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Ring-Modifying Reactions of Pyrimidines Containing a Quaternary Nitrogen

Henk C. van der Plas

Laboratory of Organic Chemistry, Agricultural University, Wageningen, The Netherlands

Since the last decade there is considerable interest in what can be considered as one of the most fascinating properties of heterocyclic systems, that is the ease by which heterocycles can be converted into other heterocycles, often by simple procedures. This field has been extensively discussed and recently reviewed in a two-volume monograph, covering the literature till 1971[1]. The growing interest in ring transformations during the last five years can be best illustrated by the number of references in the Chapter on "Ring Transformations" which appear each year in the Specialist Periodical Reports on Aromatic and Heteroaromatic Chemistry. Volume 1 (1971-1972): 183; volume 2 (1972-1973): 289; volume 3 (1973-1974): 308; volume 4 (1974-1975): 494; volume 5 (1975-1976): 579[2,3]. This interest is probably due to the fact that in this field of research many unexpected rearrangements - how beloved by organic chemists (!) - are observed. They challenge the imagination of those, being interested in unravelling mechanistic pathways. They also attract the attention of synthetic organic chemists since by these ring-modifying processes compounds can be obtained which are otherwise difficult to synthesize or even inaccessible.

Our interest in the ring transformations of pyrimidines with a quaternary nitrogen dates back to 1968. In that year we found that pyrimidines, when treated with hydrazine at high temperatures, undergo ring contraction into pyrazoles, but that the same ring contraction could also be performed under very mild conditions, when an N-alkylpyrimidinium salt is used as substrate[4]. The fact that by quaternization of the nitrogen of the pyrimidine ring the ring transformation occurs more easily, induced us to study in detail the reactivity of these systems towards nitrogen-containing nucleophiles (ammonia, hydrazine, hydroxylamine) and carbanionic reagents. As an extension of this study we also looked into the ring transformations of pyrimidine N-oxides and the N-aminopyrimidinium salts, a recently developed class of compounds[5-7]. From these studies it emerged that in general the ring transformations which take place with N-methylpyrimidinium salts, pyrimidine N-oxides and N-aminopyrimidinium salts can be divided into three categories.

A. Ring transformations in which the pyrimidine ring is converted into a six-membered heterocycle with a different ring.

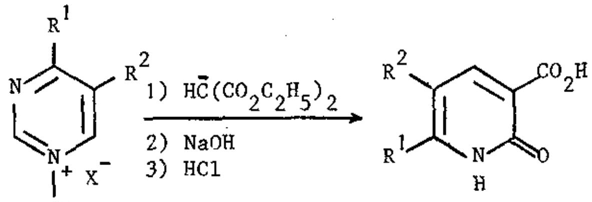
B. Ring transformations in which one or more atoms of the pyrimidine ring are replaced by one or more atoms of the reagent in such a way that the starting material and the product formed still contain the pyrimidine ring. We refer to these reactions as degenerate ring transformations.

C. Ring transformations in which the pyrimidine ring undergoes a ring contraction into a five-membered heterocycle.

Section A. Ring transformations, in which the Pyrimidine Ring is Converted into a Six-membered Heterocycle with a Different Ring.

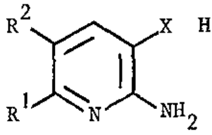
An interesting series of ring transformation reactions was observed when 1-methylpyrimidinium methylsulfate (1a, $X^- = CH_3OSO_3^-$), 1-methyl-4-phenylpyrimidinium iodide (1b, $X^- = I^-$) and 1-methyl-5-phenylpyrimidinium iodide

(1c, $X^-=I^-$) are treated with active methylene compounds CH_2XY (X=Y=CN; $X=Y=CO_2C_2H_5$; X=CN, $Y=CO_2C_2H_5$) in basic media[8]. With the carbanion of diethyl malonate these three compounds 1a-c gave reaction mixtures from which after saponification and acidification the 1,2-dihydro-2-oxonicotinic acids (2a-c) could be isolated.



1 2

a) $R^1=R^2=H$; b) $R^1=C_6H_5$, $R^2=H$; c) $R^1=H$, $R^2=C_6H_5$



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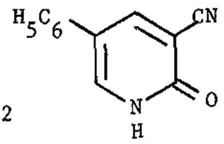
a) X=CN, $R^1=C_6H_5$, $R^2=H$
b) $X=CO_2C_2H_5$; $R^1=C_6H_5$, $R^2=H$
c) $X=CO_2C_2H_5$, $R^1=H$, $R^2=C_6H_5$



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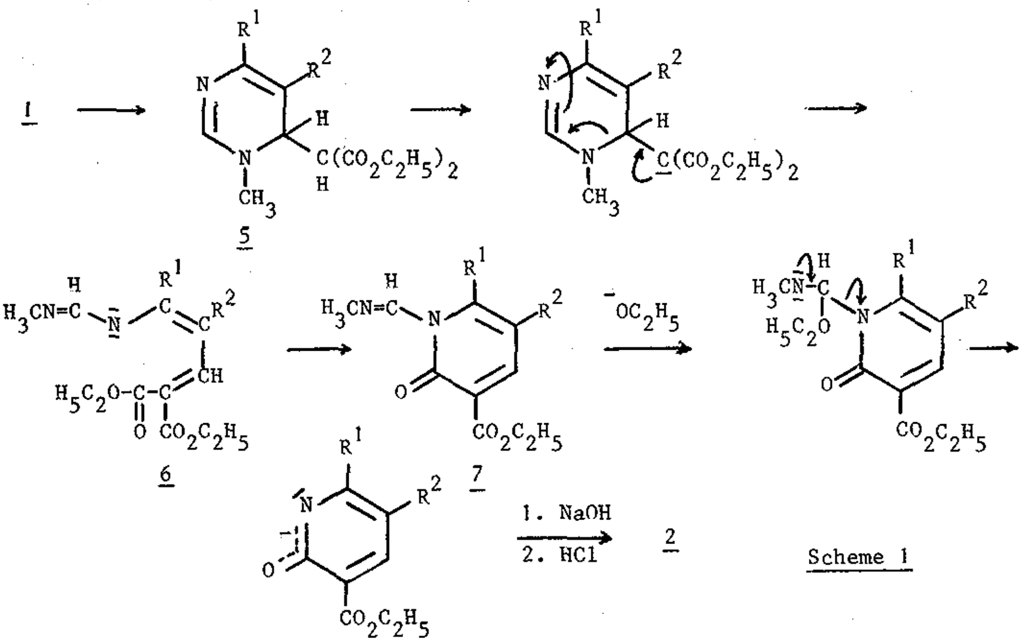
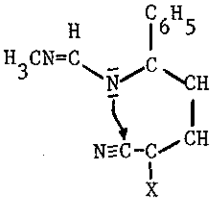
A pyrimidine-pyridine ring transformation was also observed when 1b is reacted with the carbanion of malonodinitrile and that of ethyl cyanoacetate, 2-amino-3-cyano-6-phenylpyridine (3a) and 2-amino-3-(ethoxycarbonyl)-6-phenylpyridine (3b) being obtained. Interestingly in the reaction of 1c with the carbanion of ethyl cyanoacetate not the expected 2-amino-3-(ethoxycarbonyl)-5-phenylpyridine (3c) but the 3-cyano-1,6-dihydro-2-oxo-5-phenylpyridine (4) is formed. The yields vary in all these reactions between 40-60%. It is worthwhile to mention that ethyl cyanoacetate and diethyl malonate do not react with the non-quaternised pyrimidines[9]; only malononitrile is able to convert pyrimidine and its 4-methyl derivative into 2-amino-3-cyanopyridine and its 6-methyl derivative respectively. So, first an activation of the pyrimidine ring by quaternisation and then reaction with active methylene reagents in basic medium seem to be a useful synthetic approach for the preparation of functionalized pyridines.

The ring transformation of 1 into 2, 3 and 4 respectively have all in common that the N(1)-C(2) fragment of the pyrimidine ring is replaced by two carbon atoms of the active methylene compound. Thus, the N(3)-C(4)-C(5)-C(6) fragment of the pyrimidine ring acts as a synthon for the N(1)-C(6)-C(5)-C(4) part of the novel pyridine ring. Quaternary pyrimidinium salts are able to form addition complexes with nucleophiles at the highly electron-deficient position 6. The formation of the 1,6-dihydro compound 5 seems to be a reasonable reaction step to initiate the ring transformation with the anion of diethyl malonate. Deprotonation of the acidic hydrogen of the methine group followed by ring opening yields the open-chain anion 6 which can recyclise by an intramolecular nucleophilic attack of the nitrogen at the ethoxycarbonyl group into 7. Loss of the N-substituent in 7 can be easily envisaged to occur in this basic medium by the way indicated (scheme 1).



Scheme 1

When the anion of malononitrile or ethyl cyanoacetate reacts with 1-methyl-4-phenylpyrimidinium iodide (1b, $X^-=I^-$), as intermediate is proposed 8 (X=CN or $CO_2C_2H_5$). The ring closure can now easily take place by a nucleophilic attack of nitrogen to the C≡N group. The question, why in the intermediate 9, being formed in the reaction of the 5-phenyl derivative (1c) with the anion of ethyl cyanoacetate, the cyclisation exclusively takes place by loss of an ethoxide anion and not by addition across the C≡N group is not quite understood at the moment.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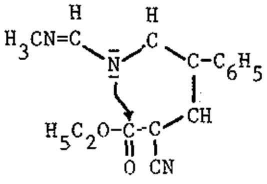
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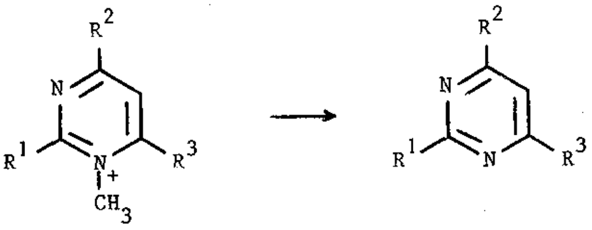
Section B. Degenerate Ring Transformations.

Degenerate ring transformations can be easily overlooked, since the heterocyclic ring in the starting material and reaction product is the same. To discover these "hidden" ring transformations, experiments with labelled compounds are often necessary. By applying these methods we have discovered a variety of degenerate ring transformations in reactions of N-methyl- and N-aminopyrimidinium salts and pyrimidine N-oxides with nucleophilic reagents. In the following sections first the degenerate ring transformations are discussed in which one nitrogen atom of the pyrimidine ring is replaced by a nitrogen atom of the reagent (ammonia, hydroxylamine, see section B.1), then the ring transformations are discussed in which more than one atom of the pyrimidine ring is replaced by the same atoms, originating from the reagent (aminocyanide, amidines and urea derivatives, see section B.2).

B.1. Degenerate ring transformations taking place under influence of ammonia and hydroxylamine.

When N-methyl pyrimidinium methylsulfate (10a, $X^- = CH_3OSO_3^-$) is dissolved in liquid ammonia at -33° and allowed to react for one hour pyrimidine (11a) is formed in a yield of 55-60%[10]. This demethylation reaction is also observed with the 1,2-dimethylpyrimidinium iodide (10b, $X^- = I^-$), 1,4,6-trimethylpyrimidinium iodide (10c, $X^- = I^-$) and 1,2,4,6-tetramethylpyrimidinium iodide (10d, $X^- = I^-$), yielding the pyrimidines (11b-d) respectively[10].

