SYNTHESIS OF N-SUBSTITUTED XANTHINES (REVIEW)

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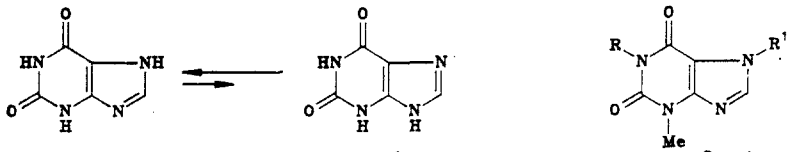
The literature on the synthesis of N-substituted xanthines by cyclization, recyclization, and N-substitution is reviewed.

Together with adenine, guanine, and uric acid, xanthine and its derivatives constitute the most important biogenic purines. Well-known xanthine derivatives include the plant alkaloids theobromine (2), theophyllin (3), and caffeine (4), which are used extensively in medicine. Some N-methylxanthines have been found in the metabolic products of animals [1].



1a 1b 2 - 4

2 R=H, R¹=Me; 3 R=Me, R¹=H; 4 R=R¹=Me

Nearly all known xanthines possess biological activity. The stimulant properties of caffeine and the cardiovascular activity of theobromine and theophyllin are well known. Derivatives of these compounds are used as drugs with antiinflammatory (pentalgin and pyraminal), psychostimulant (caffeine and caffetamine), cholinolytic and antihistaminic (dimenhydrate and dedomon), vasodilatory and spasmolytic (theodibaverine, ingexin, pentoxyphyllin, and euophyllin), and bronchodilatory and antiasthmatic activity (theophedrine, antasthman). Many N-substituted xanthines have been used as intermediates in the synthesis of compounds with potential biological activity.

Intensive examination of the chemistry of N-substituted xanthines commenced in the mid-1940s. Oddly enough, however, despite the considerable amount of work which has been carried out in this area, there have been no reviews of the synthesis of N-substituted xanthines. The available reviews of the chemistry of purines [1-5] pay little attention to this topic. The present review seeks to fill this gap. The review covers the methods of synthesis of N-substituted (N–Alk, N–Ar, N-glycosido-, N-amino-, etc.) xanthines, either by cyclization or recyclization, or by direct introduction of N-substituents into xanthine and its derivatives. The literature up to 1988, inclusive, is covered.

1. GENERAL PROPERTIES OF XANTHINES

The xanthine molecule can theoretically display two types of tautomerism, namely annular (migration of the proton of the imidazole ring between $N_{(7)}$ and $N_{(9)}$) and lactim-lactam (migration of protons between $N_{(1)}$ and $N_{(3)}$ and oxygen). A considerable amount of information is available showing that xanthines exist almost exclusively as lactams with two carbonyl groups. As far as annular tautomerism is concerned, in xanthines, as opposed to most simple purines, the 7H-form predominates. For example, the proportions of the 7H- (1a) and 9H- (1b) forms of xanthine itself in aqueous solution are 99 and 1%, respectively [6]. From the basicities of 7-methyltheophyllin (pH_a 7.60) and 9-methyltheophyllin (pK_a 9.91) in acetonitrile at 20°C, it may be concluded by analogy that the ratio of the 7H- to the 9H-forms of theophyllin under these conditions is 200:1 [7].

Four types of mono-N-substituted (1-, 3-, 7-, and 9-), five of di-N-substituted (1,3-, 1,7-, 1,9-, 3.7-, and 3,9-), and two types of trisubstituted (1,3,7- or 1,3,9-) products are possible for xanthine. Some of these compounds are readily obtainable, while others, especially the 9-substituted compounds, are relatively difficult to obtain.

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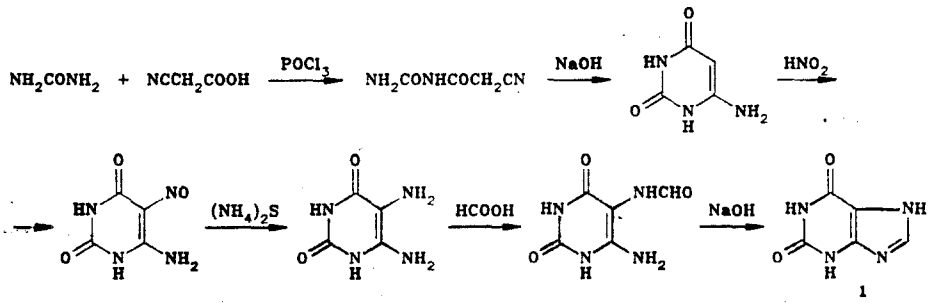
2. SYNTHESIS OF XANTHINES BY CYCLIZATION AND RECYCLIZATION

2.1. Traube Synthesis of Xanthines

The most general method of synthesis of purines is that of Traube. As applied to xanthines, this consists in the preparation of 5,6-diaminouracils from urea or N-substituted ureas, followed by cyclization [8]:



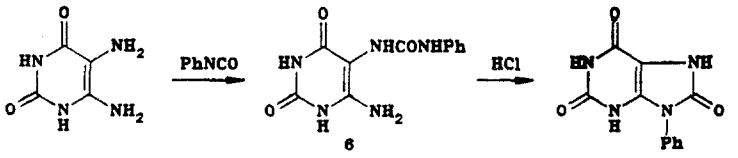
1

Similarly, sym-dimethylurea affords theophyllin (3), methylation of which gives caffeine (4). This route provides the basis for the industrial synthesis of these alkaloids [9].

The route as shown here has been considerably improved by other workers (see reviews [1, 2]). Most of the modifications of the Traube method are directed toward the synthesis of 8-substituted xanthines, usually with H or CH_3 at $N_{(1)}$ and $N_{(3)}$. This is not surprising, since most naturally occurring xanthines are of these types.

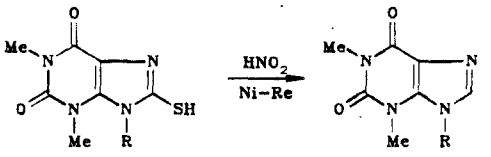
In practice, the cyanoacetic acid in the first step of the Taube synthesis is normally replaced by its ethyl ester, and the cyclization with urea is carried out in the presence of sodium alkoxides. 5,6-Diaminouracils are usually cyclized to xanthines with formamide [1]. The use of aliphatic and aromatic acids or their amides for this purpose affords 8-R-xanthines [1].

5,6-Diaminouracil reacts with phenyl isocyanate to give the ureide (6), which on treatment with 20% hydrochloric acid is converted into 9-phenyluric acid [10].



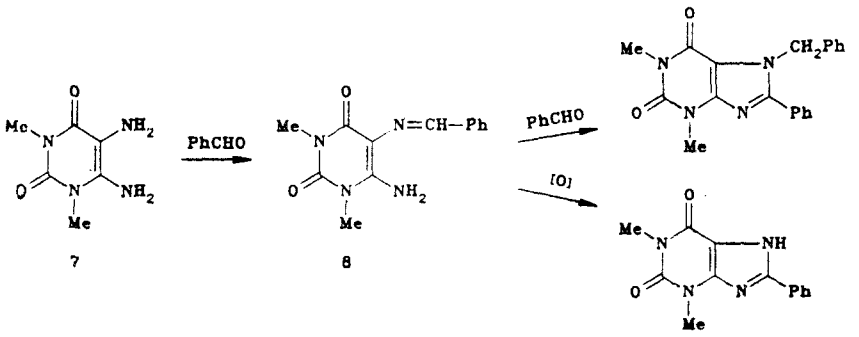
6

The use of alkyl isothiocyanates likewise gives 8-mercapto-9-alkylxanthines. Desulfurization of the latter with nitrous acid or Raney nickel gives 9-alkylxanthines [11-13].

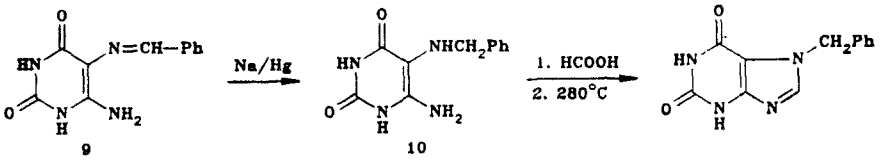


R=Me, Et, Pr, Bu, $PhCH_2$, $C_6H_{11}CH_2$

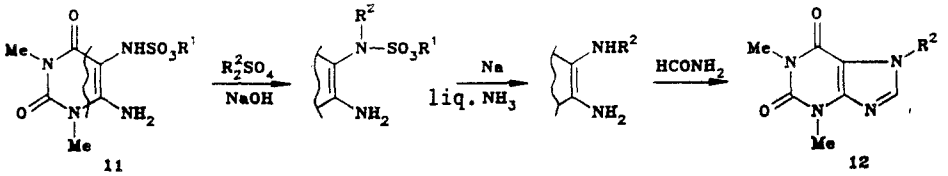
Treatment of 1,3-dimethyl-5,6-diaminouracil (7) with 1 mole of benzaldehyde gives the 5-benzylideneamino-compound (8), which on heating with 1 mole of benzaldehyde affords 7-benzyl-8-phenyltheophyllin, while treatment with oxidizing agent such as formaldehyde [14], iron(III) chloride [14], diethyl azodicarboxylate [15], thionyl chloride [16], or nitrobenzene [17-19] gives 8-phenyltheophyllin.



Reduction of (9), for example with sodium amalgam, followed by cyclization of the resulting 5-benzylamino-6-aminouracil (10), affords 7-benzylxanthine [14].

