Photochemistry of pyrimidine N-oxides and N-benzoyliminopyrimidines, and thermal reactions of N-aminopyrimidines with nitrogen-containing nucleophiles

Dit proefschrift met stellingen van Ferdinand Roeterdink,
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in de organische chemie.

De rector magnificus van de Landbouwhogeschool,
J.P.H.van der Want

Wageningen, 13 januari 1977

F.Roeterdink

Photochemistry of pyrimidine N-oxides and N-benzoyliminopyrimidines, and thermal reactions of N-aminopyrimidines with nitrogen-containing nucleophiles

Proefschrift
ter verkrijging van de graad van
doctor in de landbouwwetenschappen,
op gezag van de rector magnificus,
dr.ir.J.P.H.van der Want, hoogleraar in de virologie,
in het openbaar te verdedigen
op woensdag 13 april 1977 des namiddags te vier uur
in de aula van de Landbouwhogeschool te Wageningen

ISN = 104477-03

Dit onderzoek werd mogelijk gemaakt door financiële steun van de Nederlandse Organisatie voor Zuiver Wetenschappelijk Onderzoek (Z.W.O.) via de Stichting Scheikundig Onderzoek Nederland (S.O.N.).

NN8201 681

Stellingen

1. De veronderstelling van Buchardt et al.dat bij alle fotochemische reacties van heteroaromatische N-oxyden geen oxaziridine als intermediair optreedt is voorbarig.
   K.B.Tomer, N.Harrit, I.Rosenthal, O.Buchardt, P.L.Kumler and D.Creed, J.Amer.Chem.Soc. 95, 7402 (1973).
   Dit proefschrift.

2. Bij de fotochemie van monogesubstitueerde pyrimidine N-oxyden is de door Streith, Leibovici en Martz berekende voorkeur voor electrocyclisatie van zuurstof naar koolstofatoom 2 niet in overeenstemming met hun experimentele resultaten.
   J.Streith, C.Leibovici and P.Martz, Bull.Soc.Chim. 1971, 4152.

3. Het door Roberts, Stewart en Caserio gegeven mechanisme voor de Curtius omlegging is onjuist.
   J.D.Roberts, R.Stewart and M.C.Caserio, Organic Chemistry, Methane to Macromolecules, W.A.Benjamin, Inc. 1976, p. 430.
   W.Lwowski, Angew.Chemie 79, 922 (1967).

4. Glover en Rowbottom menen ten onrechte dat het reagens O-mesityleensulfonylhydroxylamine (MSH) minder geschikt is dan het O-p-tolueensulfonylhydroxylamine (TSH) vanwege de relatief hoge prijs.
   E.E.Glover and K.T.Rowbottom, J.Chem.Soc.Perkin I, 1976, 367.

5. Het lage percentage waarin het S_N ANRORS-mechanisme voorkomt bij de reactie van 4,5-dihalogeen-2,6-difenylpyrimidine met kaliumamide in vloeibare ammoniak kan op een andere manier verklaard worden dan voorgesteld wordt door De Valk et al.
   J.de Valk, H.C.van der Plas and J.W.A.de Bode, Rec.Trav.Chim.(Pays-Bas) 92, 442 (1973).

6. De door Mizuyama et al. geformuleerde mechanismen ter verklaring van de reactie van 3-ethoxycarbonyl-2-methylthiazolo[2,3-a] isochinolinium sulfaat met diverse nucleofielen zijn aan bedenkingen onderhevig.
K.Mizuyama, Y.Matsuo, Y.Tominaga, Y.Matsuda and G.Kobayaski,
Chem.Pharm.Bull. 24, 1299 (1976).

7. Bij het zoeken naar mogelijkheden ter ontbittering van citrussappen dient meer aandacht besteed te worden aan de bitterheid van limonine.

8. Tegen de analyse van de experimentele resultaten, die Nitsch et al. tot de bevestiging van de penetratietheorie en de verwerping van de tweefilmtheorie doet besluiten,zijn ernstige bezwaren aan te voeren.
W.Nitsch, M.Raab and R.Wiedholz, Chemie-Ing.Techn. 45, 1026 (1973).

9. Het vestigen van een record in het aantal partijen simultaan schaken is zinloos, indien er geen bepaling over de speelsterkte van de tegenstanders is vastgelegd.

F.Roeterdink
Photochemistry of pyrimidine N-oxides and N-benzoyliminopyrimidines, and thermal reactions of N-aminopyrimidines with nitrogen-containing nucleophiles

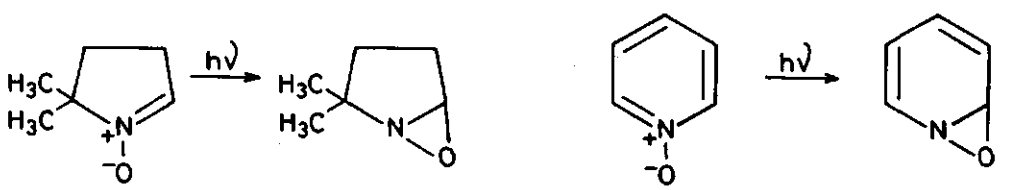
Aan mijn ouders

Aan Nita en Bennie

Contents

Introduction

During the last twenty years a growing interest in the photochemistry of heteroaromatic N-oxides[1] has developed. These compounds can formally be regarded as cyclic nitrones (1) in which the nitrone function is incorporated into an aromatic system. The relationship between nitrones (1) and heteroaromatic N-oxides is reflected in the photochemical behaviour of these systems, since on irradiation they both give oxaziridines. The oxaziridines formed from the cyclic nitrones are stable and can be isolated[2], those obtained from the heteroaromatic N-oxides however are only postulated as transient intermediates in the photoreaction.



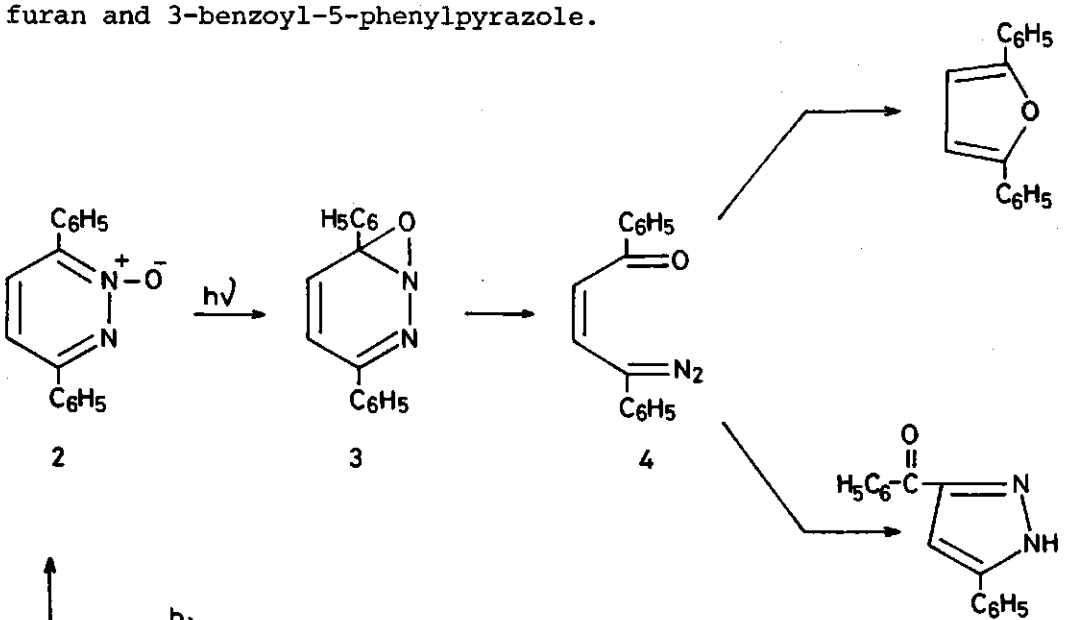
1 isolated not isolated

Despite the many efforts no one has ever succeeded in isolating these bicyclic intermediates derived from aromatic N-oxides. The reasons for this failure can be explained in several ways.

a) The oxaziridines are thermally too unstable to be isolated.
   The oxaziridine is photochemically stable when light is employed of sufficient energy to excite the aromatic N-oxide, but insufficient to excite the oxaziridine system.
b) Oxaziridines, if formed, break down photochemically with a quantum yield equal to or greater than that for their formation.
c) Transition states or species with a very short lifetime, having an excited atomic arrangement corresponding to oxaziridines may be on the reaction pathway to product formation.
d) Oxaziridines are not formed at all as intermediates, and an entirely different mechanism is operating.

Very recently in two reports the occurrence of an oxaziridine as intermediate in the photochemistry of heteroaromatic N-oxides was questioned. Studying the primary photoprocesses in isoquinoline N-oxides by laser flash photolysis technique Lohse[3] found that the isocarbostyril was formed within 20 ns. The

singlet lifetime is ~ 1 ns and the conclusion seems justified that the small time interval left for the formation of an intermediate makes the intermediacy of an oxaziridine unlikely. Investigations of the photochemical behaviour of the pyridazine N-oxide (2) by Buchardt et al[4], using the same technique, showed that the transient diazo ketone (4) was formed directly from the excited state, thus without the intermediacy of a transient oxaziridine (3) as previously believed. The diazo ketone was further converted into 2,5-diphenylfuran and 3-benzoyl-5-phenylpyrazole.



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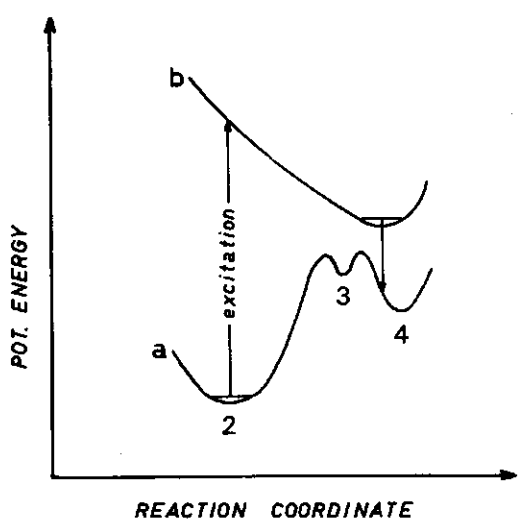


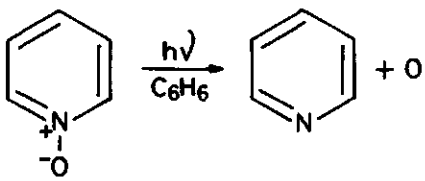
figure: Cross-section of (a) hypothetical hypersurface illustrating the thermal rearrangement of 2, via 3 to 4 and (b) excited state leading to reaction

The results of these experiments gave Buchardt et al cause for the challenging statement that product formation in the photo-irradiation of all heteroaromatic N-oxides would not occur via an oxaziridine as intermediate.

Since the mechanistic pathways in the photochemical reaction of heteroaromatic N-oxides are not completely clear at the moment it is more useful to discuss the kind of products formed in the primary photoreaction rather than the mechanism of their formation. In the following sections we refer mainly to photochemical investigations carried out with pyridine- and quinoline N-oxides, since these systems are studied in more detail. The following reactions are found to take place.

1.1 Formation of parent heterocycles

In nearly all the photoreactions of heteroaromatic N-oxides deoxygenation occurs . Only in di- and trisubstituted pyrimidine N-oxides no deoxygenation could be detected[6,7]. It is suggested that the oxygen that is liberated from the N-oxide(5)is atomic in nature and capable of oxidising the solvent. In case of (m)ethanol the corresponding aldehyde is yielded[5], while in benzene phenol (9) is obtained. The latter compound is formed by a rearrangement of the oxepine (7) and the benzene oxide (8).



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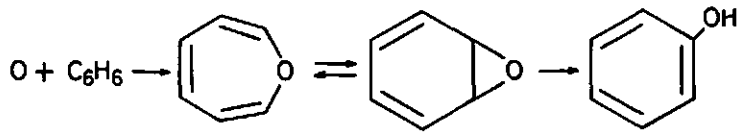


7 8 9

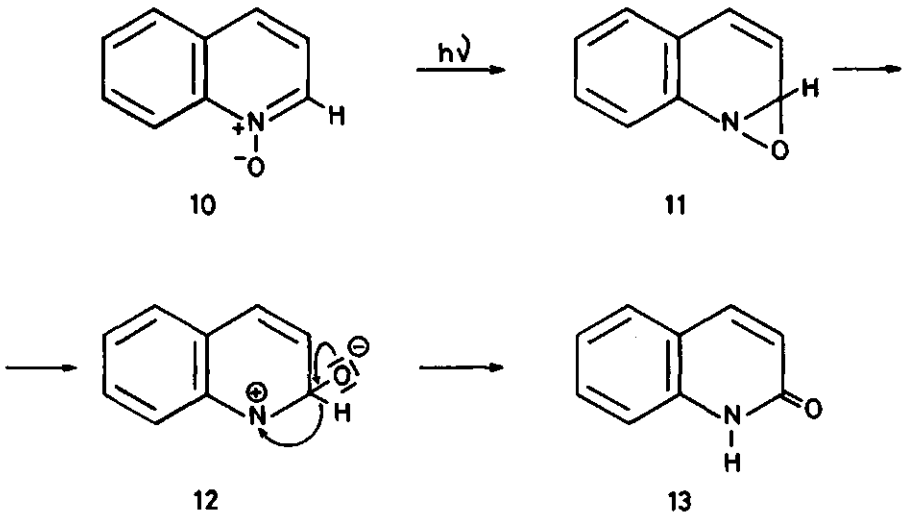
The literature on the excited states of aromatic N-oxides was rather confusing. The study of the oxygen effect on the photochemical deoxygenation of quinoline, isoquinoline and phthalazine N-oxides leads to the conclusion that the excited singlet state is responsible for this process. On the contrary, addition of benzophenone to a solution of 2,4,6-triphenylpyridine N-oxide in ethanol increases deoxygenation. This result indicates that a triplet excited state is responsible for this reaction.

