fairly large and methods for their extraction from natural sources on an industrial scale have been developed.

Uric acid is the final product of the protein metabolism of birds and reptiles and is present in large amounts in the excrement of these animals. The guano deposits, from which it is derived, have now become appreciably depleted. During the Second World War, industrial manufacture of uric acid, based on the extraction of chicken dung diluted with alkali, which contains 2–3% (relative to the dry material) of uric acid, was organised in the Soviet Union in state poultry farms. The uric acid obtained in this way served as the raw material for the synthesis of caffeine and theophylline as well as methylcaffeine; the last derivative was manufactured for several years as an independent preparation which successfully replaced caffeine in several cases[9].

This review deals with the syntheses of purines based on the reactions of uric acid. It includes also studies on the synthesis of purine derivatives from caffeine and theobromine, which are logically related to the synthesis of the same compounds from uric acids.

II. REACTIONS OF URIC ACID

Practically all known reactions of uric acid(I) which result in the derivatives of di- and monoxopurines (including xanthine and hypoxanthine), as well as oxygen-free purines can be classified into three types of reactions.

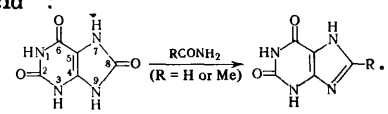
1. Interaction with Phosphoryl Chloride and Subsequent Reactions of the Resulting 2,6,8-Trichloropurine.

This series of reactions, already described by Fischer in the past century, permitted a reliable determination of the structure of uric acid and also the structures of natural purines already known at the time, such as adenine hypoxanthine, guanine, and others. The synthesis of trichloropurine and its reactions confirmed the structural relations between these natural purines and uric acid and with one another, culminated in the synthesis of the parent compound of this class (unsubstituted purine), and served as a firm foundation for a detailed elucidation of the chemistry of purines[10].

The scientific value of the brilliant studies by Fischer has persisted until the present day but the reaction between uric acid and phosphoryl chloride has been very rarely employed for preparative purposes.

2. Direct Conversion into Xanthines by Refluxing with Formamide (or Other Amides)

This completely new reaction, discovered by Bredereck and coworkers, can serve according to the authors as a quite realistic basis for a two-stage synthesis of caffeine from uric acid[11]:



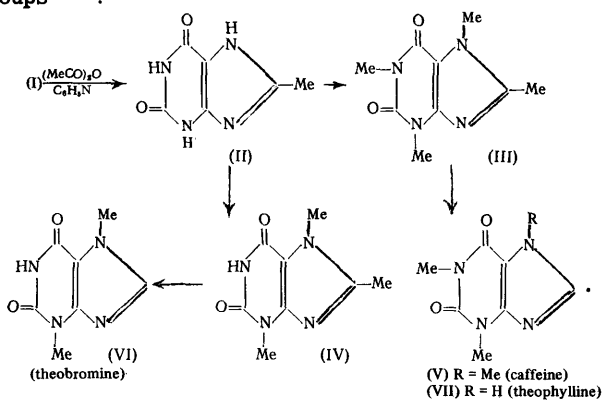
(I)

The authors convincingly disproved the possibility that the essential feature of the process is reduction by formamide of the $>C_{(8)}=O$ ($>C_{(8)}$–OH) fragment of the imidazolone ring. On the basis of the formation of 8-methylxanthine in a similar reaction with acetamide and also of a number of experimental data, they believe that, on heating with formamide, the imidazolone ring of uric acid is cleaved; this is accompanied by a reaction of the resulting 5-formylamino-4-ureidouracil culminating in ring closure. The authors assert that the precursor of the $C_{(8)}$ atom of the imidazole ring in the resulting xanthine is not the $C_{(8)}$ atom of the initial uric acid but the carbon atom of formamide.

The observation that on heating with formamide in an autoclave uric acid can be converted not only into xanthine but also into hypoxanthine is likewise noteworthy. The importance of this reaction, which has no preparative value, is due to the fact that it clearly indicates the capacity of the ureide group of both the imidazole and pyrimidine ring to react with formamide[12].

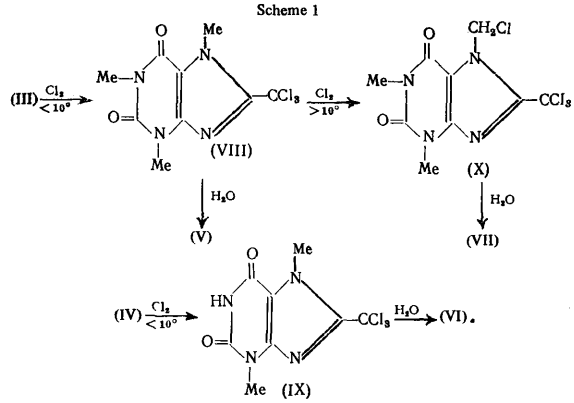
3. Interaction with Aliphatic Acid Anhydrides (Mainly Acetic Anhydride)

This reaction constitutes the basis of a whole group of patents taken out by the Boehringer Company which enabled a realistic synthesis of all three purine alkaloids (caffeine, theobromine, and theophylline) in a single common industrial scheme as early as the beginning of the present century. The first stage of this synthesis is the conversion of uric acid into 8-methylxanthine (II), which is formed in a nearly quantitative yield as a result of refluxing it for 80 h with an excess of acetic anhydride in the presence of pyridine or other pyridine bases[13]. Next, methylation of 8-methylxanthine leads to the formation of 8-methylcaffeine (III) or 8-methyltheobromine (IV) depending on the reaction conditions[14,15]. As a result of the removal of the methyl group from the $C_{(8)}$ atom in compounds (III) and (IV), caffeine (V) and theobromine (VI) are formed respectively[16,17]. In addition, methylcaffeine can be converted also into theophylline (VII) as a result of the simultaneous elimination of the $C_{(8)}$- and $N_{(7)}$-methyl groups[17,18]:



The removal of methyl groups from compounds (III) and (IV), i.e. their conversion into caffeine, theophylline, and theobromine, is achieved, in accordance with the above patents, by the substitution of hydrogen atoms in these groups by chlorine and subsequent hydrolytic removal of the chloromethyl groups from the resulting trichlorides (VIII) and (IX) and also from the tetrachloride (X)

Scheme 1

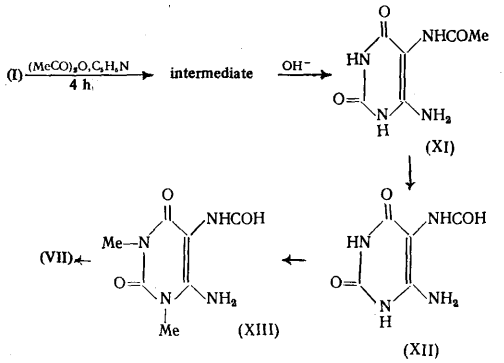


Scheme I has found wide-scale practical application and was used, in particular, in Soviet chemical-pharmaceutical industries in 1943–1953[19–29] for the synthesis of caffeine and theophylline.

Scheme 2 for the synthesis of theophylline, whereby it is also manufactured in the USSR, is based on the reaction between uric acid and acetic anhydride interrupted after a period of 4 h, the conversion of the resulting intermediate by hydrolysis into 5-acetamido-4-aminouracil (XI), and the transacylation of the latter by treatment with formic acid. 4-Amino-5-formamidouracil (XII) was methylated and the resulting 4-amino-5-formamido-1,3-dimethyluracil (XIII) was converted by cyclisation into theophylline (VII)[30–33] (Scheme 2).

Nowadays the industrial synthesis of purine alkaloids from uric acid has been displaced in many countries (and possibly throughout the world by economically more effective synthetic methods. Nevertheless the interaction of uric acid with acetic anhydride and also the substitution of hydrogen atoms in the methyl groups of *N*-methylated 8-methylxanthines by chlorine and subsequent hydrolytic

Scheme 2

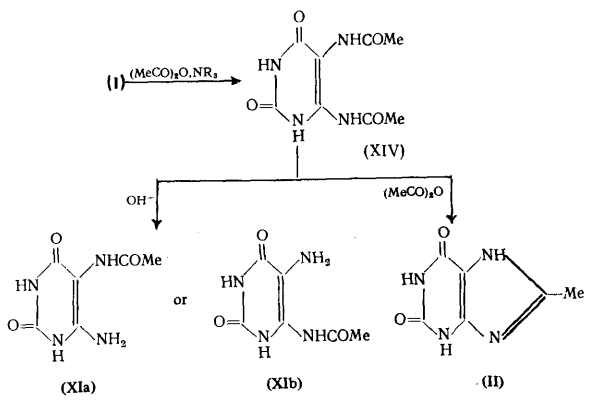


cleavage of the chloromethyl groups survived for a long time their "elimination" from industry. In particular, owing to earlier studies in connection with the needs of industry, convenient methods were found for the synthesis of a new group of derivatives of *N*-methylxanthines substituted in the 8-position (see Section III, subsection 1).

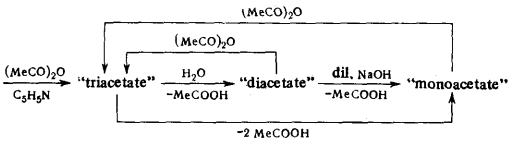
Moreover, these studies threw light on certain controversial problems concerning the structure of the compounds formed in the conversion of uric acid into 8-methylxanthine and permitted the use of the result for preparative purposes, namely for the synthesis of 9-methylpurine derivatives which had been hitherto unknown or difficult to obtain (see Section III, subsection 2).

Since the initial publication of the methods of preparation of 8-methylxanthines from uric acid[13], it has been discovered that this complex process proceeds via two stages. The first, which terminates after only brief heating with acetic anhydride (4–5 h), requires the presence of tertiary amines and is accompanied by the evolution of CO_2. The reaction product is a mixture consisting of a substance readily soluble in boiling water and a comparatively small amount of compound (II) which is virtually insoluble in it. A crystalline compound $C_8H_{10}N_4O_4$, which was believed to be an intermediate in the above process for half a century, is precipitated from the cooled aqueous filtrate.