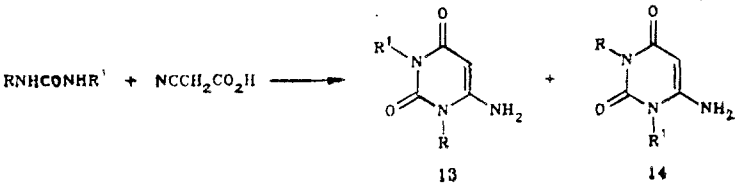


Bredereck and Gottsman [20] have proposed a route in which 5,6-diaminouracil (7) is reacted with an alkylsulfonyl chloride in pyridine to give first the 5-alkylsulfonylamino-compounds (11), which is then alkylated at the 5-$NHSO_3R^1$ group followed by cyclization to the 7-alkylxanthine (12).

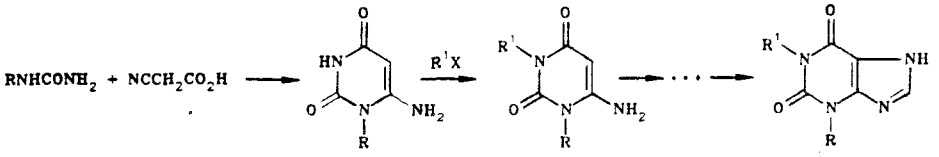


R^1=Alk, Ar; R^2=Me, Et

One drawback of the Taube method is that when unsymmetrical N,N'-dialkylureas are condensed with cyanoacetic acid, a mixture of two isomeric 6-aminouracils is obtained (13, 14), which are sometimes difficult to separate [21-23]. The isomer with the larger radical at $N_{(1)}$ predominates. Another limitation of the method is that when the condensation is carried out with monosubstituted ureas, the products are mainly the 1-alkyl-6-aminouracils (13) (R^1 = H) [24-28].

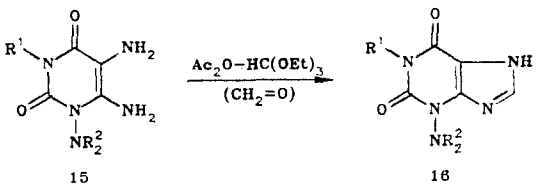


However, unsymmetrical 1,3-dialkylxanthines can be obtained from monoalkylureas, as follows [23-29]:



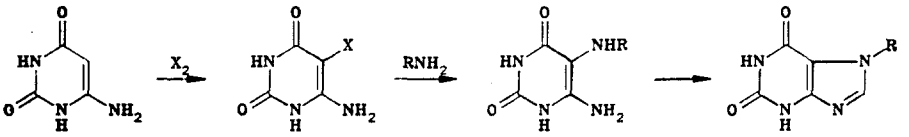
Ureas which carry bulky groups such as t-Bu at nitrogen, according to observations of the present authors, either fail to undergo condensation or do so only with difficulty.

Many 3-alkylaminoxanthines (16) have been obtained from diamines (15) by the above route [30, 31].



R^1=H, Me; NR_2^2=NMe_2, $N(CH_2Ph)_2$, piperidino, morpholino

The Traube method has been modified somewhat to obtain 7- and 9-alkylxanthines. Halogenation of the 5-position in 6-aminouracil followed by replacement of the halogen by primary alkylamines affords the 5-alkylamino-compounds (17), which are then cyclized to 7-R-xanthines in the usual way [32-37].

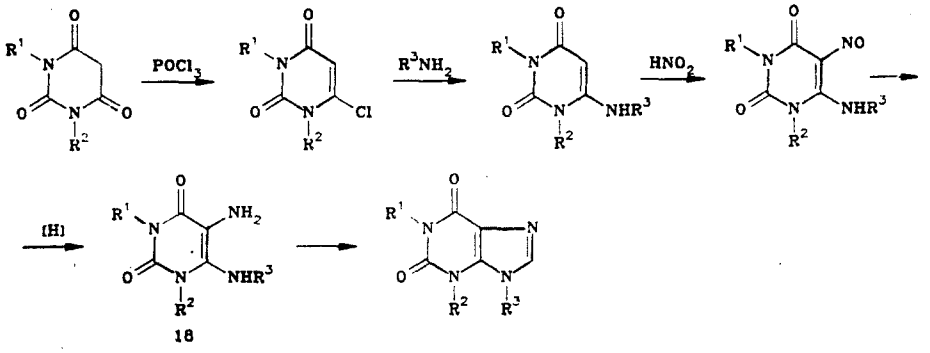


R=H, Alk, Ar

17

This method is suitable for the preparation of 3,7-dialkylxanthines (using monoalkylureas as starting materials).

9-R-Xanthines have been obtained in a similar way from 5-amino-6-alkylaminouracils (18). The latter were obtained from readily accessible barbituric acids [38-43]:

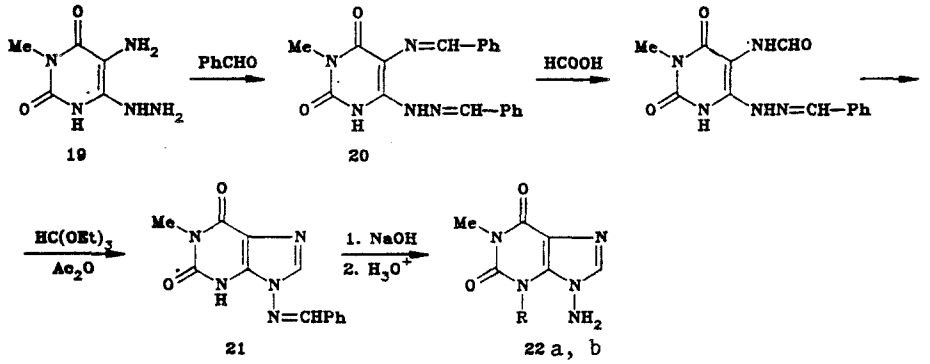


18

R^1,R^2,R^3=Alk, Ar, glycosyl

It is noteworthy that chlorination of mono-N-substituted barbituric acids affords a mixture of isomers in which the 3-R-6-chlorouracils predominate, whereas chlorination of N,N'-disubstituted barbituric acids gives mainly the isomer with the smaller substituent at $N_{(1)}$. The nitrosation step in this sequence may be replaced by nitration [44] or azocoupling [39, 45]. This route thus enables 1,9-dialkyl- and 1,3,9-trialkylxanthines to be obtained (within the limitations indicated).

9-Aminoxanthines (22) have been obtained from the aminohydrazide (19) [46] via the benzylidene compound (20):

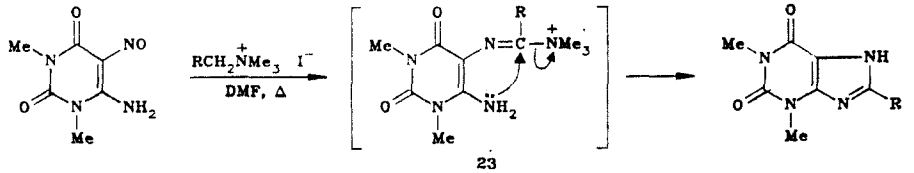


19 20 21 22 a, b

22 a R=H, b R=Me

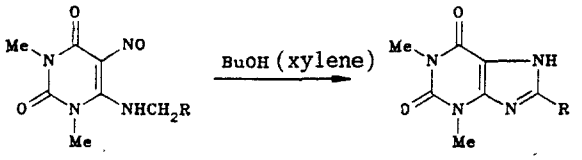
Methylation of the 9-benzylideneaminoxanthine (21) gives 9-aminotheophyllin (22b).

There have been many reports of the cyclization of 5-nitroso-6-aminouracils to xanthine avoiding the reduction step. 1,3-Dimethyl-5-nitroso-6-aminouracil reacts with quaternized Mannich bases to give 8-R-theophyllins [47].



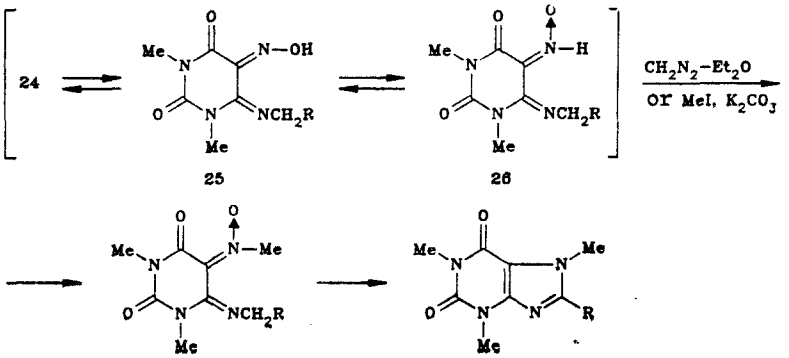
23

The facile cyclization stage is due to the presence in the anil (23) of a good leaving group, trimethylamine. 5-Nitroso-6-aminouracils may be similarly condensed with other compounds with a reactive methylene group, namely the Vilsmeier reagent [48], arylidenetriphenylphosphoranes (Wittig reagents) [49], and hydrazones of aromatic aldehydes [49, 50]. An intramolecular variation of this condensation has been reported [51-57]:

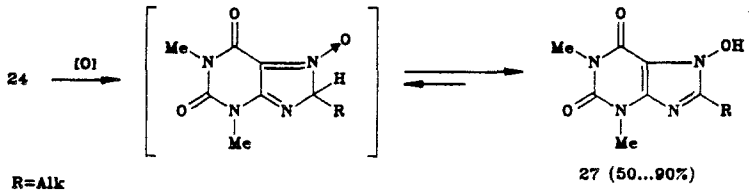


24 70...95%

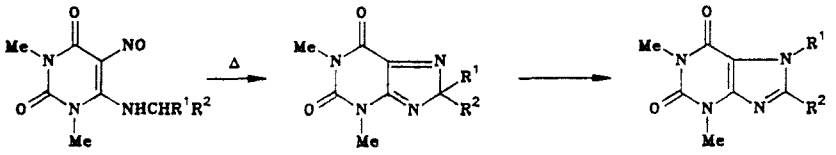
Methylation of the nitrosouracils (24) followed by cyclization affords 8-substituted caffeines [58, 59]. Compound (24) may exist as tautomers (24-26), the more acidic N-oxide form (26) apparently undergoing methylation:



When the cyclization of (24) is carried out in the presence of oxidizing agents (HNO_2, HNO_3, $KMnO_4$, or H_2O_2), 7-hydroxyxanthines (27) are obtained [60-64].