At the moment it is well established that the triplet state of isoquinoline N-oxides, pyridazine N-oxides and phthalazine N-oxides is responsible for oxygen abstraction, whereas the excited singlet state leads to isomerisations and rearrangements[1]. For pyrimidine N-oxides no results are available.

1.2 Lactam formation

This type of rearrangement is found to be especially favourable in polar solvents. The mechanism proposed for the lactam formation can in case of quinoline N-oxide be represented as follows, and involves as important intermediate the bipolar species (12).

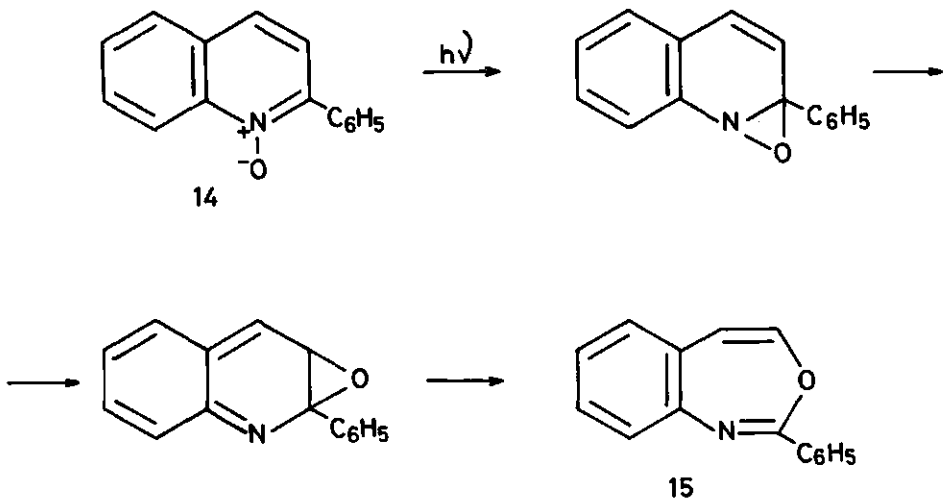
The intermediacy of (12) suggests that change of polarity of the solvent would influence the lactam formation. It was indeed found, that when (10) is irradiated in acetone instead of water, the formation of (12) would be less favourable, and thus lead to a decreased yield of (13)[8-11].



10 11 12 13

1.3 Ring expansion to seven-membered rings

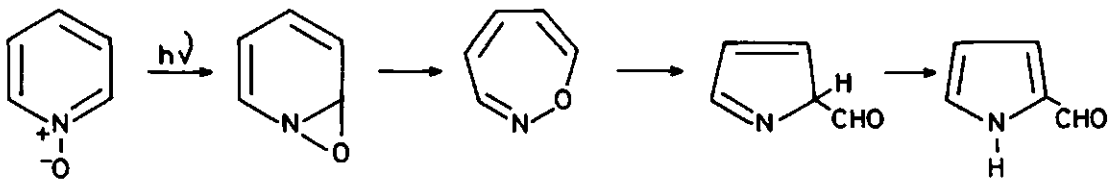
Ring expansion occurs generally when the N-oxide ring is fused with a benzene ring. Thus the 2-phenylquinoline N-oxide (14) gives the corresponding benz[d][1,3]oxazepine[12,13](15). These ring expansions are also observed with isoquinoline N-oxide[14,15], phenanthridine N-oxide[16,17], quinoxaline 1-oxide[13,18,19] and quinazoline 3-oxides[20]. Ring enlargement is also found in 2,4,6-triphenylpyridine N-oxide[21].



14 15

1.4 Ring contraction to five-membered rings

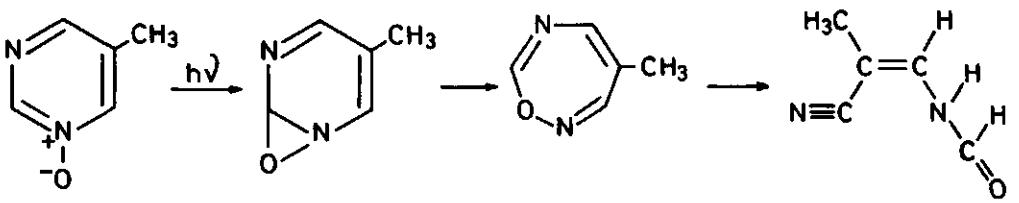
This reaction is exemplified with the conversion of pyridine N-oxide (16) into 2-formylpyrrole (20) and is thought to occur by an initial electrocyclisation into the oxaziridine (17), followed by a thermal valence tautomerism into the 1,2-oxazepine. By a thermally allowed 1,5-sigmatropic shift the 2-formylpyrrolenine (19) is yielded which undergoes prototropy into 2-formylpyrrole (20).



16 17 18 19 20

The 1,2-oxazepine (18) has never been isolated, but its existence has been proved in cases in which the N-oxide is fused with the benzene ring (see 1.3).

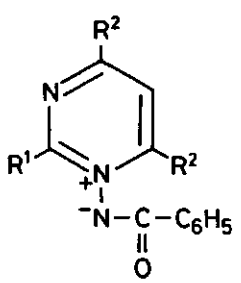
At the start of our investigations the photochemistry of pyrimidine N-oxides was a rather unexplored area. Only Streith et al[22] had studied the photochemical reactions of mono-substituted pyrimidine N-oxides, and from his results - formation of the N-formyl-eneaminonitrile (22) - he inferred a preferential electrocyclisation of oxygen to carbon atom 2, rather than to position C(6)[23].



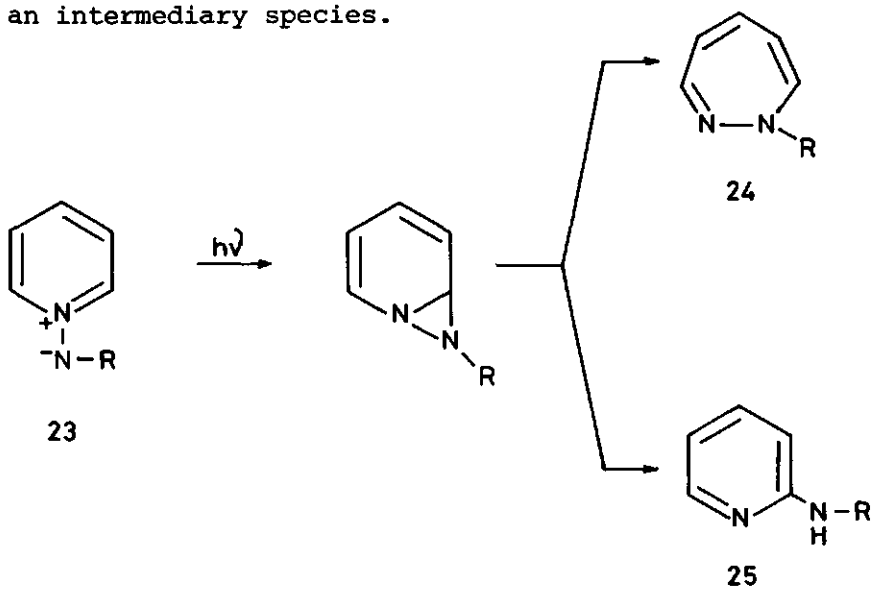
21 22

That the electrocyclisation to C(2) is indeed more favoured than electro - cyclisation to C(6) was supported by Hückel calculations. However, PPP-SCF calculations showed that the electrocyclisation has a preference for C(6)[24]. The first purpose of our work was to study which factors determine the mode of electrocyclisations in 4,6-di- and 2,4,6-trisubstituted pyrimidine N-oxides[6,7,25] and to obtain some evidence whether or not an oxaziridine is involved as transient species in the photoreactions of pyrimidine N-oxides.

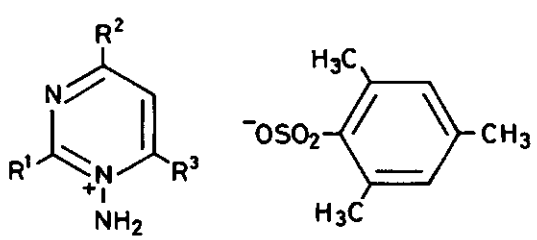
As extension of our work on pyrimidine N-oxides, we investigated N-imino derivatives of pyrimidines[26], a class of compounds which are isoelectronic with N-oxides.



The chemistry of those N-iminopyrimidines is scarcely developed - these compounds could only very recently be synthesized - in contrast to the photochemistry of N-iminopyridines (23)[27] on which some work has already been published. Ring enlargement into a 1,2-diazepine (24) and/or formation of a 2-aminopyridine (25) is observed[28-30]. It is generally accepted that a bicyclic diaziridine is an intermediary species.



Attempts to study the photochemistry of N-iminopyrimidines without a substituent on the exocyclic nitrogen - generated in situ from N-aminopyrimidinium salts by proton abstraction under influence of liquid ammonia - failed. Dark reactions occur readily and in the last part of our work the scope and limitation of these dark reactions have been studied[31].



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Photochemistry of pyrimidine *N*-oxides (IV)[1,2]

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(Received July 22nd, 1974)

Abstract. Photolysis of 2,4,6-trimethylpyrimidine 1-oxide in methanol with light of 254 nm leads to rearrangement into 4(5)-acetyl-2,5(4)-dimethylimidazole and 1,2,4-trimethyl-1,6-dihydro-6-oxopyrimidine. In benzene only the formation of the imidazole and an unknown compound X is observed. In both solvents the products are formed from the same primary photoproduct. Ring contraction into an imidazole also takes place on ultraviolet irradiation of 4-chloro-2,6-dimethylpyrimidine 1-oxide in benzene and of 2,6-dimethyl-4-methoxypyrimidine 1-oxide in methanol. Results of conventional flash photolysis applied with the aim of getting some information about the intermediary formation of oxaziridines are inconclusive. The role of possible intermediates – oxaziridines, 1,2,4-oxadiazepines or zwitter ionic species – in these rearrangement reactions is discussed.

Introduction

The photochemistry of azaaromatic *N*-oxides has been the subject of many investigations; the *N*-oxides derived from pyridine, quinoline, pyridazine, phthalazine and cinnolines especially are well studied[3]. The photochemistry of pyrimidine *N*-oxides is however much less investigated and only a few reports on the results of ultraviolet irradiations of some mono- and di-substituted pyrimidine *N*-oxides have appeared[4,5]. It was found that on irradiation of *mono*substituted pyrimidine *N*-oxides mainly open-chain products are obtained[5]. Their formation was explained by a process which involves in the excited pyrimidine *N*-oxide an electrocyclisation of the oxygen to the C(2)-atom, leading to an oxaziridinopyrimidine as intermediate. That the electrocyclisation to C(2) is indeed more favoured than cyclisation to C(6) was supported by Hückel calculations[5]. It was found in our laboratory that 4,6-*di*substituted pyrimidine *N*-oxides behave differently photochemically; they rearrange to products the formation of which involves an initial electrocyclisation of the oxygen to C(6).

Recently, arguments – based on results of conventional and nanosecond flash photolyses – have been advanced that oxaziridines are not formed as intermediates during the photolysis of isoquinoline *N*-oxides and pyridazine *N*-oxides[6,7]. The products obtained in these reactions are formed *directly* from the excited singlet state. It was suggested[7] that oxaziridines are not intermediates in the photochemistry of *all* heteroaromatic *N*-oxides. It seems to us that more experimental evidence is necessary to justify this daring suggestion, especially in cases in which monomolecular photochemical reactions are involved[8].

Since the difference in mode of electrocyclisation *i.e.* to C(2) or C(6) appears to depend on the substitution pattern in the pyrimidine *N*-oxide, it induced us to study in more detail the ultraviolet irradiation of some 4-substituted 2,6-dimethylpyrimidine 1-oxides (**1**). In those *tri*-substituted compounds the same substituent is present in positions adjacent to the *N*-oxide function so that the influence of the substituent on oxaziridino formation is in first instance the same.

Results and discussion

Photolysis of a $\sim 1.3 \times 10^{-2} M$ methanolic solution of 2,4,6-trimethylpyrimidine *N*-oxide (**1**, R=CH_3) with ultraviolet light of 254 nm until no starting material is present (21 h) yields a complex mixture of compounds. Separation on silica gel column gave compounds A and B as the two major products. The PMR spectrum of product A shows three singlets at δ = 2.45 ppm, δ = 2.56 ppm and δ = 2.58 ppm and a broad absorption peak at δ = 11.1 ppm. The IR spectrum shows *inter alia* an absorption frequency at 3425 cm^{-1}, due to the presence of a N–H group and a stretching vibration frequency at 1650 cm^{-1}, ascribed to a conjugated carbonyl group. The mass spectrum has among others, peaks at *m/e* = 138 (M^+), 123 ($M^+ - CH_3$) and 95 ($M^+ - COCH_3$). Based on all these data, the structure of the so far unknown 4(5)-acetyl-2,5(4)-dimethylimidazole (**5**, R=CH_3) was assigned to product A. The spectroscopic data of product B are in agreement with the structure 1,6-dihydro-1,2,4-trimethyl-6-oxopyrimidine (**8**, R=CH_3). The structure of this cyclic lactam was confirmed by comparison with an authentic specimen[9]. Deoxygenation – a general process in the photochemistry of heteroaromatic *N*-oxides – does not take place since 2,4,6-trimethylpyrimidine could not be detected in the reaction mixture.

Table 1 Reaction conditions of the photolysis of 4-R-2,6-dimethylpyrimidine 1-oxides (**1**) *and yield of products obtained.*

Starting substance **1**	Solvent	Reaction	Yields of products	
			5	**8**
R=CH_3	CH_3OH	21 h	15%	*
R=CH_3	C_6H_6	21 h	53%	*
R=OCH_3	CH_3OH	8 h	53%	*
R=Cl	C_6H_6	9,5 h	56%	trace**

* The yield is strongly dependent on the work-up procedure (see discussion) and varies between 5–15%.

