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Ring Transformations in Reactions of Pyrimidine and N-Alkylpyrimidinium Salts with Nucleophiles

Dit proefschrift met stellingen van Everardus Arnoldus Oostveen, doctorandus in de chemie, geboren te Utrecht op 17 september 1946, is goedgekeurd door de promotor, dr.H.C.van der Plas, hoogleraar in de organische chemie.

De rector magnificus van de Landbouwhogeschool,

J.P.H.van der Want

Wageningen, 22 maart 1977

E.A.Oostveen

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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
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Stellingen

1) De verklaring, die door J.A.Zoltewicz et al. wordt gegeven voor het verschil in reactiviteit tussen ammoniak en water tijdens reacties met quaternaire aza-aromaten, is aanvechtbaar.
J.A.Zoltewicz, T.M.Oestreich, J.K.O'Halloran en L.S.Helmick, J.Org.Chem., 38, 1949 (1973).
Dit proefschrift.

2) De bewering van J.W.Bunting et al., dat adducten van quaternaire aza-aromaten met de methoxidegroep geen ringopening kunnen ondergaan, is onvoldoende gefundeerd.
J.W.Bunting en W.G.Meathrel, Can.J.Chem., 50, 917 (1972).

3) Het door A.Kreutzberger et al. voorgestelde mechanisme voor de vorming van pyrimidine- en pyridinederivaten tijdens de reacties van s-triazine met actieve methyleenverbindingen is aan bedenkingen onderhevig.
A.Kreutzberger en D.Abel, Tetrahedron Lett., 53, 4711 (1969).
A.Kreutzberger en D.Abel, Arch,Pharmaz., 303, 715 (1970).
E.A.Oostveen en H.C.van der Plas, Recl.Trav.Chim.Pays-Bas, 93, 233 (1974).

4) De invloed van de aard van de C(4)-substituent in 4-X-6-methyl (of fenyl)-pyrimidine-1-oxiden $\left[X{=}Cl, Br, I, SC_6H_5, OC_6H_5, N^+(CH_3)_3\right]$ op de competitie tussen ringtransformatie en aminering tijdens reacties met vloeibare ammoniak of kaliumamide in vloeibare ammoniak kan op een andere manier beschreven worden dan met behulp van het "leaving group" karakter van deze substituent.
R.Peereboom en H.C.van der Plas, Recl.Trav.Chim.Pays-Bas, 93, 284 (1974).

5) Tegen het mechanisme dat door S.C.Welch et al. is voorgesteld voor de vorming van 3,4,5,5a, 8aα, 8bα - hexahydro-2aα, 5aβ-dimethyl-2H-nafto [1,8-b,c] furan-2,6(2aH)-7-enedion uit 7α, 8β -dibroom-4α, 10β -dimethyl-trans-9-decalon-4β -carbonzuur zijn bezwaren aan te voeren.
S.C.Welch, C.P.Hagan, D.H.White, W.P.Fleming en J.W.Trotter, J.Amer.Chem.Soc., 99, 549 (1977).

6) Het kleine effect, dat het toevoegen van stoffen die de waterstructuur beïnvloeden, heeft op de hydrolysesnelheid van bis(4-nitrofenyl)carbonaat, rechtvaardigt niet de aanname van F.M. Menger et al., dat veranderingen in de micro-omgeving van het actieve centrum van hydrolytische enzymen geen aanzienlijke bijdrage leveren aan de enzymkatalyse.
F.M.Menger en K.S.Venkatasubban, J.Org.Chem., 41, 1868 (1976).

7) Het effect van een toevoeging van een kleine hoeveelheid ethanol op de kritische micelvormingsconcentratie en op de micelgrootte van natriumdodecylsulfaat kan beter verklaard worden door water/ethanol interactie dan door solubilisatie zoals voorgesteld door H.Suzuki.
H.Suzuki, Bull.Chem.Soc.Japan, 49, 1470 (1976).

8) I.Alkonyi et al. maken voor de verklaring van de remming van pyruvaatdehydrogenase uit duivenborstspier onvoldoende gebruik van de door hen verkregen resultaten.
I.Alkonyi, I.Bolygo, L.Gyoesi en D.Szabo, Eur.J.Biochem., 66, 551 (1976).

9) De wijze, waarop H.Thaler et al. de samenstelling van de polysaccharidefracties in groene en gebrande koffie hebben bepaald en weergegeven is onvoldoende om tot een goed inzicht in deze samenstelling te komen.
H.Thaler, Septième colloque international sur la chimie des cafés, torrefiés et leurs derivés, Hamburg, 9-14 juni 1975 en de hierin vermelde referenties.

10. Bewoners van verpleeghuizen bezitten nog steeds onvoldoende privacy. De oplossing van dit probleem moet niet alleen gezocht worden in veranderingen in bouw en inrichting van deze huizen, maar vereist tevens een verpleegwijze, die meer rekening houdt met het totale menselijke bestaan van de bewoner.

E.A.Oostveen   Wageningen, 8 juni 1977

Ring Transformations in Reactions of Pyrimidine and N-Alkylpyrimidinium Salts with Nucleophiles

ERRATA:

Page 13, Table II

Compound 4b:

$C(CH_3)NH_3$ 2.95 should read 1.89

Compound 4c:

$C_4(CH_3)NH_3$ 2.94 should read 1.9

E.A.Oostveen Wageningen, June 8, 1977.

Ter nagedachtenis aan mijn vader
aan mijn moeder
aan Nanda

Contents

Introduction

The study of the behaviour of aza- and diazaaromatics towards nitrogen-containing nucleophiles is a subject of continuing interest in the Laboratory of Organic Chemistry at Wageningen[1]. A number of different reaction pathways have been discovered during this study, among which those leading to ring transformation are of considerable interest, since they may give products which are otherwise difficult to synthesize or even inaccessible.

The ring transformations which are observed when aza- or diazaaromatics react with ammonia or its conjugate base, the amide ion, can be divided into three main categories.

1) Ring transformations which yield azaaromatics in which the heterocyclic ring contains the same total number of atoms as the starting material, but in which the number of nitrogen atoms is reduced by or augmented with one.