The uracils (28), which have a reactive methine group, on heating in high-boiling solvents give the so-called pseudoxanthines (29). On fusion, the latter are converted into 7,8-dialkylxanthines [55, 65-68], the smaller radical normally undergoing migration

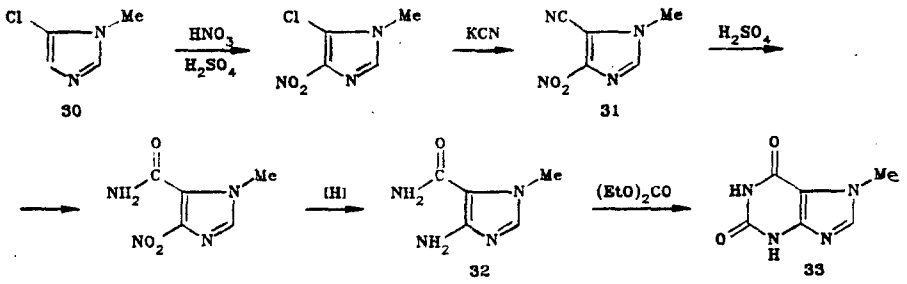


28 29

R^1, R^2= Me, Et, Pr, Bu, Ph, CH_2OH etc.

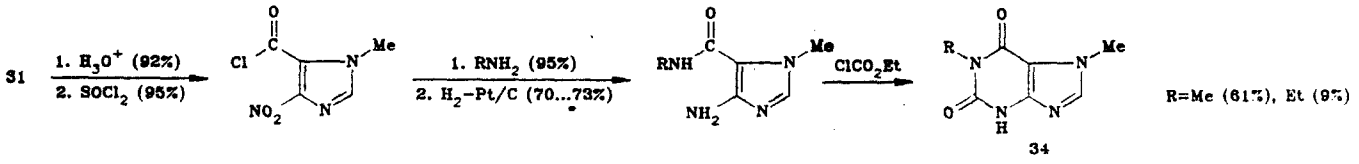
2.2. Synthesis of Xanthines from Imidazoles

The first total synthesis of a xanthine [7-methylxanthine (33)] from an imidazole derivative was carried out as follows [69]:



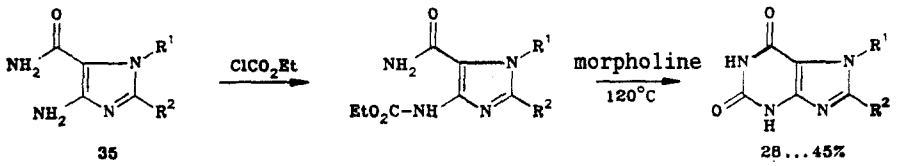
The final step in this synthesis, namely conversion of the carbamoylamino-compounds (32) to the xanthine (33), in effect imitates the biosynthesis of purines.

A similar route has been used to obtain 1,7-dialkylxanthines (34) [70, 71], which are difficult to obtain by the Traube method.



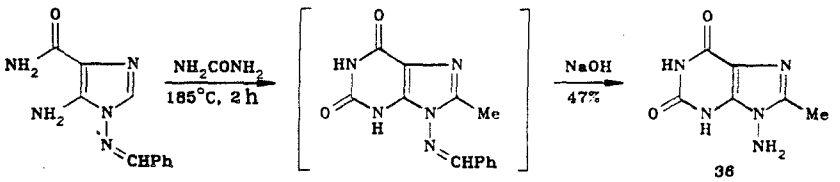
Japanese workers have obtained 7-(1-β-D-ribofuranosyl)xanthine (xanthosine) in the same way [72].

A convenient way of cyclizing 4-amino-5-carbamoylimidazoles (35) is by reaction with compounds containing a one-carbon component, namely urea [73-75], ethyl chloroformate [76], formamide [73], or cyanates [77].

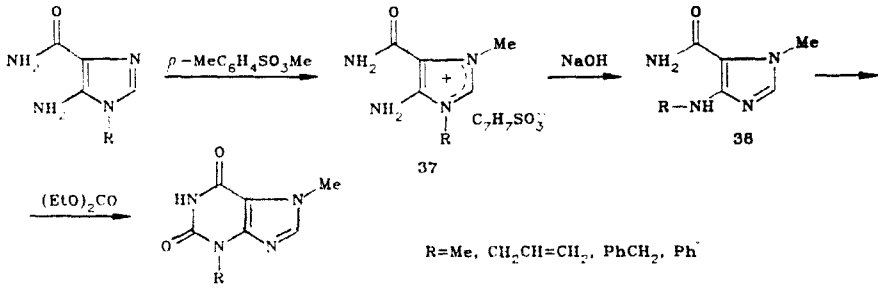


R^1,R^2=H, C_nH_{2n+1} (n=2–4)

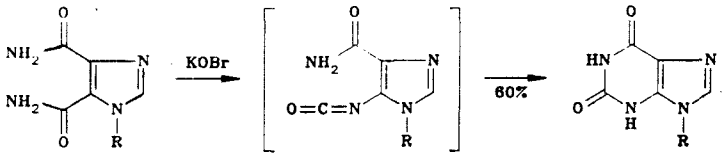
Fusion of 1-benzylideneamino-2-methyl-4-carbamoyl-5-aminoimidazole with urea, followed by alkaline hydrolysis, has given 9-amino-8-methylxanthine (36) [78].



Clearly, to obtain 3,7-dialkylxanthines by this method, it would be necessary to start from the 4-alkylamino-5-carbamoyl-1-R-imidazoles (38). However, it proved impossible [69] to obtain this compound by the method described above for (33). Sen et al. [79] have proposed a highly original method for the preparation of (38) by Dimroth cyclization of the quaternary imidazolium salts (37). The resulting compounds (38), obtained in high yield, on treatment with diethyl carbonate give the 3-alkyl-7-methylxanthines.



9-R-Xanthines (41) have been obtained by alkaline hypobromite treatment of imidazol-4,5-dicarbonamides (39). It is interesting that 7-methylxanthine was not formed. This shows that the product of this reaction is probably the isocyanate (40) [80, 81].

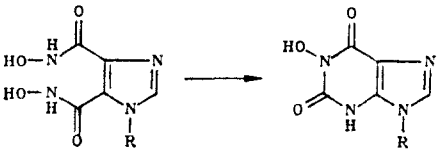


39 40 41

R=H, Me, glycosyl

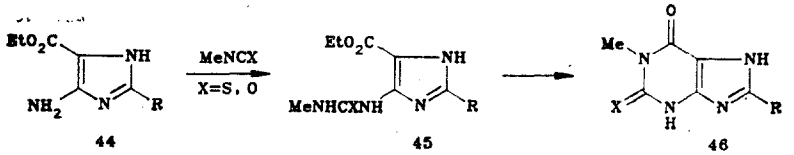
This mode of cyclization of the uracil nucleus has been used successfully for the synthesis of 9-glycosylxanthines [82-85].

The synthesis of 1-hydroxyxanthines (43) by Lossen rearrangement of the dihydroxamic acids (42) has been reported. Ring-substituted imidazole amides gave exclusively the 7-substituted xanthines [86].



42 43

4(5)-Amino-5(4)-ethoxycarbonylimidazoles (44) are readily converted into methylureido- or methylthioureido-compounds (45) on treatment with methyl isocyanate or methyl isothiocyanate. Treatment of the ureides (45) with aqueous alkali gave the 1-methylxanthines (46) [87-91].



44 45 46

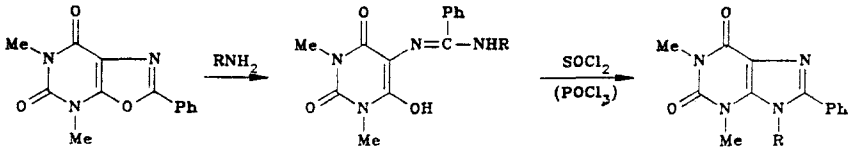
R=H, Me, Ph, CH_2Ph

1,7-Dimethylxanthine (paraxanthine) has been obtained similarly [90].

2.3. Nonstandard Methods of Synthesis of Xanthines

There have been recent reports of the preparation of xanthines by recyclization. In themselves, these methods are of little practical value, but they are of interest from the theoretical point of view.