** Observed in PMR spectrum of the crude reaction mixture obtained after irradiation.

Ring contraction into imidazoles has also been observed during the light-induced conversion of 4-chloro-2,6-dimethylpyrimidine 1-oxide (**1**, R=Cl) in benzene and of 2,6-dimethyl-4-methoxypyrimidine 1-oxide (**1**, R=OCH_3) in

[1] Part XLIX from this laboratory on pyrimidines. See for part XLVIII *R. Peereboom* and *H. C. van der Plas*, Rec. Trav. Chim. Pays-Bas **93**, 284 (1974).

[2] Part IV from this laboratory on photoreactions of diazines. See for part III: *D. A. de Bie, H. C. van der Plas* and *G. Geurtsen*, J. Chem. Soc. Perkin Transact. I, **1974**, 1363.

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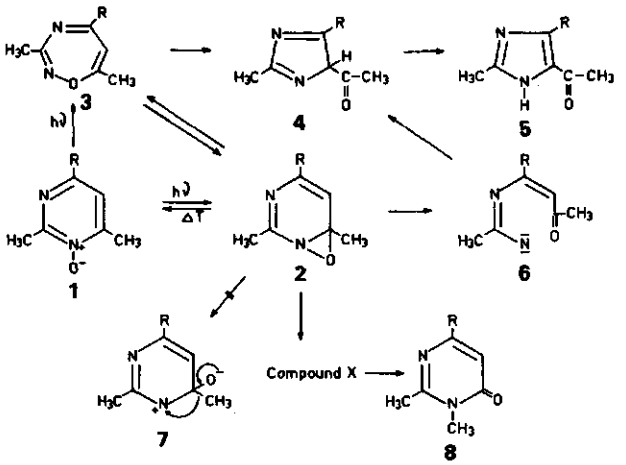
[9] *J. Maillard, R. Morin, M. Vincent* and *M. Bernard*, C.A. **58**, 1474 (1963).

methanol, 4(5)-acetyl-5(4)-chloro-2-methylimidazole (**5**, R=Cl) and 4(5)-acetyl-5(4)-methoxy-2-methylimidazole (**5**, R=OCH_3) being obtained. The structure assignments of these imidazoles were based on PMR data (see Table II in experimental part) and IR data and confirmed by conversion of **5** (R=Cl) into **5** (R=OCH_3) on treatment with methanol.



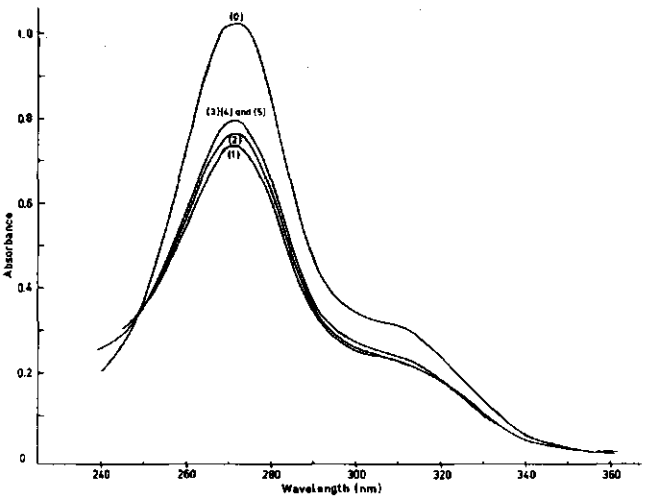
Scheme I

A mechanistic rationale to account for the formation of the rearranged products **5** and **8** is an electrocyclisation of the oxygen atom to C(6), leading to the oxaziridinopyrimidine (**2**, R=CH_3) which rearranges by different pathways into products **5** (R=CH_3) and **8** (R=CH_3). Whether these photochemical rearrangements indeed involve an oxaziridine as intermediate or occur *via* another intermediate, which is immediately formed from the excited pyrimidine *N*-oxide by vibrational relaxation – the hypersurface is then such that it bypasses the geometry corresponding to oxaziridines[11] – cannot be concluded from this work. To postulate the 1,2,4-oxadiazepine **3** or the nitrene **6** as intermediates is in accordance with results which have been obtained with other heteroaromatic *N*-oxides[3].

In order to get more information about possible intermediates we studied the photolysis of the *N*-oxides **1** by UV spectroscopy and by conventional flash spectroscopy.

Irradiation of a $10^{-4}M$ ethanolic solution of **1** (R=Cl) in a quartz cuvet at room temperature for 15 s with a high pressure mercury arc lamp (Hanau TQ 150) shows a decrease in the UV absorbance of the solution. The interesting observation was made, that after storing the irradiated solution in the dark for 1 and 2 min, the absorption of the *N*-oxide gradually increased (see Graph 1). After 3 or 4 min no increase in the absorption was observed. Irradiation of the solution at 0°C for 15 s also causes a diminution of the concentration of the *N*-oxide; however, the UV spectrum was *not* changed after storage in the dark for 2 min at 0°C. Similar observations were also made with **1** (R=CH_3).

From these results we conclude that by irradiation an intermediate is formed which at room temperature can partly revert to the starting substance **1**[10]. Since many of our



Graph 1. The progressive spectral change of a $10^{-4}M$ ethanolic solution of 4-chloro-2,6-dimethylpyrimidine 1-oxide at room temperature. (0) not irradiated solution; (1) after 15 sec of irradiation; (2) after 1 min storing in the dark; (3) after 2 min storing in the dark; (4) after 3 min storing in the dark; (5) after 4 min storing in the dark.

attempts to isolate this intermediate failed, we have no indication about its structure. Based on the results obtained thus far, the occurrence of an oxaziridino compound seems possible and cannot definitively be excluded.

On application of conventional flash-spectroscopic technique it was observed that when a degassed $10^{-4}M$ methanolic solution of **1** (R=Cl) was flashed at room temperature, no new absorption in the range of 240–650 nm could be detected 20 μ sec after flashing. Although it is known[12] that oxaziridines fused with saturated five-or six-membered heterocycles are not very unstable compounds and therefore the oxaziridines **2** can be expected to have some stability, we could not conclude from our observations whether an oxaziridine is present or not in the irradiated solution because strong absorbance of the *N*-oxide **1** (R=Cl, see Graph 1) completely masks that of the oxaziridine.

By analogy with what has been suggested in the literature for lactam formation from other heteroaromatic *N*-oxides[3], the zwitter-ionic species **7** can be proposed as intermediate in the formation of the cyclic lactam **8** (R=CH_3). The intermediacy of **7** suggests, however, that when the photoreaction is carried out in benzene instead of methanol, the formation of this zwitter-ion would be less favourable, and thus lead to a decreased yield of **8** (R=CH_3). In the crude reaction mixture, obtained on irradiation of **1** (R=CH_3) in benzene no trace of compound **8** (R=CH_3) could indeed be detected by PMR-spectroscopy. However, surprisingly, separation of the crude reaction mixture on a silica gel column yielded the pyrimidinone **8** (R=CH_3), clearly indicating that **8** (R=CH_3) is not a primary photoproduct but is probably formed by a thermal reaction on a precursor of **8** (R=CH_3). The structure of this precursor (compound X) has not yet been established in full detail. The PMR spectrum of compound X shows a doublet structure at $\delta = 2.75$ (3H, $J = 6$ Hz) which collapses to a singlet on addition of D_2O. The IR spectrum of X shows an absorption at 3450 cm^{-1}, due to a secondary amino group. These data seem to indicate the presence of a NH–CH_3 moiety in compound X. A reinvestigation of the reaction mixture obtained on photolysis of 4,6-dimethylpyrimidine 1-oxide in methanol has shown a similar result. In the reaction mixture obtained, a compound is present the PMR spectrum of which also reveals the presence of a methylamino group. After work up 1,6-dihydro-1,4-dimethyl-6-oxopyrimidine is obtained. These results strongly indicate that the lactam formed during the photolysis of the substituted pyri-

[10] Analogous results are obtained recently by *S. Yamada, M. Ishikawa* and *C. Kaneko*, J. Chem. Soc., Chem. Comm. **1972**, 1093. They found that the photoproduct of 4-chloroacridine *N*-oxide rearranges to the starting substance on heating, probably *via* an oxaziridino compound as intermediate.

[11] *J. Michl*, Mol. Photochem. **4**, 243, 257, 287 (1972). See also ref. 7.

[12] *M. Lamchen* in Mechanism of Molecular Migrations, vol. 1, Editor *B. S. Thygarajan*, 1968, Interscience Publishers, Inc., New York. See also the literature references mentioned in this survey.

midine *N*-oxide (**1**, R=CH_3) is no primary photoproduct and does not involve a zwitter-ionic species as an intermediate precursor. This in contrast to what so far has been published in the literature on cyclic lactam formation[13].

Experimental part

Melting points are uncorrected. The PMR spectra were recorded on a Jeol JNM-C 60 spectrometer, using tetramethylsilane (TMS, $\delta = 0$) as an internal standard. The IR spectra were recorded on a Hitachi model EPI-G3. The mass spectra were recorded on an AEI MS-902 instrument.
For a description of the flash-photolysis apparatus see *G. P. de Gunst*, Thesis Leiden 1971.

General procedure of the photolysis

A solution of 1.0 g of the pyrimidine 1-oxide (**1**) in 500 ml of methanol or 500 ml of benzene was irradiated under N_2 using Rayonet RPR 2537 Å lamps. During the reaction the disappearance of **1** and the formation of the products were followed by TLC. After irradiation the solution was evaporated *in vacuo* and the residue was separated on a silica gel column using eluents of different polarity (ethyl acetate with increasing amounts of ethanol).

2,4,6-Trimethylpyrimidine 1-oxide (**1**, R=CH_3) was prepared according to the procedure given in the literature[14,15]. The imidazole **5** (R=CH_3) was obtained as an oil. TLC, using different eluents, showed up no impurity in this oil.

4-Chloro-2,6-dimethylpyrimidine 1-oxide was prepared as described in the literature[16]. Compound **5** (R=Cl) obtained after evaporation of the eluent showed two different m.p.'s 137–139°C and 173–176°C. Both forms have exactly the same PMR- and IR-spectra. Probably, this compound shows another interesting case of polymorphism, being also observed with some other imidazoles[17].
IR-spectrum in $CHCl_3$: 3400 cm^{-1} (NH), 1645 cm^{-1} (C=O).
Mass spectrum: *m/e* = 160 and 158 (M^+), 145 and 143 (M^+-CH_3), 117 and 115 (M^+-COCH_3).

2,6-Dimethyl-4-methoxypyrimidine 1-oxide was prepared as previously described[18]. Compound **5** (R=OCH_3) has m.p. 165–166°C (after sublimation).
IR spectrum in $CHCl_3$: 3450 cm^{-1} (NH) and 1650 cm^{-1} (C=O).
Mass spectrum: *m/e* = 154 (M^+), 139 (M^+-CH_3), 111 (M^+-COCH_3).

Table II Chemical shifts of the protons in the imidazoles **5**.

5 (R=CH_3)	δ = 2.45 ppm (s, 3H), δ = 2.56 ppm (s, 3H), δ = 2.58 ppm (s, 3H), δ = 11.1 ppm (broad H)
5 (R=OCH_3)	δ = 2.40 ppm (s, 6H), δ = 4.02 ppm (s, 3H), δ = 8.8 ppm (broad (1H))
5 (R=Cl)	δ = 2.50 ppm (s, 3H), δ = 2.63 ppm (s, 3H), δ = 9.7 ppm (broad (1H))

Acknowledgement

We are indebted to Dr. *G. P. de Gunst* of the Gorlaeus Laboratories of The University at Leiden for the flash photolysis experiments, to Dr. *P. Smit* and Mr. *A. van Veldhuizen* for measuring PMR and IR spectra, to Drs. *C. A. Landheer* and Mr. *W. P. Combé* for the mass spectroscopic data and to Mr. *A. Harder* for technical assistance in carrying out some experiments.
This investigation was carried out under the auspices of the Netherlands Foundation for Chemical Research (SON) and with financial aid from the Netherlands Organisation for the Advancement of Pure Research (ZWO).

[13] Very recently it has been proposed that also the formation of isocarbostyril during the photolysis of quinoline *N*-oxide in aqueous solution, does not proceed through an ionic intermediate. *J. Ono* and *N. Hata*, Bull. Chem. Soc. Japan **46**, 3658 (1973).
[14] *A. Bowman*, J. Chem. Soc. **1937**, 494.
[15] *R. H. Wiley, S. C. Slaymaker*, J. Amer. Chem. Soc. **79**, 2233 (1957).
[16] *T. Kato, H. Yamanaka* and *H. Hiramuna*, Chem. Pharm. Bull. of Japan **16**, 1337 (1968).
[17] *K. Hofmann*, Imidazole and its derivatives, part I, p. 27, 1953, Interscience Publishers, Inc., New York.
[18] *M. Yamazaki, N. Honjo, K. Noda, Y. Chino* and *M. Hamana*, Yakugaku Zasshi **86**, 749 (1966); C.A. **65**, 20095e (1966).

Photochemistry of 4,6-Disubstituted Pyrimidine *N*-Oxides [1]

By **Fred Roeterdink and Henk C. van der Plas,*** Laboratory of Organic Chemistry, Agricultural University Wageningen, The Netherlands

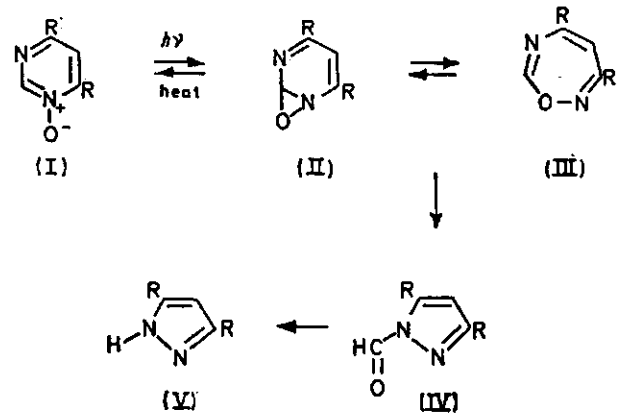
Photolysis of 4,6-di-R-pyrimidine 1-oxides (R = Ph or Bu^t) in methanol with a high-pressure mercury arc and a Rayonet RPR 2537 Å lamp, respectively, leads to 3,5-di-R-pyrazoles. In the case R = Ph, in addition to the pyrazole, 2-methoxy-4,6-diphenylpyrimidine is obtained. This compound is considered to be formed *via* an oxaziridine intermediate, the existence of which was indicated by the liberation of iodine from potassium iodide.