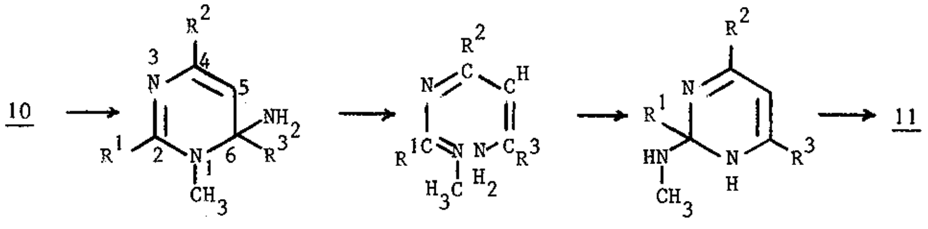


10 → 11

a) $R^1=R^2=R^3=H$; b) $R^1=CH_3$, $R^2=R^3=H$; c) $R^1=H$, $R^2=R^3=CH_3$; d) $R^1=R^2=R^3=CH_3$

The very mild conditions under which the demethylation of the pyrimidinium salts 10 occurs, are in remarkable contrast to the rather drastic conditions being generally necessary for the dealkylation of pyridinium salts by hard as well as by soft nucleophiles[11-13]. The very mild conditions found for the demethylation of 10 suggest that a mechanism is operative which is different from that given for the dealkylation of pyridinium salts. Whereas the dealkylation of the last-mentioned compounds occurs by a direct replacement of the heterocyclic ring with the nucleophile, the demethylation of 10 was considered to start by the initial formation of the 1 : 1 covalent σ-adduct 12. This adduct undergoes a ring opening into the diazatriene 13, which cyclises by a nucleophilic attack of the amino nitrogen on the azomethine N(1)-C(2) bond into the 1,2-dihydro-2-methylaminopyrimidine

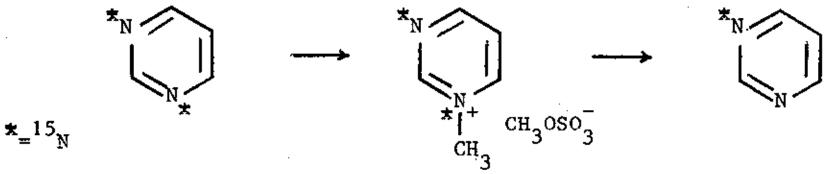
(14). Aromatisation by loss of methylamine yields 11 (scheme 2).



12 13 14

Scheme 2

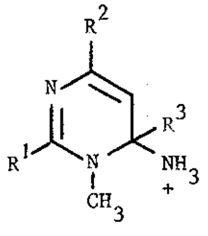
In order to verify this proposed mechanism we synthesized the double-labelled pyrimidinium salt 16 - by treatment of [1,3- ^{15}N]-pyrimidine (15) with dimethylsulfate - and subjected it to the reaction with liquid ammonia. If the mechanism given in scheme 2 is correct, it must be expected that the pyrimidine formed must contain ^{15}N at one position only, i.e. 17. This was found indeed; mass spectrometric measurements of the intensities of the M+2, M+1 and M peak in 15 and 17 showed that in 17 the M+2 peak was nearly zero, while the M+1 peak was considerably increased[10]. The decrease of the M+2 peak and the increase of the M+1 peak are balanced.



15 16 17

	15	17
M + 2	6.8	0.6
M + 1	0	6.3
M	100	100

Now the ^{15}N-labelling experiments really prove that in the demethylation of the pyrimidinium salt 10a one nitrogen atom of the pyrimidine ring is replaced by the nitrogen of the liquid ammonia and that we deal with a ring-modifying reaction, in which both starting material 10 and endproduct 11 have the *same* heterocyclic ring we call these reactions *degenerate ring transformations*. Since they can be described to occur in three consecutive steps A(ddition)N(nucleophile)-R(ing)O(pening)-R(ing)C(losure), we refer to these ring transformation as ANRORC reactions. That the initial addition of the ammonia indeed takes place at position 6 and not, for example, at position 2 has convincingly been proven by NMR spectroscopy. Following the technique given by Zoltewicz[14], we were able to measure ^{1}H- and ^{13}C-NMR spectra of 10 in liquid ammonia. The ^{1}H-NMR spectrum of a solution of 10a in liquid ammonia shows that in this solvent a compound is present of which all the hydrogen atoms of the ring resonate at a much higher field than the ones being observed in a solution of 10a in D_2O (Table I)[10]. A very similar upfield shift is observed when the pyrimidinium salts 10b and 10c are dissolved in liquid ammonia. The upfield shift is most pronounced for the hydrogen atom at position 6 (about 4.6-4.8 ppm). This is in good agreement with the formation of the 1 : 1 σ-adduct 12, since this changes the hybridisation of C(6) from $sp^2 \rightarrow sp^3$. The magnitude of the shielding ($\Delta\delta$) is in the same range as observed[15] in the covalent amination of a number of other quaternary salts derived from heteroaromatic compounds. In addition, a change in the multiplicity pattern as well as in the magnitude of the coupling constant[10] is observed, which fully support the intermediacy of 12. In the adduct 12a ($R^1=R^2=R^3=H$) no coupling between the hydrogens of the amino group at C(6) and the hydrogen at C(6) is found. This is due to the fact that the precursor of 12, i.e. the (1,6-dihydropyrimid-6-yl) ammonium ion 18, catalyses the proton exchange between the liquid ammonia and the amino group leading to decoupling[16]. The fact that in liquid ammonia only adduct 12 is present and no trace of 10 - within the limit of detection - indicates that the equilibrium between 10 and 12 is far on the side of the adduct, and in agreement with the poor leaving group mobility of an amino group.



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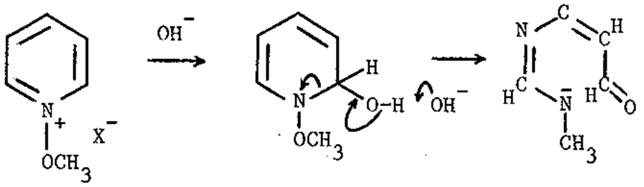
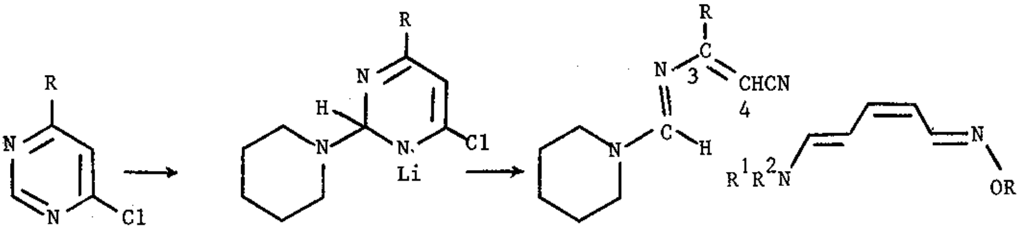


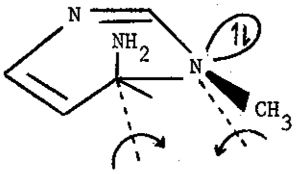
19 20 21

An interesting problem which in this connection remains to be discussed is whether the ring opening of 12 into 13 is a base-catalysed reaction or can be described as an electrocyclic rearrangement of six electrons. From earlier studies on the reaction of N-methoxypyridinium salts (19) with various nucleophiles, it was suggested that the opening of the heterocyclic ring only occurs if an acidic hydrogen is attached to the nucleophilic centre[17,18]. So, the conversion of 19 into the glutaconic dialdehyde mono-O-methyloxime (21) by sodium hydroxide is found to be a second order reaction with respect to hydroxide and involves as intermediate 20 which undergoes the ring opening as indicated (19 → 20 → 21). However, more evidence has become available[18-20] that in cases where no hydrogen is present on the nucleophilic centre, ring opening can still occur. So, 4-chloro-6-R-pyrimidine (22, R=t-C_4H_9, C_6H_5) gives with lithium piperidide at -70° the 2-aza-1,3-butadiene (24) - probably via the C(2)-adduct 23 - which in case of R=C_6H_5 proved to be a Z-E mixture around the C(3)-C(4) bond[21]. More recently it has been found that N-alkoxypyridinium salts when reacted with secondary amines (pyrrolidine, piperidine and diethylamine) give as the primary product the <u>syn-cis-trans</u> compound 25, which formation has been described to involve a disrotatory opening[22-25].



22 23 24 25

As far as the ring opening of 12 into 13 is concerned it is evident that based on the data available so far, no conclusion about either a base-catalysed and/or an electrocyclic process can be drawn. However, it seems questionable whether the weakly basic ammonia (K_B=1.8x10^{-5}) is able to perform the deprotonation of the NH_2-group at C(6), being necessary to initiate the base-catalysed ring opening. Therefore the suggestion can be made that in the liquid ammonia the ring opening of 12 → 13 occurs by a thermally allowed disrotatory process (see 26)[26].



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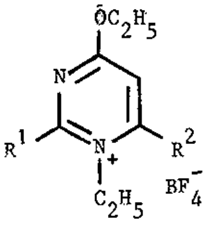
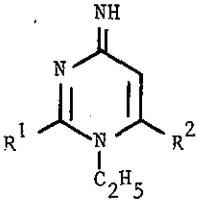
As an extension of our study on the N-demethylation of pyrimidinium salts by liquid ammonia we have investigated the 4(6)-alkoxy-1-ethylpyrimidinium tetrafluoroborates (27a and 27c) and the 4,6-dialkoxy-1-ethylpyrimidinium tetrafluoroborates (27b and 27d)[27]. These compounds - prepared by treatment of the corresponding 4-alkoxypyrimidine or 4,6-dialkoxypyrimidine with 1 equiv. of triethyloxonium tetrafluoroborate[28] - were found to give with liquid ammonia a reaction which was quite different from that observed with the 4(6)alkyl N-methylpyrimidinium salts 10. On treatment of 27a and 27c with liquid ammonia at -33° no N-de-ethylation is observed; only replacement of the ethoxy group by an amino group at position C(4) and/or C(6) is found. From 27a the 1,4-dihydro-1-ethyl-4-iminopyrimidine hydrogen tetrafluoroborate (28a, 68%) is obtained and from 27b a mixture of the 1,4-dihydro-6-ethoxy-1-ethyl-4-iminopyrimidine (28b, 55%) and 1,6-dihydro-4-ethoxy-1-ethyl-6-iminopyrimidine (29b, unspecified yield) respectively. It was proved, using ^{15}N-labelled ammonia, that the amino-de-ethoxylation reaction does not involve ring opening[27,29,30].