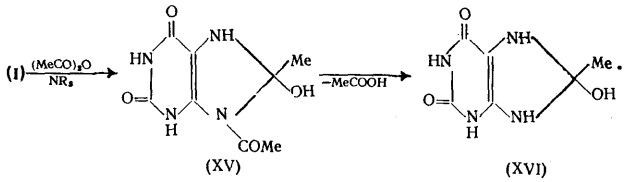
Indeed, it can be converted into compound (II) on prolonged heating with acetic anhydride. The second stage no longer requires the presence of tertiary amines and proceeds with elimination of acetic acid[34]. The first views concerning the course of the process were expressed at the same time[35] and a process mechanism was put forward, according to which the structure of 4,5-diacetamidouracil (XIV) was attributed to the intermediate and the compound $C_6H_8N_4O_3$ obtained from it by the hydrolytic elimination of one acetyl group in an alkaline medium was assumed to be the monoacetyl derivative of 4,5-diaminouracil (XIa or XIb).



In the first place we must note that fifty years later Bredereck et al.[36] established that the intermediate in the conversion of uric acid into 8-methylxanthine is not the compound $C_8H_{10}N_4O_4$, as believed previously, but a compound containing a further acetyl group ($C_{10}H_{12}N_4O_5$). It was found that it hydrolyses with elimination of one mole of acetic acid after only brief heating with water. They isolated this substance directly from the mixture which was untreated with water and was formed in the interrupted synthesis of compound (II) and also by treating with acetic anhydride the "intermediate compound" crystallised from water or the compound $C_6H_8N_4O_3$ obtained from the latter by alkaline hydrolysis†.



In 1923 Biltz and Schmidt published their first detailed study of the structures of "diacetate" and "monoacetate".[37] They suggested that both "diacetate" and "monoacetate" are bicyclic carbinols, namely, 9-acetyl-8-hydroxy-8-methyl-8,9-dihydroxanthine (XV) and 8-hydroxy-8-methyl-8,9-dihydroxanthine (XVI):



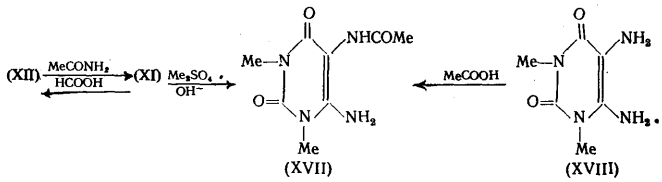
In 1953–1954, i.e. 30 years later, the structures of "triacetate", "diacetate", and "monoacetate" were revised in studies published almost simultaneously in the German Federal Republic[36,38,39] and in the Soviet Union[40–43].

It is remarkable that although their results were closely interrelated and many of their fundamental aspects were identical, their authors arrived at opposite conclusions concerning the "closed" (i.e. bicyclic) or "open" (i.e. uracil) structures of "diacetate" and "triacetate". "Monoacetate" was shown unanimously and by different methods to have the uracil structure (XI) and not the bicyclic carbinol structure (XVI).

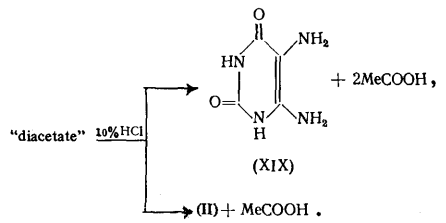
Structure (XI) of "monoacetate" was confirmed by many reactions, including the quantitative isolation of one mole of acetic acid at low pH, its formation from 4-amino-5-formamidouracil (XII) known previously[44] on treatment with acetamide, and finally its conversion into compound (XII) by heating with an excess of formic acid[33,36]. In addition, two specimens of "1,3-dimethylmonoacetate" (XVII) were

† For brevity, they suggested that the following names be given to the three compounds (these have been adopted in subsequent descriptions): "triacetate"—the true intermediate, "diacetate"—obtained by the crystallisation of "triacetate" from water, and "monoacetate"—obtained from "triacetate" or "diacetate" by the hydrolytic removal of two or one acetyl groups.

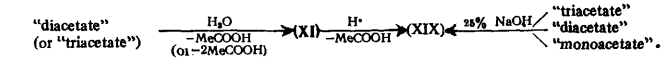
identified; one of them was obtained by heating 4,5-diamino-1,3-dimethyluracil (XVIII) with acetic acid and the other by methylating "monoacetate" (XI)[41]:



Both series of studies described demonstrated the error of Biltz and Schmidt's assertion[37] that "diacetate" is incapable of splitting off both acetyl groups on hydrolysis. The exact determination of the amounts of acetic acid distilled off during the hydrolysis of "diacetate" at low pH showed that it indeed never reaches two moles and is approximately one and a half moles. This was convincingly explained by the fact that, when "diacetate" is heated with inorganic acid, it can cyclise with formation of 8-methylxanthine[45]. The measured amounts of distilled acetic acid showed that in the acid hydrolysis of "diacetate", two parallel processes take place: (a) the hydrolysis of both acetyl groups and (b) the hydrolysis of one acetyl group accompanied by the formation of 8-methylxanthine via the second group. 8-Methylxanthine could be always isolated from the "diacetate" hydrolysis mixture[41]:

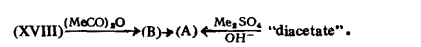


The quantitative isolation of two moles of acetic acid as a result of the hydrolysis of "diacetate" (and correspondingly three moles from "triacetate") can be achieved by their prolonged refluxing with water, which results in the formation of "monoacetate"[43], and subsequent hydrolysis of the latter in the presence of inorganic acids. On the other hand, 4,5-diaminouracil (XIX) was obtained in a yield exceeding 90% by treating "monoacetate", "diacetate", and "triacetate" with 25% sodium hydroxide solution[45]:



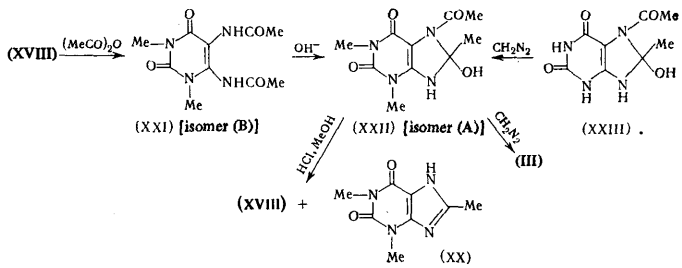
The preparation of the following methylated derivatives of "diacetate" was described in both studies: "tetramethyldiacetate" and two isomeric "dimethyldiacetates" (A) and (B), one of which was obtained by methylating "diacetate" with dimethyl sulphate in an alkaline medium [compound (A)]; its properties differed from those of the second dimethyl derivative obtained by heating 4,5-diamino-1,3-dimethyluracil (XVIII) with acetic anhydride [compound (B)].

It was shown that this is not a consequence of the different positions of the *N*-methyl groups, because compound (B) is readily converted into compound (A) by dissolution in dilute alkali and subsequent precipitation with acid or by refluxing in butyl alcohol[38,40]:

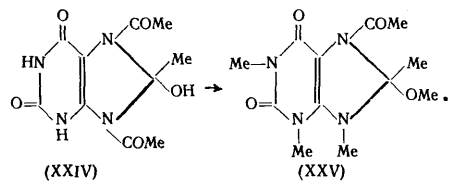


Compound (B) does not react with diazomethane and is readily hydrolysed by HCl in methanol with evolution of two molecules of acetic acid and by 20% acetic acid with evolution of one molecule of CH_3COOH.

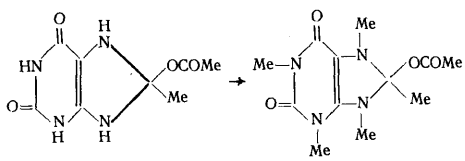
In contrast to (B), its isomer (A) readily reacts with diazomethane and is converted thereby into 1,3,7,8-tetramethylxanthine (III), but does not react at all with 20% acetic acid. The reaction with HCl in methanol results in the elimination of only 1.5 moles of acetic acid and the formation of a mixture consisting of a diamino-derivative (XVIII) and 1,3,8-trimethylxanthine (XX), i.e. behaves in the same way as the initial non-methylated "diacetate". The chemical behaviour of the isomer (B) led the German workers (Bredereck and coworkers) to the hypothesis that it is 4,5-diacetamido-1,3-dimethyluracil (XXI), which cyclises under the influence of alkali with formation of the dihydropurine isomer (A) (XXII). The fact that the latter can be obtained from "diacetate" by methylation of diazomethane suggested that the initial non-methylated "diacetate", obtained in the conversion of compound (I) into compound (II), has a bicyclic carbinol structure like "triacetate":



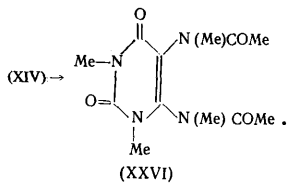
The German workers disagreed with Biltz and Schmidt[37] only as regards the position of the "hydrolysable" acetyl groups—at $N_{(7)}$ and not at $N_{(9)}$—and attributed structures (XXIII) and (XXIV) to "diacetate" and "triacetate" and structure (XXV) to "tetramethyldiacetate" obtained from them[38]:



They did not notice that not even traces of a methoxy-group could be detected in "tetramethyldiacetate" by analytical methods, although this finding ruled out the validity of their hypothesis concerning the structure of (XXV). The possibility of another bicyclic structure of "tetramethyldiacetate", which they did not consider, where the "hydrolysable" acetyl group is joined to the dihydroimidazole ring by an ester and not an amide linkage and all four methyl groups are joined to the ring nitrogen atoms, was disproved by an infrared spectroscopic study of "diacetate" and all its methylated derivatives[40].