DI- AND TRI-SUBSTITUTED pyrimidine *N*-oxides have been shown to rearrange photochemically by a process probably involving an initial attack of the oxygen atom at C(6),[1a] resulting in a 1a*H*-oxaziridino[2,3-*a*]pyrimidine intermediate. No indication of attack of the oxygen at C(2) of the pyrimidine ring was observed. This regiospecificity is in good agreement with the results of PPP–SCF calculations,[2] but contradicts those based on LCAO–MO theory, predicting a preferential addition to C(2).[3] Although the products obtained on irradiation of monosubstituted pyrimidine *N*-oxides [3] seem to confirm the latter theory, a recent report reveals that in these compounds also there is a tendency for the oxygen atom to attack at C(6).[4]

Since in the reactions of the pyrimidine 1-oxides described so far the substituents at positions 2, 4, and 6 have been relatively small, we became interested in the behaviour of 4,6-disubstituted pyrimidine *N*-oxides in which the 4- and 6-substituents are bulky, hoping that steric interference at these positions would direct the cyclisation to the unsubstituted position 2. We therefore studied the photochemical behaviour of the 4,6-di-R-pyrimidine 1-oxides (I; R = Ph or Bu^t).

The photolysis of 4,6-diphenylpyrimidine 1-oxide in acetone is reported to yield a complex mixture from which no product was isolated.[5] In our hands photolysis of a methanolic 5×10^{-3}M-solution of 4,6-diphenylpyrimidine 1-oxide (I; R = Ph) with a high-pressure mercury arc (Hanau TQ 150) yielded a mixture from which, by t.l.c., two main products, *i.e.* 3,5-diphenylpyrazole (V; R = Ph) (11%) and 2-methoxy-4,6-diphenylpyrimidine (X) (6%) could be isolated. No indication of the formation of 4,6-diphenylpyrimidine was obtained. Both products were identified by comparison (^{1}H n.m.r., i.r., and mass spectra) with authentic compounds.

To our knowledge, this is the first example of a photochemically induced ring contraction of a pyrimidine *N*-oxide to a pyrazole. In this reaction the initia lattack of the oxygen must take place at C(2). Apparently attack at C(6) is strongly disfavoured owing to steric hindrance by the phenyl group.† Although the mechanism of this ring contraction is not completely elucidated, we suggest the following pathway: (*a*) cyclisation at C(2); (*b*) ring expansion to a 1,2,6-oxadiazepine (III); (*c*) ring contraction to a 3,5-disubstituted *N*-formylpyrazole (IV), which undergoes deformylation to (V).



SCHEME 1

An equilibrium between the oxaziridinopyrimidine (II) and the 1,2,6-oxadiazepine (III) has been proposed but never established; however, it shows a great similarity to the equilibrium between a 1,3-oxazepine and its oxanorcaradiene isomer, which was recently established [6] in the thermal rearrangement of 2-phenyl-1,3-oxazepine to *N*-formyl-2-phenylpyrrole. In order to investigate the feasibility of the photodeformylation (IV) ⟶ (V) (as recently observed during the photolysis of 6-methyl- and 6,9-dimethyl-purine 1-oxides [7]) attempts were made to prepare (IV) by a procedure analogous to that for the preparation of *N*-formylindole.[8] These attempts failed, however (see Experimental section). The possibility that (V) is formed from an intermediate 4,6-diphenyl-

† Ground-state addition of an amide ion to a pyrimidine ring usually takes place at position 4(6); in the case of 4,6-diphenylpyrimidine the addition of an amide ion has been found to occur at C(2) (J. P. Geerts and H. C. van der Plas, unpublished data).

[1] This paper is regarded as Part LII of the series 'Pyrimidines' and Part VI of 'Photoreactions of Diazines.' For Part LI(V) see (*a*) F. Roeterdink and H. C. van der Plas, Contributed Paper of the Euchem Research Conference: Useful Preparative Aspects of Photochemistry, Gent, 1975; for Part L see (*b*) J. P. Geerts, H. C. van der Plas, and A. van Veldhuizen, *Org. Magnetic Resonance*, 1975, **7**, 85.

[2] C. Kaneko, S. Yamada, H. Ischikawa, and T. Kubota, Abstracts, Third International Congress of Heterocyclic Chemistry, Japan, B, 1971, p. 215.

[3] J. Streith, C. Leibovici, and P. Martz, *Bull. Soc. chim. France*, 1971, 4152.

[4] F. Bellamy, P. Martz, and J. Streith, *Tetrahedron Letters*, 1974, 3189.

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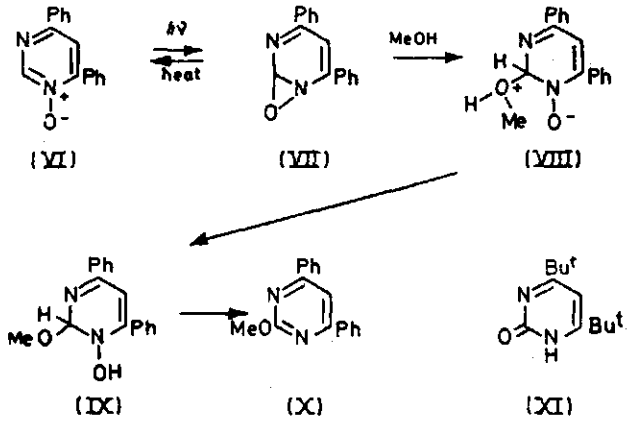
[6] T. Tezuka, O. Seshimoto, and T. Mukai, *Tetrahedron Letters*, 1975, 1067.

[7] F. C. Lam and J. C. Parham, *J. Amer. Chem. Soc.*, 1975, **97**, 2839.

[8] L. Alessandri and M. Passerini, *Gazzetta*, 1921, **51**[I], 262.

pyrimidin-2-one was ruled out by irradiation of this compound under the same conditions; only starting material was recovered.

The intermediate formation of an oxaziridine in the photoreactions of heteroaromatic *N*-oxides is generally accepted,[5] but despite many efforts these species have never been isolated; even recent nanosecond flash photolysis experiments gave no indication of its intermediary existence.[9,10] The only chemical 'proof' hitherto available is the 'trapping' of the oxaziridine by primary or secondary amines during the photolysis of 2-cyanoquinoline 1-oxides.[11,*] We believe that the formation of 2-methoxy-4,6-diphenylpyrimidine (X) in the present reaction can also be considered as a good indication of the intermediary existence of an oxaziridine. Furthermore, irradiation of 4,6-diphenylpyrimidine 1-oxide in the presence of a seven-fold molar amount of



SCHEME 2

potassium iodide in water produced iodine. Since 4,6-diphenylpyrimidine 1-oxide shows no oxidising properties towards iodide ion in the dark, and oxaziridines are known to be strong oxidising agents which are capable of liberating iodine from potassium iodide,[13] this experiment strongly supports the presence of an oxaziridine as intermediate. Since no deoxygenation was observed, the oxaziridine intermediate is the oxidising species and not atomic oxygen. Identical experiments were performed with 2,4,6-trimethylpyrimidine 1-oxide and 4-chloro-2,6-dimethylpyrimidine 1-oxide. In both experiments a twelve-fold molar amount of potassium iodide was needed to liberate iodine. This can be considered as an indication that in the case of the 4-R-2,6-dimethylpyrimidine 1-oxides (R = Me or Cl) the oxaziridine has a shorter lifetime. It has been reported that during the irradiation of 3,6-diphenylpyridazine *N*-oxide no oxaziridine intermediate is formed.[10] Photolysis of this *N*-oxide, in our hands, in the presence of a fifty-fold molar amount of potassium iodide in water did not produce iodine. From these results we conclude 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.

The possibility that the methoxy-derivative (X) is formed from 4,6-diphenylpyrimidine arising by deoxygenation of the *N*-oxide was ruled out by irradiation of 4,6-diphenylpyrimidine in methanol: no 2-methoxy-4,6-diphenylpyrimidine 1-oxide was formed. Irradiation of 4,6-diphenylpyrimidine 1-oxide in benzene gave as main product only 3,5-diphenylpyrazole (V; R = Ph) (9%).

In agreement with the foregoing results, pyrazole formation was also observed during the light-induced conversion of 4,6-di-t-butylpyrimidine 1-oxide (I; R = Bu^t) in methanol with light of wavelength 254 nm. Besides the pyrazole (V; R = Bu^t) (23%) 4,6-di-t-butylpyrimidin-2-one (XI) (10%) was also isolated. No indication of the formation of 2-methoxy-4,6-di-t-butylpyrimidine was obtained. The formation of both products (V; R = Bu^t) and (XI) indicates that in this case also the attack of the oxygen atom takes place at C(2).

EXPERIMENTAL

^{1}H N.m.r. spectra were recorded with a JEOL JNM-C60 spectrometer (Me_4Si as internal standard). Mass spectra were recorded with an A.E.I. MS902 instrument.

General Photolysis Procedure.—A solution of 4,6-diphenylpyrimidine 1-oxide (I; R = Ph) (0.4 g) in methanol (500 ml) or benzene (500 ml) was irradiated under nitrogen with a Hanau TQ 150 high-pressure mercury arc through a quartz filter. 4,6-Di-t-butylpyrimidine 1-oxide (I; R = Bu^t) was irradiated under the same conditions as reported earlier.[12]

The intermediacy of the oxaziridine during photolysis was indicated as follows. A solution of 4,6-diphenylpyrimidine 1-oxide (3.5 mg) and potassium iodide (15.8 mg) in water (4 ml) was irradiated for 5 min with the mercury arc. The formation of iodine was proved by addition of this solution, directly after irradiation, to an aqueous starch solution, which immediately gave the typical blue colour. The same solution did not produce iodine when kept in the dark. Also, irradiation of an aqueous solution of potassium iodide did not give iodine.

Starting Materials.—(1) 4,6-Diphenylpyrimidine [14] and 3,6-diphenylpyridazine *N*-oxide [10] were prepared as described in the literature.

(2) 4,6-*Diphenylpyrimidine* 1-*oxide* (I; R = Ph). 30% Hydrogen peroxide (12.5 g) was slowly stirred into a solution of maleic anhydride (84 g) in chloroform (280 ml) cooled in ice. After stirring for 2 h 4,6-diphenylpyrimidine (8.2 g) was added. The mixture was kept in a refrigerator for 5 days. The precipitated maleic acid was filtered off, and the filtrate was washed with aqueous potassium carbonate.

* It was reported recently [12] that 4-alkoxyisoquinolines are formed in the photolysis of isoquinoline 2-oxide derivatives.

[9] C. Lohse, *J.C.S. Perkin II*, 1972, 229.
[10] K. B. Tomer, N. Harrit, J. Rosenthal, O. Buchardt, P. L. Kumler, and I. Creed, *J. Amer. Chem. Soc.*, 1973, **95**, 7402.
[11] C. Kaneko and I. Yokoe, *Tetrahedron Letters*, 1967, 5355.
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[13] J. S. Splitter and M. Calvin, *J. Org. Chem.*, 1965, **30**, 3427.
[14] H. Bredereck, R. Gompper, and G. Morlock, *Chem. Ber.*, 1957, **90**, 942.

The chloroform layer was dried (K_2CO_3), filtered, and evaporated *in vacuo*. Recrystallisation of the residue from light petroleum (b.p. 60—80 °C) gave the 1-*oxide* (I; R = Ph) (3.2 g, 37%); m.p. 107—108 °C; δ ($CDCl_3$) 7.4—7.5 (m), 7.75 [H(5), s], 7.9—8.1 (m), and 9.00 [H(2), s] (Found: C, 77.15; H, 5.1. $C_{16}H_{12}N_2O$ requires C, 77.4; H, 4.85%).

(3) 2-*Methoxy*-4,6-*diphenylpyrimidine* (X). A solution of 2-chloro-4,6-diphenylpyrimidine (484 mg) in methanol containing sodium methoxide (204 mg) was refluxed for ½ h. After neutralisation with CO_2 the solution was evaporated and the residue recrystallised from light petroleum (b.p. 60—80 °C) to give the *methoxy-derivative* (381 mg, 80%), m.p. 81—82 °C; δ ($CDCl_3$) 4.20 (OCH_3, s), 7.5—7.65 (m), 7.82 [H(5), s], and 8.1—8.3 (m); *m/e* 262 (M^+) and 232 ($M^+ - CH_2O$) (Found: C, 77.9; H, 5.4. $C_{17}H_{14}N_2O$ requires C, 77.85; H, 5.4%).

(4) 3,5-*Diphenylpyrazole* (V; R = Ph). This compound was prepared according to a modified procedure.[15] Hydrazine sulphate (9.75 g) was dissolved in 2.5N-sodium hydroxide (60 ml). Dibenzoylmethane (17 g) and ethanol (50 ml) were added. The mixture was stirred at 50—60 °C for 4 h, and the temperature was then slowly raised till the solvent evaporated off. 3,5-Diphenylpyrazole crystallised out and was recrystallised from light petroleum (b.p. 100—140 °C); yield 6 g (36%), m.p. 199 °C (lit.,[16] 199 °C).

(5) 4,6-*Di-t-butylpyrimidine* (with A. Koudijs). To a solution of pyrimidine (3.20 g), pivalic acid (20.6 g), and silver nitrate (0.6 g) in sulphuric acid (10%; 40 ml) at 70 °C, ammonium peroxodisulphate (27.4 g) was added during 1 h.[17] The mixture was then stirred for another ½ h. After neutralisation with 25% sodium hydroxide the solution was extracted with ether. Evaporation of the extract left a residue which was purified on a silica gel column (eluant $CHCl_3$). Distillation *in vacuo* yielded 4,6-di-t-butylpyrimidine (4.7 g, 61%), b.p. 101—102 °C at 13 mm Hg; δ ($CDCl_3$) 1.40 (CMe, s), 7.33 [H(5), s], and 9.11 [H(2), s]; *m/e* 192 (M^+), 177 ($M^+ - CH_3$), and 150 ($M^+ - C_3H_6$) * (Found: C, 75.25; H, 10.5. $C_{12}H_{20}N_2$ requires C, 74.95; H, 10.5%).