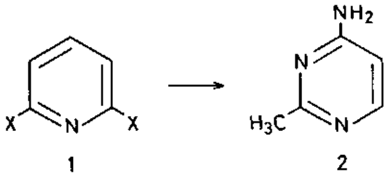
2) Ring modifying processes in which one nitrogen atom in the ring of the starting material is exchanged for one nitrogen atom of the nucleophile, leading thus in fact to the same heterocyclic ring system. We refer to this type of ring interconversion as a degenerate ring transformation.

3) Ring interconversions which yield products in which the heterocyclic ring contains one atom less than the starting substance.

Some examples, demonstrating the general principles of these different types of ring transformations, are treated below.

Category 1. The results of the extensive investigations by Den Hertog and coworkers[2] on the behaviour of halogenopyridines towards potassium amide have revealed that these compounds generally undergo substitution reactions without ring-opening.

An interesting exception was found however with 2,6-dibromopyridine (1), which with potassium amide in liquid ammonia at -33° undergoes a ring transformation into a pyrimidine derivative i.e. 4-amino-2-methylpyrimidine (2)[3]. In this and similar transformations the number of nitrogen atoms in the ring are



X = Cl, Br

Scheme 1

thus augmented with one and one carbon atom of the pyridine ring becomes exocyclic. The formation of 2 has been explained by an initial addition of the amide ion to C(4) followed by a cleavage of the pyridine ring between C(3) and C(4).

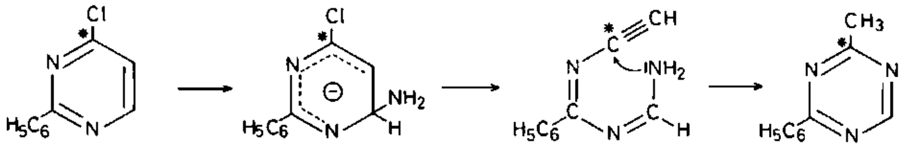
The reverse ring transformation, that is of pyrimidines into pyridines has been discovered independently by a research group of the John Curtin School in Canberra (Australia) and in the Laboratory of Organic Chemistry in Wageningen (The Netherlands). The Australian group found[4] that when 5-aryl-2-methoxypyrimidine (3) was heated with ethanolic ammonia 3,5-diarylpyridine (4) is obtained. The Dutch group discovered[5] that pyrimidine (5), when heated with aqueous methylamine or aqueous ammonia at 190°C, was converted into 5-ethyl-2-methylpyridine (6). Insight into the mechanism of this last-mentioned remarkable ring transformation was obtained by an extensive study of the reaction with the labelled compounds $\left[1,3\text{-}^{15}N\right]$ pyrimidine, $\left[4,6\text{-}^{14}C\right]$ pyrimidine and $\left[5\text{-}^{14}C\right]$ pyrimidine. The results of this study are published in paper VIII[6].


3 4 5 6

X = C_6H_4-p-R

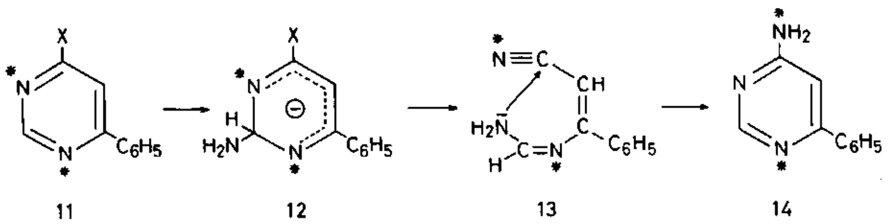
Scheme 2

Halogenopyrimidines are more inclined to ring transformations than halogenopyridines when reacted with potassium amide in liquid ammonia. For example treatment of 4-chloro derivatives of 2-methyl-, 2-ethyl-, 2-phenyl-, 2-N-methylanilino-, 2-N,N-dimethylamino-, 2-morpholino- and 2-piperidinopyrimidine with potassium amide gave reasonable to good yields of the 2-substituted 4-methyl-s-triazines as compared to only traces of the corresponding 4-amino compounds[7,8,9]. By means of ^{1}H-NMR[10] and ^{13}C-NMR[11] spectroscopy, in combination with the results of tracer experiments with 4-chloro-2-phenylpyrimidine-^{14}C (7), convincing evidence was obtained that in these ring transformations the initial attack of the amide ion takes place on position 6. The anionic 1:1 σ-adduct (8) being formed, undergoes a subsequent ring-opening by cleavage of the C(5) - C(6) bond into the intermediary 1-amino-4-ethynyl-diazabutadiene derivative (9). Recyclisation into the s-triazine (10) then occurs by an internal nucleophilic attack of the amidine nitrogen at the sp-carbon atom of the triple bond.