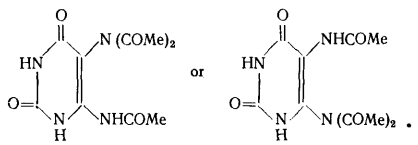


The absence of the methoxy-group from "tetramethyldiacetate" and the spectroscopic data thus disproved the possibility of any bicyclic structure of "tetramethyldiacetate" and suggested that it is 1,3-dimethyl-4,5-di(methylacetamido)uracil (XXVI), which in turn constituted important evidence in support of the validity of the structure (XIV) proposed initially for "diacetate"[40]:



(XXVI)

This structure of "diacetate" was confirmed by its capacity, mentioned above, to be hydrolysed comparatively readily with evolution of two moles of acetic acid when conditions ruling out the possibility of cyclisation are observed. The elimination of one acetyl group and the formation of "monoacetate", i.e. 5-acetamido-4-aminouracil (XXI) take place under such mild conditions (heating with water) that the opening of the imidazole ring in this reaction is unlikely[43]:

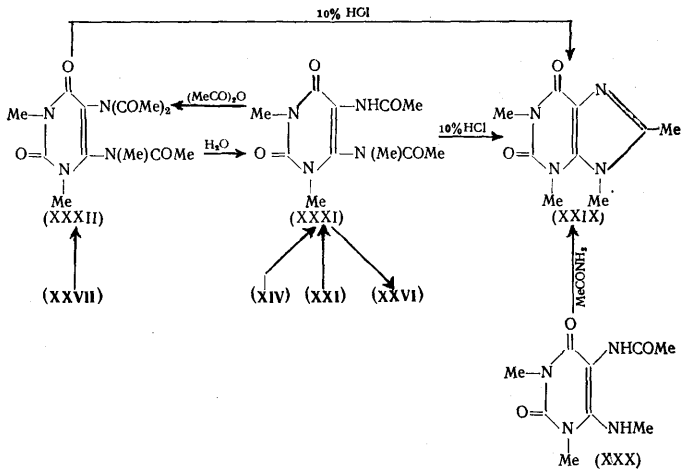


(XXVII) (XXVIII)

The choice between the two possible structures of "triacetate", (XXVII) and (XXVIII), was made by studying the reactions of "trimethyldiacetate", which was isolated for the first time from the reaction mixture obtained in the methylation of "diacetate". It was obtained also from "1,3-dimethyldiacetate" (XXI) and its methylation yielded "tetramethyldiacetate" (XXV).

It was found that the third methyl group of "trimethyldiacetate" is at the amino-group joined to $C_{(4)}$ (the position of the two other methyl groups at $N_{(1)}$ and $N_{(3)}$ gave rise to no doubts), since on heating with 10% hydrochloric acid a single molecule of acetic acid is split off and cyclisation with formation of 1,3,8,9-tetramethylxanthine (XXIX) takes place[42]. The latter was identified with methylisocaffeine, synthesised from 1,3-dimethyluramil[46] and also by condensing 5-acetamido-4-methylamino-1,3-dimethyluracil (XXX) with acetamide[38].

On the basis of the uracil structure of "tetramethyldiacetate" and the formation of methylisocaffeine as a result of the cyclisation of "trimethyldiacetate", the latter is 5-acetamido-4-acetylmethylamino-1,3-dimethyluracil (XXXI). When it is treated with acetic anhydride, it is acetylated to "trimethyltriacetate", the only possible structure of which is 5-diacetamido-4-acetylmethylamino-1,3-dimethyluracil (XXXII). It was identified with "trimethyltriacetate" obtained by methylating "triacetate" isolated directly from the reaction mixture obtained when uric acid interacts with acetic anhydride. This showed that the acetyl groups in "triacetate" are located in the same positions as in compound (XXXII), which fully confirmed that their structure is (XXVII)[47,48] and not (XXVIII)[42].



The cyclisation of (XXXI) and (XXXII) on treatment with inorganic acids led to the possibility of employing this reaction as a convenient method of synthesising methylisocaffeine (XXIX) which was previously difficult to obtain. The solutions formed as a result of the methylation of "diacetate" or "triacetate" are heated with an acid for this purpose. The highly soluble "trimethyldiacetate" (XXI) contained in these solutions is then converted into the comparatively sparingly soluble compound (XXIX), which crystallises in its entirety on cooling[49]. Its yield is 60–65% with respect to two stages (methylation and cyclisation) or 40–45% relative to uric acid (i.e. with respect to all three stages).

Methylisocaffeine (XXIX) obtained in this way subsequently serves as the starting material for the synthesis of hitherto unknown derivatives of 9-methylpurine.

III. SYNTHESES BASED ON *N*-METHYLATED 8-METHYLXANTHINES

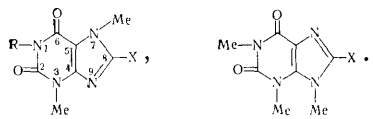
Both isomeric tetramethylxanthines synthesised from uric acid, i.e. 8-methylcaffeine (III) and 8-methylisocaffeine (XXIX), as well as 3,7,8-trimethylxanthine, i.e. 8-methyltheobromine (IV), were employed successfully to synthesise *N*-methylated purines: (1) xanthines (2,6-dioxopurines) substituted at $C_{(8)}$ and (2) 1,9-dimethylhypoxanthines (6-mono-oxopurines) and 9-methylpurines substituted at the carbon atoms of the pyrimidine ring‡.

1. Methylated Xanthines Substituted at $C_{(8)}$

In accordance with the difference between the positions of the *N*-methyl group of the imidazole ring (7- or 9-) in the initial compounds (III) or (IV) and (XXIX), these are

‡ In accordance with the aim of this review, it does not include questions concerning the synthesis of the isomeric derivatives of 3,7-dimethylhypoxanthine and 7-methylpurine, since the starting material for their synthesis is theobromine, which is not as a rule obtained from uric acid.

the parent compounds of two isomeric α- and β-series of $C_{(8)}$-substituted xanthines with different positions of the double bond in the ring, which sometimes differ significantly in their properties. The results of methylation in an aqueous alkaline medium[50,51], the rate of hydrolytic cleavage of the pyrimidine ring under the influence of alkaline agents[52], ultraviolet spectra[53,54], and certain other chemical and physical properties can serve as examples of such differences for α- and β-xanthines, in particular for compounds (III)–(VI), (XXIX), and (XXXIII):



(III, R = X = Me) (V, R = Me, X = H) (XXIX, X = Me)
(IV, R = H, X = Me) (VI, R = X = H) (XXXIII, X = H)

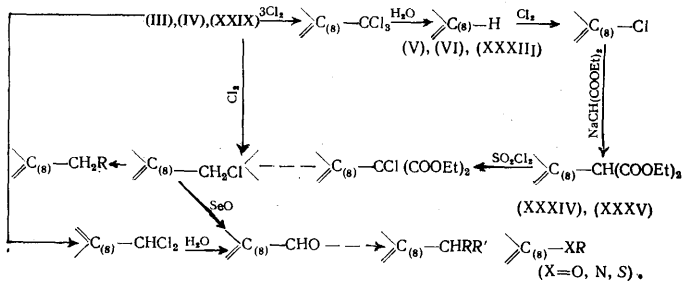
The first widely occurring stage in the reactions of all three 8-methyl derivatives of N-methylated xanthines (III), (IV), and (XXIX) is the substitution of the hydrogen atoms in the $C_{(8)}$-methyl group by chlorine. Such substitution is as a rule achieved by treatment with chlorine or sulphur chloride[15,18,24-28,55-60] and does not require vigorous heating[18,25,27]. The substitution of one or two hydrogen atoms in this methyl group by chlorine leads to the formation of mono- and di-chlorides[15,58-60,66] and the replacement of chlorine in such groups by other substituents leads to the synthesis of a wide variety of $C_{(8)}$ derivatives of caffeine (V)[56], theobromine (VI)[58,60-62], and isocaffeine (XXXIII)[59,63]. Compounds of this type may be obtained from 8-methylderivatives of N-methylxanthines also by another longer but more universal procedure based on the preliminary elimination of the $C_{(8)}$-methyl group by complete substitution with chlorine and subsequent hydrolysis[15,16,18,24-28,55-58].

The substitution of a hydrogen atom in the 8-position by halogen[55,64-68] in compounds (V), (VI), and (XXIII) formed§ and condensation of 8-halogeno-N-methylxanthines with sodiomalonic and sodioalkylmalonic esters also makes it possible to prepare various $C_{(8)}$-derivatives. Caffeine-8-malonic ester (XXXIV) and isocaffeine-8-malonic ester (XXXV) exhibit a fairly high acidity[65,69], exceeding that of other monosubstituted malonic esters and of malonic ester itself and are produced in the condensation reaction as crystalline sodium derivatives, which are formed from the unreacted part of the sodiomalonic ester. Therefore the normal termination of the reactions always requires the use of two moles of sodiomalonic ester per mole of the chloride:

$$\rangle C_{(8)}-Cl + 2NaCH(COOEt)_2 \xrightarrow{-NaCl} \rangle C_{(8)}-CH(COOEt)_2 + NaCH(COOEt)_2 \rightarrow \rangle C_{(8)}-C(Na)(COOEt)_2 + CH_2(COOEt)_2.$$

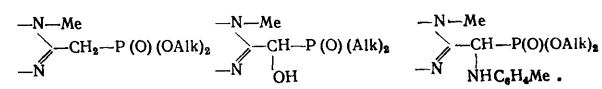
The electron-accepting properties of the purine molecule lead to an enhancement of the polarity of the C–H bond of the malonic acid group in compounds (XXIV) and (XXXV). This influence is general and is observed for other C-malonic acid derivatives of various purine systems, regardless of the position of the malonic acid residue in the purine molecule—at $C_{(8)}$,[70-73] at $C_{(6)}$,[74,75] or at $C_{(2)}$.[76-78] This influence is shown also by the fact that the halogen atom in the malonic acid residue in purinylhalogenomalonic esters reacts as a halogen cation[79] and also by the capacity of purinylmalonic, alkylmalonic, and acylaminomalonic esters to split off, on heating with alkoxides in an alcoholic medium, one of the two ethoxycarbonyl groups with formation of esters of the corresponding purinylmonocarboxylic acids and of the carbonic ester[80-82].

Subsequent reactions of the malonic acid residue in the diesters (XXXIV) and (XXXV) as well as the conversion of 8-monochloro- and dichloro-methyl derivatives obtained by direct chlorination of compounds (III), (IV), and (XXIX), permitted a fairly wide variation of the nature of the substituent linked to $C_{(8)}$ in N-methylated xanthines and the synthesis via the two schemes discussed above of compounds with a wide variety of substituents R—derivatives of alkanoic acids with straight or branched chains[63,65,69,71-73,83-90], aldehydes, alcohols[59,60,61,72,85,87-90], amines[52,63,85,88-92], derivatives of α-alanine substituted with a xanthine molecule at the β-carbon atom[58,59,88,92] (cf. Refs. 74–78), and certain others (see, for example, Refs. 93–95):



Lugovkin synthesised a group of purinylphosphonic acid esters from 8-monochloro and dichloromethyl-N-methylxanthines (1,3,7-, 1,3,9-, and 3,7-derivatives) via the Arbuzov reaction. Diesters of the corresponding purinylmethylphosphonic acids (XXXVI) were obtained by the condensation of 8-monochloromethylcaffeine[96] (and later also 2-chloro-6-monochloromethyl-9-methylpurine[74,97]) with trialkyl phosphites and diesters of α-hydroxy-8-purinylmethylphosphonic acids (XXXVII) were obtained by the reaction of dialkylphosphorous acids with caffeine-8-aldehyde and theobromine-8-aldehyde[98,99].