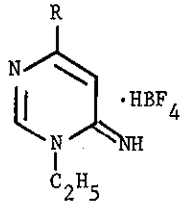
27

a) $R^1=R^2=H$
b) $R^1=H,\ R^2=OC_2H_5$
c) $R^1=C_6H_5,\ R^2=H$
d) $R^1=C_6H_5,\ R^2=OC_2H_5$



28

a) $R^1=R^2=H$
b) $R^1=H,\ R^2=OC_2H_5$
c) $R^1=C_6H_5,\ R^2=H$



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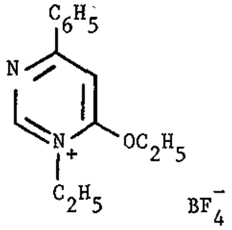
a) $R=C_6H_5$
b) $R=OC_2H_5$



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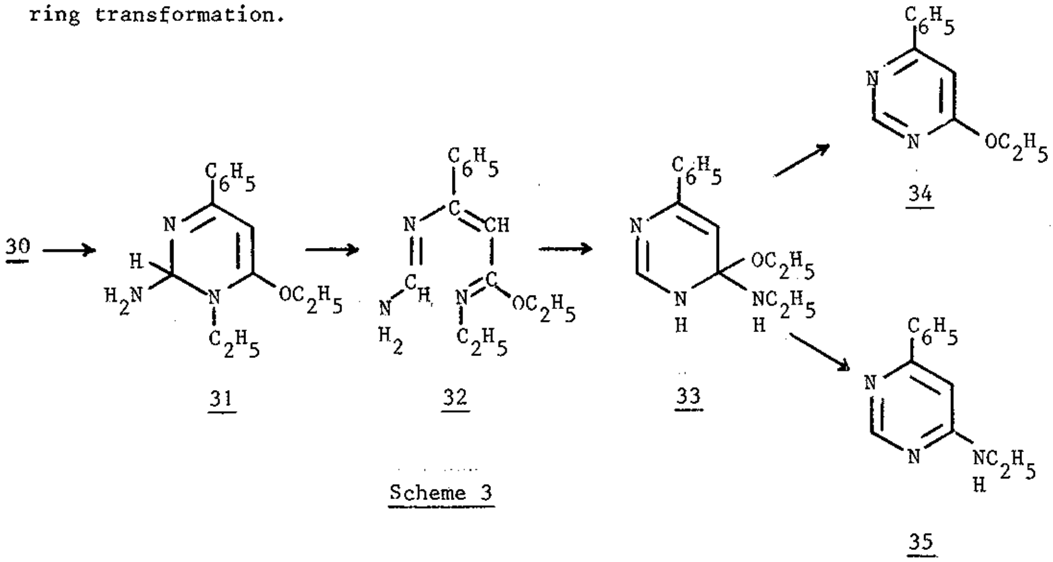
4-Ethoxy-1-ethyl-2-phenylpyrimidinium tetrafluoroborate (27c) shows with liquid ammonia a more complex behaviour; besides amino-de-ethoxylation into 28c, N-de-ethylation into 4-ethoxy-2-phenylpyrimidine occurs. When this N-de-ethylation reaction was investigated with ^{15}N-labelled ammonia it was found that the 4-ethoxy-2-phenylpyrimidine contained the same excess of ^{15}N as present in the labelled ammonia. Thus, the de-ethylation occurs via the same type of ring opening - ring closure mechanism as depicted in Scheme 2 for the N-demethylation of 10 and presents another example of a degenerate ring transformation[27]. Interestingly, from 6-ethoxy-1-ethyl-4-phenylpyrimidinium tetrafluoroborate (30) - being isomeric with 27c - three different products are obtained. One product is 29a, formed by amino-de-ethoxylation, the second product is 4-ethoxy-6-phenylpyrimidine (34) and the third product is 4-(ethylamino)-6-phenylpyrimidine (35). The formation of a product with an 4(6)-ethylamino substituent, accompanied by an N-de-ethylation product is also observed with 4,6-dimethoxy-1-ethyl-2-phenylpyrimidinium tetrafluoroborate, 4,6-dimethoxy-2-phenylpyrimidine and 4-(ethylamino)-6-methoxy-2-phenylpyrimidine being obtained[27]. These observations make it reasonable to assume that the N-de-ethylation of 30 into 34 and the formation of the 4-(ethylamino)pyrimidine derivative 35 proceed *via* a common intermediate 33. It is formed by a subsequent series of reactions involving addition at C(2), ring opening of the covalent adduct 31 into the diazahexatriene 32 by cleavage of the N_1-C_2 bond and recyclisation by addition of the amino group to the iminoether moiety. Loss of ethylamine and ethanol respectively from 33 yields the compounds 34 and 35 (scheme 3). It is evident that both compounds are formed by a *degenerate* ring transformation.



Scheme 3

It is of interest to note the remarkable difference in the regiospecificity of the addition of ammonia between the 4-alkoxypyrimidinium salts 27 which give adducts at C(2) and the alkylpyrimidinium salts 10 which give adducts at C(6). To substantiate this further we measured the ^1H- and ^{13}C-spectra of solutions of 27a and 27b in liquid ammonia and compared the chemical shifts of the ring protons with those found in solutions of 27a and 27b in acetone-d_6 (see Table I). It showed that in liquid ammonia the absorption of

Table I

Chemical shifts (δ) of the ring H-atoms of the N-alkylpyrimidinium salts 10a-c, 27a-b, 36 and 40 (R=H)

Compound	Solvent	H(2)	H(4)	H(5)	H(6)
10a ($X^- = CH_3OSO_3^-$)	D_2O	9.60	9.39	8.17	9.21
	NH_3	6.94	6.27	4.91	4.57
10b ($X^- = I^-$)	D_2O	-	9.0	8.01	9.2
	NH_3	-	6.15	4.84	4.42
10c ($X^- = I^-$)	D_2O	9.34	-	8.00	-
	NH_3	6.82	-	4.48	-
27a	acetone-d_6	9.36	-	7.45	8.90
	NH_3	5.37	-	4.57	6.84
27b	acetone-d_6	9.05	-	6.92	-
	NH_3	5.26	-	4.10	-
36	acetone-d_6	9.50	-	6.80	8.20
	NH_3	5.25	-	4.50	6.85
40 (R=H)	acetone-d_6	9.50	-	6.14	-
	NH_3	5.20	-	4.12	-

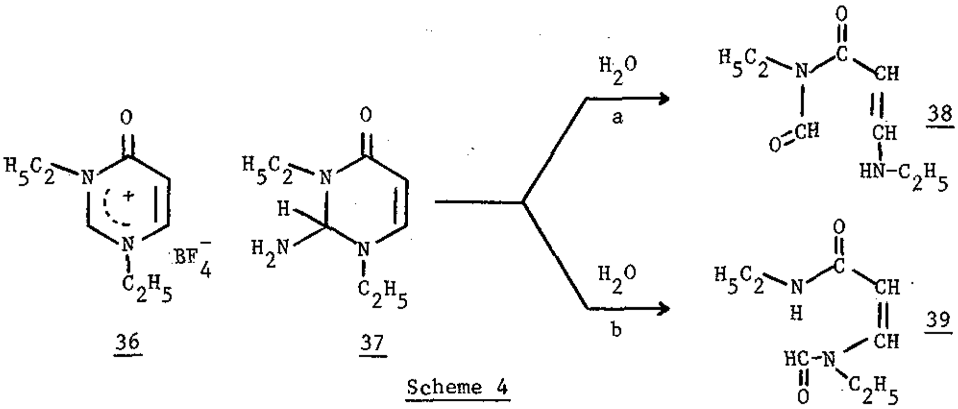
the ring hydrogen atoms lie at a much higher field than in acetone-d_6 and that the upfield shifts are most pronounced for the H(2)-atoms. This is ascribed to the formation of a covalent adduct at C(2) leading to rehybridisation of C(2) ($sp^2 \rightarrow sp^3$). This was also confirmed by measurements of the ^{13}C-NMR spectra in acetone-D_6 and in liquid ammonia (Table II). The chemical shift difference (Δδ) is for C(2) the largest and amounts to 77.3 ppm. This value is in good agreement with the shielding difference of about 90 ppm which is found on adduct formation between a 2-substituted 4-chloropyrimidine and an amide ion[31]. Further spectroscopic evidence for adduct formation at C(2) is the significant change of ^1J C(2)H from 210 Hz (acetone-d_6) to 152 Hz (NH_3), being in agreement with the formation of an sp^3-carbon atom at C(2)[31-32].

Table II

Chemical shifts (ppm) and coupling constants of the ring carbon atoms of 27a-b, 36 and 40 (R=H) in acetone-d_6 and in liquid ammonia

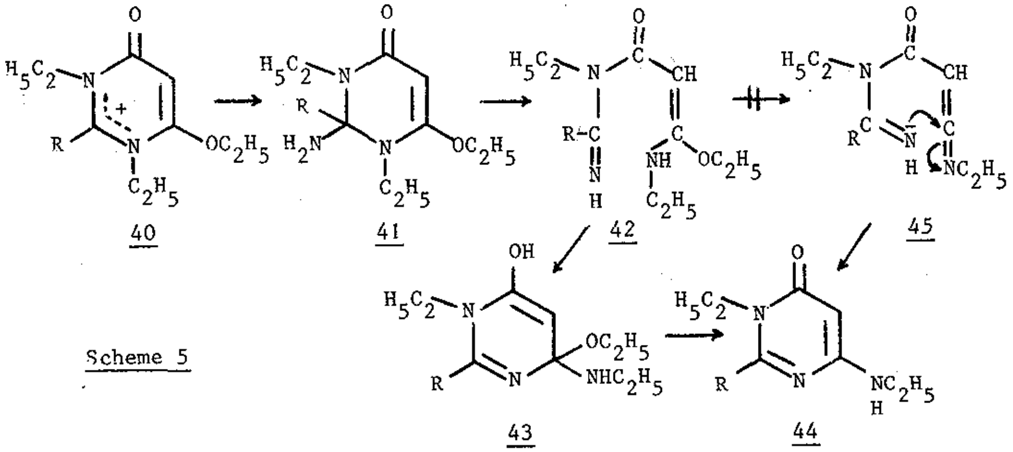
Compound	Solvent	C(2)	C(4)	C(5)	C(6)	^1J C(2)H	^1J C(5)H	^1J C(6)H
27a	acetone-d_6	156.2	172.8	111.9	151.4	210	180	192
	NH_3	78.3	162.1	83.1	144.4	165	170	172
27b	acetone-d_6	154.9	174.7	91.2	165.2	216	178	-
	NH_3	81.0	164.2	62.8	160.8	163	170	-
36	acetone-d_6	155.8	158.5	117.6	145.1	210	180	192
	NH_3	78.5	164.3	89.8	145.7	152	170	172
40	acetone-d_6	154.7	161	91.8	161	214	174	-
(R=H)	NH_3	79.1	166.1	69.8	161.8	160	170	-

The 1,3-diethyl-1,4(3,4)-dihydro-4-oxopyrimidinium salt (36) and its 2-phenyl,6-phenyl and 6-methyl derivative were also subjected to treatment with ammonia[33]. Reaction of 36 with aqueous ammonia resulted in the formation of a mixture of Z- and E-isomers of N-formyl-N-ethyl-3(ethylamino)-acrylamides (38) together with the Z-isomer of N-ethyl-3-(formylethylamino)-acrylamide (39). The formation of these products was explained by a decomposition of the C(2)-adduct 37 either by fission of the N(1)-C(2) bond (route a) and/or by cleavage of the N(3)-C(2) bond (route b); see scheme 4. Similar results are obtained with the 2-phenyl,6-phenyl and 6-methyl derivative of 36.