7 8 9 10

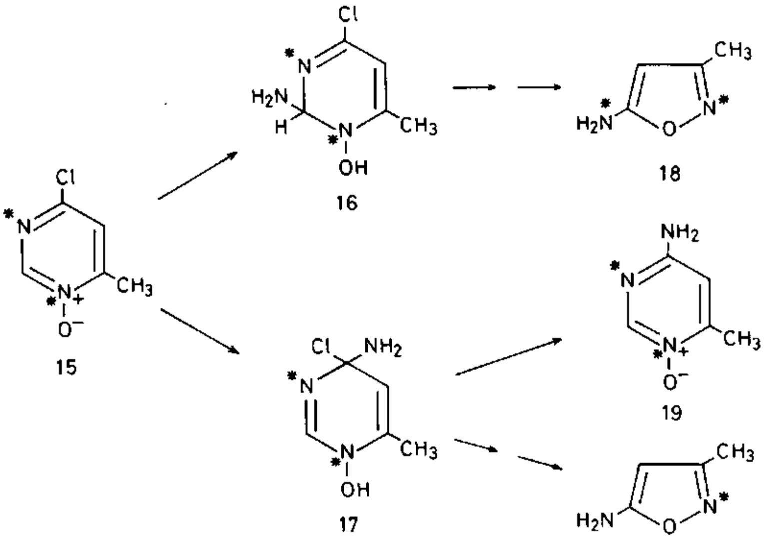
Scheme 3

Category 2. The 4-X-6-phenylpyrimidines (11, X=F, Cl, Br) also undergo easily addition of the amide ion at the "free" position C(2)[13-16]. The anionic σ-adduct (12) can undergo ring-opening into 13. An interesting difference between the open-chain compounds 13 and 9 is that by ring closure of 13 a pyrimidine ring is formed again. That the formation of the 4-aminopyrimidine (14) can indeed proceed according to the pathway 11 ⟶ 12 ⟶ 13 ⟶ 14 and not by an S_NAr substitution was proved by ^{15}N labelling (See Scheme IV). This reaction presents an interesting example of a degenerate ring transformation, leading to a nucleophilic substitution. This substitution mechanism, referred to as an S_N(ANRORC) mechanism, is also found with the 2-X-4-phenylpyrimidines (X=F, Cl, Br, J, SCH_3)[17-20] and with 2-methylthio-1,2,4-triazine[21].



Scheme 4

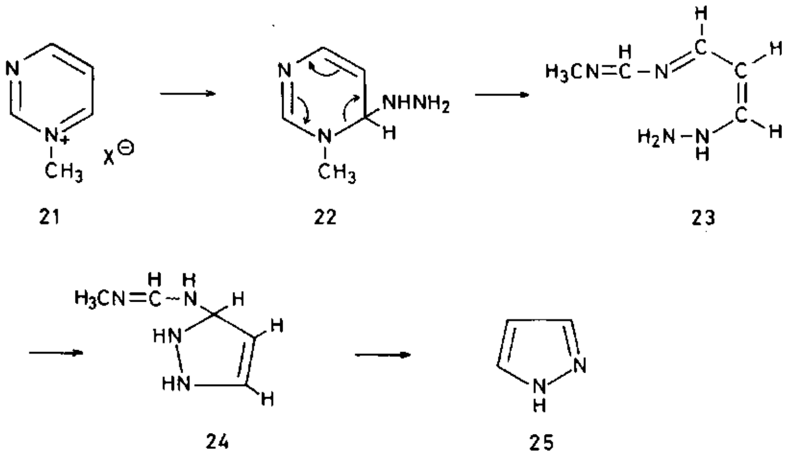
Category 3. When one of the nitrogen atoms of the ring in 4-X-6-phenyl(methyl)pyrimidines is quaternised by oxidation, the reactivity towards liquid ammonia (-33°C) and potassium amide (-75°C) is changed considerably[22,23]. The 4-X-6-phenyl(methyl)pyrimidine 1-oxides give the ring contracted products 5-amino-3-phenyl(methyl)isoxazoles, besides the corresponding 4-aminopyrimidine 1-oxides.
An investigation of this reaction with the ^{15}N-labelled substrates (15) revealed[23] that the conversion into the 4-amino-6-methylpyrimidine 1-oxide (19) does not occur according to an S_N(ANRORC) process. Furthermore it was established that in the 5-amino-3-methylisoxazole the nitrogen-15 is present exocyclic as well as in the ring. Apparently a mixture of 18 and 20 is present. The formation was explained by two concurrent pathways. One involves addition of the nucleophile to the C(2) atom i.e. 16, which by a number of consecutive steps is converted into the isoxazole (18). In the other route an addition to the C(4) atom is the initial step, leading to 17,which finally gives 5-amino-3-methylisoxazole (20).



Scheme 5

The above-mentioned examples show that the ring interconversions of the pyrimidines require drastic conditions when weak nucleophiles (aqueous methylamine, aqueous ammonia) are used and mild conditions with the strongly nucleophilic amide ion. Thus, the ring contraction of 4-X-6-phenyl(methyl)pyrimidine 1-oxides into 5-amino-3-phenyl(methyl)isoxazole can already take place in liquid ammonia at -33°C. Apparently the electrophilic character of the pyrimidine ring is enhanced by the presence of the N-oxide function which is known to have electron-accepting and electron-donating properties[24].

A similar enhancement of the reactivity of the pyrimidine ring towards nucleophiles has been observed when one or two of the nitrogen atoms of the pyrimidine ring are quaternized. Whereas hydrazinolysis of pyrimidine to pyrazole requires high temperatures[25,26] the same ring contraction can be performed at room temperature, when a 1-methylpyrimidinium salt[26] or N-aminopyrimidinium salt[27] is used as substrate. The reaction with the N-alkylpyrimidinium salt (21) can be described to occur by an initial addition of the nucleophile to position 6, yielding a 1,6-dihydropyrimidine derivative (22) which after ring fission between N(1) - C(6) gives a functionalized three-carbon fragment (23). Recyclisation and elimination of the N(1) - C(2) - N(3) fragment gives pyrazole (25).



Scheme 6

Analogously, 1-methylpyrimidinium iodide or 1,3-diethylpyrimidinium tetrafluoroborate on treatment with hydroxylamine at room temperature give isoxazole[28] while with pyrimidine itself a temperature of about 125° is needed.

The recognition of the general principle that quaternisation of the pyrimidine ring makes the molecule more susceptible to nucleophilic reactions, induced us to study the reactions of N-methylpyrimidinium salts and their C-methyl or C-aryl derivatives with different types of nucleophilic reagents in detail.

The results of the reactions of pyrimidinium salts with liquid ammonia and with carbanions are described in paper I[29] and II[30] respectively, and those obtained with benzamidine, pivalamidine, O-methylisoureum, S-methylisothioureum and cyanamide are brought together in paper III[31]. From these studies it became evident that it was worthwhile to undertake a study of the reaction between ammonia and N-alkylpyrimidinium salts, which contain substituents different from an alkyl and/or aryl group.
The syntheses, chemical and physical properties of pyrimidinium salts derived from 4-alkoxy-, 4,6-dialkoxy- and 4-oxopyrimidines are described in paper IV[32]. In paper V[33] the results are given of an X-ray study intended to establish unequivocally the structure of the pyrimidinium salts 4,6-diethoxy-1-ethylpyrimidinium tetrafluoroborate and the isomeric 1,3-diethyl-1,4(3,4)-dihydro-6-ethoxy-4-oxopyrimidinium tetrafluoroborate. The behaviour of the 1,3-diethyl-1,4(3,4)-dihydro-4-oxopyrimidinium salts, and the N-ethylalkoxy- and N-ethyl-4,6-dialkoxypyrimidinium salts towards ammonia is described in paper VI[34] and VII[35] respectively.