A series of dimethyl esters of 8-purinyl-(*p*- and *m*-tolylamino)methylphosphonic acids (XXXVIII) were synthesised by treating with dialkylphosphorous acids 8-xanthinylazomethines obtained by the condensation of the above aldehydes with *m*- or *p*-toluidine[100]:

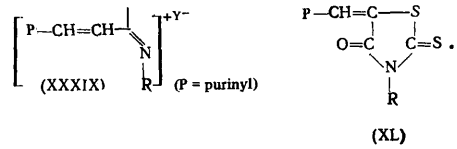


(XXXVI) (XXXVII) (XXXVIII)

Lugovkin investigated the condensation of N-methylated xanthine-8-aldehydes with the active methylene groups of the alkiodides of α- and β-picolines, quinaldine, lepidine, and 2-methylbenzothiazole and its derivatives[101-103] and also with 3-alkyl- and 3-phenylrhodanines[104], which yielded the quarternary salts of various heterocyclic systems with N-methylated xanthine-8-ylidene substituents

§ It is self-evident that the synthesis of uric acid is not obligatory for the synthesis of caffeine which is nowadays manufactured by another synthetic procedure or isolated from natural materials. However, this scheme may be regarded as entirely reliable for the preparation of derivatives of 9-methylpurines, and it has many advantages over other versions of their synthesis.

(XXXIX) and also purine rhodanines with the general formula (XL):



(XXXIX) (P = purinyl)

(XL)

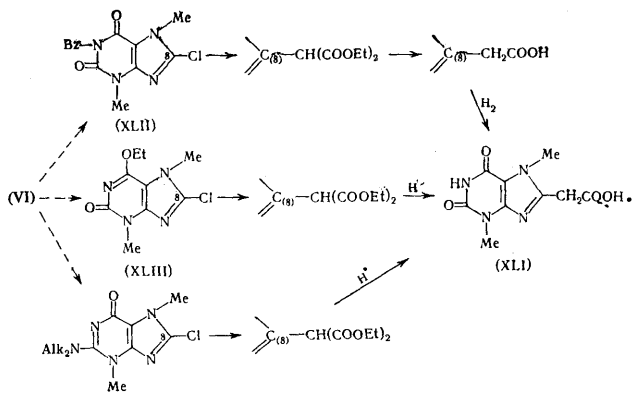
The interaction of *N*-methylated 8-chloroxanthines with amines, alkoxides, and other nucleophilic agents leads readily to the formation of the corresponding xanthines with C–N, C–O, and C–S bonds at the $C_{(8)}$ carbon atom.

Such reactions and also the direct substitution of the hydrogen atoms of the $C_{(8)}$-methyl group by chlorine discussed above and the subsequent conversion of the mono-, di-, and tri-chlorides takes place in more or less the same manner for *NNN*-trimethylxanthines and those *N*-methylated xanthines where one or two ring hydrogen atoms are unsubstituted (see, for example, Golovchinskaya et al.[52]).

In contrast to these reactions, the condensation of 8-chloro-derivatives of *NN*-dimethylxanthines and *N*-monomethylxanthines with sodiomalonic ester is much more complicated than the analogous condensation of *NNN*-trimethylxanthines, i.e. of 8-chlorocaffeine and 8-chloroisocaffeine, since it requires a preliminary introduction of protecting groups. *N*-Benzylation or the introduction of *C*-alkoxy groups are usually employed for this purpose. Catalytic reduction is used to remove the benzyl group[62,72,89,105,106] and the alkoxy-group is eliminated hydrolytically[71–73,88].

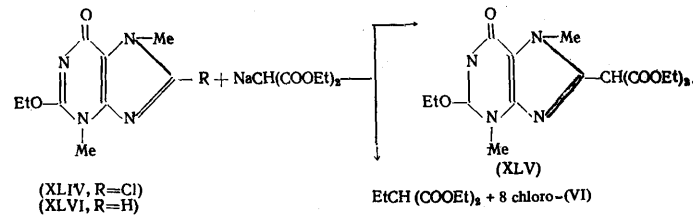
Both methods of protection can be clearly illustrated by the synthesis of theobromine-8-acetic acid (XLI) and its derivatives from 1-benzyl-8-chlorotheobromine (XLII) and from 8-chloro-6-ethoxy-3,7-dimethylhypoxanthine (XLIII)[72,107].

Recently yet another method of synthesising theobromine-8-acetic acid from theobromine (VI) has been discovered; it is based on the fact that the alkylamino-groups linked to the $C_{(2)}$ atom of 3,7-dimethylhypoxanthine are readily split off on heating with inorganic acids[108]. Therefore such groups can be successfully employed at $C_{(2)}$ instead of alkoxy-groups at $C_{(6)}$ for protection in the condensation of 8-chlorotheobromine with sodiomalonic ester. They are eliminated with regeneration of the xanthine structure and simultaneous hydrolytic cleavage of the malonic acid residue[109]:



(XLII) (XLIII) (XLI)

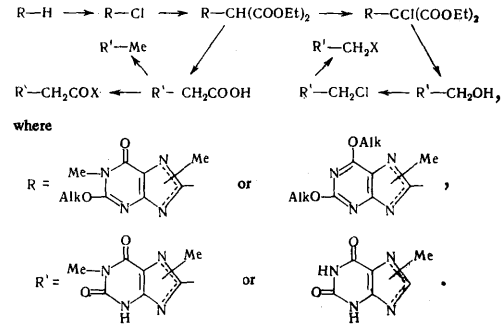
An interesting fact was observed in an attempt to synthesise the acid (XLI) from 8-chloro-2-ethoxytheobromine or 8-chloro-2-ethoxy-3,7-dimethylhypoxanthine[110–111] (XLIV), i.e. from an isomer of compound (XLIII). The yield of the condensation product, 2-ethoxytheobromine-8-malonic ester (XLV), was found to be appreciably lower than the yield of the condensation product obtained from the 6-ethoxy-derivative (50% instead of 80%), because the condensation of (XLIV) was accompanied by a parallel reaction involving the ethylation of the malonic ester owing to the cleavage of the ethoxy-group at $C_{(2)}$. In this case, the final reaction products were, apart from (XLV), ethylmalonic ester (yield 42%) and 8-chlorotheobromine:



(XLIV, R=Cl) (XLVI, R=H) (XLV) $EtCH(COOEt)_2$ + 8 chloro-(VI)

The yield of ethylmalonic ester increases and reaches 92% when the possibility of the competing condensation reaction is excluded, i.e. when 2-ethoxy-theobromine (XLVI), which does not contain a chlorine atom at $C_{(8)}$, is allowed to react with sodiomalonic ester. The capacity of compounds (XLIV) and (XLVI) to behave as ethylating agents has been confirmed also in other reactions[112].

The isomeric 2-ethoxy-1,9-dimethylhypoxanthine (XLVII) and 2-ethoxy-1,7-dimethylhypoxanthine (XLVIII) and their 8-chloroderivatives (XLIX) and (L)[113–116] also alkylate malonic ester, but the main reaction products formed are the corresponding 2-ethoxypurinyl-8-malonic esters[112]. As a result, both 2-alkoxydimethylhypoxanthines [(XLVII and XLVIII) and also 2,6-dialkoxy-7-methylpurine (LI) and 2,6-dialkoxy-9-methylpurine (LII); see below] were used as the starting materials for the synthesis in satisfactory yields of a series of derivatives of 1,7- and 1,9-dimethylxanthines and also 7- and 9-monomethylxanthines substituted by various groups in the 8-position[72,113]:



where

It was suggested that the reason why 2-ethoxytheobromine (XLVI) and its 8-chloro-derivative (XLIV) are more active ethylating agents than compounds (XLVII)–(L) is associated with the *p*-quinonoid structure of the pyrimidine part of the molecule, which entails an additional decrease of electron density at $C_{(2)}$ and a consequent loosening of the bond between the oxygen in the ethoxy-group and the carbon atom of the alkyl group.

The real reason for the inability of 8-chloro-6-ethoxy-theobromine (XLIII), mentioned above, to alkylate malonic ester is probably the steric effect of the $N_{(7)}$-methyl group, which is in the *peri*-position relative to the $C_{(8)}$ reaction centre[112].

LCAO-MO calculations using the parameters of Pullman's system for the compounds (XLVI), (XLIV), (XLVII)–(L), 1,7-, 1,9-, and 3,7-dimethylhypoxanthines, 3,7-dimethyl-2-oxo-2,3-dihydropurine [67–69] and the study of their ^{1}H NMR spectra yielded a satisfactory qualitative correlation between the experimental and calculated data characterising the reactivity of the substituents (the ethoxy-group at $C_{(2)}$ and the chlorine atom at $C_{(8)}$) in the reactions discussed above [117].

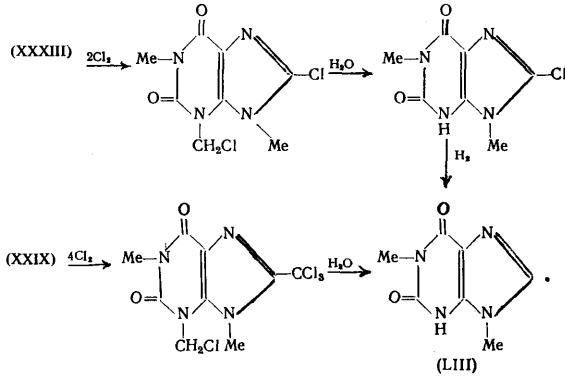
In conclusion of this section, it should be noted that the difference between α- and β-xanthines is shown to only a slight degree in the reactions enumerated above.

2. 9-Methylpurine Derivatives Substituted in the Pyrimidine Ring

a. Preparation of 1,9-dimethylxanthine from 8-methylisocaffeine. Substitution of tetramethylxanthines with chlorine in the $C_{(8)}$-methyl group and directly at $C_{(8)}$ in *NNN*-tri- and *NN*-di-methylxanthines takes place in the α- and β-series without significant differences, while in the substitution with chlorine in the *N*-methyl groups (reactions requiring higher temperatures [18,25,118–121] and the use of an excess of the chlorinating agent) certain differences are observed.