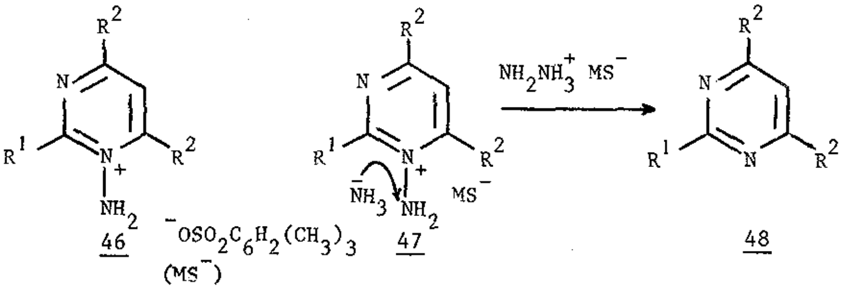
Scheme 4

Degenerate ring transformations have been observed when the 6-ethoxy-4-oxopyrimidinium tetrafluoroborates (40, R=H, CH_3, C_6H_5) are reacted with liquid ammonia. Besides the formation of open-chain compounds the 1,6-dihydro-1-ethyl-4(ethylamino)-6-oxopyrimidine (44) is obtained. The presence of the ethylamino group as substituent indicates that a degenerate ring transformation has occurred. The C(2) adduct 41 is intermediate which undergoes a N(1)-C(2) bond fission yielding 42. It is suggested that 42 gives ring closure into the 1,4-dihydro intermediate 43 which then loses ethanol to give 44. It can be suggested that by loss of ethanol the ketenimine 45 is formed which could be intermediate in the formation of 44 (see scheme 5). However, since ketenimines undergo addition of alcohols in basic solution[34], it seems very unlikely that the reversed reaction into 45 will take place under these conditions. ^1H-NMR data and ^{13}C-NMR data of solutions of the 4-oxopyrimidinium tetrafluoroborates 36 and 40 (R=H) in liquid ammonia supports unequivocally the formation of a C(2)-adduct (see Tables I and II).



Scheme 5

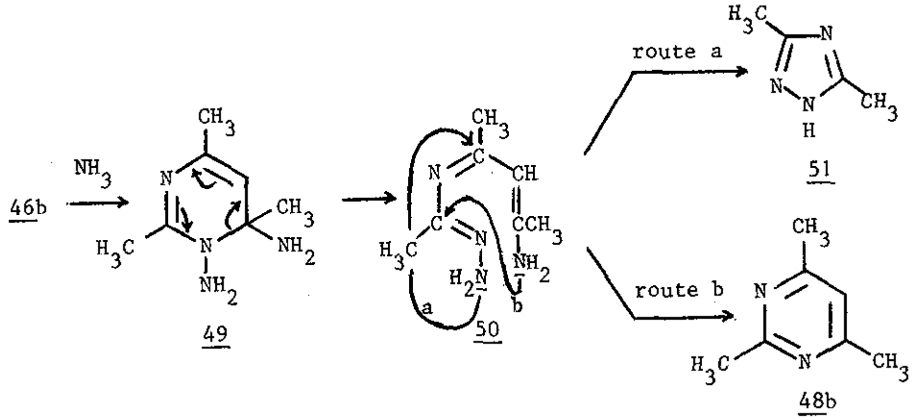
The ANRORC mechanism being found for the N-demethylation of N-methylpyrimidinium salts by liquid ammonia induced us to study whether N-aminopyrimidinium salts could undergo N-deamination. It was observed[7] that treatment of N-amino-4,6-diphenylpyrimidinium mesitylene sulfonate (46a) with liquid ammonia gives a quantitative deamination into 4,6-diphenylpyrimidine (48a). When the reaction was carried out with ^{15}N-labelled liquid ammonia (containing 9.9% of excess of ^{15}N) we found[7] that 4,6-diphenylpyrimidine contained 2.7% of excess of ^{15}N indicating that about 27% (neglecting isotope effects) of the deamination had occurred according to the ANRORC mechanism. An attempt to establish the structure of the adduct by ^1H-NMR spectroscopy failed *due to the low solubility of 46a. Therefore it is impossible to conclude* whether the ammonia adds to C(2) or C(6) before ring opening occurs. Since it is found[35] by ^1H-NMR spectroscopy that 4,6-diphenylpyrimidine in $K^+NH_2^-$/NH_3 easily gives a σ-adduct at C(2) we may cautiously conclude that also the adduct formation of ammonia to 46a preferentially occurs at C(2). From the result of the experiment with labelled $^{15}NH_3$ it is evident that the major pathway for deamination is not a ring opening reaction but an S_N2 nucleophilic attack of ammonia on the N-amino group (47).



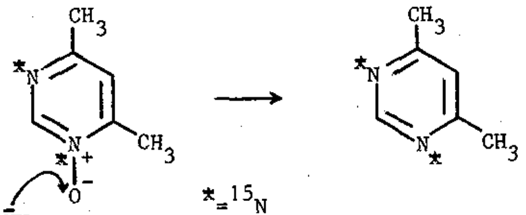
a) R^1=H, R^2=C_6H_5; b) R^1=R^2=CH_3; c) R^1=H, R^2=CH_3

The reaction of N-amino-2,4,6-trimethylpyrimidinium mesitylene sulfonate (46b) with liquid ammonia shows to be more complex[7]. Deamination is the main reaction - 2,4,6-trimethylpyrimidine (48b) is formed in a 40% yield - but also ring contraction into 3,5-dimethyl-1,2,4-triazole (51, 12%) is observed. It was established by carrying out experiments with $^{15}NH_3$, that the deamination occurs to the extent of ∿80% by a direct nucleophilic attack of the ammonia to the N-amino group in 47b and 20% by the ANRORC mechanism. The formation of 1,2,4-triazole 51 indicates that the ring opening must occur by an initial addition of the NH_3 at C(6)! The formation of both 51 and 48b could then be explained via the common intermediates 49 and 50 which recyclise via the routes a and b into 51 and 48b respectively.

In the reaction mixture obtained when N-amino-4,6-dimethylpyrimidinium mesitylene sulfonate (46c) is reacted with liquid ammonia no trace of 4,6-dimethylpyrimidine could be discovered. The reaction takes a quite different



course, leading to dimerisation and ring contraction (see section C). Attempts were undertaken to perform deoxygenation of pyrimidine N-oxides by treatment with liquid ammonia. 4,6-Dimethylpyrimidine N-oxide was found to be fully stable in liquid ammonia at -33° and at 70° but to lose the oxygen if heated with liquid ammonia at 160°(!) for 2 h[36]. These rather drastic conditions recall those being necessary for the demethylation of N-methylpyridinium salts with hard and soft nucleophiles[11-13]. A same type of mechanism can therefore be expected i.e. a direct nucleophilic attack of the NH_3 at the oxygen of the N-oxide. Reaction of $\left[1,3\text{-}^{15}N\right]$-dimethylpyrimidine N-oxide (52) with unlabelled ammonia showed that in the 4,6-dimethylpyrimidine (53) obtained the same percentage of ^{15}N-enrichment is present as in the starting material 52[36]. It leads to the conclusion that no ring opening is involved in the deoxygenation!



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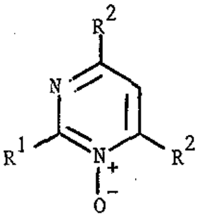

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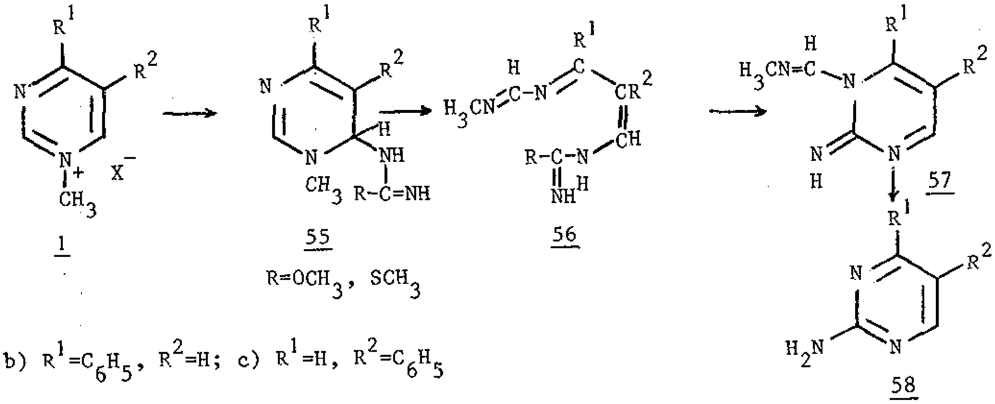
An interesting degenerate ring transformation, being of preparative value for the synthetic organic chemistry is the conversion of the N-aminopyrimidinium salts (46) into the corresponding pyrimidine N-oxides (54) by a reaction with hydroxylamine. This conversion occurs in reasonable to high yield (46a → 54a, 35%; 46b → 54b, 90%; 46c → 54c, 85%)[37]. This method of formation of pyrimidine N-oxides is a valuable addition to the more classical oxidation method with peracids, since the yields obtained are usually higher and it opens up the possibility of synthesizing pyrimidine N-oxides containing substituents which are sensitive for oxidation.

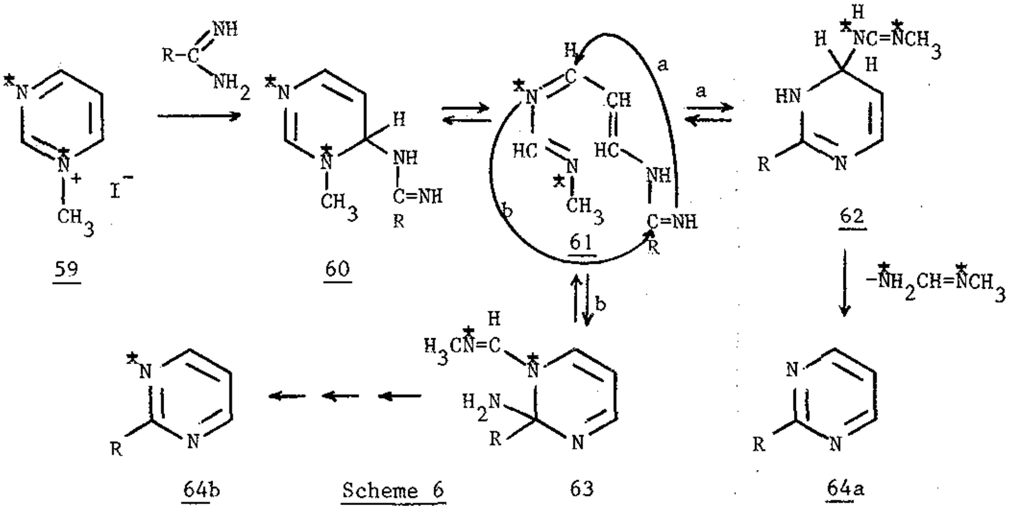
Section B.2 Degenerate ring transformations under influence of cyanamide, urea- and thiourea-derivatives and amidines

Reaction of 1-methyl-4-phenylpyrimidinium iodide (1b, $X^-=I^-$) and 1-methyl-5-phenylpyrimidinium iodide (1c, $X^-=I^-$) with O-methylisourea leads to a complicated reaction mixture from which we were able to isolate as main product 2-amino-4-phenylpyrimidine (58b) (35%) and 2-amino-5-phenylpyrimidine (58c) (15%) respectively[38]. The corresponding reaction of 1b and 1c with S-methylisourea also gives 58b and 58c respectively; the yields, however, were much higher (70% and 40%). In the reaction mixtures no detectable amounts of 2-methoxy- or 2-(methylthio)pyrimidine derivatives were present. It is evident that both 2-amino compounds are formed by an overall displacement of the C(2)-N(1) fragment of the pyrimidinium salt by the N-C fragment of the nucleophile applied. It is the first example of a nucleophilic substitution - leading to the introduction of an amino group at position 2 of the pyrimidine ring - which involves a degenerate ring transformation, replacing two atoms of the pyrimidine ring by two atoms of the reagent[38]. The reaction can be described to occur by a ring opening of the C(6)-σ-adduct (55) into the open-chain diamidine 56 (R=OCH_3, SCH_3) and subsequent ring closure by loss of the methoxide or thiomethoxide ion. In the intermediary 1,2-dihydro-2-iminopyrimidine (57) the side-chain is lost by a base-catalysed fragmentation (compare 7 in Scheme 1). Attempts to prepare 58a and 58b by a reaction of 1a and 1b with guanidine failed. With cyanamide however, reasonable yields of 58a and 58b were obtained (60% and 35% respectively)[38].



b) $R^1=C_6H_5$, R^2=H; c) R^1=H, $R^2=C_6H_5$

Other interesting examples of reactions which lead to a nucleophilic substitution at position 2 of the pyrimidine ring by a degenerate ring transformation have been observed in the reaction of 1-methylpyrimidinium salt 1a with amidine. The reaction of 1a with a solution of benzamidine in basic medium has been found to give in a reasonable yield 2-phenylpyrimidine (64, R=C_6H_5, 45%). The reaction of 1a with aliphatic amidines is less satisfactory. With acetamidine a complicated reaction mixture was obtained in which, if present, only a trace (< 1%) of 2-methylpyrimidine was found. With pivalamidine, 2-t-butylpyrimidine (64, R=tBu) could be isolated in a small yield (10%). The mechanism of this reaction is advanced to occur in the manner shown below (scheme 6).