(6) 4,6-*Di-t-butylpyrimidine* 1-*oxide* (I; R = Bu^t) (with A. Koudijs). This compound was prepared by the procedure given for 4,6-diphenylpyrimidine 1-oxide [see section (2)]. 4,6-Di-t-butylpyrimidine (4.0 g) gave the *N-oxide* (1.8 g, 42%), m.p. 115—116 °C; δ ($CDCl_3$) 1.40 (CMe_3, s), 1.58 CMe_3, s), 7.30 [H(5), s], and 8.88 [H(2), s]; *m/e* 208 (M^+) and 193 ($M^+ - CH_3$) (Found: C, 68.85; H, 9.7. $C_{12}H_{20}N_2O$ requires C, 69.2; H, 9.7%).

(7) 4,6-*Di-t-butylpyrimidin*-2-*one* (with A. Koudijs). According to the procedure given in section (5), t-butylation of 2-ethoxypyrimidine (2.0 g) gave 2-ethoxy-4,6-di-t-butylpyrimidine (2.6 g, 68%). The product (300 mg) was refluxed with concentrated hydrochloric acid (25 ml) during 1 h. Evaporation followed by neutralisation with ammonia and extraction with chloroform gave 4,6-*di-t-butylpyrimidin*-2-*one* (100 mg, 38%), m.p. 223—224 °C, δ ($CDCl_3$) 1.34 (CMe_3, s), 4.9br (NH), and 6.45 [H(5), s]; *m/e* 208 (M^+), 193 ($M^+ - CH_3$), and 166 ($M^+ - C_3H_6$) (Found: C, 69.0, H, 9.54. $C_{12}H_{20}N_2O$ requires C, 69.2; H, 9.7%).

Attempt to prepare 1-*Formyl*-3,5-*diphenylpyrazole*.[6]—3,5-Diphenylpyrazole (6.00 g) in absolute ether was treated, with cooling, with the Grignard reagent obtained from magnesium (0.65 g) and methyl iodide (4.04 g) in ether. After completion of the reaction by heating, isopentyl formate (3.54 g) was added dropwise and with cooling. Immediately after the initial addition of the formate the mixture changed from a yellow-brown suspension to a dark red solution. After 80 min, crushed ice was added. A precipitate was obtained and the supernatant ethereal layer was separated. This layer was combined with ethereal extracts of the aqueous layer. On evaporation the starting material was nearly quantitatively recovered.

We thank Mr. C. A. Landheer for mass spectroscopic data, Mr. H. Jongejan for microanalyses, and Mr. A. van Veldhuizen for measuring ^1H n.m.r. spectra. We also thank Miss C. L. Habraken (Gorlaeus Laboratory, Leiden) for providing a sample of 3,5-di-t-butylpyrazole This investigation was carried out under the auspices of the Netherlands Foundation for Chemical Research (S.O.N.) and with financial aid from the Netherlands Organisation for the Advancement of Pure Research (Z.W.O.).

[5/2168 *Received*, 7th *November*, 1975]

* It is generally observed that compounds containing a t-butyl group in a position adjacent to nitrogen undergo a fragmentation with loss of C_3H_6.

[15] A. I. Vogel, 'A Textbook of Practical Organic Chemistry,' 3rd edn., London, 1957, p. 842.
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PHOTOCHEMISTRY OF N-BENZOYLIMINOPYRIMIDINES[1,2]

Short communication

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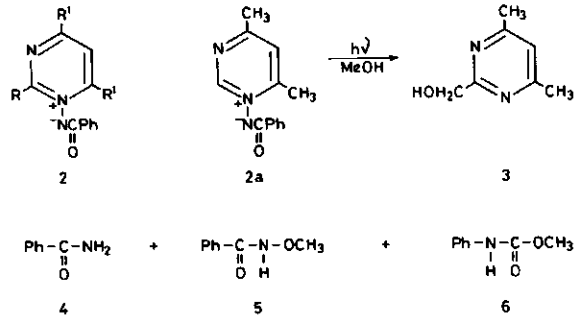
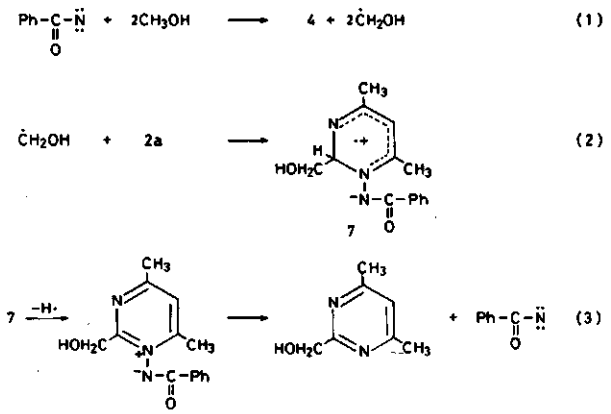
Recently there is strong interest in the photochemistry of N-iminoylides derived from pyridine, quinoline, isoquinoline, benzocinnoline and triazoles[3]. From these studies it appeared that the six-membered ring systems are inclined to give ring enlargements[4] and that the five-membered ring systems show N-N bond cleavage as the favourite process[3]. Ring contraction - a well-known reaction in the photochemistry of heteroaromatic N-oxides - is not observed with the N-iminoylides.

In connection with our investigations on the photochemical reactions of pyrimidine N-oxides, we became interested in the behaviour of the isoelectronic N-iminopyrimidines, a class of compounds of which the photochemistry has not been studied so far. For our purpose we synthesized three N-benzoyliminopyrimidines i.e. 2a (R=H, R^1=Me), 2b (R=H, R^1=Ph) and 2c (R=R^1=Me) from the corresponding N-aminopyrimidinium mesitylene sulfonate (1) (see Experimental part).

Irradiation of a solution of 2a (1.00 g in 950 ml MeOH)during 12 h gave as main product 4,6-dimethyl-2-hydroxymethylpyrimidine 3 (27%) and as minor products benzamide 4 (14%), N-benzoyl O-methylhydroxylamine 5 (9%) and methyl N-phenylcarbamate 6 (7%). Moreover some tarry material is formed during the irradiation. All the reaction products were characterized by comparison of the ^{1}H-NMR, IR and mass spectra with those of authentic samples (see for compound 3, literature reference 5).



The formation of the 2-hydroxymethylpyrimidine derivative 3 is of interest, since its formation must take place according to a reaction type which to our knowledge has never been observed before in the field of the photochemistry of N-benzoylheteroaromatics. Its formation can be postulated to occur as follows. After excitation of 2a rupture of the N-N bond occurs, yielding among others the benzoylnitrene in its triplet state. Since triplet benzoylnitrenes behave as radical species[6], they are able to abstract hydrogen atoms from the solvent, yielding hydroxymethylene radicals (reaction 1). Addition to 2a gives the N-iminoylid radical 7 (reaction 2) which by loss of an H-atom yields the 2-hydroxymethyl derivative 2a. Again an N-N bond rupture can occur, generating benzoylnitrene and the endproduct 3 (reaction 3). It cannot definitively be excluded that formation of the H atom and benzoylnitrene does not occur sequential but concerted.



Compound 3 is also formed when a solution of 4,6-dimethylpyrimidine in methanol is irradiated in the presence of the radical initiator dibenzoylperoxide. Thus, the possibility that . CH_2OH radicals react with 4,6-dimethylpyrimidine - formed by the cleavage of the N-N bond in 2a - to form 3 cannot be excluded. However, since in the reaction mixture obtained by irradiation of 2a no trace of 4,6-dimethylpyrimidine could be detected, we feel that the reaction mechanism discussed above in Scheme II is more valid. Further indications for the formation of benzoylnitrene is of course the formation of product 5 (addition of methanol); 6 is produced by addition of methanol to phenylisocyanate, obtained by a photo-Curtius rearrangement of the N-iminoylid.

No indication was obtained for a migration of the iminobenzoyl group to position 2, yielding 2-benzoylamino-4,6-dimethylpyrimidine. Although an authentic specimen of this compound showed to be very photolabile under our conditions, its photo-products could not be detected however (by means of ^{1}H-NMR) in the photolysis of 2a.

Photolysis of 2b (0.285 g in 900 ml MeOH) during 15½ h, yields as main products benzamide (36%) and the carbamic ester 6 (11%). Only a trace of 4,6-diphenyl-2-hydroxymethylpyrimidine could be detected. The structure of this last-mentioned product was proved by mass spectrometry (exact mass: found 262, 1096, calcd. 262, 1106) and the ^{1}H-NMR spectrum (absorptions at δ 5.00 ppm (CH_2OH) and δ 7.3-8.4 ppm (phenyl pattern)). The signal of H(5) has disappeared in the phenyl multiplets.

Photolysis of 2c (0.84 g in 900 ml MeOH) during 12 h showed a very different pathway. Since positions 2, 4 and 6 are blocked by the methyl group no substitution reaction can occur. The main reaction product is benzamide (84%); two minor products were isolated i.e. 2,4,6-trimethylpyrimidine (11%) and 6 (11%). In the photolyses of both 2b and 2c tarry materials were found.

Experimental part

3.0 g of the corresponding N-aminopyrimidinium mesitylene sulfonate (1)[7] was dissolved in 15 ml of benzoylchloride and stored overnight. This solution was poured into water and slightly basified with K_2CO_3. This solution was extracted with chloroform; after distilling off the solvent the residue was purified by column chromatography, using Al_2O_3 as adsorbent and chloroform or acetone as eluent. Compound 2a, R=H, R^1=CH_3, yield 75%, m.p. 155°C; m/e 227 (M^+); ^{1}H-NMR: δ 2.55 ppm (6H), δ 7.2-7.4 ppm and δ 8.0-8.2 ppm (phenyl pattern), δ 9.10 ppm (H(2)). Although the CH_3 signals coincide in the ^{1}H-NMR spectrum, in the ^{13}C-NMR spectrum the absorptions of two CH_3 substituents are different, they are observed at δ 18.8 ppm and δ 24.1 ppm. The NMR spectra were recorded in $CDCl_3$, with TMS (δ=0) as internal standard. (Found: C 68.55, H 6.0; calcd. for $C_{13}H_{13}N_3O$: C 68.7, H 5.75). Compound 2b, R=H, R^1=Ph, yield 25%, m.p. 187-188°C; ^{1}H-NMR: δ 7.3-8.3 ppm (phenyl pattern), δ 9.35 ppm (H(2)); the absorption of the H(5) proton has disappeared under the absorption of the phenyl pattern. (Found: C 78.5, H 4.9; calcd. for $C_{23}H_{17}N_3O$: C 78.6, H 4.9). Compound 2c, R=R^1=CH_3, yield 47%; ^{1}H-NMR: δ 2.60 ppm (6H), δ 2.80 ppm (3H), δ 7.3-7.5 ppm and δ 8.0-8.2 ppm (phenyl pattern). M.p. picrate 192°C (from methanol). (Found: C 50.9,

H 3.9; calcd. for $C_{20}H_{18}N_6O_8$: C 51.05, H 3.85.

General procedure for the photolysis:
A methanolic solution of 2a-c was irradiated with an Hanau high-pressure mercury arc, using a quartz filter till no starting material was present. The reaction was stopped when by tlc no starting material could be discovered.

Acknowledgment

We are indebted to Mr.A.van Veldhuizen for measuring NMR and IR spectra, to Drs. C.A.Landheer for the mass spectroscopic data and to Mr.H.Jongejan for microanalyses. This investigation has been carried out under the auspices of the Netherlands Foundation for Chemical Research (SON) and with financial aid from the Netherlands Organisation for the Advancement of Pure Research (ZWO).

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Ring transformations in reactions of heterocyclic compounds with nucleophiles (XV)[1] Reactions of *N*-aminopyrimidinium salts with liquid ammonia[2]

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(Received June 15th, 1976)

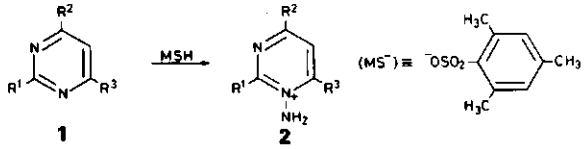
Abstract. *N*-Aminopyrimidinium salts, *e.g.* 4,6-dimethylpyrimidinium (**2a**), 4,6-diphenylpyrimidinium (**2b**) and 2,4,6-trimethylpyrimidinium mesitylenesulfonates (**2c**), show a very divergent behaviour towards liquid ammonia at −33°. *1)* Proton abstraction takes place from the amino group of **2a**,resulting in the formation of a 1,3-dipolar intermediate, which under the reaction conditions dimerises. *2)* Adduct formation is observed on C(2) of **2a** or C(6) of **2c**, resulting in the formation of a pyrazole or a 1,2,4-triazole ring. *3)* Deamination occurs with **2b** and **2c**, *via* two pathways, namely, a nucleophilic attack of ammonia on the nitrogen atom of the amino group or by a ring opening/ring closure sequence. This last-mentioned mechanism has been proved by use of ^{15}N-labelled ammonia.

In connection with our current research on ring-opening reactions of pyrimidine *N*-oxides[3] and *N*-methylpyrimidinium salts[4] by the action of liquid ammonia we became interested in the reactivity of the *N*-aminopyrimidinium salts. In quaternised pyrimidines the addition of a nucleophilic reagent to the N(1)–C(6) azomethine bond takes place readily. A σ-adduct is formed, the formation of which has in several cases been confirmed by ^{1}H-NMR spectroscopy[4,5]. After addition, ring opening can occur yielding an open-chain intermediate, which can either recyclise into a heteroaromatic system *different*[3] from that of the starting substance or return to the *same* ring system[4] present in the starting substance (a "degenerate" ring transformation).
The purpose of the present investigation was to explore whether quaternisation of the nitrogen of the pyrimidine ring by an amino group – instead of an oxygen atom or alkyl group – changes its reactivity towards liquid ammonia. It was considered that besides addition to the polarised N(1)–C(6) bond, deprotonation of the N^+-NH_2 group to an *N*-ylide (being able to react as a 1,3-dipole) could be a competitive process. We synthesized therefore several *N*-aminopyrimidinium mesitylenesulfonates (**2**) and examined the behaviour of these compounds towards liquid ammonia.