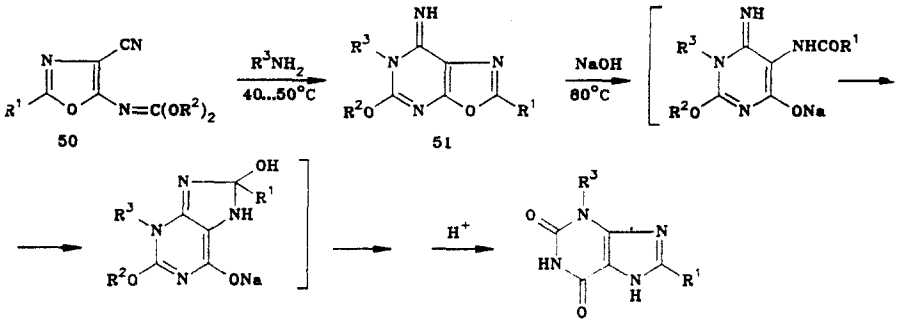
Treatment of the oxazolopyrimidine (47), with alkyl- or arylamines, results in opening of the oxazole ring to give the amidines (48), which on treatment with thionyl chloride or phosphoryl chloride cyclize to 9-R-8-phenyltheophyllins (49) [92].



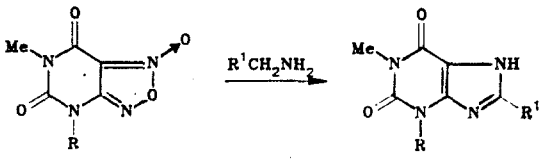
47 48 49

R=C_6H_5; *p*-Br-, *p*-Cl-, *p*-Me-, *p*-$MeOC_6H_4$; $PhCH_2$; Me

A Japanese patent [93] describes the preparation of xanthines by successive treatment of the oxazoles (50) (R^1, R^3 = H or alkyl; R^2 = alkyl) with primary alkylamines and alkali with brief heating. The intermediate oxazolopyrimidines (51) on treatment with caustic alkali undergo fission of the oxazole ring followed by cyclization at the imino-group.



Yoneda et al. [94] report the conversion of the [1,2,5]oxadiazolo[3,4-d]pyrimidine 1-oxides (52) into the xanthines (53) by treatment with arylalkylamines.

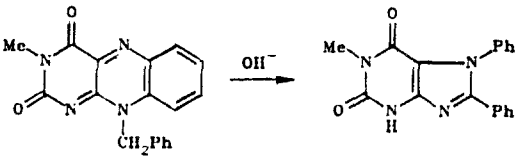


52

53 (22...55%)

R=H, Me; R^1=Ph, $PhCH_2$

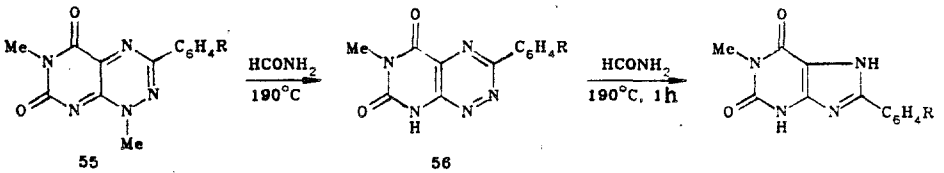
Alkaline hydrolysis of 3-methyl-9-phenylbenzo[g]pteridine-2,4-dione (54) affords 1-methyl-7,8-diphenylxanthine [95].



54

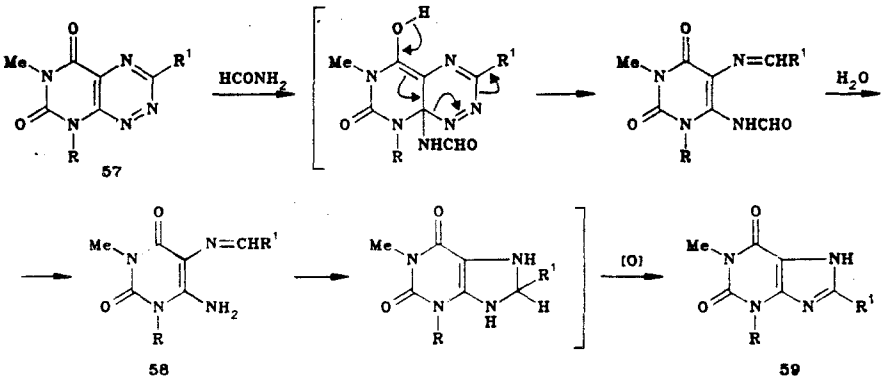
A similar recyclization of pteridine $N_{(5)}$-oxides has been reported [96, 97].

The imidazole ring may be formed by contraction of the triazine ring, as shown by the reaction of 3-aryl derivatives of the antibiotic toxoflavin (55) with formamide [98].



55 56

This reaction commences with the demethylation of the toxoflavins (55) to give 3-aryl derivatives of the antibiotic rheumycin (56). A similar reaction of 3-arylfervenulins (57) with formamide at 190°C has given 8-aryltheophyllins (59).

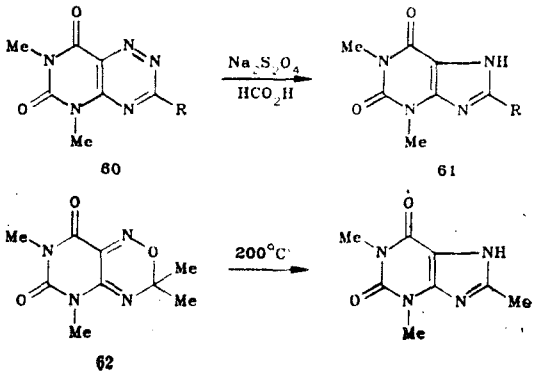


57 58 59

R=H, Me; R^1=Ph, p-ClC_6H_4, 3,4-$Cl_2C_6H_3$

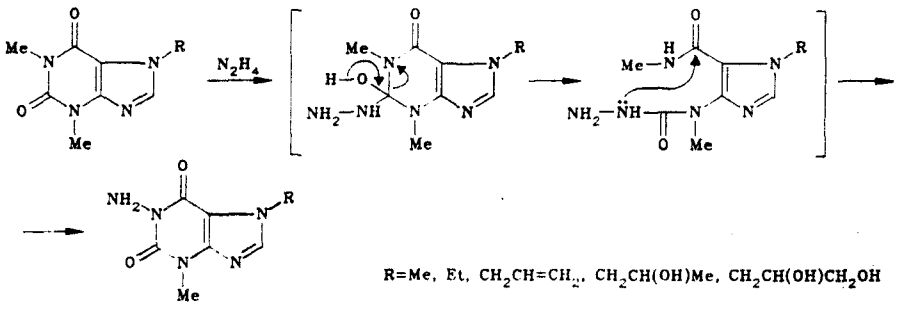
Both reactions appear to involve nucleophilic attack of formamide on the 8a position followed by elimination of a molecule of nitrogen and recyclization of the intermediate 6-amino-5-benzylideneaminouracils (58).

Of rearrangements of other systems constructed from two six-membered rings, reported examples are the transformation of 3-R-isofervenulins (60) into 8-substituted theophyllins (61) on reduction [99], and the conversion of the pyrimido[5,4-c]oxadiazine (62) into 8-methyltheophyllin, which occurs at 200°C with loss of a molecule of formaldehyde [100].



60 61 62

1-Aminoxanthines (63) have been synthesized by recyclization of 1,3,7-trialkylxanthines, by treatment with hydrazine hydrate [101-103]:



63 (28...42%)

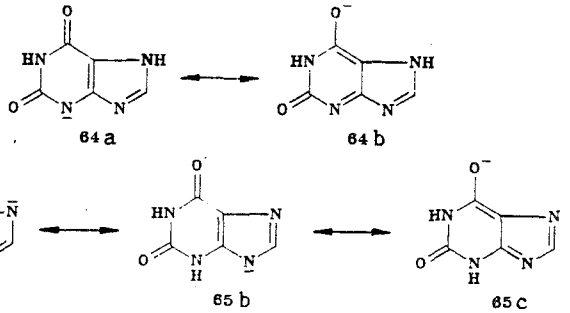
Theophyllin does not react in this way, apparently as a result of the formation in the first step of the N-anion, which is inert to further addition of the nucleophile, whereas theobromine on treatment with hydrazine hydrate is converted into 1-aminotheobromine.

Of other syntheses based on recyclization reactions, the synthesis of xanthines from uric acid may be mentioned, but this has formed the subject of a separate review [4].

3. DIRECT N-SUBSTITUTION IN XANTHINES

3.1. General Features

Methods involving direct N-substitution are especially convenient for the preparation of large series of compounds, so that they largely supplement methods involving cyclization. However, not all N-substituted xanthines by any means are



64 a 64 b

65 a 65 b 65 c

TABLE 1. NH-Acidity of Xanthines and Their Anions, Measured Spectrophotometrically (water, 20°C) [104]

Xanthine	pK_a	MS*	Xanthine	pK_a	MS*
Unsubstituted	7,7±0,1	O	9-Methyl-	6,12±0,04	O
	11,94±0,02	A		13,00	A
1-Methyl-	7,90±0,1	O	1,3-Dimethyl-	8,68±0,04	O
	12,23±0,1	A	1,7-Dimethyl-	8,65±0,05	O
3-Methyl-	8,45±0,03	O	1,9-Dimethyl-	5,99±0,04	O
	11,92±0,06	A	3,7-Dimethyl-	10,00±0,05	O
7-Methyl-	8,42±0,04	O	3,9-Dimethyl-	10,14±0,04	O
	13,00	A			

*MS) Molecular state; O) neutral molecule; A) anion.

available by this method. The xanthine molecule contains four potential sites for N-substitution, and only in a few cases are the reactions regioselective. This is especially true of the most commonly used method of alkylation of xanthines in alkaline solution, in which ambident anions of different structure are involved. It will be seen from Table 1 that xanthines are highly NH-acidic, more acidic by 1.5-2 orders of magnitude than phenol. This favors the effective delocalization of the negative charge, in which the carbonyl groups are involved.