Scheme 6

The transient intermediate 60 being formed by attack of the nucleophilic nitrogen of the amidine at C(6) is in a tautomeric ring-chain equilibrium with 61. This can revert to either 60 or cyclise to the 3,4-dihydropyrimidine 62 (route a) or 2,3-dihydropyrimidine 63 (route b). By a base-catalysed loss of N-methylformamidine aromatisation into the 2-substituted pyrimidine 64 takes place.

In order to differentiate between the two possible reaction pathways a and b, N-methyl-[1,3-^{15}N]-pyrimidinium iodide (59), containing an excess of 5% ^{15}N, was synthesized. We observed that after the reaction with benzamidine unlabelled 2-phenylpyrimidine is obtained[38]. From this result we have to conclude that this degenerate ring transformation proceeds via the pathway involving the reaction intermediates 60, 61 and 62. In the conversion of 59 into 64a ($R=C_6H_5$) we encountered the first example of a nucleophilic substitution in which the three-atom N-C-N fragment of the amidine replaces the three-atom N(1)-C(2)-N(3) fragment of the pyrimidine ring.

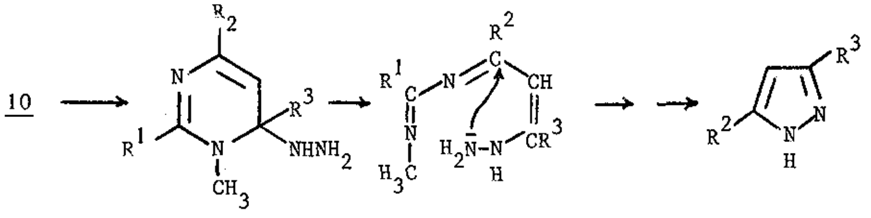
Section C Ring Contraction Reactions into Five-Membered Hetrocycles

In this section first the ring contractions of pyrimidinium salts are discussed which take place under influence of different nucleophiles (section C.1). The conversion into pyrazoles and 1,2,4-triazoles is discussed in section C.1.1, into isoxazoles in section C.1.2 and into oxazolidines in section C.1.3. In section C.2 the ring contractions are discussed which take place when pyrimidine N-oxides are irradiated with light.

Section C.1 Ring Contraction under Influence of Nucleophiles

C.1.1 Formation of Pyrazoles and 1,2,4-Triazoles

Reaction of an aqueous solution of 1-methylpyrimidinium methylsulfate (10a, $X^-=CH_3OSO_3^-$) and 1,2-dimethylpyrimidinium iodide (10b, $X^-=I^-$) with hydrazine hydrate at room temperature gives in good yield pyrazole (66, $R^2=R^3=H$). From 1,4,6-trimethylpyrimidinium iodide (10c, $X^-=I^-$), 3,5-dimethylpyrazole (66, $R^2=R^3=CH_3$) and from 1-methyl-4-phenylpyrimidinium iodide (10, $R^1=R^3=H$, $R^2=C_6H_5$, $X^-=I^-$) 3-phenylpyrazole (66, $R^2=C_6H_5$; $R^3=H$) is obtained[4,39a,b]. This ring contraction can also be performed when reacting the non-quaternized pyrimidines with hydrazine; however, the temperature being required is then high (about 180°-200°). The rate enhancement observed with the quaternized compounds is due to the presence of the electron attracting positive nitrogen which depletes the N(1)-C(6) bond from electrons, making addition of nucleophiles favourable. The ring contraction is described to start with an initial addition at C(6) and follows the pathway given in scheme 7. Substantial evidence for this mechanism was given by studying the course of the reaction with ^{1}H-NMR spectroscopy[39b]. In order to obtain somewhat simp-



65 66

Scheme 7

lified ^{1}H-NMR spectra we used as substrate the N-methylpyrimidinium iodide (10a, $X^- = I^-$) instead of 10a ($X^- = CH_3OSO_3^-$) and as reagent fully deuterated hydrazine hydrate ($N_2D_4 \cdot D_2O$). After allowing 10a ($X^- = I^-$) to react with $N_2D_4 \cdot D_2O$ at -30^o for about 10 min we observed in the ^{1}H-NMR spectrum that all absorptions of the ring hydrogen are shifted upfield in comparison with those measured in D_2O (see Table III). From the chemical shift differences ($\Delta\delta$) it is evident that an adduct is formed at C(6), i.e. 65 ($R^1 = R^2 = R^3 = H$). The values are very similar to those observed for the adducts formed from compound 10a and liquid ammonia (see Tables I and IV). After increasing the temperature of the reaction mixture to -5^o and allowing it to react for some additional time, it was observed[39b] that weak absorptions appear between δ5.5-8.0. After standing overnight the spectrum of the reaction mixture featured besides signals at δ2.45 and δ7.04 the H(3) and H(5) hydrogen atoms of pyrazole at δ7.82. Surprisingly, the H(4) hydrogen of the pyrazole ring was only present as a weak triplet at δ6.30. After isolation of the pyrazole it became evident that position 4 is deuterated for about 75%. Since pyrazole

Table III

Chemical shifts of the ring hydrogen atom of 10 in D_2O and in $N_2D_4\cdot D_2O$

Compound	Solvent	H(2)	H(4)	H(5)	H(6)
10a $(X = I^-)$	D_2O $N_2D_4\cdot D_2O$	9.70(s) 7.42(s)	9.30(d) 6.70(d)	8.25(t) ca.5.0[*]	9.48(d) ca.5.0[*]
10b $(X = I^-)$	D_2O $N_2D_4\cdot D_2O$	-	9.15(d) 6.58(d)	8.06(t) ca.5.0[*]	9.32(d) ca.5.0[*]
10c $(X^- = I^-)$	D_2O $N_2D_4\cdot D_2O$	9.34(s) 7.30(s)	- -	7.95(s) 4.52(s)	- -
10 $(X^- = I^-)$ $(R^1=R^3=H,\ R^2=C_6H_5$	D_2O $N_2D_4\cdot D_2O$	9.47(s) 7.72(s)	- -	8.46(d) 5.42(d)	9.05(d) 5.02(d)

[*] Peaks are partly overlapped by the HOD (H_2O) being present in small amounts in the $N_2D_4\cdot D_2O$.

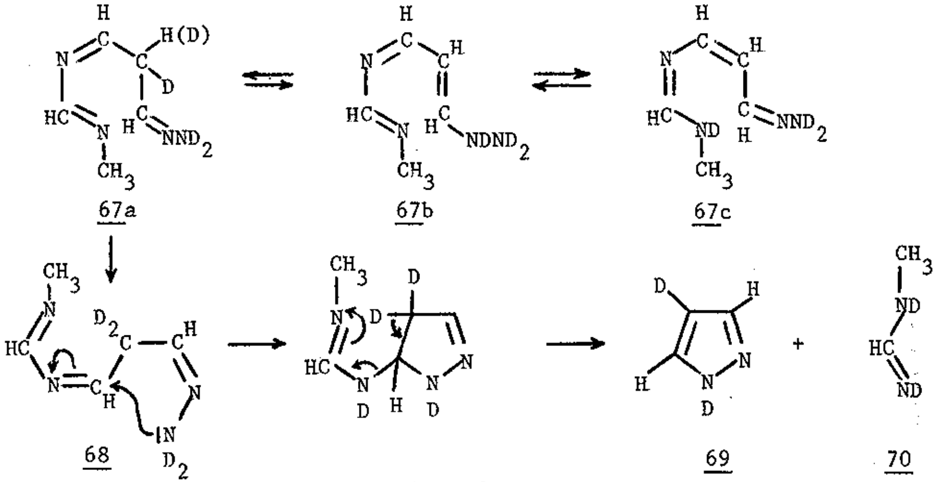
Table IV

Chemical shift differences (Δδ) between the ring protons in the compound <u>10</u>, when dissolved in D_2O and in $N_2D_4 \cdot D_2O$. The number in brackets refers to the Δδ observed between solutions of <u>10</u> in D_2O and liquid ammonia

Compound	H(2)	H(4)	H(5)	H(6)
<u>10a</u> ($X^- = I^-$)	2.28(2.66)	2.60(3.12)	ca.3.3(3.26)	ca.4.5(4.64)
<u>10b</u> ($X^- = I^-$)	--	2.57(2.8)	ca.3.1(3.17)	ca.4.3(4.8)
<u>10c</u> ($X^- = I^-$)	2.04(2.52)	--	3.43(3.52)	--
<u>10</u> ($X^- = I^-$) ($R^1 = R^3 = H$; $R^2 = C_6H_5$	1.75 (*)	--	3.04 (*)	4.03 (*)