References

1) See for a survey:
   a) H.C.van der Plas, Ring Transformations of Heterocycles, vol.1 and 2, Academic Press, London and New York, 1973.
   b) H.C.van der Plas, Lectures in Heterocyclic Chemistry, vol. II, Ed. R.N.Castle and F.Elslager, Utah (1974).
2) M.J.Pieterse and H.J.den Hertog, Recl.Trav.Chim.Pays-Bas 80, 1376 (1961).
3) H.J.den Hertog, H.C.van der Plas, M.J.Pieterse and J.W.Streef, Recl.Trav.Chim.Pays-Bas 84, 1569 (1965).
4) D.J.Brown and B.F.England, Austr.J.of Chem. 23, 625 (1970).
5) H.C.van der Plas, H.Jongejan, G.Geurtsen and Miss M.C.Vollering, Recl. Trav.Chim.Pays-Bas 90, 1246 (1971).
6) E.A.Oostveen and H.C.van der Plas, Recl.Trav.Chim.Pays-Bas 95, 104 (1976).

7) H.C.van der Plas, B.Haase, B.Zuurdeeg and M.C.Vollering, Recl.Trav.Chim.Pays-Bas 85, 1101 (1966).

8) H.C.van der Plas and B.Zuurdeeg, Recl.Trav.Chim.Pays-Bas 88, 426 (1969).

9) H.C.van der Plas, B.Zuurdeeg and H.W.van Meeteren, Recl.Trav.Chim.Pays-Bas 88, 1156 (1969).

10) J.P.Geerts, H.C.van der Plas and A.van Veldhuizen, Recl.Trav.Chim.Pays-Bas 92, 1232 (1973).

11) J.P.Geerts, H.C.van der Plas and A.van Veldhuizen, Org.Magn.Reson. 7, 86 (1975).

12) H.W.van Meeteren and H.C.van der Plas, Recl.Trav.Chim.Pays-Bas 86, 15 (1967).

13) J.de Valk and H.C.van der Plas, Recl.Trav.Chim.Pays-Bas 90, 1239 (1971).

14) J.de Valk and H.C.van der Plas, Recl.Trav.Chim.Pays-Bas 91, 1414 (1972).

15) J.de Valk and H.C.van der Plas, Recl.Trav.Chim.Pays-Bas 92, 145 (1973).

16) J.de Valk, H.C.van der Plas and J.W.A.de Bode, Recl.Trav.Chim.Pays-Bas 92, 442 (1973).

17) A.P.Kroon and H.C.van der Plas, Recl.Trav.Chim.Pays-Bas 92, 1020 (1973).

18) A.P.Kroon and H.C.van der Plas, Recl.Trav.Chim.Pays-Bas 93, 111 (1974).

19) A.P.Kroon and H.C.van der Plas, Recl.Trav.Chim.Pays-Bas 93, 227 (1974).

20) A.P.Kroon and H.C.van der Plas, Recl.Trav.Chim.Pays-Bas 93, 325 (1974).

21) A.Rykowski and H.C.van der Plas, Recl.Trav.Chim.Pays-Bas 94, 204 (1975).

22) R.Peereboom, H.C.van der Plas and A.Koudijs, Recl.Trav.Chim.Pays-Bas 93, 58 (1974).

23) R.Peereboom and H.C.van der Plas, Recl.Trav.Chim.Pays-Bas 93, 277 (1974).

24) A.R.Katritzky and J.M.Lagowski, Chemistry of Heterocyclic N-oxides, Ed. A.T.Blomquist, Academic Press, New York (1972), p 4-12.

25) H.C.van der Plas and H.Jongejan, Tetrahedron Lett, 44, 4385 (1967).

26) H.C.van der Plas and H.Jongejan, Recl.Trav.Chim.Pays-Bas 87, 1065 (1968).

27) F.Roeterdink and H.C.van der Plas, unpublished results.

28) H.C.van der Plas, Miss M.C.Vollering, H.Jongejan and B.Zuurdeeg, Recl.Trav.Chim.Pays-Bas 93, 225 (1974).

29) E.A.Oostveen, H.C.van der Plas and H.Jongejan, Recl.Trav.Chim.Pays-Bas 93, 114 (1974).

30) E.A.Oostveen and H.C.van der Plas, Recl.Trav.Chim.Pays-Bas 93, 233 (1974).

31) E.A.Oostveen, H.C.van der Plas and H.Jongejan, Recl.Trav.Chim.Pays-Bas 95, 209 (1976).

32) E.A.Oostveen and H.C.van der Plas, Recl.Trav.Chim.Pays-Bas 96, 64 (1977).

33) D.Heydenrijk, C.H.Stam, E.A.Oostveen and H.C.van der Plas, Recl.Trav.Chim.Pays-Bas, in the press.

34) E.A.Oostveen and H.C.van der Plas, Recl.Trav.Chim.Pays-Bas 96, 68 (1977).

35) E.A.Oostveen and H.C.van der Plas, Recl.Trav.Chim.Pays-Bas, in the press.