The acidities of the three N–H bonds in the xanthine molecule decrease in the sequence $N_{(3)}$–H ≥ $N_{(7)}$–H > $N_{(1)}$–H. N-Substitution follows approximately the same sequence. It is interesting in this connection that, in living organisms, the reverse process of transmethylation of xanthines occurs [105]:

Xanthine ⇀ 7-methylxanthine ⇀ 3,7-dimethylxanthine (theobromine) ⇀ 1,3,7-trimethylxanthine (caffeine).

The nucleophilicity of $N_{(9)}$ is very low, and it undergoes attack by electrophiles only under special circumstances. Reaction at the oxygen atoms is just as rare, despite the fact that they probably carry a substantial part of the negative charge. However, such behavior is well known in the alkylation of the antions of α- and γ-oxo-N-heteroaromatic systems [106].

Attention is drawn to the small differences in the acidity of the $N_{(3)}$–H and $N_{(7)}$–H bonds. There can, therefore, be little doubt that ionization of xanthine in alkaline solution results in the formation of comparable amounts of both the $N_{(3)}$- and $N_{(7)}$-anions (64, 65). The difficulty of selective alkylation of xanthine to give the 3- or 7-monosubstituted compounds is therefore understandable.

The second acidic ionization constant has also been measured for xanthine and its N-monosubstituted derivatives (Table 1). It lies in the region of pK_a 12, showing that in strongly alkaline solutions xanthine will be converted into the dianion. We are not aware of any reports of the formation of a xanthine trianion, although such a possibility cannot be excluded, for example in solutions of potassium amide in liquid ammonia, or KOH in DMSO. It would be of interest to carry out a systematic examination of the alkylation of the di- and trianions of xanthine.

Xanthines are of low basicity, the pK_a of caffeine and other xanthines in water being <1 [107] (for data for acetonitrile, see Sec. 1). Protonation of xanthine occurs at the nitrogen atoms of the imidazole ring, alkylation occurring here in neutral or acidic media. The reaction is, however, slow, and requires high temperatures and prolonged reaction times.

In addition to the alkylation of xanthine via the anions and the neutral molecule, a third method of N-substitution has been used, namely via salts of xanthines with heavy metals (such as mercury and silver), or via the trimethylsilyl derivatives. The latter method is most frequently used for the synthesis of N-glycosidoxanthines.

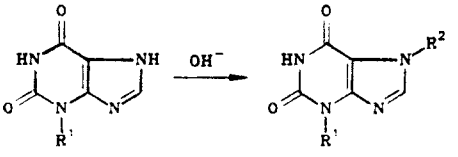
3.2. N-Substitution under Alkaline Conditions

The earliest work on the methylation of xanthine was carried out as long ago as the turn of the century. It was found, and confirmed by later work, that it was easiest to carry out either exhaustive methylation of xanthine to caffeine, or partial methylation to theobromine. For example, xanthine is methylated in alkali to caffeine by methyl iodide [108, 109], dimethyl sulfate (optimum conditions: pH 8-9, 30-35°C, yields up to 90%) [110-113], and methyl toluene-p-sulfonate (yields 62%) [114].

The methylation of xanthine and 8-methylxanthine with dimethyl sulfate affords theobromine [113, 115] and 8-methyltheobromine [116], respectively. The reaction is carried out in aqueous or aqueous-alcoholic alkali at 60-70°C and pH 6.0-6.5, yields 60-68%. It has been reported [117-119] that 8-methyltheobromine is obtained when authentic disodium and di-potassium salts of xanthine are alkylated with methyl iodide or methyl toluene-p-sulfonate in ether, xylene, or dichlorotoluene.

There have been no reports of the selective methylation of xanthine to 3-methylxanthine. 3-Ethylxanthine (12% yield) was obtained by treating xanthine with an excess of ethyl iodide in the presence of 1 mole of KOH [120]. Under the same conditions, in the presence of 2 moles of KOH there was obtained an equimolar mixture of 3- and 3,7-diethylxanthines in an overall yield of 13%. When an excess of both ethyl iodide and KOH was used, 1,3,7-triethylxanthine was obtained in 11-16% yield [120].

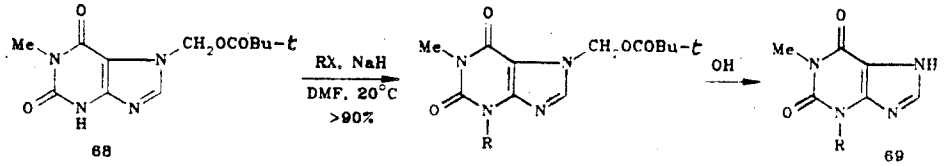
This largely covers the available information on the alkylation of xanthine itself by standard methods. Less information is available on the alkylation of N-monosubstituted xanthines. Methylation of 3-methylxanthine with dimethyl sulfate in aqueous (pH 7.6-9.0, 60°C, yield 60-70%) [116, 121], or aqueous-alcoholic alkali (yield 90%) gives theobromine [113]. Similar alkylation of 3-R-xanthines gives 3,7-dialkylxanthines (67) in 80-95% yield [122].



66 67

R^1, R^2 =Me, CH_2CH_2OH, $CH_2CH(OH)CH_2OH$

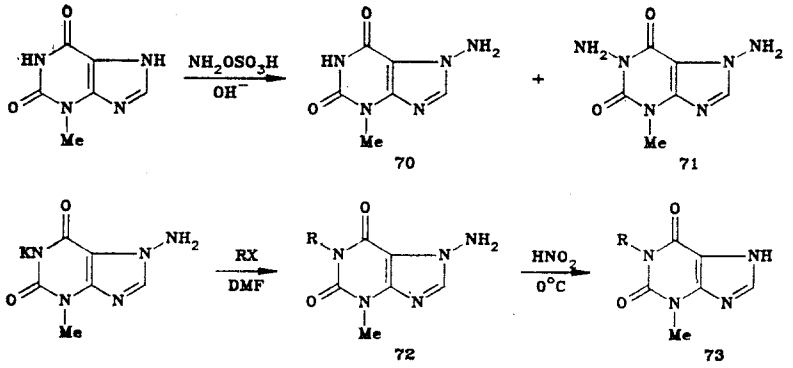
Controlled alkylation of 1-methylxanthine to 1-methyl-3-R-xanthines has not been possible, mixtures of 1,7-di- and 1,3,7-trialkylxanthines being obtained under a variety of experimental conditions [123]. Attempts have been made to introduce a protecting group into the 7-position as a preliminary. The use of trialkylsilyl protection for this purpose failed to give satisfactory results [124]. Somewhat better results were obtained using the pivaloyloxymethyl group [123]. Treatment of 1-methylxanthine with pivaloyloxymethyl chloride in DMF gave a mixture of 1-methyl-7-(pivaloyloxymethyl)xanthine (68) and 1-methyl-3,7-di(pivaloyloxymethyl)xanthine in 41 and 39% yield, respectively. After separation, (68) was converted into the 1,3-dialkylxanthines (69):



68 69

R=Me, *i*-Bu, $(CH_2)_3CO_2Et$, CH_2CH_2CN

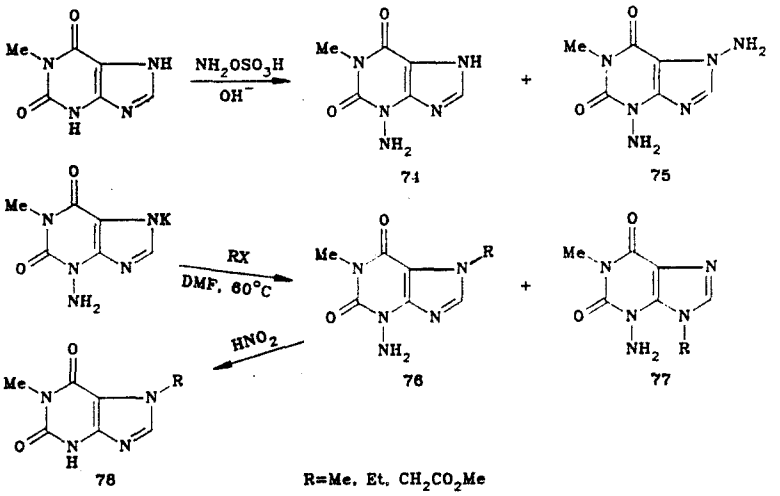
Much more effective was the use of the N-amino group as the protecting group for the preparation of unsymmetrical 1,3-dialkylxanthines from 3-methylxanthine [125]. Amination of 3-methylxanthine with hydroxylamine-O-sulfonic acid in aqueous alkali gave a readily separable mixture of 3-methyl-7-amino- (70) (yield 67%) and 3-methyl-1,7-diaminoxanthines (71) (7%). Alkylation of the potassium salt of the amine (70) followed by deamination of (72) afforded the 1-R-3-methylxanthines (73) in high yields.