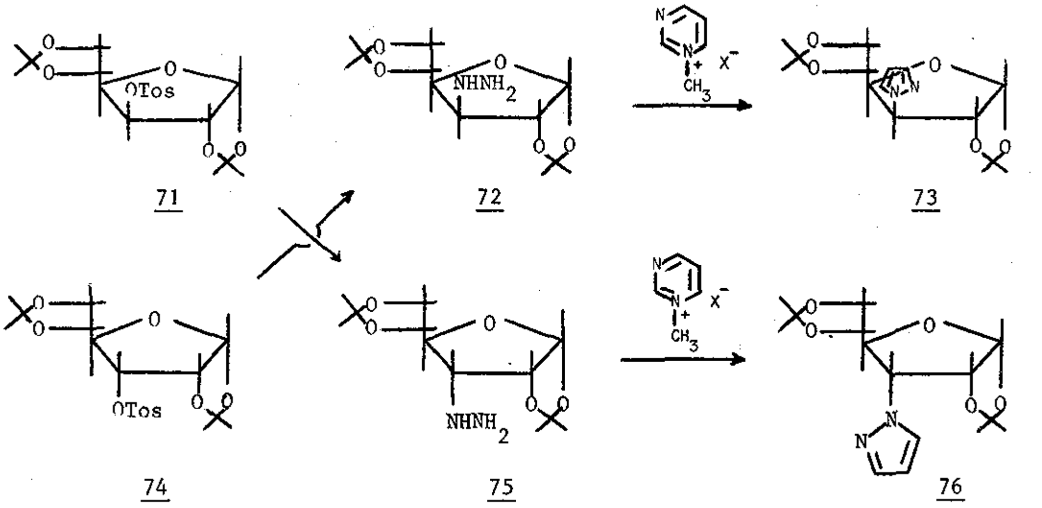
* = not measured

does not undergo an H/D exchange with $N_2D_4.D_2O$ under the very mild conditions which have been applied for the ring contraction, in the pathway leading to the ring contraction an intermediate must be formed which easily undergoes an H/D exchange. It is likely the tautomeric mixture of the open-chain intermediates 67a-c, formed after the ring opening (see for the discussion on the ring opening Section B.1) which undergoes H/D exchange with the deuterated hydrazine hydrate[40,41]. Cyclisation of the rotamer 68 and subsequent loss of deuterated N-methylformamidine 70 (or N-methylformamide) leads to the pyrazole 69 containing deuterium at position 4. We assume that the ^{1}H-NMR signals observed at δ2.45 and δ7.04 in the spectrum obtained after standing of the reaction mixture overnight (see before) are originated from the peaks of the N-methyl and the H-C= group in 70 respectively[42]. Pyrazoles, being deuterated at position 4 have also been found when reacting 10b, 10c and 1-methyl-4-phenylpyrimidinium iodide (10, $R^1=R^3=H$, $R^2=C_6H_5$, $X^-=I^-$) with $N_2D_4.D_2O$. Since also these compounds form a covalent σ-adduct at C(6) when dissolved in $N_2D_4.D_2O$ (see Table III) the ring contraction into the 4-D-pyrazoles must take place according to the pathway described in scheme 8.



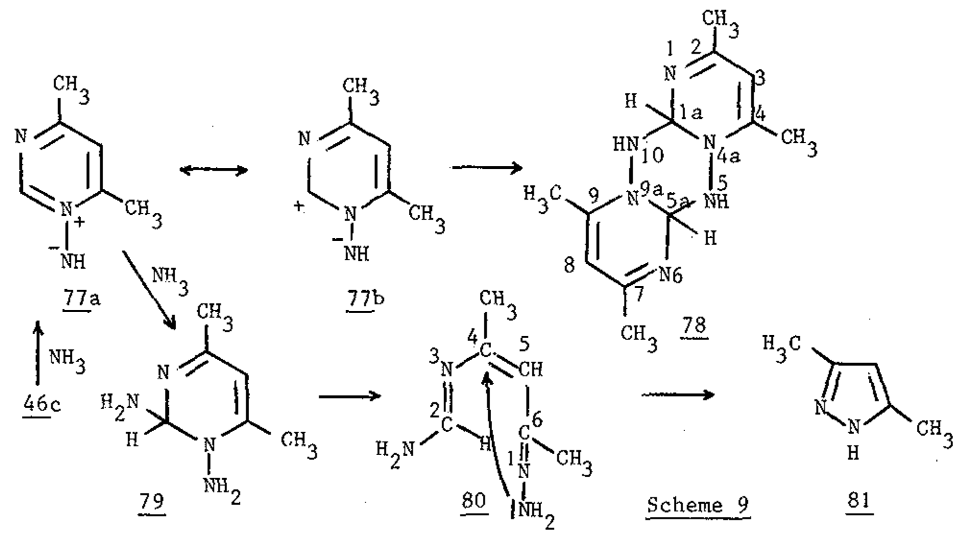
Scheme 8

An interesting example of a useful synthetic application of the ring contraction of pyrimidinium salts into pyrazoles can be demonstrated[43] by the preparation of 1,2;5,6-di-O-isopropylidene-3-deoxy-3-(N-pyrazolyl)glucose (73) and the 1,2;5,6-di-O-isopropylidene-3-deoxy-3(N-pyrazolyl)allose (76). Attempts to introduce the pyrazolyl group at position 3 of the tetrahydrofuran ring via a displacement of a 3-O(p-tolylsulfonyl)group in 71 and in 74 by the sodium salt of pyrazole, failed. Since this method could succesfully be applied to introduce a pyrazolyl group at position 6 of a glucose derivative[43,44], apparently the back-side approach of the rather bulky pyrazolyl anion to the secondary carbon at position 3 is sensitive for steric interference. However, reaction of the 3-allohydrazino compound 75 - being easily obtained by hydrazinolysis of the 3-glucotosylate - with N-methylpyrimidinium sulfate gave the 3-allopyrazolyl derivative 76 in excellent yield. Similarly, reaction of this N-methylpyrimidinium salt with the 3-glucohydrazino derivative 72 yields the 3-glucopyrazolyl compound 73.



Several ring contractions have also been reported with N-aminopyrimidinium salts. When the yellow 4,6-dimethyl-N-aminopyrimidinium salt (46c) is reacted for 1 h with liquid ammonia at -33° two products i.e. the 2,4,7,9-tetramethyldipyrimido[1,2-b; 1',2'-c]hexahydrotetrazine (78, 20%) and 3,5-dimethylpyrazole (81, 13%) were obtained[7]. The formation of dimer 78 can be rationalized by an initial deprotonation of the N-amino group leading to the intermediary formation of the N-ylide 77 which acts as a 1,3-dipolar intermediate resulting in dimerisation. Dimerisation of N-ylides derived from isoquinoline and quinoline has been reported[45].

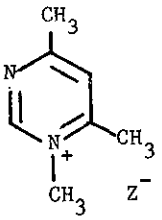
The concurrent formation of 81 present a new type of pyrimidine-pyrazole ring transformation. It involves the N(1)-C(6)-C(5)-C(4) fragment of the pyrimidine ring, which serves as a four atom synthon in the construction of the pyrazole ring. In the conversion of the N-methylpyrimidinium salts into pyrazole with hydrazine (10 → 66) it is the C(4)-C(5)-C(6) moiety of the pyrimidine ring which is incorporated in the pyrazole ring[4]. We postulate in the conversion of 46c → 81 an initial formation of a σ-adduct at C(2) i.e. 79 which, after ring opening, gives an N-(hydrazonoalkenyl)formamidine 80 ; 81 is formed by attack at C(4) of the amino group of the hydrazono moiety. From this postulate it is apparent that the ammonia is considered as necessary for the addition, preceding ring opening, but that it does not play a role in the cyclisation. In agreement with this result it is found that treatment of 46c with a dilute solution of sodium hydroxide also leads to the formation of 81[46]. Attempts to obtain by ^{1}HNMR spectroscopy some data on the intermediary adduct 79 failed; the spectrum is considerably confused probably due to the formation of the dimer.



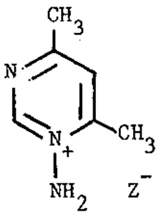
Scheme 9

The reaction of the N-amino-2,4,6-trimethylpyrimidinium salt (46b) into the 1,2,4-triazole (51) is another example of a ring contraction reaction which N-aminopyrimidinium salts can undergo[7]. The interesting point is that in this reaction the initial addition must take place at position 6. The 1 : 1 covalent σ-adduct 49 undergoes ring opening at the N(1)-C(6) bond into the N-amino-N'-(aminoalkenyl) formamidine (50). Ring closure by attack of the amino group of the hydrazino moiety at C=N (see route a) yields 51. Also in this case the ammonia is necessary for the formation of the adduct but does not take part in the cyclisation.

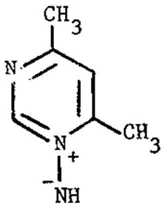
The results discussed before raises the important question why the 1,4,6-trimethylpyrimidinium salt (10c) gives reactions being initiated by an addition at C(6) whilst the reaction of the 1-amino-4,6-dimethylpyrimidinium salt (46c) starts by an addition at C(2). By application of the Frontier orbital Theory of Fukui[47], using as frontier orbitals the LUMO of the substrate and the HOMO of the nucleophile, it was calculated[48,49] that in both compounds C(2) and C(6) have about equal reactivity - but lower than C(4)! - and that in the N-ylid (77) the reactivity at C(2) is greater than at C(2) in 46c. Therefore we postulate that the formation of the pyrazole 81 starts by an addition of ammonia at C(2) in the N-ylide 77 (Scheme 9). The formation of the dimer 78 proves that in liquid ammonia the deprotonation of 46c into the ylide 77 can indeed takes place. Since N-ylides are isoelectronic with N-oxides it can be expected that the pyrimidine N-oxides will also show reactions in which addition at C(2) is the introductory step. In the following section C.1.2. it will be shown that the conversion of the 4-substituted pyrimidine 1-oxides (86) into the 5-aminoisoxazole (87) by a reaction with liquid ammonia indeed starts by the initial addition of the ammonia at C(2).



10c



46c



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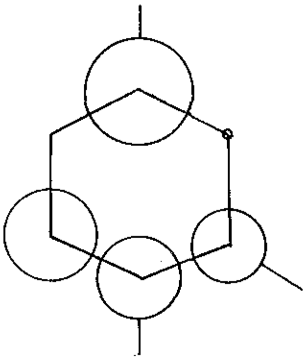
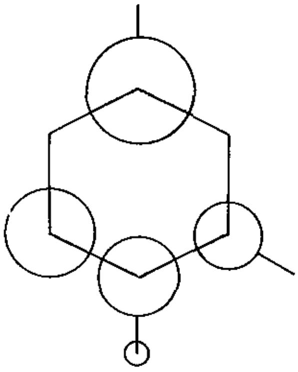
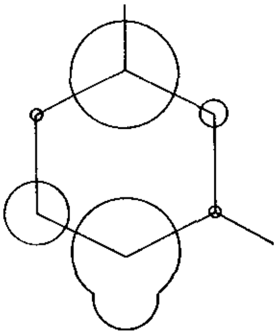
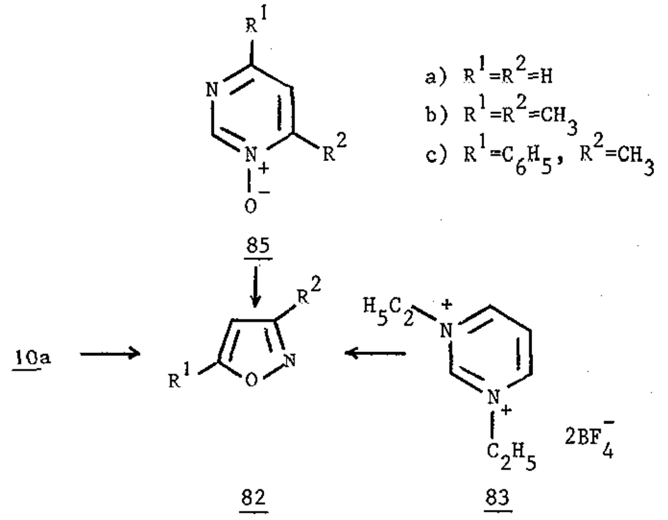