The replacement by chlorine of some of the hydrogen atoms in the *N*-methyl group of 8-chlorocaffeine [118–120] and 8-trichloromethylcaffeine [18,24,25] with subsequent hydrolytic elimination of the *N*-monochloromethyl group constitutes the basis of the methods of industrial synthesis of theophylline (VII) from caffeine [122] or uric acid, which have been known for a long time.

The chlorination of isocaffeine (XXXIII) and its 8-methyl derivative (XXIX) and subsequent hydrolysis yielded 8-chlorodimethylxanthine and dimethylxanthine containing *N*-methyl groups in the 9-position; on the other hand, the chloromethyl groups at $N_{(3)}$ in the pyrimidine ring were eliminated [53,123–129]:



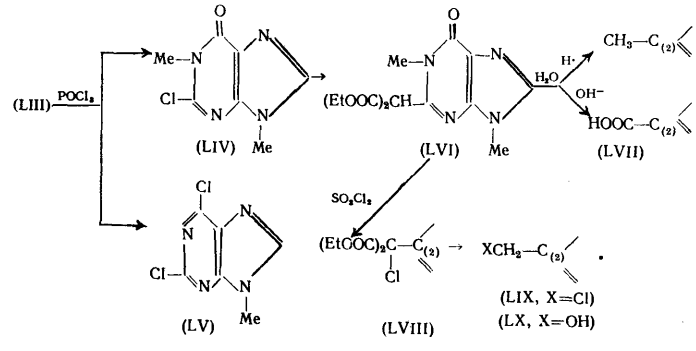
The observed difference in the order of substitution by chlorine of the hydrogen atoms in the *N*-methyl groups of *NNN*-trimethylxanthines of the α- and β-series led to a comparatively simple and short method for the conversion of compound (XXIX) into 1,9-dimethylxanthine (LIII) [130], which had been synthesised hitherto by more time-consuming procedures [127,128,131]. Owing to the ease of the new method of synthesising (LIII), it has become the starting material for the synthesis of many derivatives of 1,9-dimethylhypoxanthine substituted at $C_{(2)}$ and also of 9-methylpurine substituted at $C_{(2)}$ and at $C_{(6)}$.

b. Synthesis of derivatives of 1,9-dimethylhypoxanthine substituted at $C_{(2)}$. When 1,9-dimethylxanthine is heated with phosphoryl chloride, 2-chloro-1,9-dimethylhypoxanthine (LIV) is formed in 55% yield with an admixture of about 10% of 2,6-dichloro-9-methylpurine (LV). [128] When the monochloro-derivative (LIV) is heated with aqueous solutions of ammonia and primary and secondary amines and also with alcoholic solutions of thiourea and sodium alkoxides at temperatures below 100°C, derivatives of 1,9-dimethylhypoxanthine substituted at $C_{(2)}$ by various groups via the N, S, and O heteroatoms are formed comparatively readily [113]. 2-Amino-1,9-dimethylhypoxanthine had been obtained previously by the methylation of methylguanine [51].

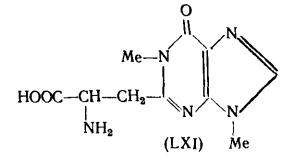
The high reactivity of chlorine in 2-chloro-1,9-dimethylhypoxanthine (LIV) was employed for malonic ester synthesis [76].

Like *NNN*-trimethylxanthine-8-malonic ester and *NN*-dimethyl- and *N*-monoethyl-hypoxanthine-8-malonic esters mentioned above, the diester (LVI), obtained in this process has a relatively high acidity constant and therefore two moles of sodiomalonic ester are employed per mole of (LIV) to obtain a high yield of the diester. Hydrolysis of compound (LVI) in an alkaline medium yielded 1,9-dimethylhypoxanthine-2-acetic acid (LVII), its esters, and amides. In contrast to xanthine-8-acetic acids, this acid readily splits off CO_2 at a low pH and therefore hydrolysis of the diester in the presence of inorganic acids leads to the formation of 1,2,9-trimethylhypoxanthine.

When the diester (LVI) is treated with sulphuryl chloride, 1,9-dimethylhypoxanthine-2-chloromalonic ester (LVIII) is obtained; depending on the conditions, the latter can be hydrolysed to the chloromethyl derivative (LIX) or the hydroxymethyl derivative (LX):



A group of derivatives of 1,9-dimethylhypoxanthine substituted at $C_{(2)}$ via a C–C bond, including β-(1,9-dimethylhypoxanthin-2-yl)-α-alanine (LXI), an analogue of β-(8-purinyl)-α-alanine mentioned above, was obtained by treating the chloro-derivative (LIX) with various nucleophilic agents [76]:

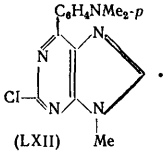


c. Synthesis of 9-methylpurine derivatives substituted at $C_{(2)}$ and at $C_{(6)}$. 9-Methylpurine derivatives substituted at $C_{(2)}$(R) and at $C_{(6)}$(R′) were obtained from 1,9-methylxanthine via two procedures:

with intermediate formation of 2,6-dichloro-9-methylpurine (LV) or from compound (LIV) by substituting the chlorine at $C_{(2)}$ with subsequent conversion of 2-R-1,9-dimethylhypoxanthine into 2-R-6-chloro-9-methylpurine and the subsequent replacement of chlorine by the required substituent R'.[114]

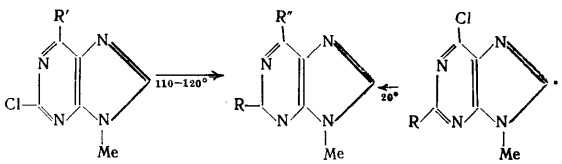
The formation of 2,6-dichloro-9-methylpurine (LV)[128] as the main product from compound (LIII) is a complicated process requiring heating with phosphoryl chloride at a high temperature (about 160°C)[132] or the addition of agents such as tertiary amines or phosphorus pentachloride.

Dimethylxanthine (LIII) can be converted into dichloropurine (LV) by heating with phosphoryl chloride in the presence of dimethylaniline, by analogy with the synthesis of 2,6-dichloro-7-methylpurine from theobromine[133], but the yield of the dichloro-derivative does not exceed 30–32%. The product is a bright-yellow substance (LXII), which was identified by ^{1}H NMR spectroscopy with a substance which had been obtained by the interaction of 2-chloro-1,9-dimethylhypoxanthine (LIV) with $POCl_3$ and dimethylaniline[134–136]:



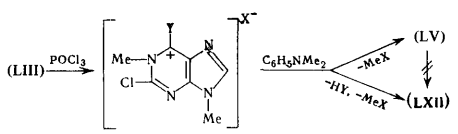
(LXII)

The structure of compound (LXII) is confirmed by its similarity to 2-chloro-6-R'-9-methylpurines in which R' is a dimethylamino- or a benzylamino-group (the substitution of chlorine by amines requires prolonged heating at 110–120°C). The reactivity of compound (LXII) is very much lower than that of the highly reactive 2-R-6-chloro-9-methylpurines, which undergo nucleophilic exchange reactions even at room temperature[137]:



Condensation with dimethylaniline was found to be a side reaction taking place simultaneously and not a secondary process involving the final dichloro-derivative (LV) after its formation. Its comparatively high reactivity of the chlorine atom at $C_{(8)}$ in this dichloro-derivative was still found to be inadequate to ensure para-condensation with dimethylaniline, as shown by experiments in which compound (LV) was heated with dimethylaniline in phosphoryl chloride.

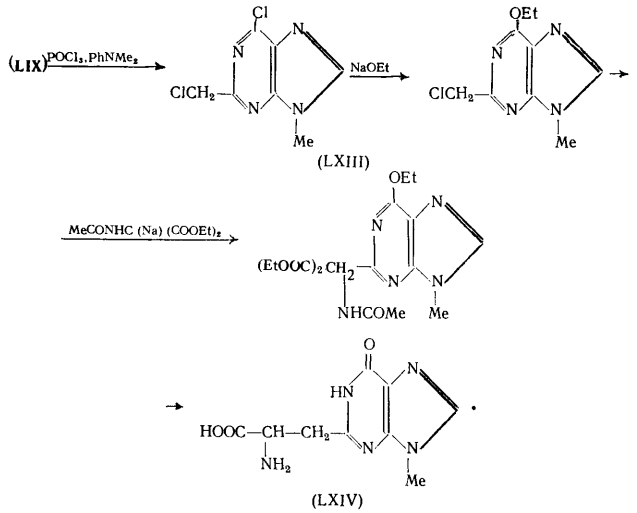
Evidently a purine compound in which the $C_{(8)}$ atom is more electrophilic takes part in the para-condensation reaction. It was suggested that an intermediate of the amidochloride type[138–140], which is partly cleaved with formation of a dichloro-derivative and partly condenses with dimethylaniline and only then splits off the $N_{(1)}$-methyl group, should be regarded as responsible for the formation of the para-condensation product. The primary product of such para-condensation is a precursor of compound (LXII), which was isolated[138]:



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

The validity of this interpretation of the process is partly confirmed by the analogy with the isomeric dimethylxanthine of the α-series, namely theobromine: its reaction with dimethylaniline and phosphoryl chloride led to the isolation, apart from 2,6-dichloro-7-methylpurine, of the primary para-condensation products retaining the $N_{(3)}$-methyl group in the pyrimidine ring[141].

Certain derivatives of 1,9-dimethylhypoxanthine containing substituents at $C_{(2)}$ and linked to the purine molecule via a heteroatom split off the $N_{(1)}$-methyl group comparatively readily and are converted into the corresponding 2-R-6-chloro-9-methylpurines as a result of heating with phosphoryl chloride without the addition of tertiary amines or phosphorus pentachloride[142]. However, when there is a carbon–carbon bond at $C_{(2)}$, the reaction requires the presence of dimethylaniline and takes place with charring. For example, 2-chloromethyl-1,9-dimethylhypoxanthine (LIX) gives not more than 40% of 6-chloro-2-chloromethyl-9-methylpurine (LXIII)—a compound from which yet another purinylalanine (LXIV) was synthesised according to the following scheme[143]:

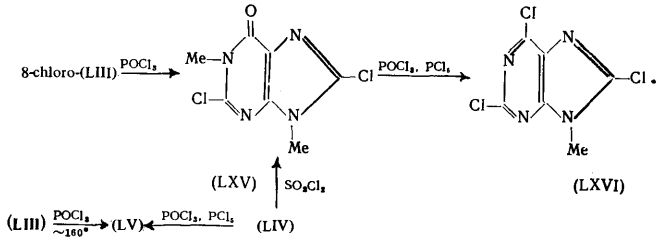


(LXIV)

The replacement of dimethylaniline by other tertiary amines (cf., for example, Robins and Christensen[144]) in order to eliminate the parallel para-condensation process mentioned above leads to a considerable increase of the yield of the dichloro-derivative (LV). Thus, when dimethylxanthine (LIII) was heated with phosphoryl chloride and triethylamine hydrochloride, compound (LV) was obtained in 70–75% yield[109]. This compound can be obtained also in satisfactory yield (60–65%) when phosphorus pentachloride is employed instead of tertiary amines.