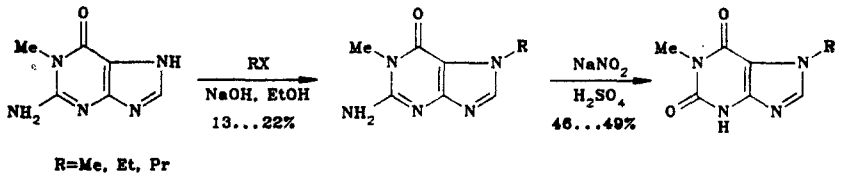
70 71 72 73

R=Me, Et, CH_2Ph, CH_2CN, CH_2CO_2Me

The use of N-amino-1-methylxanthines provides a route to the difficultly accessible 1,7-dialkylxanthines. Treatment of 1-methylxanthine with hydroxyalmine-O-sulfonic acid gives 1-methyl-3-amino- (74) and 1-methyl-3,7-diaminoxanthine (75) in yields of 55 and 10%, respectively [126]. Alkylation of the potassium salt of the amine (74) gave a mixture of 1-methyl-7-R- (76) and 1-methyl-9-R-3-aminoxanthine (77), in which the 7-isomer greatly predominated. Deamination of (76) with nitrous acid afforded the 1-methyl-7-R-xanthines (78) in high yields.



Another approach to the synthesis of 1,7-dialkylxanthines uses 1-methylguanine as starting material [70, 127]:

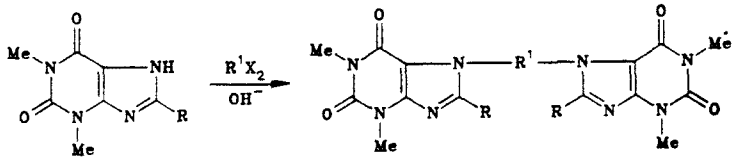


A drawback of this method is, however, that low yields of products are obtained at all stages of the synthesis.

The alkylation of N,N'-dimethylxanthines could form the subject of a separate review, since N-substituted derivatives of theophyllin, theobromine, and 1,7-dimethylxanthine (paraxanthine) are of pharmacological interest, and are frequently used in the synthesis of drugs with bronchospasmolytic [128, 129], diuretic [130], psychotonic [131], cardiotonic [132, 133], hypotensive [133, 134], antihistaminic [133], and analeptic activity [135]. Dimethylxanthines are usually alkylated with alkyl halides in aqueous or alcoholic solution in the presence of caustic alkali [136-146]. Good results are obtained by alkylation in dry DMF in the presence of potassium carbonate [128, 147-150]. Authentic, isolated potassium or sodium salts of xanthines are frequently alkylated in an excess of alkyl halide [132, 134, 151-155], in alcohols [156, 157], in DMF [158], or in toluene [159]. In this way, the reactions can be controlled, avoiding strongly basic conditions in which xanthines are prone to undergo cleavage of the uracil ring.

In addition to alkyl halides, effective alkylating agents for xanthines are the alkyl esters of phosphoric, phosphonic, and phosphinic acids [160-162], and onium hydroxides ($Me_3Se^+OH^-$, $PhN^+Me_3OH^-$, $Me_3S^+OH^-$, etc.) [163]. Sulfonium salts make good alkylating agents [164, 165], these, as is well known, functioning as alkyl carriers in the living cell. Treatment of xanthine with an excess of trimethylsulfonium fluoride at 90-100°C in DMF gives 67-85% yields of caffiene [164]. It is interesting that trimethylsulfonium iodide either fails to methylate xanthines, or the course of methylation is quite different. This is due to the fact that the fluoride ion forms strong N···H···F⁻ hydrogen bonds, thereby raising the nucleophilicity of the imide group undergoing attack by the sulfonium cation. A similar effect of the fluoride ion has been reported [166, 167]. These workers showed that xanthines are alkylated by the usual alkylating agents (alkyl iodides, alkyl sulfates, and alkyl phosphates) in the presence of tetrabutylammonium fluoride at 20°C for 1 h, often in quantitative yields.

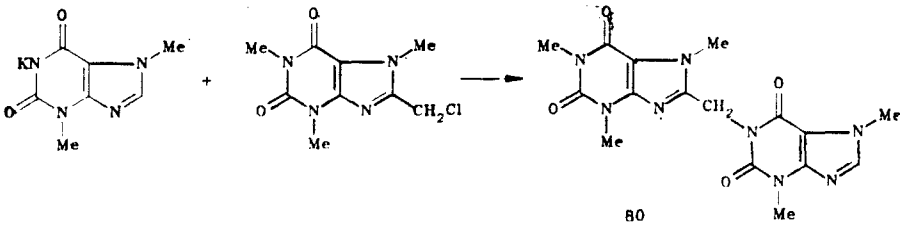
Alkylation of theophyllin with bifunctional alkylating and acylating agents (dihaloalkanes, dihaloalkenes [168, 169] and dicarboxylic acid chlorides [170, 171]), used in deficient amounts with respect to the substrate, result in linkage of two molecules of theophyllin at the 7-position. The longer the separating carbon chain, the greater the yield of product. Compound (79) possesses antiasthmatic activity.



79

Bistheobrominylalkanes analogous to (79) have been reported [172].

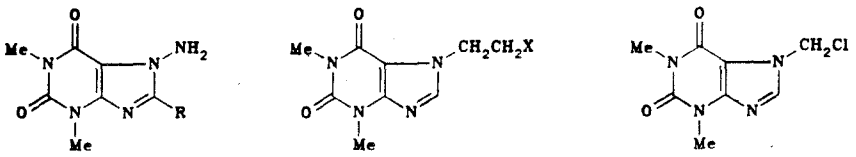
Unsymmetrical dixanthylmethanes (80) have been obtained by alkylation of the potassium salt of theobromine with 8-chloromethylcaffeine [173]. Several similar reactions have been reported [168, 173, 174]. Compounds of similar structure have shown high stimulant activity [174].



80

Xanthines undergo electrophilic N-amination by hydroxyalmine-O-sulfonic acid in alkaline solution [125, 126, 175, 176]. In this way, theobromine afforded 1-aminotheobromine [175], 1-methylxanthine a mixture of mono- and diamines (75, 76) [126], and 3-methylxanthine-7-amino- (70) and 1,7-diamino-3-methylxanthene (71) [125]. Theophyllin and some 8-substituted theophyllins have been likewise converted into 7-aminotheophyllins (81) [174-180].

O-Diphenylphosphinylhydroxylamine has also been used as an electrophilic N-aminating agent [181, 182]. Reaction of this compound with theophyllin sodium salt in N-methylpyrrolidone under mild conditions afforded 7-aminotheophyllin [isolated as its benzylidene derivative (82) in 72% yield]. Similarly, theobromine sodium salt gave 1-aminotheobromine in 71% yield.



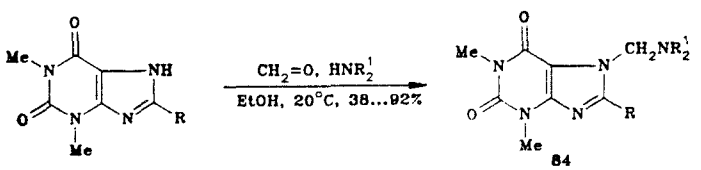
81 82 83

R=H, Br, Me, NH_2; X=CN, CO_2Et, 2-pyridyl, etc.

In the presence of basic catalysts ($Me,\overset{+}{N}CH_2PhOH^-$, pyridine, sodium methoxide), theophyllin adds to the double bond in acrylonitrile [151, 183, 184], ethyl acrylate [151], 2-vinylpyridine [151], vinyl ketones [151, 185, 186], and ethylene propylene carbonates [187] to give compounds (82) in 53-95% yields. Also reported is the addition of theophyllin to the double bond in isocyanates [152, 188] and in 2,3-dihydropyran [189]. Theobromine reacts similarly [190-192].

On treatment with formalin and hydrochloric acid, theophyllin undergoes facile (20°C, 20 min) chloromethylation at the 7-position to give 7-chloroemthyltheophyllin (83) [193].

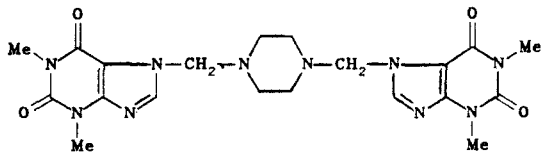
Both theophyllin and its derivatives [193-197] and theobromine [196] participate in the Mannich reaction to give, in the case of theophyllins, the compounds (84).



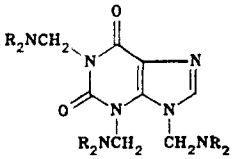
84

R=H, Cl; NR_2^1=Et_2N, 1-pyrrolidinyl, piperidino, 4-methylpiperazin-1-yl, etc.

When bifunctional amines such as piperazine are employed, the compounds such as (85) are obtained [193, 197].



85



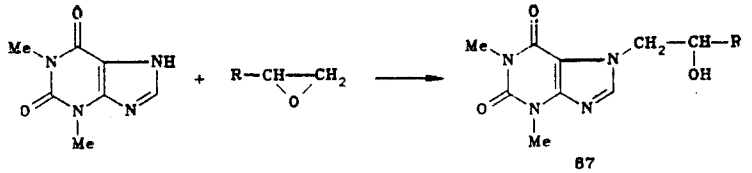
86

NR_2= piperidino, morpholino

It is interesting that replacement of the formaldehyde by paraformaldehyde, and extended heating of the reaction mixture, results in aminomethylation of theophyllin at the 8-position [197]. This is in agreement with the finding that on heating caffeine with paraformaldehyde and HCl at 170°C the product obtained is 8-hydroxymethylcaffeine. It is likely that under these conditions the 7-hydroxymethyl derivatives are thermodynamically unstable [198].