Ring transformations in reactions of heterocyclic compounds with nucleophiles [VII][1] *N*-demethylation during the reaction of *N*-methylpyrimidinium salts with liquid ammonia[2]

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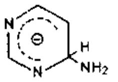
Laboratory of Organic Chemistry, Agricultural University, Wageningen, The Netherlands

(Received October 16th, 1973)

Abstract. On treatment with liquid ammonia at −33°C, the quaternary pyrimidinium salts, *i.e.* 1-methylpyrimidinium methyl sulfate (**4a**), 1,2-dimethylpyrimidinium iodide (**4b**), 1,4,6-trimethylpyrimidinium iodide (**4c**) and 1,2,4,6-tetramethylpyrimidinium iodide (**4d**) demethylate yielding pyrimidine, 2-methyl-, 4,6-dimethyl- and 2,4,6-trimethylpyrimidine, respectively. It was observed that under these conditions 1-methyl-[1,3-^{15}N]-pyrimidinium methyl sulfate yields [1-^{15}N]-pyrimidine. By measuring the PMR spectra of above-mentioned pyrimidinium salts in liquid ammonia it is shown that these salts undergo covalent amination on the 1,6-azomethine bond. These results indicate that the demethylation reaction occurs *via* an Addition-Nucleophile-Ring-Opening-Ring Closure mechanism.

There is a current interest in this laboratory on the occurrence of ring transformations, which take place in reactions of pyrimidines with hydrazine[1] and hydroxylamine[3]. These ring transformations, leading to pyrazoles, 1,2,4-triazoles and isoxazoles, are postulated to be initiated by an attack of the nycleophile at position 2 or 4 of the pyrimidine ring. That addition of a nucleophile to an azomethine bond in diazines can easily take place has recently been proved by PMR studies, showing the formation of anionic σ-addition complexes between an amide ion and pyrimidine (**1**)[4], pyrazine[4], pyridazine[4], 2-substituted 4-chloropyrimidines (**2**)[5] and 2-chloro-3,6-diphenylpyrazine (**3**)[6].



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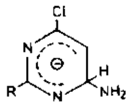

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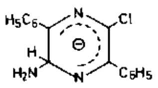
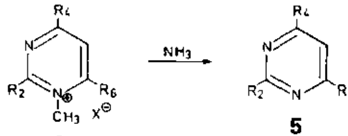


3

In extension of our work on complex formation between diazines and amide ions we became interested in the reactivity of quaternary pyrimidinium salts towards liquid ammonia (thus free of amide ions!).

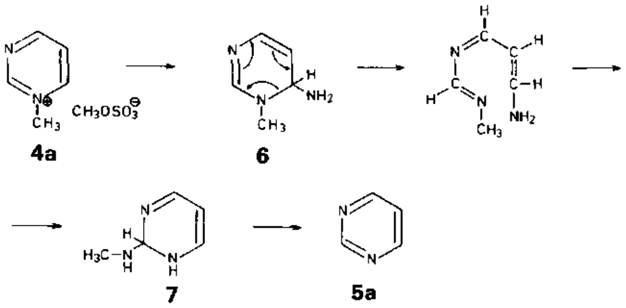
When 1-methylpyrimidinium methyl sulfate (**4a**) is dissolved in liquid ammonia at −33° and this solution is kept at this temperature for 1 h, pyrimidine (**5a**) is formed in a yield of 55–60%. A similar demethylation reaction also occurs on treatment of the 1,2-dimethyl-, 1,4,6-trimethyl- and 1,2,4,6-tetramethylpyrimidinium iodides, (**4b**), (**4c**) and (**4d**), respectively, with liquid ammonia, the corresponding alkylpyrimidines **5b**, **5c** and **5d** being formed in yields of 10–15%, 45–50% and 65–70%.



4 **5**

a) $R_2=R_4=R_6=H$ b) $R_2=CH_3, R_4=R_6=H$
c) $R_2=H, R_4=R_6=CH_3$ d) $R_2=R_4=R_6=CH_3$

The occurrence of a demethylation reaction under such moderate conditions is quite unexpected, but can be understood, when one bears in mind that the formation of σ-complexes of compounds like **4** with liquid ammonia is easily possible – due to a strong polarisation of the azomethine bond in the quaternary salt – leading to covalent amination of the N(1)–C(6) bond. From **4a** 6-amino-1-methyl-1,6-dihydropyrimidine (**6**) is produced from which, after a subsequent ring opening – ring closure sequence the 2-methylamino-1,2-dihydropyrimidine (**7**) is formed, which aromatizes into pyrimidine (**5a**).



Scheme 1

Table I

Intensities of the M + 2-, M + 1- and M-peak in the compounds **8** and **10**			
Compound	M + 2	M + 1	M
8	6.8	0.0	100
10	0.6 (0.6)*	6.3 (7.1)*	100

* This intensity refers to a duplicate experiment.

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[1] See part VI in these series: *H. C. van der Plas* and *H. Jongejan*, Recl. Trav. Chim. Pays-Bas **91**, 336 (1972).

[2] Part XXXVIII on Pyrimidines from this laboratory, see for Part XXXVII *A. P. Kroon* and *H. C. van der Plas*. Recl. Trav. Chim. Pays-Bas **93**, 111 (1974).

[3] Unpublished results.

[4] *J. A. Zoltewicz* and *L. S. Helmick*, J. Amer. Chem. Soc. **94**, 682 (1972).

[5] *J. P. Geerts*, *H. C. van der Plas* and *A. van Veldhuizen*, Recl. Trav. Chim. Pays-Bas **92** (1973).

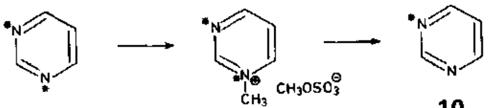
[6] *P. J. Lont* and *H. C. van der Plas*, Recl. Trav. Chim. Pays-Bas **92**, 449 (1973).