Results and discussion

a) *Synthesis of the* N-*aminopyrimidinium salts* (**2a-c**)

It has recently been shown that the previously inaccessible *N*-aminopyrimidinium salts can be synthesized by amination with *O*-mesitylenesulfonylhydroxylamine[6,7] (see Scheme 1).



	yield
a) $R^2=R^3=CH_3$, $R^1=H$	65% (lit.[7] 66%)
b) $R^2=R^3=C_6H_5$, $R^1=H$	75%
c) $R^1=R^2=R^3=CH_3$	80%
d) $R^2=R^3=$ t-Bu, $R^1=H$	—
e) $R^2=R^3=CH_3$, $R^1=C_6H_5$	—
f) $R^1=R^2=R^3=C_6H_5$	—

Scheme 1

It seemed to us that the mechanism of the formation of the *N*-aminopyrimidinium mesitylenesulfonates is analogous to that of the formation of the *N*-oxides of heteroaromatic compounds[8]. Both reactions involve an electrophilic attack at the nitrogen of the pyrimidine ring. Our results show, however, that the *N*-amination is more sensitive for steric effect than the *N*-oxidation. This can be illustrated on 4,6-di-*t*-butylpyrimidine (**1d**) which is easily converted into its *N*-oxide[9] but which cannot be converted into the corresponding *N*-aminopyrimidinium salt. In accordance with results reported in the literature about the inertness of 2-phenylpyrimidines[10] as regards oxidation into their *N*-oxides, we observed that neither is the *N*-amination of 4,6-dimethyl-2-phenylpyrimidine and 2,4,6-triphenylpyrimidine possible.

b) *Reactions with liquid ammonia*

When the yellow compound **2a** is dissolved in liquid ammonia at −33° the colour immediately changes to red. After 1 h a reaction mixture is obtained, from which we could isolate two products, a dimer (**4**, 20% *m/e* = 246) and 3,5-dimethylpyrazole (**8**, 13%). No indications for the presence in the reaction mixture of 4,6-dimethylpyrimidine and the dimer **5** could be obtained. The structure assignment to **4** was essentially based on ^{1}H-NMR data ($CDCl_3$). Besides methyl singlets at δ 1.85 (6H) and δ 1.90 (6H) and sharp singlets at δ 6.82 (1H) and δ 6.94 (1H) we observed at δ 4.38 a singlet (2H) which could be ascribed only to C(1a) and C(5a) in **4**. In the case of **5** an absorption at much lower field for the hydrogen atom at C(1) and C(7) would have

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[1] Part LVII from this laboratory on Pyrimidines. See for part LVI *F. Roeterdink* and *H. C. van der Plas*, Tetrahedron Lett. **1976**, 3337.
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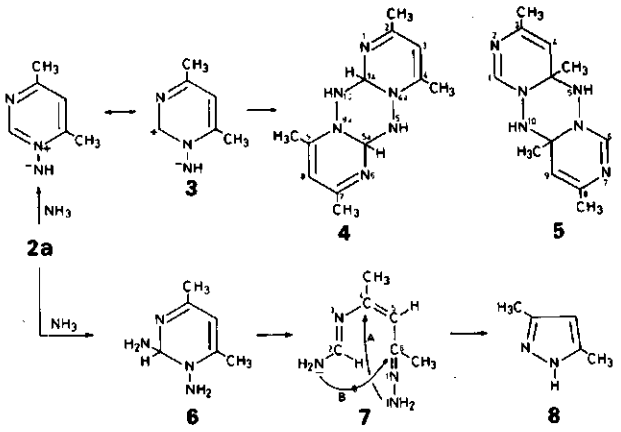


Scheme 2

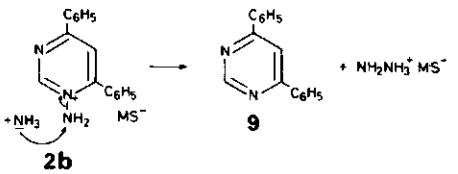
been expected than is in fact observed. Moreover, in structure **5** the two methyl groups can be expected to lie further apart than has been found.

The formation of dimer **4** can be rationalized by an initial deprotonation of the *N*-amino group leading to the intermediary formation of the *N*-ylide **3**, which acts as a 1,3-dipolar intermediate resulting in dimerisation. Dimerisation of *N*-ylides derived from isoquinoline and quinoline has already been reported[11].

The concurrent formation of **8** is of interest and deserves attention since it presents 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 building block for construction of the pyrazole ring. There are two other different fragmentations of a pyrimidine ring already reported which also led to pyrazoles. The most common of these is the one in which the C(4)–C(5)–C(6) of the pyrimidine ring is incorporated in the pyrazole ring[12]. The other ring transformation, which is less frequently observed, is the one in which loss of the N(1)–C(2) moiety occurs and the remaining N(3)–C(4)–C(5)–C(6) fragment takes part in the formation of a 5-aminopyrazole[13].

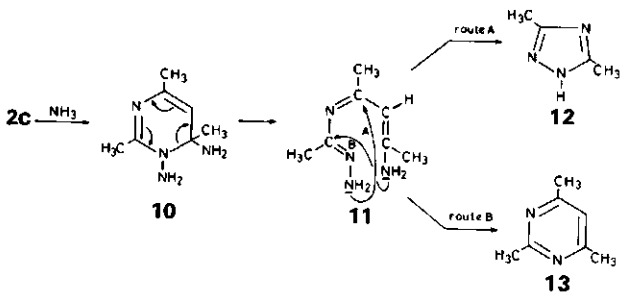
We postulate in the conversion of **2a** → **8** an initial formation of a σ-adduct at C(2) *i.e.* **6** which, after ring opening, gives an *N*-(hydrazonoalkenyl)formamidine (**7**). **8** is formed by attack at C(4) of the amino group of the hydrazono moiety (route A). Thus the ammonia is necessary for addition preceding ring opening, but does not play a role in the cyclisation. Similar examples have been observed in the ring transformation of 4-chloropyrimidine *N*-oxides with liquid ammonia into 5-aminoisoxazoles[3] and in the ring transformation of 2-chloropyrazine into imidazole and 2-cyanoimidazole by potassium amide[14]. Attempts to obtain by ^{1}H-NMR spectroscopy some data on the intermediary adduct **6** failed. This is probably due to the formation of the dimer which considerably confuses the spectrum.

A completely different behaviour was observed in the reaction of the *N*-amino-4,6-diphenylpyrimidinium salt (**2b**) with liquid ammonia. No trace of a dimer or a pyrazole was found, only a quantitative deamination into 4,6-diphenylpyrimidine was observed. When the reaction was carried out with ^{15}N-labelled liquid ammonia (containing 9.9% of excess of ^{15}N) surprisingly we found that the 4,6-diphenylpyrimidine contained 2.7% of excess of ^{15}N indicating that about 27% (neglecting isotope effects) of the deamination had occurred *via* an addition, ring opening/ring closure sequence [(ANRORC) mechanism]. This mechanism is very similar to that postulated for the demethylation of *N*-methylpyrimidinium salts by liquid ammonia which was proved to occur quantitatively with ring opening[4]. An attempt to establish the structure of the adduct by ^{1}H-NMR spectroscopy failed due to the low solubility of **2b**. Therefore it is impossible to conclude whether the ammonia adds to C(2) or C(6) before ring opening occurs[15]. From the result of the labelling experiment with $^{15}NH_3$ 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 (see Scheme 3). This mechanism for deamination shows a close similarity to the recently discovered deoxygenation of pyrimidine *N*-oxide by heating with ammonia. In this case it was established that the pyrimidine obtained after treatment of the ^{15}N-labelled pyrimidine *N*-oxide with unlabelled ammonia has the same ^{15}N-percentage of enrichment as in the starting material[16].



Scheme 3

The reaction of **2c** with liquid ammonia also shows a complex reaction pattern. Deamination is the main reaction pathway: 2,4,6-trimethylpyrimidine (**13**) is formed in 40% yield. 3,5-Dimethyl-1,2,4-triazole (**12**, 12%) was formed as minor product in the reaction. Applying the same technique as described above for **2b** – use of $^{15}NH_3$ – it was established that this deamination occurs to the extent of ~80% by a nucleophilic attack of the NH_3 on the *N*-amino group and 20% by an ANRORC mechanism (**1** → **11** $\xrightarrow{\text{route B}}$ **13**).



Scheme 4

The formation of **12** is of considerable interest since it presents a new type of a pyrimidine/1,2,4-triazole ring transformation. As can be seen from Scheme 4 it involves incorporation in the 1,2,4-triazole ring of the N(1)–C(2)–N(3)–C(4) fragment of the pyrimidine ring as observed previously.

Known examples of pyrimidine/1,2,4-triazole conversions are those in which, by action of hydrazine, the C(6)–N(1) moiety of the pyrimidine ring is lost and C(5) is incorporated

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[15] The ^{1}H-NMR spectrum of a solution of 4,6-diphenylpyrimidine in $K^+NH_2^-/NH_3$ strongly supports the formation of a σ-adduct at C(2). Adducts at C(6) is apparently unfavourable probably due to steric effects. From this result we may cautiously conclude that adduct formation of ammonia to **1b** preferentially occurs at C(2).

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in the methyl group of 3-methyl-1,2,4-triazole[12,17] and the very recent one in which N(1) and N(3) are lost and the C(4)–C(5) moiety is incorporated in an acetohydrazino group being attached to a 1,2,4-triazole ring[18].
In conclusion, the *N*-aminopyrimidinium salts are found to react by a variety of reaction pathways. Some reactions show similarities with those of the heteroaromatic *N*-oxides, others with the *N*-alkylpyrimidinium salts. This interesting bivalent behaviour of the *N*-aminopyrimidinium salts deserves further attention.

Experimental part

All melting points are uncorrected. The ^{1}H-NMR spectra were recorded on a Jeol JNM-C 60 spectrometer, using TMS ($\delta = 0$) as internal standard. In the case of adduct measurements the apparatus was equipped with a JES-V.T-3 variable temperature controller. The measurements of the ^{15}N contents were carried out on an AEI-MS 902 mass spectrometer. The IR spectra were recorded on an Hitachi model EPI-G3. GLC analyses were carried out with a Becker gaschromatograph (Delft, The Netherlands, using a copper column, length 200 cm, internal diameter 0.4 cm, containing 20% Carbowax-20M on Kieselguhr 60–80 mesh and 10% Na_2CO_3).

a. Preparation of the starting materials

1. *Mesitylenesulfonylhydroxylamine* (MSH) was prepared as described in the literature[6].

Caution: MSH is explosive on standing for several days in the refrigerator at −20°. Therefore it is strongly advised to use MSH immediately after its preparation.

2. N-*Aminopyrimidinium mesitylenesulfonates* (**2a-c**). To a solution of the appropriate pyrimidine (5×10^{-2} mol) in CH_2Cl_2 (70 ml), while cooled in ice, a solution of MSH (5×10^{-2} mol) in CH_2Cl_2 (50 ml) was added drop by drop. The reaction mixture was allowed to stand at room temperature for 2 h. Addition of ether caused crystallisation. The crystals were collected and recrystallised from isopropyl alcohol.

N-*Amino-4,6-dimethylpyrimidinium mesitylenesulfonate* (**2a**), m.p. 142° (lit. [7] 141–143°).

N-*Amino-4,6-diphenylpyrimidinium mesitylenesulfonate* (**2b**), m.p. 162°. Found: C 67.15, H 5.8; calc. for $C_{25}H_{25}N_3O_3S$: C 67.1, H 5.65.

N-*Amino-2,4,6-trimethylpyrimidinium mesitylenesulfonate* (**2c**), m.p. 175°. Found: C 57.15, H 7.15; calc. for $C_{16}H_{23}N_3O_3S$: C 56.95, H 6.85.

The above-mentioned compounds show the ^{1}H-NMR characteristics of the mesitylenesulfonate anion at $\delta = 2.12$–2.18 (CH_3), $\delta = 2.47$–2.50 ($2 \times CH_3$) and $\delta = 6.72$–6.75 (2H). In addition the chemical shifts of the protons of the pyrimidine ring and substituents are summarized.

Table I Chemical shift values of the hydrogens of the ring and substitutents in the pyrimidinium ion of **2a-c**.

Compound	H_2	H_5	Substituents
2a	9.56	8.00	2.60 (R^2); 2.68 (R^3)
2b	9.70	*	7.5–8.0 (m); 8.3–8.7 (m)
2c	–	7.82	2.84 (R^1); 2.57 (R^2); 2.70 (R^3)

* This ^{1}H-NMR signal is not observed since it is overlapped by the multiplet of the hydrogens of the phenyl group.

b. General procedure for the reaction with liquid ammonia

1.0 g of the salt was added to 60–70 ml of liquid ammonia. After standing for 1 h the ammonia had evaporated, and the residue was mixed with 40 ml of water. This solution was continuously extracted with chloroform for 24 h. After drying the chloroform extracts over $MgSO_4$, the solvent was distilled off, and the oil obtained was, if necessary, separated by column chromatography on a silica gel column, using eluents of different polarity (chloroform with increasing amounts of ethyl acetate). The reaction products, *i.e.* 3,5-dimethylpyrazole[19], 4,6-diphenylpyrimidine[20], 2,4,6-trimethylpyrimidine[21] and 3,5-dimethyl-1,2,4-triazole[22] which were already known, were characterized by identity with ^{1}H-NMR and IR spectra of authentic specimens.
Dimer of *N*-imino-4,6-dimethylpyrimidine (**4**), m.p. 285° (from ethanol). Found: C 58.5, H 7.55; calc. for $C_{12}H_{18}N_6$: C 58.5, H 7.35.

c. Reaction of 2b and 2c with ^{15}N-labelled ammonia

The reaction was carried out as described in section b for unlabelled ammonia. 4,6-Diphenylpyrimidine and 2,4,6-trimethylpyrimidine were purified by GLC before ^{15}N measurements.