The Mannich reaction with xanthine gives 1,3,9-triaminomethyl derivatives (86) [199].

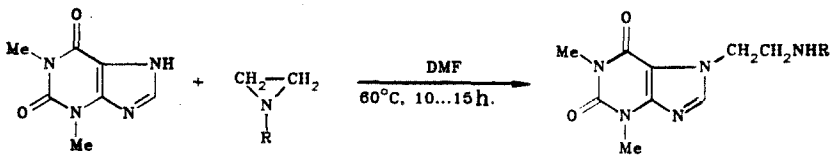
Theophyllin, theobromine, and their 8-halo-derivatives react with 1,2-epoxides in the presence of basic catalysts to give quantitative yields of the 7-(β-hydroxyalkyl) derivatives (87) [174, 200-207], which have coronary dilating activity [202].



87

R=H, Me, CH_2OH, CH_2Cl, Ph, CH_2OPh etc.

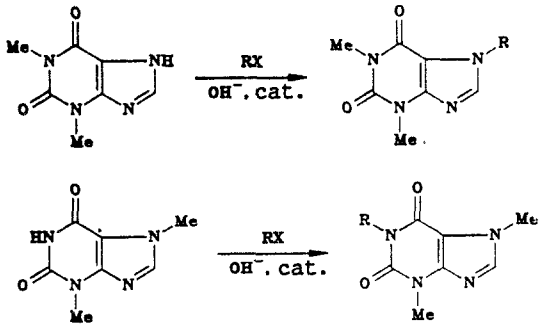
On prolonged heating of theophyllin with ethyleneimine (or its N-alkyl derivatives), the 7-(2-aminoethyl)theophyllins (88) are obtained [208]:



R=H, CH_2CH_2Ph, CH_2CH_2CN 88

The procedure for the N-alkylation of xanthines has been much simplified by the use of phase-transfer catalysis. It has been shown that treatment of xanthine with methyl bromide in aqueous alkali in the presence of catalytic amounts of tetrabutylammonium bromide in methylene chloride affords quantitative yields of caffeine [209, 210]. Under these conditions, 1,3,7-triethylxanthine is obtained in 45% yield.

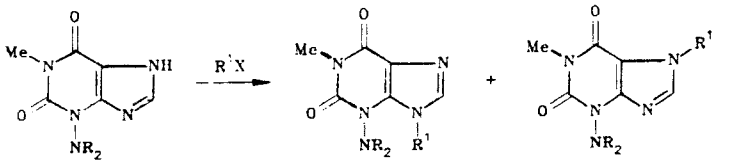
Alkylation of theophyllin and theobromine by catalytic solid-liquid transfer has been reported [211, 212]. The phase-transfer catalysts employed are usually quaternary ammonium salts or crown ethers:



RX	T, C°	Yield %
Me_2SO_4	20	90
$PhCH_2Cl$	20	75
$C_8H_{17}Br$	80	96
$C_{18}H_{37}Br$	80	96
$PhCH_2Cl$	80	97
$C_{18}H_{37}Br$	80	87
$C_8H_{17}Br$	80	75

In theory, alkylation of 1,3-disubstituted xanthines should give the 7- and 9-isomers. As noted above, theophyllin is substituted at position $N_{(7)}$ only. However, when 3-dialkylaminoxanthines (89) are alkylated, the 9-alkylated product (90) predominates [30]. It may be that the dialkylamino group provides anchimeric assistance for alkylation of $N_{(9)}$ in the appro-

priate anion. Proof of the structures of (90) and (91) was based on the differences in the UV spectra of 7-R- and 9-R-xanthines [104, 126].

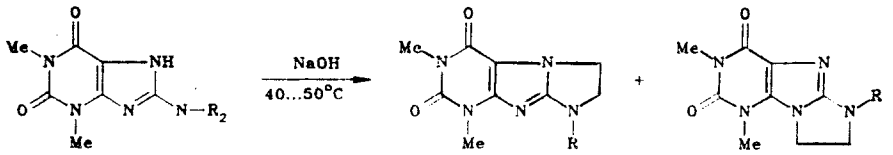


89 90 (40...80%) 91 (<15%)

NR_2=NMe_2, piperidino, morpholino ; R^1=Me, CH_2CH_2OH

As mentioned above, 9-R-xanthines are also formed in small amounts on alkylation of 1-methyl-3-aminoxanthine [126].

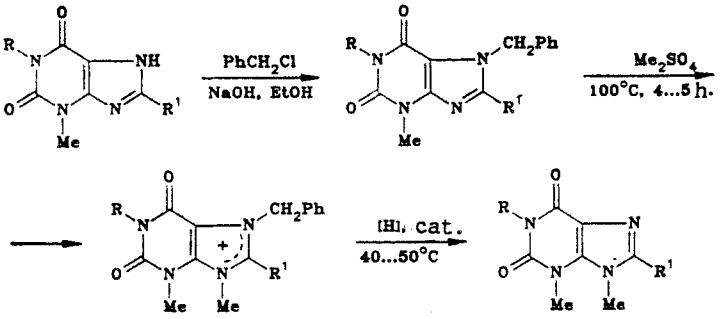
Simultaneous formation of both 7- and 9-R-xanthines has been noted in some intramolecular alkylation reactions [213]. For example, treatment of 8-di-(β-chloroethyl)aminotheophyllin with NaOH solution (0.1 mole/liter) resulted in a mixture of the 7- (92) and 9-isomers (93) in yields of 50 and 26%, respectively.



R=CH_2CH_2Cl 92 93

9-Substituted xanthines are relatively unstable, undergoing rearrangement to the 7-substituted compounds on heating in aprotic solvents in the presence of alkyl halides [214, 215], on melting [216] or on heating in pyridene [216]. Transalkylation of 9-R-xanthines to 7-R-xanthines has been reported [215, 217]. For example, 1,9-dimethyl-8-phenylxanthine gives 71% of 1-methyl-3,7-diethyl-8-phenylxanthine on heating with ethyl iodide in DMF in the presence of potassium carbonate.

Simple 9-R-xanthines are difficult to obtain by direct alkylation. A straightforward procedure has, however, been described for the methylation of 1,3-dialkylxanthines at the 9-position, involving benzyl protection of the 7-position [218, 219]:



R=Me, Et, Pr, Bu, C_6H_{13}; R^1=Ph, *m*-MeOPh, $PhCH_2$, Ph_2CH

3,9-Dimethylxanthine has been obtained in this way from 3-methylxanthine [220]. The protecting group can also be methoxymethyl [219].

3.3. N-Alkylation via Heavy Metal Salts

Alkylation of the lead and silver salts of xanthines frequently gives anomalous results. Attempts [221] to obtain theobromine by treating xanthine silver salt with methyl iodide gave a compound which was termed pseudotheobromine. The same compound was obtained by methylating xanthine lead salt with methyl iodide or dimethyl sulfate (together with unidentified xanthine quaternary salts) [110]. These workers assumed pseudotheobromine to be 3,9-dimethylxanthine.

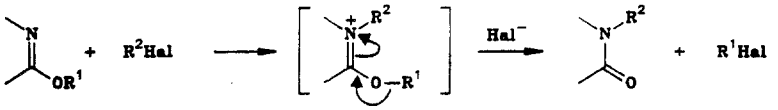
Alkylation of theophyllin silver salt affords 7-glycosylxanthines [222, 223]. These are also obtained by fusing theophyllin with glycosides [224, 225] or reaction of theophyllin with tetraacetylglycosides in dioxane in the presence of boron trifluoride [226]. Silver salts have been frequently used for the synthesis of compounds such as (79) and (80) [169, 172, 173].

Reports have recently appeared on the alkylation of "coordinated" xanthines, namely complexes in which xanthine is the ligand. The metal center, as might be expected, accepts negative charge from nitrogen less readily than does hydrogen, so that the reactivity of the xanthine in these complexes is comparable with that of the xanthine anion. Complexes with the composition [bis(theophyllinato)metal(II)], where the metal is Cu(II) or Hg(II), in which the theophyllin is deprotonated and the metal is coordinated at $N_{(7)}$, are highly unstable and sparingly soluble, which hinders their alkylation [227, 228]. Alkylation of the complex [bis(dimethylglyoxoimato)(xanthinato)(tributylphosphine)cobalt(III)] gives exclusively the 7-R-xanthines (R = $PhCH_2$, p-$NCC_6H_4CH_2$, p-$PhC_6H_4CH_2$, p-$ClC_6H_4CH_2$) in 77-86% yields [229]. This mode of reaction was attributed by these authors to coordination of the cobalt at $N_{(9)}$, which is more nucleophilic than the other heteroatoms and is less sterically hindered. Consequently, alkylation occurs at $N_{(7)}$, which is situated at the "surface" of the complex. It is interesting that theophyllin does not form such a complex, coordination in this case at $N_{(9)}$ being hindered by the methyl group in the 3-position.