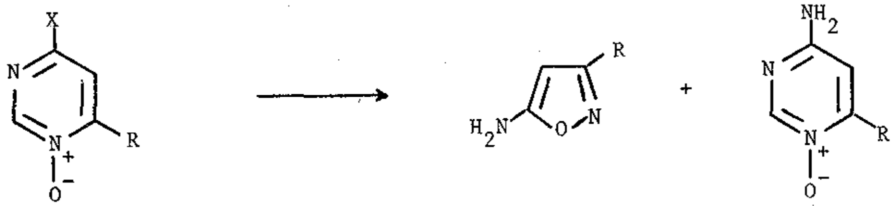


Section C.1.2 Formation of Isoxazoles

The fact that quaternary pyrimidinium salts are able to undergo a smooth ring contraction into pyrazoles in reactions with hydrazine has induced a study on the ring contraction into isoxazoles by hydroxylamine. When 1-methylpyrimidinium methylsulfate (10a, $X^- = CH_3OSO_3^-$) or 1,3-diethylpyrimidinium tetrafluoroborate (83) is reacted with hydroxylamine hydrochloride at room temperature for 1 h in a 55-65% yield isoxazole (82, $R^1=R^2=H$) is formed[50]. The malonic dialdoxime (84) is side-product and was found to be an intermediate in the formation of isoxazole. Quite similarly pyrimidine N-oxide (85a), 4,6-dimethylpyrimidine N-oxide (85b) and 6-methyl-4-phenylpyrimidine 1-oxide (85c) can also undergo ring contraction with hydroxylamine hydrochloride, yielding the isoxazoles (82a-c) respectively[50]. The ring contraction of the pyrimidine N-oxides 85 into the isoxazoles 82 raises the interesting question whether the N-O moiety in the isoxazole originates from the hydroxylamine or from the N^+-O^- function. In order to



solve this problem 4,6-dimethyl$\left[1(3)\text{-}^{15}N\right]$pyrimidine N-oxide was synthesized and the presence of ^{15}N in the resultant isoxazole was investigated. We observed that the ratio of the M/M + 1 peak (determined by mass spectrometry) in the 4,6-dimethylpyrimidine N-oxide was 100:8.0, in the isoxazole formed 100:0.6[50]. It unequivocally leads to the conclusion that in the formation of the isoxazole ring the hydroxylamine and not the $N^+\text{-}O^-$ function provides the N-O fragment in the isoxazole. These results clearly indicate that the mechanism of the ring contraction of the N-oxides into the isoxazoles is essentially the same as given in schemes 7 and 8 for the formation of pyrazoles from the N-methylpyrimidinium salts by hydrazine. An unexpected ring contraction with pyrimidine N-oxides was found when the 4-X-6-R-pyrimidine 1-oxides (86) were treated with potassium amide in liquid ammonia at -75° or in boiling liquid ammonia at -33°. Besides amination into the corresponding 4-amino-6-R-pyrimidine N-oxide (88) the 3-R-5-aminoisoxazole (87) was formed.[51,53]. The ratio 87/88 is strongly dependent on the leaving group R (see Table V). It was the first example of a base-catalysed ring contraction of a pyrimidine N-oxide into an isoxazole. The data in Table V show that the 4-phenoxy compounds 86c and



86

a) X=Cl, $R=CH_3$
b) X=J, $R=CH_3$
c) $X=OC_6H_5$, $R=CH_3$
d) $X=SC_6H_5$, $R=CH_3$
e) $X=N^{\oplus}(CH_3)_3$, $R=CH_3$
f) X=Cl, $R=C_6H_5$
g) X=Br, $R=C_6H_5$
h) X=J, $R=C_6H_5$
i) $X=OC_6H_5$, $R=C_6H_5$

87

a) $R=CH_3$
b) $R=C_6H_5$

88

a) $R=CH_3$
b) $R=C_6H_5$

Table V

Reaction conditions and yields of the products obtained on conversion of 4-X-6-R-pyrimidine 1-oxides with liquid ammonia and - in parentheses - with potassium amide in liquid ammonia

Substrate 86	Reaction time (min)	Reaction temp. (0^{o}C)	Yields of the products (%)	
			87	88
a	120(1)	-33(-75)	a: 23(62)	a: 52(12)
b	240(3)	-33(-75)	a: 33(15-20)	a: 51(5-10)
c	1200(210)	-33(-33)	a: np(50-55)	a: np(np)
d	[*] (210)	-33(-33)	a: np(50-55)	a: np(np)
e	30([*])	-33(-75)	a: np(np)	a: 23(np)
f	120(5)	-33(-75)	b: 25(12)	b: 65[**](30)[+]
g	120(3)	-33(-75)	b: 30-35(13)	b: 60[**](26)[+]
h	60(3)	-33(-75)	b: 35-40(12-15)	b: 55[**](17)[+]
i	[*] (210)	-33(-33)	b: np(60)	b: np(np)

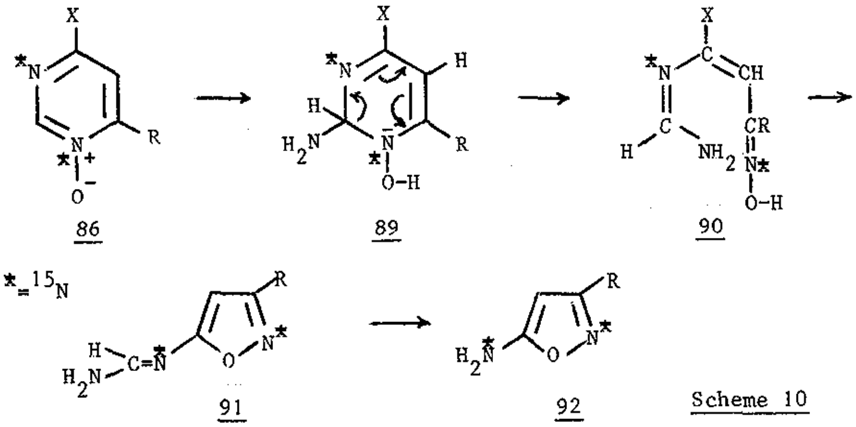
np Not present.

[*] Reaction has not been carried out.

[**] In addition, 5% of 4-amino-6-phenylpyrimidine was present.

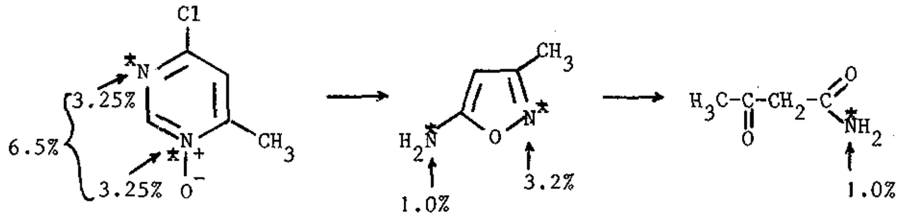
[+] In addition, 20% of 4-amino-6-phenylpyrimidine was present.

86i and the 4-(phenylthio) compound 86d do not undergo amination to the corresponding 4-aminopyrimidine 1-oxides, but only give ring contraction into the 5-aminoisoxazole 87. The ring contraction was originally proposed to occur by the initial addition of the ammonia (or amide ion) to position 2[51]. After ring opening of 89 into the oximinoalkenylformamidine (90) ring closure occurs into the *N-5-(isoxazolyl)formamidine* (91). Aminolysis of the formamidine group gives the amino group at C(5) (scheme 10).



Scheme 10

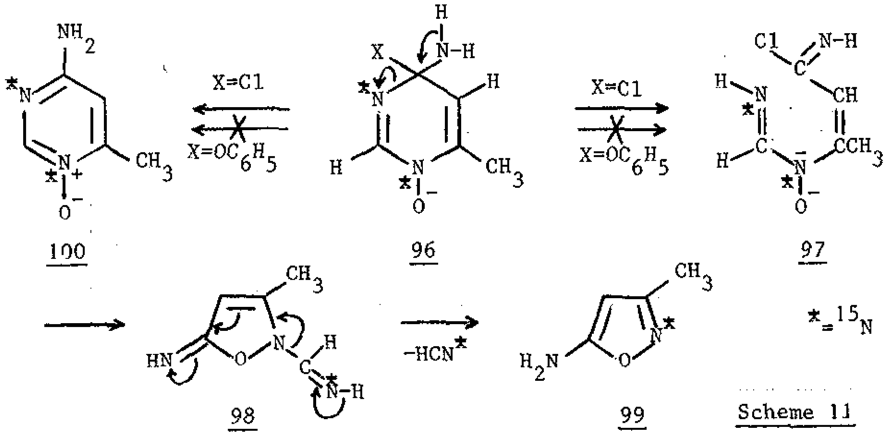
In order to establish more firmly this hypothetical mechanism, experiments were carried out with 4-chloro-6-methyl[1(3)-^{15}N]pyrimidine 1-oxide (93)[52]. From scheme 10 it is evident that if one starts with a 1(3)-^{15}N-labelled pyrimidine 93 the aminoisoxazole 92 must have the same excess of ^{15}N as present in the starting material and the ^{15}N label must be distributed equally over the ring nitrogen and the amino group. It was observed however that starting with 93 containing 6.5% of excess of ^{15}N, the excess of ^{15}N in the aminomethylisoxazole formed i.e. 94, is considerably lower (4.2%).



93 94 95

The distribution of the ^{15}N-label over the N atom in the ring and in the amino group was established by measuring the M + 1/M ratio in the 3-oxobutyramide (95) which was obtained on treatment of 94 with Raney Nickel and hydrogen, and hydrolysis of the intermediary 3-iminobutyramide. It was found to contain 1% of excess of ^{15}N. The ring nitrogen in 94 contains thus 3.2% of excess of ^{15}N. The fact that the ring nitrogen of 94 has exactly half of the original amount of ^{15}N present in 93 unequivocally proves that the decrease of excess of ^{15}N observed in the conversion of 93 → 94 must take place in the formation of the amino group[52,53].

The decrease of the ^{15}N-enrichment in the conversion of 93 → 94 has been proved not to take place by a ^{15}N-exchange in the amino group of 5-amino-3-methylisoxazole by the nitrogen of liquid ammonia. Therefore it is assumed that the ring contraction must occur by a second mechanism different from that given in scheme 10. It is given in scheme 11. In this mechanism the resonance-stabilized Meisenheimer-type anionic intermediate 96 (X=Cl) plays an important role. Opening of the ring of this σ-anionic adduct by C(4)-N(3) fission yields the open-chain intermediate 97. Ring closure into the 2-formimidoyl-5-imino-3-methyl-3-isoxazoline (98) followed by aromatisation through loss of HCN yields 99. It is evident that this pathway leads to a compound in which the N(3) atom of the pyrimidine ring is not incorporated in the amino group of the isoxazole. We suggest that the two pathways given in the schemes 10 and 11 both occur and therefore explain a lowering of the ^{15}N label during the conversion of 93 → 94.