Acknowledgement

We are indebted to Dr. *P. Smit* and Mr. *A. van Veldhuizen* for measuring PMR and IR spectra, to Drs. *C. A. Landheer* for the mass spectroscopic data, to Mr. *W. Ch. Melger* for his advice on the chromatographic part and to Mr. *K. van Dijk* for technical assistance in carrying out some experiments.
This investigation was carried out under the auspices of the Netherlands Foundation for Chemical Research (SON) and with financial aid from the Netherlands Organisation for the Advancement of Pure Research (ZWO).

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Tetrahedron Letters No. 37, pp 3337 - 3338, 1976

A NEW SYNTHESIS OF PYRIMIDINE 1-OXIDES[1,2]

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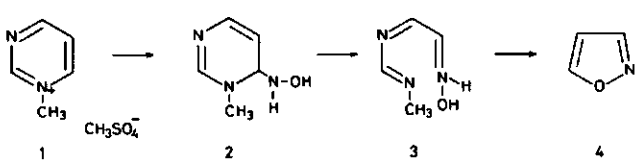
(Received in UK 20 July 1976; accepted for publication 20 July 1976)

In our current research on the behaviour of diazines with nucleophiles, it was recently found that pyrimidines, 1-methylpyrimidinium methosulfate (1) and pyrimidine 1-oxides are converted into isoxazoles (4) by the action of hydroxylamine[3]. The mechanism for the conversion of 1 into isoxazole (4) occurs via the intermediates 2 and 3 (see scheme below). The first step common to these reactions is an addition of the nucleophile at C(6). Ring-opening by fission of the C-N bond in (2) gives (3), which cyclises into (4) by a nucleophilic attack of the oxygen lone pair on C(4). Subsequent aromatisation occurs by loss of N-methylformamidine.

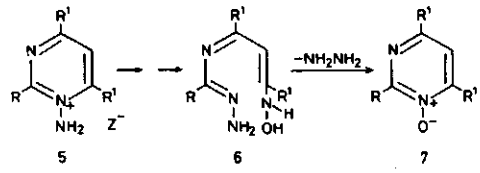


In principle the nitrogen lone pair of the hydroxylamino group in an open-chain compound like (3) is also able to perform the cylisation leading to a heteroaromatic N-oxide. For example pyrylium salts can easily be converted into either isoxazoles or pyridine N-oxides[4]. 3-Azapyrylium salts however, failed to give pyrimidine N-oxides[5], isoxazoles being formed instead.

We wish to report now on a new, non-oxidative conversion of pyrimidine N-oxides, observed on treatment of 1-aminopyrimidinium mesitylenesulfonates (5)[6] ($Z^{\ominus}=^{\ominus}OSO_2C_6H_2(CH_3)_3$) with hydroxylamine.

Reaction of 3×10^{-3} mol of 5 in water with a fivefold molar amount of NH_2OH . HCl for 15 min gave a solution, which was neutralized with K_2CO_3 and extracted with ether. After drying and distilling off the solvent the pyrimidine N-oxides (7) were isolated in moderate to high yields (7a: R=H, $R^1=CH_3$, 85%; 7b: $R=R^1=CH_3$, 90%; 7c: R=H, $R^1=C_6H_5$, 35%).

We assume that the intermediate 6 is formed from 5 by the same mechanism as reported above, after which ring closure yields the pyrimidine 1-oxides (7). No trace of a corresponding isoxazole could be detected.



In the cases of 7a and 7b this new method gives yields, which are higher than the ones obtained in the direct oxidation of pyrimidines, moreover this non-oxidative method opens up the possibility of synthesizing pyrimidine 1-oxides with substituents which are sensitive for oxidation.

Acknowledgement

We are indebted to Dr.P.Smit and Mr.A.van Veldhuizen for measuring ^{1}H-NMR and IR spectra and to Mr.K.van Dijk for technical assistance.

This investigation has been carried out under the auspices of the Netherlands Founda-

tion for Chemical Research (SON) and with financial aid from the Netherlands Organisation for the Advancement of Pure Research (ZWO).

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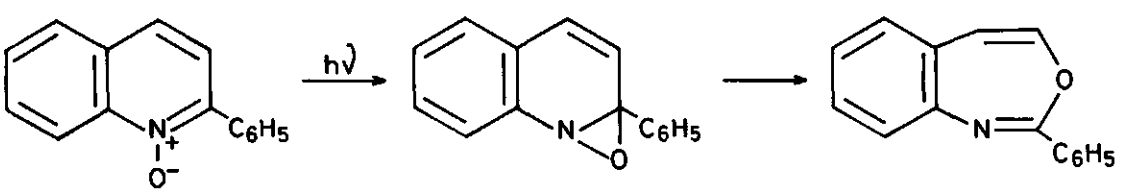
7. The ^{1}H-NMR, IR spectra and melting points were identical with those of the authentic compounds.

Discussion

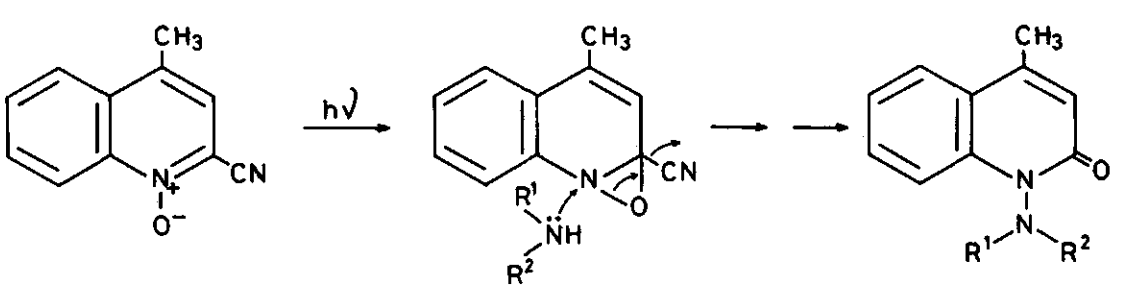
At the start of our investigations on the photochemistry of pyrimidine N-oxides the crucial question was whether an oxaziridine exists or not as intermediate in the photochemical rearrangements of heteroaromatic N-oxides[1]. Since Todd et al.[2] were able to isolate bicyclic oxaziridines from cyclic nitrones, it induced the idea that oxaziridines may also be formed as transient intermediates in the irradiation of heteroaromatic N-oxides. However, despite many efforts nobody succeeded to isolate an oxaziridine in the last-mentioned reactions, although for a short time it was believed that on irradiation of the quinoline N-oxide (1) the oxaziridinoquinoline (2) was obtained[3]. This was proved to be false since by means of an X-ray study this compound was identified as the isomeric benz[d] [1,3]oxazepine (3)[4].



1 2 3

Experimental results which support the hypothesis of an oxaziridine as intermediate in the photoreactions of heteroaromatic N-oxides are:

a) Irradiation of 2-cyano-4-methylquinoline N-oxide (4) in the presence of amines leads to the corresponding N-aminocarbostyril (6)[5]. Since aliphatic oxaziridines are known to undergo ring-opening on treatment with hydrazine, it was assumed that the transient oxaziridine (5) was intermediate in this photoconversion.



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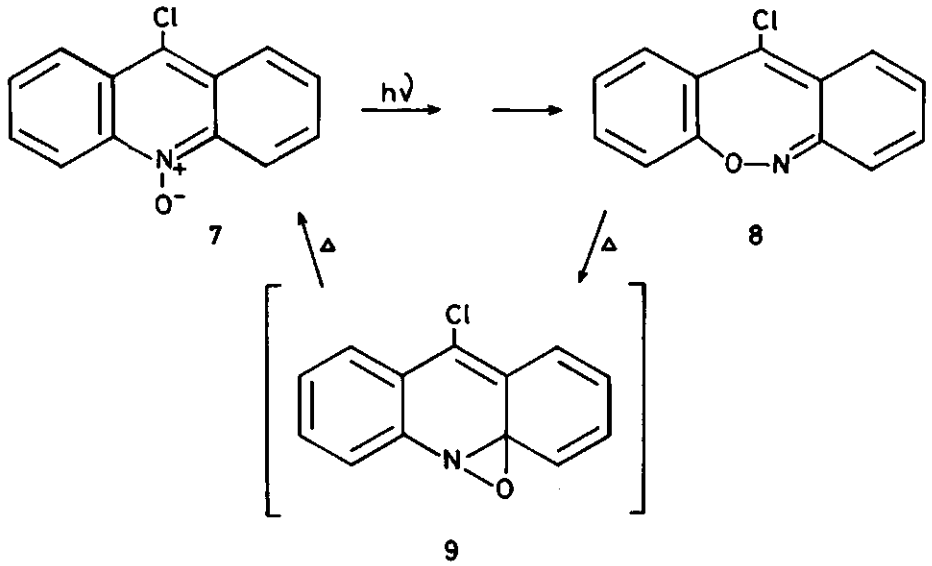
b) Photolysis of 9-chloroacridine N-oxide (7) leads to the corresponding dibenz[c,f]-1,2-oxazepine (8)[6]. This compound can isomerize thermally to the N-oxide (7), which process can be explained via the intermediate oxaziridine (9).



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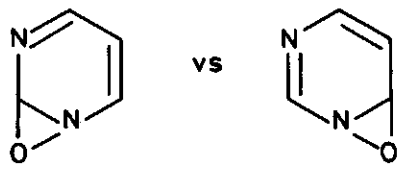
In 1972 and 1973 strong evidence arose that the proposal of oxaziridine intermediates in the photochemistry of heteroaromatic N-oxides was premature. As mentioned in the introduction Lohse[7] and Buchardt et al.[8] obtained results with laser flash photolysis experiments which made the existence of oxaziridines doubtful.

From the results of our work on cuvet irradiation experiments with 2,4,6-trisubstituted pyrimidine N-oxides (chapter 1) we have to conclude that during the irradiation an intermediate is formed. This intermediate can revert thermally to the starting material. Attempts to characterize this intermediate with the aid of conventional flash photolysis failed. However, the fact that by irradiation of 4,6-diphenylpyrimidine N-oxide in methanol i.a. 2-methoxy-4,6-diphenylpyrimidine is yielded (see chapter 2) is considered as a strong indication for the occurrence of an oxaziridine intermediate, since ring-opening of oxaziridines by methanol is well established[9]. Additional evidence for the intermediary existence of oxaziridines is obtained from irradiation experiments which are carried out in the presence of potassium iodide (chapter 2). Iodine is liberated,what also points to the intermediacy of oxaziridines as they are known to be strongly oxidising agents[10]. Control experiments indicate that pyrimidine N-oxides do not react with potassium iodide in a dark reaction. A combination of all these above-mentioned results (the cuvet irradiation experiment, formation of 2-methoxy-4,6-diphenylpyrimidine and liberation of iodine from potassium iodide) can in our opinion be considered as an unambiguous proof that in the photochemistry of pyrimidine N-oxides the first step is oxaziridine formation. Interestingly, 3,6-diphenylpyridazine N-oxide - a compound which with the aid of flash photolysis was proved <u>not</u> to react via an oxaziridine[8] - also does <u>not</u> liberate iodine during irradiation in the presence of potassium iodide.

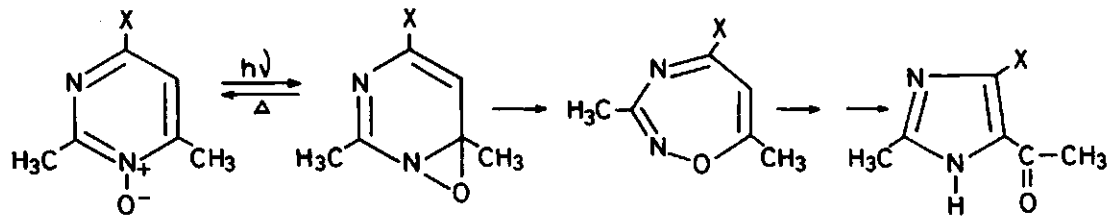
From these results we must conclude that the statement that in the photo-

chemical reactions of all heteroaromatic N-oxides no oxaziridines are involved[8] cannot be generally accepted. Now the occurrence of an oxaziridine intermediate in the photochemistry of pyrimidine N-oxides has been established, the question arises which oxaziridine is formed, (10) or (11).



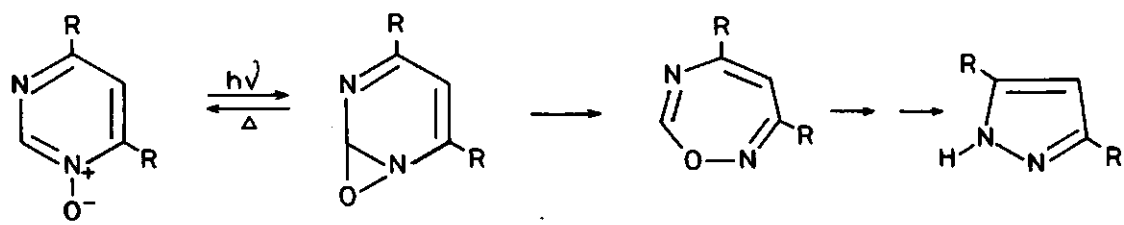
10 11

Based on Hückel calculations a preference for electrocyclisation to C(2) was predicted[11]. In contrast PPP-SCF calculations showed a tendency for electrocyclisation to C(6)[12]. From the fact that a 4(5)-acetylimidazole derivative (15) could be isolated from 4-X-2,6-dimethylpyrimidine 1-oxides (12, X=CH_3, Cl, OCH_3) in all cases, clearly supports the intermediacy of oxaziridine (13),which by a thermal ring expansion into the 1,2,4-oxadiazepine (14) followed by ring contraction is converted into the imidazole (15).