If phosphorus pentachloride is present in the reaction mixture from the very beginning of the heat treatment of compound (LIII) in the presence of phosphoryl chloride, a parallel process involving electrophilic substitution by chlorine at $C_{(8)}$ takes place, the 8-chloro-derivative of compound (LIII) undergoing subsequently the same reactions as the initial compound (LIII). Therefore ultimately, when phosphoryl chloride and phosphorus pentachloride act simultaneously on compound (LIII), one obtains from the reaction mixture, after treatment with water, a mixture which is difficult to resolve and which consists of the monochloro-derivative (LIV), the dichloro-derivative (LV), 2,8-dichloro-1,9-dimethylhypoxanthine (LXV), and 2,6,8-trichloro-9-methylpurine (LXIV)[145,146].

The chloro-derivatives (LXV) and (LXVI) proved to be identical with the specimens of the same compounds synthesised in other ways:



On the other hand, derivatives of 9-methylpurine containing a chloro-substituent in the pyrimidine ring, namely the chloro-derivatives (LIV) and (LV), are incapable of being substituted by chlorine at $C_{(8)}$ on treatment with PCl_5, in contrast to the initial xanthine (LIII), and therefore cannot serve as the starting materials for the synthesis of compounds (LXV) and (LXVI) in this reaction.

These observations agree with the general rules of electrophilic halogenation of the purine system in the 8-position according to which this is possible only when the molecule contains electron-donating groups capable of compensating the electron-accepting influence of the pyrimidine ring relative to the imidazole ring[147]. According to this rule, the presence of a chlorine atom in the pyrimidine ring decreases the nucleophilicity of the $C_{(8)}$ ring carbon atom and prevents halogenation at this position. The chloro-derivative (LIV) can be converted into the 8-chloro-derivative (LXV) only as a result of a prolonged reaction with SO_2Cl_2 (in a yield not exceeding 25%) but not by treatment with PCl_5. The dichloro-derivative (LV) does not react even with SO_2Cl_2.

A method for the synthesis of the dichloro-derivative (LV) from dimethylxanthine (LIII) is based on such relations; it consists in heating compound (LIII) with $POCl_3$ until the disappearance of the initial xanthine from the reaction sphere and the subsequent interaction of the reaction mixture with PCl_5.[133]

The replacement of the chlorine atoms in the dichloro-derivative in compound (LV) by identical or different atoms or groups makes it possible to obtain derivatives of 9-methylpurine with various combinations of substituents at the carbon atoms of the pyrimidine ring.

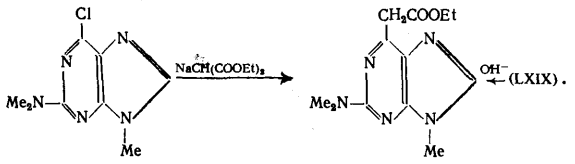
Owing to the much higher reactivity of the chlorine linked to $C_{(6)}$ in the initial chloro-derivative compared with the chlorine at $C_{(2)}$, it is possible to obtain from this compound 6-R′-2-chloro-9-methylpurines (R′ = OAlk, NHR″, SH, etc.) under very mild conditions after which the chlorine at $C_{(2)}$ can be reduced or replaced by other groups under more severe conditions[137,148]. It is self-evident that, when R = R′, both chlorine atoms are substituted simultaneously.

The non-equivalence of the chlorine atoms in the initial compound (LV) makes it possible to obtain from it derivatives of 9-methylpurine substituted at $C_{(6)}$[149,150] via the scheme adopted for the condensation of halogenopurines with sodiomalonic ester (see above). In 2-chloro-9-methylpurine-6-malonic ester (LXVII), the chlorine atom at $C_{(2)}$ may be reduced or replaced by another substituent [for example $N(CH_3)_2$] with formation of the corresponding diesters (LXVIII) and (LXIX). When the diesters (LXVII)–(LXIX) are heated with a dilute inorganic acid, 6,9-dimethylpurine (LXX), 2-R- (LXX), (LXXI, R = Cl), and [(LXXXII, R = $N(CH_3)_2$] are obtained.

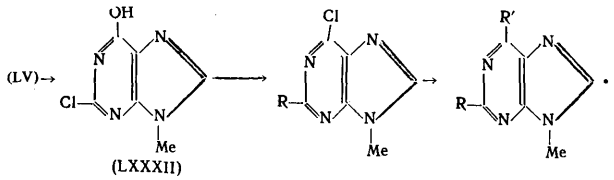
On treatment with SO_2Cl_2, the diesters (LXVII)–(LXIX) are converted into the corresponding purine-6-chloromalonic esters (LXXIII)–(LXXV), which are converted by hydrolysis at a low pH into 6-chloromethylpurines (LXXVI)–(LXXVIII). The yield of the conversion of (LXXIV) into (LXXVII) does not exceed 18%, since the main reaction product is found to be 6-hydroxy-9-methylpurine (LXXIX)[149], which is formed as a result of the cleavage of the C–C bond between $C_{(6)}$ of the 9-methylpurine molecule and the carbon atom of the chloromalonic group. Such hydrolytic cleavage of this bond is evidently a result of the high electrophilicity of the $C_{(6)}$ ring carbon atom. It is apparently also responsible for the capacity of the chlorine in the chloromethyl and chloromalonic groups of compounds (LXXIII)–(LXXVIII) to react vigorously as halogen cations and in particular to be reduced rapidly in KI solution with evolution of I_2 (see Scheme 3).

The chlorine in 6-chloromethylpurines (LXXVI)–(LXXVIII) can be substituted comparatively readily whereby the synthesis of a wide variety of $C_{(6)}$ derivatives of 9-methylpurine, including three β-(9-methyl-2-R-purin-6-yl)-α-anilines [(R = Cl, H, and $N(CH_3)_2$] can be achieved comparatively readily.

2-Chloro-9-methylpurine-6-carboxylic acid (LXXX) was obtained by the oxidation of the dichloro-derivative (LXXVI) in an alkaline medium and was converted into 2-dimethylamino-9-methylpurine-6-carboxylic acid (LXXXI). It is decarboxylated only on fairly strong heating, in contrast to the corresponding 2-R-9-methylpurine-6-acetic acids [R = Cl, H, and $N(CH_3)_2$], which split off CO_2 extremely readily. Quite stable esters of the latter were obtained from the diesters (LXVII)–(LXIX) by hydrolysis with NaOH in an aqueous-alcoholic medium[150] and one of them [R = $N(CH_3)_2$] is formed also by the condensation of 6-chloro-2-dimethylamino-9-methylpurine with sodiomalonic ester, since the reaction is accompanied by the splitting off of the ethoxycarbonyl group:

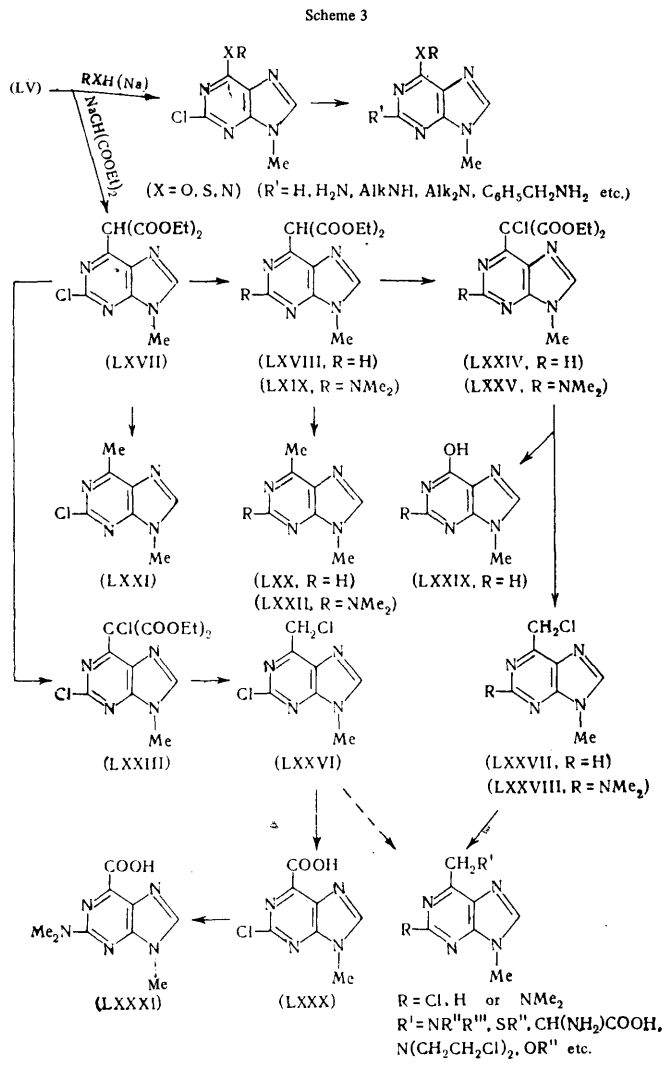


2,6-Disubstituted 9-methylpurines with various substituents at $C_{(2)}$ and $C_{(6)}$ can be synthesised from the dichloro-derivative (LV) also via another scheme with the intermediate formation of 2-chloro-6-hydroxy-9-methylpurine (LXXXII). The replacement of the chlorine in this compound at $C_{(2)}$ by various groups and subsequent introduction of chlorine at $C_{(6)}$ by treatment with $POCl_3$ and its subsequent substitution yield 2,6-disubstituted derivatives of 9-methylpurine containing all kinds of substituents at $C_{(6)}$, including the most reactive groups[113]:



The chloro-derivative (LXXXII) is formed in 82% yield after heating the dichloro-derivative (LV) for 5 h with 1 *N* acid. More prolonged heat treatment or the use of more

Scheme 3

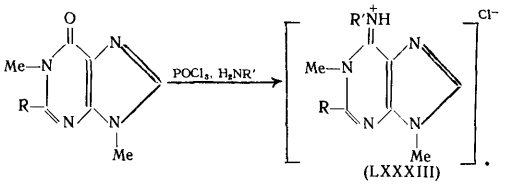


concentrated acid leads to the hydrolytic elimination of the second chlorine atom too, i.e. to the regeneration of the xanthine structure.