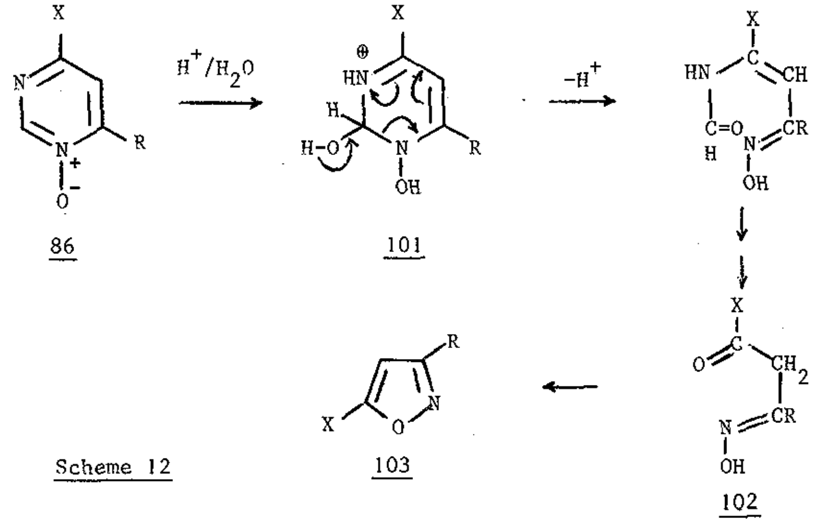


Scheme 11

It could be proved that the 4-amino-6-methylpyrimidine 1-oxide (88, R=CH_3) is formed by an $S_N(AE)$ process - and thus not by a process involving ring opening - since all ^{15}N is still present in the pyrimidine ring (see 100). This may indicate that 96 is also intermediate in the formation of 100. It strongly suggests that the ring contraction of 4-phenoxypyrimidine 1-oxide (86c) which - as we have seen - does not give a 4-aminopyrimidine 1-oxide, must completely take place by an initial addition at position 2 and thus follow the reaction pathway given in scheme 10. This has indeed been found: reaction of 6-methyl-4-phenoxy-$\left[1(3)\text{-}^{15}N\right]$-pyrimidine 1-oxide (86, X=OC_6H_5, R=CH_3; 8.1% ^{15}N) led to the isoxazole (92, R=CH_3) with nearly the same amount of ^{15}N (8.0%) as present in 86[52,53].

An acid-catalysed hydrolytic ring contraction of the 4-X-6-R-pyrimidine 1-oxide (86, X=C_6H_5, R=H; X=C_6H_5, R=CH_3; X=R=CH_3) into the corresponding 3-X-5-

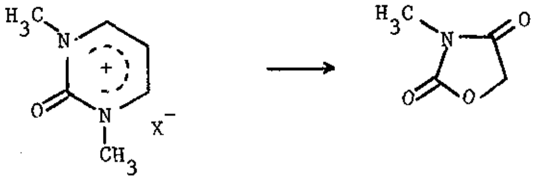
R-isoxazole (103) is reported[54]. The reaction is described by an attack of water on the 2-position of the conjugate acid of the N-oxide i.e. 101. According to this mechanism (see Scheme 12) the N^+-O^- function of the pyrimidine N-oxide forms the N-O moiety of the isoxazole. The ring closure of one of the intermediates i.e. 102 is reported[55] to occur easily in case of $X=C_6H_5$, R=H.



Scheme 12

Section C.1.3 Formation of Oxazolidines

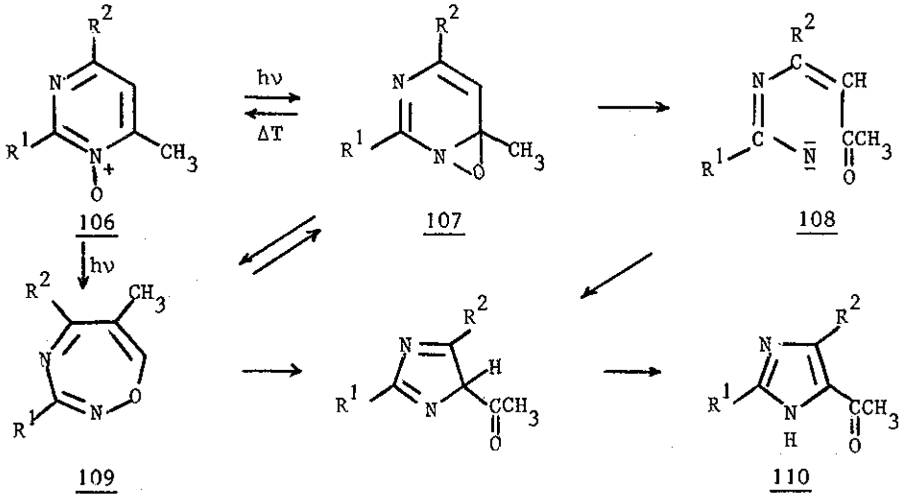
There is a single report[56] that oxidation of the 1,3-dimethyl-2-oxopyrimidinium bisulphate (104, $X^-=HSO_4^-$) with hydrogen peroxide in acetic acid at 60-65° for 2 h does not give the expected 1,3-dimethyluracil but instead 3-methyloxazolidine-2,4-dione (105). This compound is not formed from 1,3-dimethyluracil or another potential oxidation intermediate such as 1,3-dimethylbarbituric acid. The mechanism is mentioned to be "obscure"; it certainly involves pseudo-base formation as the initial step. It is recently found[57], however, that by oxidation - under the same conditions - of the iodide salt 104 ($X^- = I^-$) instead of the bisulfate salt 104 ($X = HSO_4^-$), 5-iodo-1,3-dimethyluracil was easily obtained.



104 105

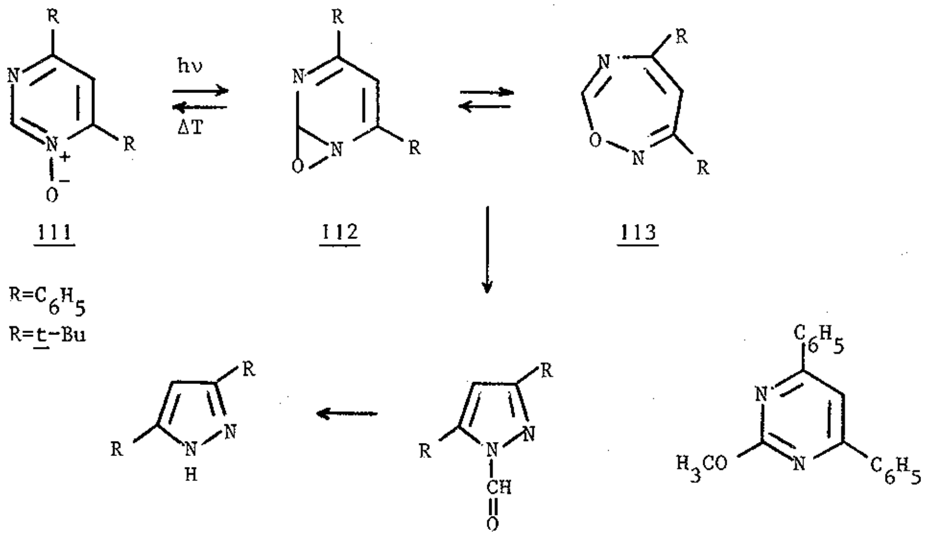
Section C.2 Ring Contraction of Pyrimidine N-oxides under Influence of Light

2-R^1-4-R^2-6-methylpyrimidine 1-oxides (106) were found to rearrange by irradiation with an Hanau TQ 150 high-pressure mercury arc through a quartz filter into 2-R^1-4(5)-acetyl-5(4)-R^2-imidazole (110), 1,6-dihydro-6-oxopyrimidine derivatives and some unidentified material[58,59]. The formation of 110 occurred in a reasonable yield and is of synthetic value. In contrast, irradiation of 2-mono substituted pyrimidine N-oxides did not lead - in general - to ring contracted products but gave in almost all cases enaminonitriles[60,61]. A mechanistic rationale to account for the formation of the imidazole (110) is an initial electrocyclisation of the oxygen atom to C(6), leading to the *1aH-oxaziridino*[2,3-*c*]pyrimidine intermediate (107). A subsequent rearrangement of 107 by possibly different pathways - such as valence-tautomerisation into the 1,3,4-oxadiazepine (109) or via the nitrene (108) - yields (110). Application of conventional flash-spectroscopic technique with the aim of getting some information about the intermediary formation of an oxaziridine gave - unfortunately - inconclusive results.



a) R^1=H, R^2=CH_3; b) R^1=H, R^2=C_6H_5 c) R^1=R^2=CH_3 d) R^1=CH_3, R^2=Cl e) R^1=CH_3, R^2=OCH_3

No evidence was found for the formation of an oxaziridinopyrimidine initiated by an electrocyclisation of the oxygen to C(2) of the pyrimidine ring in 106. This regiospecificity to C(6) is in good agreement with the results of PPP-SCF calculations[62], but contradicts those based on the LCAO-MO theory predicting a preferential addition at C(2)[60]. A study of the photochemistry of 4,6-disubstituted pyrimidine N-oxides (111) in which the 4- and 6-substituents are bulky (C_6H_5 or t-C_4H_9) indicates that steric interference at these positions directs the electrocyclisation to the unsubstituted position 2[63]. Photolysis of a methanolic solution of 111a yielded a reaction mixture from which the two main products i.e. 3,5-diphenylpyrazole (115, R=C_6H_5) and 4,6-diphenyl-2-methoxypyrimidine (116) could be isolated. This first example of a photochemically induced ring contraction of a pyrimidine N-oxide into a pyrazole must be explained by an initial electrocyclisation at C(2) yielding 112. This undergoes a ring expansion to a 1,2,6-oxadiazepine 113, which by a 1,5-sigmatropic shift gives the N-formylpyrazole (114). Photodeformylation yields 115.



111 112 113

a) R=C_6H_5
b) R=t-Bu

115 114 116

A very recent focal point of attention in the photochemistry of heteroaromatic N-oxides is the uncertainty about the structure of the primary intermediate formed. Whereas in the photoreactions mentioned in this section the initial step was assumed to be electrocyclisation to C(6) or C(2), it has been proved - using nano second flash photolysis - that in the photoirradiation of 3,6-diphenylpyridazine N-oxide[64a] and isoquinoline N-oxides[64b] not an oxaziridine is intermediate, but a compound which is formed immediately from the excited N-oxide by vibrational relaxation[64,65]. The hypersurface is then such that it bypasses the geometry corresponding to oxaziridines.

The formation of the 2-methoxy compound 116 in the photoreaction of 111a however, can be considered as a good indication for the intermediary existence of the oxaziridine 112, being "trapped" by the solvent methanol[66,67]. Furthermore, irradiation of 111a in the presence of a seven-fold molar amount of potassium iodide in water produced iodine. Since 4,6-diphenylpyrimidine N-oxide shows no oxidising properties towards iodide ion in the dark, and oxaziridines are known to be strong oxidising agents[68] which are capable of liberating iodine from potassium iodide, this experiment strongly supports the presence of an oxaziridine as intermediate. Since no deoxygenation was observed, the oxaziridine intermediate must be the oxidising species and not atomic oxygen. Identical experiments were performed with the N-oxides 106c and 106d. In both experiments a twelve-fold molar mount of potassium iodide was needed to liberate iodine. It has also been found that irradiation of 3,6-diphenylpyridazine N-oxide in the presence of a fifty-molar amount of potassium iodide in water did not produce iodine, indicating the absence of an oxaziridine and being in agreement with the nano second flash photolysis experiments[64]. From these results it is concluded that the photochemical behaviour of heteroaromatic N-oxides is not uniform. In some cases the first step is oxaziridine formation; in others the products are formed directly from the excited state of the N-oxide[69,70].

In agreement with the foregoing results, pyrazole formation was also observed during the light-induced conversion of 4,6-di-t-butylpyrimidine N-oxide (111b) in methanol with light of wavelength 254 nm[63]. Besides the pyrazole (115b) (23%) 4,6-di-t-butylpyrimidin-2-one (10%) was also isolated. No indication of the formation of 2-methoxy-4,6-di-t-butylpyrimidine was obtained.

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