12 13 14 15

Evidence for an intermediate like (10) was obtained from experiments in which pyrimidine N-oxides containing bulky substituents (t-butyl and phenyl group) at positions 4 and 6 (16)are irradiated. We observed that electrocyclisation takes place exclusively to carbon atom (2). As was proved by the formation of pyrazole (19), this can only be explained via the intermediate (17) and the 1,2,6-oxadiazepine (18).



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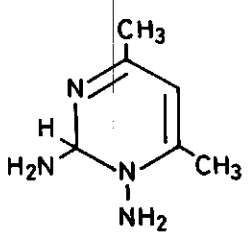
As an extension of our investigations on the photochemical reactions of pyrimidine N-oxides, we studied the photochemistry of N-imino pyrimidines, these being isoelectronic with the N-oxides. Whereas with pyridine N-benzoylimines ring

enlargement and/or rearrangement into a 2-aminopyridine derivative is observed[13], with pyrimidine N-benzoylimines no ring enlargement or migration of the benzoylimino group is found. Only rupture of the N-N bond - being so characteristic for N-aminotriazole ylides - is the most common reaction pattern. Benzoylnitrene is yielded, which is converted into several phenyl derivatives by the solvent methanol.
The photochemical formation of 2-hydroxymethyl-4,6-dimethylpyrimidine from N-benzoylimino-4,6-dimethylpyrimidine, proved to occur by a radical process, is to our knowledge without precedent and shows a new mode of reaction of these N-iminoylides. In summary we can conclude that the reactivity of the excited state of pyrimidine N-oxides and pyrimidine N-imines is quite different.

The second part of our investigation has been devoted to the study of the thermal behaviour of N-aminopyrimidinium salts towards nucleophiles, NH_3 (chapter 4) and NH_2OH (chapter 5). From the results reported in chapter 4 we conclude that there is a tendency for NH_3 to undergo an addition reaction at position 2. The formation of 3,5-dimethylpyrazole from N-amino-4,6-dimethylpyrimidinium mesitylenesulfonate can only be explained via the intermediate formation of (20).



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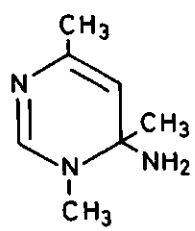

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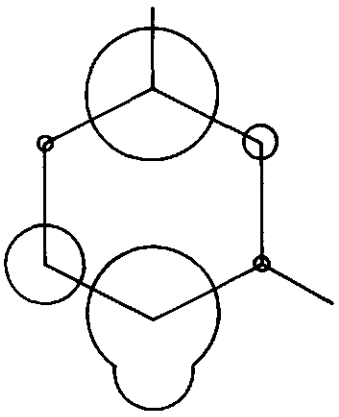
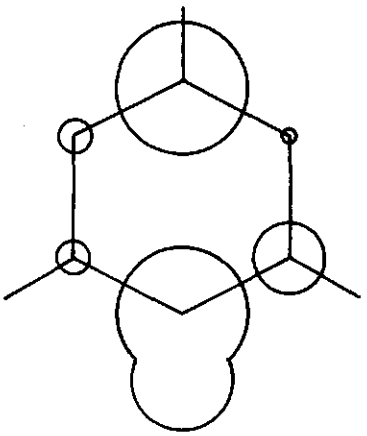
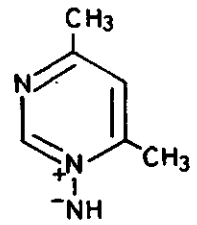
This exclusive addition at position 2 is of considerable interest, since the 1,4,6-trimethylpyrimidinium salt shows a very exclusive addition at position 6 (21)[14] towards NH_3 and a number of other nucleophilic reagents.
However, ammonia forms an adduct at position 6 with N-amino-2,4,6-trimethylpyrimidinium mesitylenesulfonate. Clearly the difference in substitution pattern influences the adduct formation of N-aminopyrimidinium mesitylenesulfonates. This preferential attack of NH_3 is supported by SCF-PPP calculations[15].

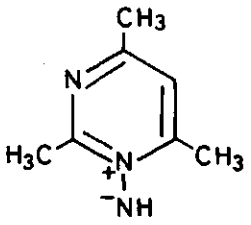
The reactivity of the atoms was determined with the aid of the frontier molecular orbital theory of Fukui[16], giving parameters for the frontier orbital density and superdelocalizability for nucleophilic attack. From these calculations the following conclusions can be drawn.

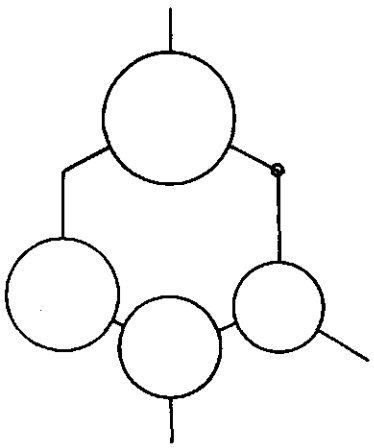
1) In liquid ammonia the imino form is the reactive species. The calculations indicate that the N-methyl and the N-aminopyrimidinium salts have a similar reactivity pattern. Since the N-methylpyrimidinium salts show an exclusive addition at C(6) in the N-amino salts the same position of attack would be

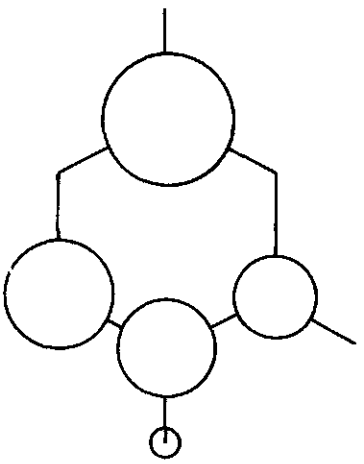


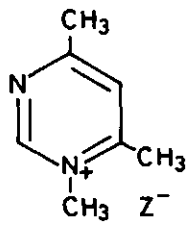


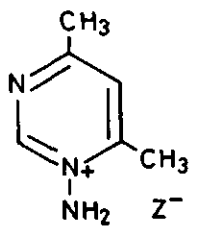












expected. This has not been found.

2) In all the compounds mentioned above, position C(4) is the most reactive, however, no reaction product was found which is obtained from an initial attack at that position.

The importance of ring transformations for the synthetic organic chemistry can be demonstrated by the $N^+-NH_2 \longrightarrow N^+-O^-$ replacement, which occurs in high yield when N-aminopyrimidinium salts are reacted with hydroxylamine into pyrimidine N-oxides (chapter 5). This non-oxidative method of preparation of pyrimidine N-oxides may become a useful synthetic method since it makes it possible to prepare pyrimidine N-oxides, containing substituents which are sensitive to oxidation.

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Samenvatting

Het in dit proefschrift beschreven onderzoek vormt een onderdeel van een onderzoek dat op het laboratorium voor Organische Chemie te Wageningen wordt verricht naar de inwerking van licht en nucleofielen op aza-aromaten. Het onderzoek valt daarom in twee gedeelten uiteen. In de eerste drie hoofdstukken wordt het fotochemisch gedrag van di- en trigesubstitueerde pyrimidine-N-oxiden en van N-benzoyliminopyrimidinen beschreven. In de twee laatste hoofdstukken zijn enige thermische reacties van N-aminopyrimidiniumzouten met stikstofhoudende nucleofielen vermeld.

De verkregen resultaten van het door ons uitgevoerde onderzoek kunnen als volgt worden samengevat.

hoofdstuk 1: Bestraling van 2,4,6-trimethylpyrimidine-1-oxyde in methanol met Rayonet RPR 2537 Å lampen geeft 4(5)-acetyl-2,5-(4)-dimethylimidazool en 1,2,4-trimethyl-1,6-dihydro-6-oxopyrimidine. In benzeen wordt alleen de vorming van het imidazool en een onbekende verbinding X waargenomen. In beide oplosmiddelen worden echter de produkten uit hetzelfde primaire fotoprodukt gevormd. Ringcontractie tot een imidazoolderivaat treedt ook op bij uv-bestraling van 4-chloor-2,6-dimethylpyrimidine-1-oxyde in benzeen en bij 2,6-dimethyl-4-methoxypyrimidine-1-oxyde in methanol. Uit de resultaten van conventionele flitsfotolyses, die uitgevoerd zijn met het doel een inzicht te krijgen over het optreden van een oxaziridine intermediair, kunnen geen conclusies worden getrokken. De rol van enige mogelijke intermediairen, zoals oxaziridines, 1,2,4-oxadiazepines of zwitter ionen, die bij deze omleggingen een rol spelen, is besproken.

hoofdstuk 2: Bestraling van 4,6-di-R-pyrimidine-1-oxyden (R=C_6H_5- of t-Bu) in methanol met een Hanau-hogedrukkwiklamp, respectievelijk in een Rayonet met RPR 2537 Å lampen, geeft 3,5-di-R-pyrazolen.
In het geval R = C_6H_5- wordt er naast het 3,5-difenylpyrazool o.a. het 2-methoxy-4,6-difenylpyrimidine verkregen. Dat deze verbinding via een oxaziridine-intermediair wordt gevormd, werd waarschijnlijk gemaakt door de bestraling uit te voeren in aanwezigheid van kaliumjodide, waarbij jodium wordt gevormd. In de literatuur is vermeld dat er bij de bestraling van 3,6-difenylpyridazine-N-oxyde geen oxaziridine wordt gevormd. Onze bestralingsexperimenten met kaliumjodide zijn hiermee in overeenstemming, aangezien er geen jodium wordt vrijgemaakt.

Een combinatie van de resultaten beschreven in de hoofdstukken één en twee geven naar onze mening een ondubbelzinnig bewijs voor het optreden van een oxaziridine-intermediair tijdens de bestraling van pyrimidine-N-oxyden. Tevens is aangetoond dat de oxaziridinevorming niet algemeen optreedt bij de bestraling van heteroaromatische N-oxyden.

hoofdstuk 3: Bestraling van N-benzoylimino-4,6-dimethylpyrimidine in methanol met een Hanau-hogedrukkwiklamp en een kwartsfilter geeft als hoofdprodukt 2-hydroxymethyl-4,6-dimethylpyrimidine en als bijprodukten - die ontstaan zijn door een splitsing van de stikstof-stikstofbinding - benzamide (14%), N-benzoyl-O-methylhydroxylamine (9%) en methyl-N-fenylcarbamaat (7%). Bij de bestraling van de N-iminoyliden van 4,6-difenyl- en van 2,4,6-trimethylpyrimidine treedt op analoge wijze de splitsing van de N-N-binding op, terwijl geen enkele aanwijzing voor de vorming van de overeenkomstige 2-hydroxymethylpyrimidineverbinding verkregen werd. Er treedt een aanzienlijke teervorming op.

hoofdstuk 4: N-aminopyrimidiniumzouten, zoals 4,6-dimethylpyrimidinium (I)- 4,6-difenylpyrimidinium (II)- en 2,4,6-trimethylpyrimidinium-mesityleensulfonaat (III), vertonen een sterk uiteenlopend gedrag t.o.v. vloeibare ammoniak bij -33^{o}.

1) Er treedt een protonabstractie op van de aminogroep in I, waardoor een 1,3-dipolair deeltje ontstaat, dat onder de reactie-omstandigheden dimeriseert.
2) Adductvorming wordt waargenomen op C(2) bij I of C(6) bij III, hetgeen resulteert in de vorming van pyrazool resp. 1,2,4-triazoolderivaten.
3) Deaminering treedt op bij II en III volgens twee reactiewegen, namelijk één waarbij een nucleofiele aanval van ammoniak op het stikstofatoom van de aminogroep optreedt en één welke plaatsvindt volgens een ringopening/ringsluiting (ANRORS) mechanisme. Het optreden van laatstgenoemd mechanisme is bewezen m.b.v. ^{15}N gemerkt ammoniak.

hoofdstuk 5: N-aminopyrimidiniumzouten geven met hydroxylamine in hoge opbrengst pyrimidine-N-oxyden. Deze niet oxydatieve methode maakt het in principe mogelijk pyrimidine-N-oxyden, met substituenten die gevoelig zijn voor oxydatie, te synthetiseren.

Op deze plaats wil ik allen, die hebben bijgedragen aan het tot stand komen van dit proefschrift daarvoor hartelijk danken.
In de eerste plaats gaat mijn dank uit naar mijn promotor, Prof.Dr.H.C.van der Plas voor zijn stimulerende invloed en grote belangstelling voor het door mij verrichtte onderzoek.
Naast de personen genoemd in de publikaties gaat mijn dank uit naar de heren ir.L.J.H.Martens voor de medewerking aan het onderzoek gedurende zijn ingenieurs-practicum en G.P.Lelyveld voor het vervaardigen van de d.l.c.-platen.
Naar mevrouw M.Snell en de heer B.H.J.van Amersfoort voor het typen van het manuscript en de heer A.Schuchhard voor het verzorgen van de tekeningen.
Naar alle leden van de vakgroep Organische Chemie voor de prettige samenwerking.

Curriculum vitae

De schrijver van dit proefschrift behaalde in 1965 aan de Gemeente H.B.S. te Utrecht zijn diploma H.B.S.-B. In datzelfde jaar begon hij met de scheikunde-studie aan de Rijksuniversiteit te Utrecht. Het kandidaatsexamen (S1) werd afgelegd in december 1969, het doctoraalexamen met hoofdvak organische scheikunde (Prof.Dr.J.F.Arens en Dr.H.J.T.Bos) en bijvak analytische scheikunde (Prof.Dr. G.Dijkstra en Dr.J.H.van der Maas) in mei 1972.
Sinds november 1972 is de auteur verbonden aan het Laboratorium voor Organische Chemie van de Landbouwhogeschool te Wageningen, aanvankelijk in dienst van Z.W.O., vanaf november 1976 in dienst van de Landbouwhogeschool.
Het in dit proefschrift beschreven onderzoek werd uitgevoerd onder leiding van Prof.Dr.H.C.van der Plas.