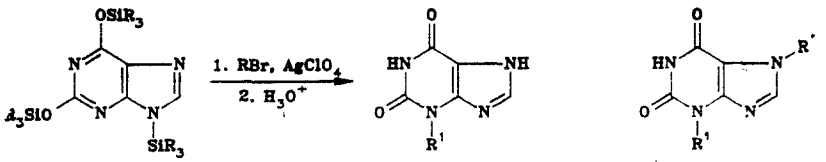
3.4. Use of Silylation in the Synthesis of N-Substituted Xanthines

Alkylsilyl derivatives of xanthines may be obtained by direct silylation with trialkylsilylamines or trialkylchlorosilanes, or by the Traube method [230]. Attention is drawn to the fact that these compounds are O-trialkylsilyl derivatives (94), as a result of the Si–O bond being stronger than Si–N. Treatment of 2,6,7-tris(triethylsilyl)xanthine with methyl iodide in the presence of silver perchlorate at ambient temperature affords 66% of 7-methylxanthine, while at 60°C 55% of theobromine is obtained. It is interesting that the reaction with acetobromoglucose under these conditions gives 3-glycosylxanthine only [230].

The mechanism of this substitution may be shown as follows:



The silylation method has been used extensively in the synthesis of N-glycosylxanthines. The first nucleoside to be obtained by direct glycosylation of xanthine was 3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)xanthine (95), obtained by treatment of (94b) with 2,3,4,6-tetra-O-acetyl-D-glucopyranosyl bromide in nitromethane in the presence of silver perchlorate [230, 231]. When this reaction was carried out in acetonitrile, the product was the 3,7-diglucoside (96) [232].

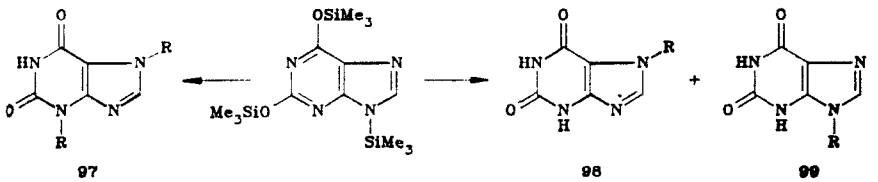


94 a,b 95 96

94 a R=Me; b R=Et; R¹= 2,3,4,6-tetra-O-acetyl-D-glucopyranosyl

The 3,7-disubstituted xanthine (97) is also formed in the reaction with 3,5-di-O-p-toluoyl-2-desoxy-D-ribofuranosyl chloride in acetonitrile at 35 or 65°C. Under milder conditions (benzene, 20°C) the products of this reaction are 7-(2-desoxyribosyl)xanthine, or a mixture of the 7-(98) and 9-derivatives (99) [232].

Reaction of 2,6,9-tris(trimethylsilyl)xanthine with 3,4,6-tri-O-acetyl-2-desoxy-2-(2,4-dinitroanilino)glucopyranosyl bromide affords a mixture of products, in which the $N_{(1)}$- and $N_{(7)}$-glucosides have been identified [232].

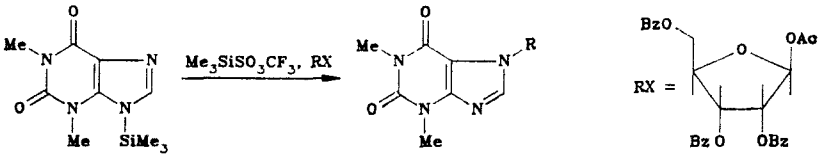


97 98 99

R=3,5-di-O-p-toluoyl-2-desoxy-D-ribofuranosyl

Xanthosine was obtained in 49% yield (following removal of the protecting groups) by reaction of 2,6,9-tris(trimethylsilyl)xanthine with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose in boiling 1,2-dichloroethane in the presence of trimethylsilyl trifluoromethanesulfonate [233].

The 7-β-D-nucleoside (101) was obtained from 9-trimethylsilyltheophyllin (100) and 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose in 1,2-dichloroethane in the presence of trimethylsilyl triflate [233].

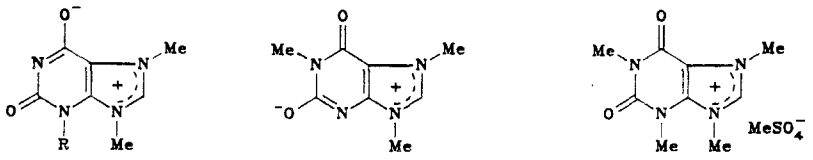


100 101

Reaction of (100) with penta-O-acetyl-α-D-mannopyranose in acetonitrile in the presence of stannic perchlorate gives 7-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)theophyllin in 70% yield [234], as against the 40% yield obtained on fusing theophyllin with the glycoside [235]. 7-β-Nucleosides are obtained in high yield by the reaction of (100) under similar conditions with 1,2,3-tri-O-acetyl-4,6-O-ethylidene-β-D-glucose or 1,3,4-tetra-O-2-desoxy-D-arabinohexopyranose. In the latter case, however, a mixture of the two nucleosides is obtained in a ratio of 85:15. The minor component of the mixture was not identified [236].

3.5. N-Substitution in Neutral and Acidic Media

The reaction of xanthine with methyl iodide in an ampul [237, 238], with dimethyl sulfate in dimethylacetamide or DMSO (140°C, 2 h) [239], or with methyl toluene-p-sulfonate (170°C, 1.5 h) [240] gives the betaine (102a) as the sole product



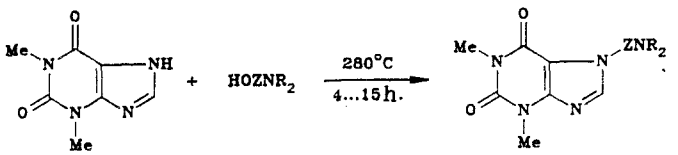
102 a R=H; b R=Me 103 104

7-Methylxanthine and 9-methylxanthine are converted into (102a) under any of the above conditions [239, 240]. It is noteworthy that the methylation product of 9-methylxanthine, originally described as 3,9-dimethylxanthine, was later found to be the betaine (102a).

Further alkylation of (102a) gives the betaine (103), also obtained from 1-methyl- or 1,9-dimethylxanthine and methyl toluene-p-sulfonate [240-242]. Similarly, the betaine (102b) was obtained either from 3-methyl- [240], or from 3,7-dimethylxanthine [240, 242].

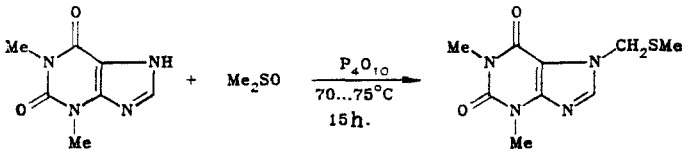
On heating caffeine with dimethyl sulfate in nitrobenzene (100°C , 12 h), the quaternary salt (104) is obtained [242].

Under severe conditions (280°C, ampul), theophyllin condenses with N-substituted aminoalcohols to give 7-aminoalkyl derivatives in 10-85% yield [243].



Z=CH_2CH_2, $(CH_2)_3$, $CH_2CH(CH_3)_2$; NR_2=NEt_2, NBu_2, $N(CH_2Ph)_2$, piperidino

Reaction of theophyllin with DMSO in the presence of phosphorus pentoxide affords 7-methylmercaptotheophyllin [244].



On treatment with acetic anhydride, theophyllin is acylated at the 7-position [245].

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SYNTHESIS AND STRUCTURE OF DIETHYL 2-OXO-1-OXASPIRO[4,5]DECANE-3,4-DICARBOXYLATE

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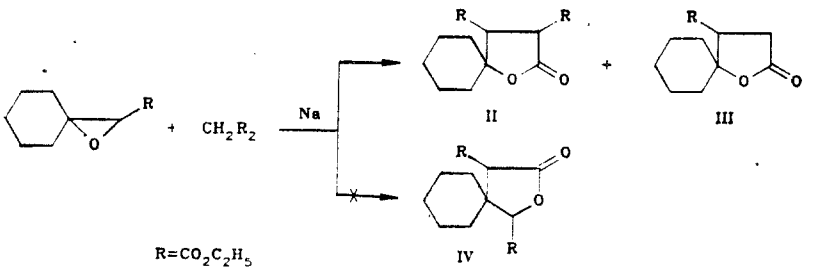
Ethyl 1-oxaspiro[2,5]octane-2-carboxylate reacts with diethyl sodiomalonate in toluene to give diethyl 2-oxo-1-oxaspiro[4,5]decane-3,4-dicarboxylate, which on distillation undergoes partial de-ethoxycarbonylation to give ethyl 2-oxo-1-oxaspiro[4,5]decane-4-carboxylate.

Decarboxylation of glycidic (2,3-epoxypropionic) acids results, depending on their structure, in either β_{C-O} or α_{C-O} cleavage of the oxirane ring [1]. If the glycidic acid has two substituents in the β-position while being unsubstituted in the α-position, cleavage of the oxirane ring occurs exclusively at the β_{C-O} bond. It would be interesting to know whether this behavior is also applicable when the oxirane ring is cleaved by carbanions. If this is so, then the glycidyl esters from cyclic ketones and malonic ester should give spirolactones, namely diethyl 3-oxo-2-oxaspiro[4,5]decane-1,4-dicarboxylates (IV).

It has been reported [2] that β-phenylglycidyl ester reacts with malonic ester to give 3,4-diethoxycarbonyl-5-phenylbutyrolactone, i.e., these workers assume rupture of the α_{C-O} bond, but no evidence in support of the structure of the product was adduced. We have found that when ethyl 1-oxaspiro[2,5]octane-2-carboxylate (I) reacts with diethyl sodiomalonate the oxirane ring is cleaved at the α_{C-O} bond exclusively to give diethyl 2-oxo-1-oxaspiro[4,5]decane-3,4-dicarboxylate (II), as follows:



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