---o0o---

The reactions of 1,9-dimethylxanthine described in this section do not exhaust the wide variety of processes in which the compound may be involved and all the possibilities of its employment for synthetic purposes. In particular, it does not include certain aspects of the reaction of 1,9-dimethylxanthine with phosphorus chloro-compounds, which require separate consideration and do not fit within the framework of the present review.

Brief mention should also be made of the synthesis of 6-imino(or alkylamino-)-1,9-dimethylpurines (LXXXIII)—analogues of 1-alkyl-6-iminopurines, which were obtained for the first time in the 1960's either by the alkylation of adenosine[151-154] or by synthesis from 3-amino-2-cyano-1-methyl-imidazole[155]. The hydrochlorides (LXXXIII) were formed as a result of treatment with aqueous solutions of ammonia or amines of compounds of the amidochloride type obtained by treating 1,9-dimethylxanthine (LIII) or 2-R-1,9-dimethylhypoxanthines (R = Cl, CH_3, NHAlk, etc.) with phosphoryl chloride[156]:



In contrast to the syntheses described previously, this scheme makes it possible to vary widely the substituents in the exocyclic imino-group of compound (LXXXIII) and at $C_{(2)}$ (cf. Nikolaeva et al.[157]).

REFERENCES

1. J. H. Lister, Rev. Pure Appl. Chem., 11, 178 (1961).
2. J. H. Lister, Rev. Pure Appl. Chem., 13, 30 (1963).
3. H. Bredereck, F. Effenberger, G. Rainer, and H. P. Schosser, Annalen, 659, 133 (1962).
4. "Heterocyclic Compounds" (Translated into Russian), Izd. Mir, Moscow, 1969, Vol. 8, p. 130.
5. J. Montgomery and H. I. Hewson, Adv. Carbohydrate Chem., 17, 301 (1962).
6. H. Bredereck, O. Christmann, and W. Koser, Ber., 93, 1206 (1960).
7. W. Pfleiderer, Annalen, 647, 167 (1961).
8. D. Akkerman and P. H. List, A. physiol. Chem., 323, 192 (1961).
9. E. S. Golovchinskaya and O. Yu. Magidson, USSR P. 64625; Byul. Izobret., No. 3–4, 35 (1945).
10. E. Fischer, "Untersuchungen in der Puringruppe", Berlin, 1904.
11. H. Bredereck, H. G. Schuh, and A. Martini, Ber., 83, 201 (1950).
12. H. Bredereck, R. Gompper, H. G. Schuh, and G. Theilig, Angew. Chem., 71, 753 (1959).
13. German P. 121 224; Frdl., VI, 1182 (1902).
14. German P. 128 212; Frdl., VI, 1187 (1902).
15. German P. 534 907; Frdl., XVIII, 2896 (1933).
16. German P. 146 714; Frdl., VII, 670 (1904).
17. German P. 151 133; Frdl., VII, 672 (1904).
18. German P. 146 715; Frdl., VII, 672 (1904).
19. E. S. Golovchinskaya, Zhur. Prikl. Khim., 19, 1173 (1946).
20. E. S. Golovchinskaya, USSR P. 63603; Byul. Izobret., No. 4–5 (1944).
21. I. T. Strukov and L. S. Diskina, USSR P. 67605; Byul. Izobret., No. 1, 8 (1947).
22. E. S. Golovchinskaya, USSR P. 104 833; Byul. Izobret., No. 12, 13 (1956).
23. E. S. Golovchinskaya, Zhur. Prikl. Khim., 30, 1347 (1957).
24. E. S. Golovchinskaya, R. G. Glushkov, and A. A. Chemerisskaya, Zhur. Prikl. Khim., 30, 1806 (1957).
25. E. S. Golovchinskaya, O. Yu. Magidson, and T. N. Kudinova, USSR P. 66308; Byul. Izobret., No. 5, 15 (1946).
26. E. S. Golovchinskaya, Zhur. Prikl. Khim., 31, 918 (1958).
27. V. M. Fedosova and O. Yu. Magidson, USSR P. 99992; Byul. Izobret., No. 2, 8 (1954).
28. E. S. Golovchinskaya, V. M. Fedosova, and A. A. Cherkasova, Zhur. Prikl. Khim., 31, 1241 (1958).

29. E. S. Golovchinskaya, V. M. Fedosova, and A. A. Cherkasova, USSR P. 105279; Byul. Izobret., No. 2, 15 (1957).
30. V. I. Khmelevskii, Med. Prom. SSSR, 12, (4), 11 (1958).
31. V. I. Khmelevskii, USSR P. 102848; Byul. Izobret., No. 3, 10 (1956).
32. V. I. Khmelevskii, USSR P. 106606; Byul. Izobret., No. 6, 26 (1957).
33. V. I. Khmelevskii, USSR P. 106378; Byul. Izobret., No. 3, 26 (1957).
34. I. T. Strukov and L. S. Diskina, Farmatsiya, 6, 16 (1945).
35. German P. 126797; Frdl., VI, 1165 (1902).
36. H. Bredereck, J. Hennig, and W. Pfleiderer, Ber., 86, 321 (1953).
37. H. Biltz and W. Schmidt, Annalen, 431, 94 (1923).
38. H. Bredereck, J. Hennig, W. Pfleiderer, and G. Weber, Ber., 86, 333 (1953).
39. H. Bredereck, J. Hennig, W. Pfleiderer, and O. Muller, Ber., 86, 850 (1953).
40. E. S. Golovchinskaya, Zhur. Obshch. Khim., 24, 136 (1954).
41. E. S. Golovchinskaya, Zhur. Obshch. Khim., 24, 146 (1954).
42. E. S. Golovchinskaya, Zhur. Obshch. Khim., 29, 1213 (1959).
43. E. S. Golovchinskaya and F. L. Kolodkin, Zhur. Obshch. Khim., 29, 1650 (1959).
44. W. Traube, Ber., 33, 1380, 3041 (1900).
45. German P. 144761; Frdl., VII, 681 (1904).
46. H. Biltz and I. Sauer, Ber., 64, 765 (1931).
47. V. I. Khmelevskii and O. I. Durnitsyna, Zhur. Obshch. Khim., 26, 755, 867 (1956).
48. V. I. Khmelevskii, Zhur. Obshch. Khim., 31, 3123 (1961).
49. E. S. Golovchinskaya and F. L. Kolodkin, USSR P. 11370; Byul. Izobret., No. 6, 27 (1958).
50. H. Biltz and I. Sauer, Ber., 64, 752 (1931).
51. W. Pfleiderer, Annalen, 647, 161, 167 (1961).
52. E. S. Golovchinskaya, O. A. Kalganova, L. A. Nikolaeva, and E. S. Chaman, Zhur. Obshch. Khim., 33, 1650 (1963).
53. E. S. Golovchinskaya and E. S. Chaman, Zhur. Obshch. Khim., 30, 1873 (1960).
54. W. Pfleiderer and G. Nubel, Annalen, 647, 155 (1961).
55. E. S. Golovchinskaya and O. Yu. Magidson, USSR P. 89103; Byul. Izobret., No. 2, 13 (1950).
56. E. S. Golovchinskaya, Zhur. Obshch. Khim., 18, 2129 (1948).
57. E. S. Golovchinskaya, Zhur. Obshch. Khim., 26, 2367 (1956).
58. E. S. Chaman, A. A. Cherkasova, and E. S. Golovchinskaya, Zhur. Obshch. Khim., 30, 1878 (1960).
59. E. S. Chaman and E. S. Golovchinskaya, Zhur. Obshch. Khim., 32, 2015 (1962).
60. E. S. Golovchinskaya, M. Ebed, and E. S. Chaman, USSR P. 163185; Byul. Izobret., No. 12, 23 (1964).
61. E. S. Golovchinskaya, M. Ebed, and E. S. Chaman, Zhur. Obshch. Khim., 32, 4097 (1962).
62. H. Bredereck, E. Siegel, and B. Föhlisch, Ber., 95, 403 (1962).
63. E. S. Golovchinskaya and E. S. Chaman, Zhur. Obshch. Khim., 32, 3245 (1962).
64. E. Fischer and L. Reese, Annalen, 221, 336 (1884).
65. E. S. Golovchinskaya, Zhur. Obshch. Khim., "Sbornik Statei po Obshchei Khimii" (Collected Papers on General Chemistry), 1953, Vol. I, p. 692.
66. M. Ebed, E. S. Chaman, and E. S. Golovchinskaya, Zhur. Obshch. Khim., "Sbornik Statei. Problemy Organicheskogo Sinteza" (Collected Papers. Problems of Organic Synthesis), 1965, p. 198.
67. E. S. Golovchinskaya, I. M. Ovcharova, and E. S. Chaman, USSR P. 135084; Byul. Izobret., No. 2, 16 (1961).
68. E. S. Golovchinskaya, I. M. Ovcharova, and E. S. Chaman, USSR P. 135085; Byul. Izobret., No. 2, 17 (1961).
69. E. S. Golovchinskaya and E. S. Chaman, Zhur. Obshch. Khim., 30, 3628 (1960).
70. E. S. Golovchinskaya, USSR P. 93548; Byul. Izobret., No. 4, 7 (1952).
71. L. A. Nikolaeva and E. S. Golovchinskaya, Zhur. Obshch. Khim., 34, 1137 (1964).
72. L. A. Nikolaeva, M. Ebed, and E. S. Golovchinskaya, Zhur. Obshch. Khim., "Sbornik Statei. Sintez Prirodnykh Soedinenii, Ikh Analogov i Fragmentov" (Collected Papers. The Synthesis of Natural Products, Their Analogues, and Fragments), 1965, p. 245.
73. V. B. Kalcheva and E. S. Golovchinskaya, Khim. Geterotsikl. Soed., Collection I, 469 (1967).
74. E. S. Chaman and E. S. Golovchinskaya, Zhur. Obshch. Khim., 33, 3342 (1963).
75. E. S. Chaman and E. S. Golovchinskaya, Zhur. Obshch. Khim., 36, 1608 (1966).
76. I. M. Ovcharova and E. S. Golovchinskaya, Zhur. Obshch. Khim., 34, 3254 (1964).
77. I. M. Ovcharova, L. N. Babenko, and E. S. Golovchinskaya, Khim.-Farm. Zhur., No. 3, 37 (1967).
78. I. M. Ovcharova, L. N. Babenko, and E. S. Golovchinskaya, Khim.-Farm. Zhur., No. 7, 26 (1970).
79. E. S. Chaman and E. S. Golovchinskaya, Zhur. Obshch. Khim., 31, 2645 (1961).
80. E. S. Golovchinskaya, Zhur. Obshch. Khim., "Sbornik Statei po Obshchei Khimii" (Collected Papers on General Chemistry), 1953, Vol. I, p. 702.
81. L. A. Gutorov and E. S. Golovchinskaya, Khim.-Farm. Zhur., No. 6, 13 (1971).
82. L. A. Gutorov and E. S. Golovchinskaya, Khim.-Farm. Zhur., No. 7, 13 (1972).
83. G. Bargioni, Chem. Zentr., I, 2096 (1936).
84. E. S. Golovchinskaya and E. S. Chaman, Zhur. Obshch. Khim., 22, 528 (1952).
85. M. Ebed, E. S. Chaman, and E. S. Golovchinskaya, Khim. Geterotsikl. Soed., Collection I, 462 (1967).
86. L. A. Gutorov and E. S. Golovchinskaya, Khim.-Farm. Zhur., No. 7, 45 (1967).
87. E. S. Golovchinskaya and E. S. Chaman, Zhur. Obshch. Khim., 22, 2220 (1952).
88. L. A. Nikolaeva and E. S. Golovchinskaya, Zhur. Obshch. Khim., "Sbornik. Statei. Problemy Organicheskogo Sinteza" (Collected Papers. Problems of Organic Synthesis), 1965, p. 192.
89. M. Ebed, E. S. Chaman, and E. S. Golovchinskaya, Zhur. Obshch. Khim., 36, 816 (1966).
90. E. S. Golovchinskaya and E. S. Chaman, Zhur. Obshch. Khim., 22, 2225 (1952).
91. E. S. Golovchinskaya and E. S. Chaman, Zhur. Obshch. Khim., 22, 535 (1952).
92. I. M. Ovcharova, E. S. Chaman, and E. S. Golovchinskaya, Khim. Geterotsikl. Soed., 1129 (1967).
93. R. G. Glushkov, E. S. Golovchinskaya, and O. Yu. Magidson, Zhur. Obshch. Khim., 29, 3742 (1959).
94. G. M. Borodina, Khim. Nauka i Prom., 3, No. 5, 681 (1958).