Table II Chemical shifts (δ) of the H-atoms in the compounds **4a**, **4b** *and* **4c** *in D_2O and their corresponding 6-amino-1,6-dihydro compounds in NH_3*

Compound	Solvent	2-H	4-H	5-H	6-H	Others
4a	D_2O NH_3	9.60 $\Delta = 2.66$ 6.94	9.39 $\Delta = 3.12$ 6.27	8.17 $\Delta = 3.26$ 4.91	9.21 $\Delta = 4.64$ 4.57	$N(CH_3)\,D_2O: 4.37$ $N(CH_3)\,NH_3: 2.95$
4b	D_2O NH_3		9.0* $\Delta = 2.8$ 6.15	8.01 $\Delta = 3.17$ 4.84	9.2* $\Delta = 4.8$ 4.42	$N(CH_3)\,D_2O: 4.30$ $N(CH_3)\,NH_3: 2.95$ $C(CH_3)\,D_2O: 3.05$ $C(CH_3)\,NH_3: 2.95$
4c	D_2O NH_3	9.34 $\Delta = 2.52$ 6.82		8.00 $\Delta = 3.52$ 4.48		$N(CH_3)\,D_2O: 4.20$ $N(CH_3)\,NH_3: 2.94$ $C_4(CH_3)\,D_2O: 2.83$ $C_4(CH_3)\,NH_3: 2.94$ $C_6(CH_3)\,D_2O: 2.79$ $C_6(CH_3)\,NH_3: < 1.8$

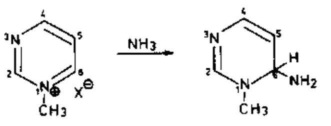
* The position of these peaks cannot be measured accurately because of overlap between the 4-H and 6-H signals.

In order to verify this hypothetical mechanism, we synthesized the double labelled 1-methyl-[1,3-^{15}N]-pyrimidinium salt **9**. If the above-mentioned mechanism (see Scheme 1) is correct, the pyrimidine formed must contain only on *one* position ^{15}N *i.e.* **10**. It was found that this is indeed the case. Mass spectrometric measurements of the intensity of the M + 2, M + 1 and M peak in **8** and in **10** showed that the intensity of the M + 2 peak in **10** was nearly decreased to zero while the M + 1 peak was considerably increased (see Table I). These results fully support the mechanism given in Scheme 1.

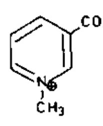


8 **9** **10**

Evidence for the intermediary formation of the dihydro compound **6** in the proposed mechanism was obtained by measuring the PMR spectrum of the solution of the quaternary salt **4a** in liquid ammonia. A solution of the cation **4a** in liquid ammonia at −33° showed a PMR spectrum in which the protons 2-H, 4-H, 5-H and 6-H appear at a much higher field than those observed in solutions of the cation **4a** in D_2O*. As can be seen from the data in Table II this upfield shift is the most pronounced for 6-H (about 4.8 ppm). Also the coupling pattern has changed considerably. The multiplicity of 6-H – being a double multiplet in solution of **4a** in D_2O, due to coupling of 6-H with the 5-H, 4-H and 2-H proton – is reduced to a doublet in liquid ammonia; the 5-H is now coupled with 4-H and 6-H with different coupling constants (7 and 4.5 Hz, respectively) (see Table III). This change in multiplicity combined with the considerable upfield shifts can only be explained by a σ-complex formation between ammonia and **4a**, leading to **6**, in which the hydrogen, attached to the tetrahedral carbon atom is apparently coupled with 5-H only and not with the hydrogen atoms of the amino group, attached to the same carbon; this is probably due to an ammonium ion catalysed proton exchange between solvent and amino group, leading to spin decoupling[7]. The coupling constant $J_{4,5} = 7$ Hz for the vinyl protons 4-H and 5-H in the non aromatic ring fully confirms the proposed structure **6**.



4a **6**



11

Measurements of the PMR spectra of solutions of **4b** and **4c** in liquid ammonia also indicate the occurrence of a covalent amination at position 6. That in **4c** position 6 is occupied by the methyl group does not prevent addition to that site; no indication for the presence of the free cation **4c** in liquid ammonia is observed.

Table III Coupling constants (Hz) for the ring protons of the compounds **4a** *and* **4 b** *and their corresponding 6-amino-1,6-dihydro compounds.*

Compound	Solvent	$J_{4,5}$	$J_{5,6}$
4a	D_2O	5	5
	NH_3	7	4.5
4b	D_2O	5	5
	NH_3	7	4.5

Covalent hydration with pyrimidinium salts has never been observed, but is well-established in *bi*cyclic systems containing the pyrimidine ring[8] (quinazolines, 1,3,x-triazanaphthalenes, pteridines, etc.). Apparently pyrimidinium salts are more inclined to covalent amination than covalent hydration. This phenomenon has been discussed, ascribing to the polar covalent adduct a higher stability in the moderately

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* Changing the solvent from NH_3 to D_2O has no influence on the chemical shifts of the ring hydrogens, as was established by measuring the PMR spectrum of pyrimidine in NH_3 and D_2O.

[7] *R. A. Ogg* Jr., Discuss. Faraday Soc. **17**, 215 (1954); *D. R. Cluther* and *T. J. Swift*, J. Amer. Chem. Soc. **90**, 601 (1968).

[8] *W. L. F. Armarego*, Advan. Heterocycl. Chem. **1**, 253 (1963); *A. Albert* and *W. L. F. Armarego*, Advan. Heterocycl. Chem. **4**, 1 (1965); *D. D. Perrin*, Advan. Heterocycl. Chem. **4**, 43 (1965); *A. Albert*, Angew. Chem. Int. Ed. Engl. **6**, 919 (1967).

polar ammonia than in the very polar solvent water[9]. When this work was finished a publication of *Zoltewicz* appeared[9], in which by PMR spectroscopy the covalent amination of a number of quaternary salts derived from pyridine, quinoxaline and 1,4,5-triazanaphthalene was proved. These results are in excellent agreement with those discussed in this paper. It was further reported that 1-methylpyridinium iodide does not show covalent amination and that those pyridinium salts which contain an electron-withdrawing substituent at position 3 (NO_2, $COCH_3$, SO_2CH_3) give, when reacted with liquid ammonia at *room* temperature, a 3-substituted pyridine. A similar behaviour was observed by us with trigonelline (**11**) which demethylated after treatment with liquid ammonia at −33° into nicotinic acid (yield 30–35%). The demethylation reaction observed with all these pyridinium salts will very probably occur by the same type of mechanism as given in Scheme 1 for the demethylation of the pyrimidinium salts. The primary step is addition of ammonia to the N(1)—C(6) azomethine bond[9].

Experimental part

All melting points are uncorrected.
The measurements of the ^{15}N-contents were carried out on an AEI 902 mass spectrometer. The PMR spectra were recorded on a Jeol JNM-C60 spectrometer, equipped with a JES-VT-3 variable temperature controller. If D_2O was used as solvent, 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) was the internal standard, in liquid ammonia trimethylamine ($\delta = 2.13$) was used as shift standard. 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 FFAP on gaschrom Q 60–80 mesh, weight ratio 20:80.

1. Preparation of the starting materials

a. [1,3-^{15}N]-Pyrimidine was prepared by a procedure similar to that described in the literature for the unlabelled compound[10,11,12].

b. Pyrimidine[13], 1-methylpyrimidinium methyl sulfate[14], 4,6-dimethylpyrimidine[13], 1,4,6-trimethylpyrimidinium iodide[15], 2,4,6-trimethylpyrimidine[16] and trigonelline[17] were synthesized as described in the literature.

c. *1,2-Dimethylpyrimidinium iodide.* A solution of 4.0 g of 4-chloro-2-methylpyrimidine[18] in 30 ml of ethanol was refluxed with 7.7 g of benzenesulphohydrazide for 1–2 hrs. A precipitate was obtained. This whole mixture was evaporated to dryness, after which the residue was boiled with 260 ml of 1*N*-NaOH-solution for 6–7 h. After perforating the solution with ether, drying with $MgSO_4$ and evaporating of the ether, 2,3 g of crude 2-methylpyrimidine were obtained.
2.0 g of this crude product were heated under reflux with 10 ml of methyl iodide for 6 h, 3.3 g of a precipitate were formed which was collected and recrystallised from ethanol. M.p. 173–174° (with decomposition).
Analysis: $C_6H_9IN_2$ (236.07); calc. C 30.52, H 3.84; found C 30.54, H 4.30.

d. *1,2,4,6-Tetramethylpyrimidinium iodide.* 1,0 g of 2,4,6-trimethylpyrimidine was heated under reflux with 9 ml of methyliodide for 20 h; 1.0 g of a precipitate was collected. M.p. 257–258° (with decomposition) (recrystallised from ethanol). $C_8H_{13}IN_2$ (264.12); calc. C 36.37, H 4.96; found C 36.53, H 5.10.

2. Demethylation of the quaternary salts 4a, 4b, 4c, 4d and 11 on reaction with liquid ammonia at −33°

1.0–1.5 g of the quaternary salt were dissolved in 60–80 ml of liquid ammonia. After one hour the liquid ammonia was evaporated, and to the residue obtained 30–40 ml of water were added. This solution was perforated with ether for 24 h. After drying the ethereal extracts with $MgSO_4$, the solvent was distilled off and in the residual oil the yields of demethylated products were determined by GLC and by weight, after isolation by column chromatography. In the case of trigonelline the residue, which was obtained after evaporating off the liquid ammonia, was dissolved in a small amount of water and the pH was adjusted to 3.4. By cooling at 0° a voluminous precipitate was formed, which was collected and recrystallised from water. Yield 30–35%.

Acknowledgement

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We are indebted to Mr. *A. van Veldhuizen* and Dr. *P. Smit* for their help during the PMR measurements, to Drs. *C. A. Landheer* and Mr. *W. P. Combé* for mass spectrometric data and to Mr. *W. Ch. Melger* for his advice on the chromatographic part of this study.

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[9] *J. A. Zoltewicz, T. M. Oestrich, J. K. O'Halloran* and *L. S. Helmick*, J. Org. Chem. **38**, 1949 (1973).

[10] *J. B. Dickey* and *A. R. Gray*, Org. Synth. **18**, 8 (1938).

[11] *J. Baddily* and *A. Topham*, J. Chem. Soc. **1944**, 678.

[12] *N. Whittaker*, J. Chem. Soc. **1951**, 1565.

[13] *H. Bredereck, R. Gompper* und *G. Morlock*, Chem. Ber. **90**, 942 (1957).

[14] *H. Bredereck, R. Gompper* und *H. Herlinger*, Chem. Ber. **91**, 2832 (1958).

[15] *H. C. van der Plas* and *H. Jongejan*, Recl. Trav. Chim. Pays-Bas **87**, 1065 (1968).

[16] *A. Bowman*, J. Chem. Soc. **1937**, 494.

[17] *A. Hautasch*, Chem. Ber. **19**, 31 (1886).

[18] *H. J. den Hertog, H. C. van der Plas, M. J. Pieterse* and *J. W. Streef*, Recl. Trav. Chim. Pays-Bas **84**, 1569 (1965).

Ring transformations in reactions of heterocyclic compounds with nucleophiles (IX)[1]
Conversion of *N*-methylpyrimidinium salts into pyridines by carbanions[2]

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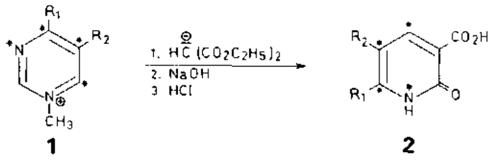
(Received February 18th, 1974)

Abstract. On treatment with active methylene compounds in basic media the quaternary pyrimidinium salts, *i.e.* methyl 1-methylpyrimidinium sulfate, 1-methyl-4-phenylpyrimidinium iodide and 1-methyl-5-phenylpyrimidinium iodide are converted into pyridine derivatives. The mechanism of the reaction is discussed.