95. E. S. Golovchinskaya, USSR P. 93549; Byul. Izobret., No. 4, 8 (1952).
96. B. P. Lugovkin, Zhur. Obshch. Khim., **27**, 1524 (1957).
97. B. P. Lugovkin and E. S. Chaman, see Ref. 72, p. 278.
98. B. P. Lugovkin, Zhur. Obshch. Khim., **30**, 2427 (1960).
99. B. P. Lugovkin, Zhur. Obshch. Khim., **31**, 3406 (1961).
100. B. P. Lugovkin, Khim. Geterotsikl. Soed., 900 (1969).
101. B. P. Lugovkin, Zhur. Obshch. Khim., **32**, 452 (1962).
102. B. P. Lugovkin, Zhur. Obshch. Khim., **33**, 2942 (1963).
103. B. P. Lugovkin, Zhur. Obshch. Khim., **33**, 3205 (1963).
104. B. P. Lugovkin, Khim. Geterotsikl. Soed., No. 4, 61 (1969).
105. BRD P. 1 140 581, (1963); Chem. Abs., **58**, 10 217 (1963).
106. N. Ya. Vel'kina, E. S. Chaman, and M. Ebed, Zhur. Obshch. Khim., **37**, 50 (1967).
107. L. A. Nikolaeva and E. S. Golovchinskaya, Khim.-Farm. Zhur., No. 4, 32 (1968).
108. L. A. Gutorov and E. S. Golovchinskaya, Khim.-Farm. Zhur., No. 6, 13 (1971).
109. L. A. Gutorov and E. S. Golovchinskaya, USSR P. 311 917; Byul. Izobret., No. 25, 99 (1971).
110. I. M. Ovcharova, L. A. Nikolaeva, and E. S. Golovchinskaya, Khim.-Farm. Zhur., No. 2, 18 (1968).
111. E. S. Golovchinskaya, L. A. Nikolaeva, and I. M. Ovcharova, USSR P. 202 153; Byul. Izobret., No. 19, 36 (1967).
112. V. S. Korsunskii, O. V. Kozlova, T. D. Pervacheva, and E. S. Golovchinskaya, Khim.-Farm. Zhur., No. 11, 20 (1969).
113. I. M. Ovcharova, L. A. Nikolaeva, E. S. Chaman, and E. S. Golovchinskaya, Zhur. Obshch. Khim., **32**, 2010 (1962).
114. E. Fischer, Ber., **30**, 2400 (1897).
115. I. M. Ovcharova and E. S. Golovchinskaya, Khim.-Farm. Zhur., No. 3, 32 (1967).
116. E. S. Golovchinskaya and L. A. Nikolaeva, USSR P. 162 851; Byul. Izobret., No. 11, 19 (1964).
117. T. N. Ul'yanova, G. G. Dvoryantseva, N. P. Kostryuchenko, and Yu. N. Sheinker, Khim. Geterotsikl. Soed., No. 2, 265 (1971).
118. German P. 153 122; Frdl., VII, 677 (1904).
119. J. H. Lister, "Purines. The Chemistry of Heterocyclic Compounds" (Edited by A. Weissberger); E. C. Taylor, "Fused Pyrimidines", Part II, (Edited by D. J. Brown), 1971.
120. German P. 151 190; Frdl., VII, 676 (1904).
121. German P. 105 050; Frdl., V, 850 (1901).
122. German P. 145 880; Frdl., VII, 676 (1904).
123. E. S. Golovchinskaya, I. M. Ovcharova, and A. A. Cherkasova, Zhur. Obshch. Khim., **30**, 3332 (1960).
124. W. Schwabe, Arch. Pharm., **245**, 398 (1907).
125. W. Pfleiderer, Ber., **90**, 2272 (1957).
126. K. A. Chkhikvadze and O. Yu. Magidson, Med. Prom. SSSR, No. 9, 16 (1958).
127. H. Biltz, K. Strufe, E. Topp, M. Heyn, and R. Robl., Annalen, **423**, 200 (1921).
128. Y. M. Gulland and L. F. Story, J. Chem. Soc., 692 (1938).
129. German P. 120 437; Frdl., VI, 1180 (1902).
130. E. S. Golovchinskaya, I. M. Ovcharova, E. S. Chaman, and A. A. Cherkasova, USSR P. 129 658; Byul. Izobret., No. 13, 23 (1960).
131. A. H. Cook, J. D. Downer, and I. Heilbron, J. Chem. Soc., 1069 (1949).
132. L. A. Nikolaeva, I. M. Ovcharova, E. S. Chaman, and E. S. Golovchinskaya, USSR P. 141 870; Byul. Izobret., No. 20, 19 (1961).
133. D. Ya. Uretskaya, E. I. Rybkina, and G. P. Men'shikov, Zhur. Obshch. Khim., **30**, 327 (1960).
134. F. Bergel and H. Döring, Chem. Ber., **61**, 844 (1928).
135. O. Hess, Chem. Ber., **18**, 685 (1885).
136. S. Kawai and T. Miyoshi, Sci. Paper Inst. Phys. Chem. Research (Tokyo), **16**, 20 (1951); Chem. Abs., **25**, 5676 (1931).
137. I. M. Ovcharova and E. S. Golovchinskaya, Zhur. Obshch. Khim., **34**, 3247 (1964).
138. E. S. Golovchinskaya, L. A. Nikolaeva, I. M. Ovcharova, and E. S. Chaman, Symposium, "Puti Sinteza i Izyskaniya Protivoopukholevykh Preparatov" (Methods of Synthesising and Employment of Antitumour Preparations), Medgiz. Moscow, 1962, p. 134.
139. H. Ellingsfeld, M. Seefelder, and H. Weidinger, Angew. Chem., **72**, 836 (1960).
140. H. H. Basshard and H. Zollinger, Helv. Chem. Acta, **42**, 1659 (1959).
141. L. A. Gutorov and E. S. Golovchinskaya, Khim.-Farm. Zhur. (in the Press).
142. I. M. Ovcharova and E. S. Golovchinskaya, Khim.-Farm. Zhur. (in the Press).
143. I. M. Ovcharova and E. S. Golovchinskaya, Khim.-Farm. Zhur. (in the Press).
144. R. K. Robins and B. E. Christensen, J. Amer. Chem. Soc., **74**, 3625 (1952).
145. Y. Satcliff and R. K. Robins, J. Org. Chem., **28**, 1662 (1963).
146. E. Fischer, Ber., **31**, 2658 (1898).
147. J. H. Lister, Adv. Heterocycl. Chem., **6**, 30 (1966).
148. V. S. Korsunskii, E. S. Chaman, and E. S. Golovchinskaya, Khim.-Farm. Zhur., No. 3, 10 (1972).
149. E. S. Chaman and E. S. Golovchinskaya, Zhur. Obshch. Khim., **33**, 3342 (1963).
150. E. S. Chaman and E. S. Golovchinskaya, Zhur. Obshch. Khim., **34**, 1608 (1964).
151. P. Brooks and P. D. Lawley, J. Chem. Soc., 539 (1960).
152. H. G. Windqueller and N. O. Kaplan, J. Biol. Chem., **236**, 2716 (1961).
153. J. W. Jones and P. K. Robins, J. Amer. Chem. Soc., **85**, 193 (1963).
154. H. Bredereck, H. Hass, and A. Martini, Ber., **81**, 307 (1948).
155. E. C. Taylor and P. K. Loffler, J. Amer. Chem. Soc., **82**, 3147 (1960).
156. I. M. Ovcharova and E. S. Golovchinskaya, Zhur. Obshch. Khim., **34**, 2472 (1964).
157. L. A. Nikolaeva, I. M. Ovcharova, and E. S. Golovchinskaya, Khim.-Farm. Zhur., No. 8, 21 (1969).

Ordzhonikidze All-Union Institute
of Chemistry and Pharmacology,
Moscow