Recently[3] we reported that some quaternary *N*-methylpyrimidinium salts on treatment with liquid ammonia demethylate into the corresponding pyrimidines. Strong evidence, based on the results of PMR-spectroscopy has been presented that these *N*-demethylation reactions are initiated by an addition of the nucleophile ammonia to the C_6-position of the strongly polarised N_1-C_6 azomethine bond. A subsequent opening of the 1,6-dihydropyrimidine ring, followed by ring closure and aromatisation through loss of methylamine explains how the $\overset{\oplus}{N}-CH_3$ moiety of the pyrimidinium salt is replaced by the N atom of the ammonia. In the present work we report on the generality of this replacement reaction on showing that the $-C_2-\overset{\oplus}{N}-CH_3$ part of *N*-methylpyrimidinium salts can be replaced by a two-carbon fragment, leading thus in fact to a ring transformation of a pyrimidine derivative into a pyridine derivative.



a) $R_1=R_2=H$ b) $R_1=C_6H_5$, $R_2=H$ c) $R_1=H$, $R_2=C_6H_5$

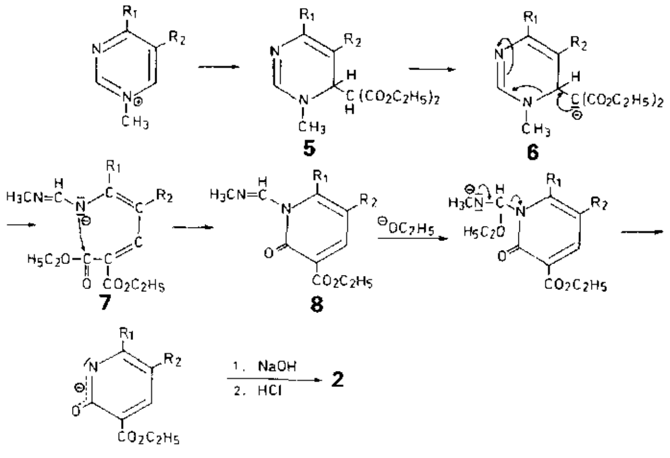
Scheme 1

Methyl 1-methylpyrimidinium sulfate (**1a**), 1-methyl-4-phenylpyrimidinium iodide (**1b**) or 1-methyl-5-phenylpyrimidinium iodide (**1c**), when reacted with the carbanion of diethyl malonate, gave products, which after saponification were identified as 1,2-dihydro-2-oxonicotinic acid (**2a**), its 6-phenyl derivative (**2b**) and its 5-phenyl derivative (**2c**), respectively. A similar ring transformation was observed, when 1-methyl-4-phenylpyrimidinium iodide (**1b**) is reacted with the carbanions of malonodinitrile and ethyl cyanoacetate, 2-amino-3-cyano-6-phenylpyridine (**3a**) and 2-amino-3-(ethoxycarbonyl)-6-phenylpyridine (**3b**) being obtained. Surprisingly, in the reaction of 1-methyl-5-phenylpyrimidinium iodide (**1c**) with the carbanion of ethyl cyanoacetate not the expected 2-amino-3-(ethoxycarbonyl)-5-phenylpyridine (**3c**), but 3-cyano-1,6-dihydro-2-oxo-5-phenylpyridine (**4**) was obtained

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) $X=CO_2C_2H_5$; $R_2=C_6H_5$; $R_1=H$

Scheme 2

All the pyrimidine-to-pyridine ring transformations, mentioned in this paper, show the characteristic feature that the



Scheme 3

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[1] Part IX in these series on ring transformations, see for part VIII *H. C. van der Plas, Miss M. C. Vollering, H. Jongejan* and *B. Zuurdeeg*, Recl. Trav. Chim. (Pays-Bas) **93**, 225 (1974). See for a general review on this subject, *H. C. van der Plas*, "Ring transformations of Heterocycles", Vol. I and II, Academic Press (London and New York) 1973.

[2] Part XLIII on pyrimidines from this laboratory, see for part XLII *J. P. Geerts, C. A. H. Rasmussen, H. C. van der Plas* and *A. van Veldhuizen*, Recl. Trav. Chim. (Pays-Bas) **93**, 231 (1974).

[3] *E. A. Oostveen, H. C. van der Plas* and *H. Jongejan*, Recl. Trav. Chim. (Pays-Bas) **93**, 114 (1974).

Table I Physical properties of the pyridinederivatives.

Starting Substances	Structure	Yield %	Recryst. from	Observed m.p. (°C)	Lit. m.p. (°C)	Products: PMR spectra Chem. shifts (δ values) and coupling constants *(J)* of the pyridine ringprotons	Products: IR spectra
1a + A[a]	**2a**	40–45	X[b]	256–258[c] (dec)	255[10] (dec)	7.73 (d); $J_{4,5}=J_{5,6}=6.0$ cps 6.50 (t)	C=O 1720–1730 cm^{-1}
1b + A[a]	**2b**	45–50	X[b]	305–306 (dec)	302–303[10] (dec)	6.86 (d)[d] $J_{4,5}=7.5$ cps	C=O 1750 cm^{-1}
1c + A[a]	**2c**	45–50	X[b]	296–298	283[11]	7.95 (d) $J_{4,6}=3.0$ cps 8.23 (d)	C=O 1710 cm^{-1}
1b + B[a]	**3b**	35–40	Y[b]	107–108	108[10]	7.02 (d) $J_{4,5}=7.6$ cps 8.15 (d)	C=O 1690 cm^{-1} NH_2 3380 cm^{-1} 3500 cm^{-1}
1b + C[a]	**3a**	55–60	Y[b]	149–150		7.10 (d) $J_{4,5}=7.6$ cps 7.72 (d)	NH_2 3400 cm^{-1} 3500 cm^{-1}
1c + B[a]	**4**	45–50	Z[b]	241–242	232–233[11]	8.07 (d) $J_{4,6}=3.0$ cps 8.32 (d)	C≡N 2220 cm^{-1}

[a] A: diethyl malonate; B: ethyl cyanoacetate; C: malonodinitrile.
[b] X: glacial acetic acid; Y: ethanol (abs); Z: methanol.
[c] Mixed melting-point determination gave no depression.
[d] The position of the other doublet cannot be measured because of overlap with the phenyl protons.

$N_3-C_4-C_5-C_6$ fragment of the pyrimidine ring forms the $N_1-C_6-C_5-C_4$ part of the new pyridine ring and the N_1-C_2 fragment of the pyrimidine ring is replaced by two carbonatoms of the active methylene compound.

The fact that quaternary pyrimidinium salts are capable of forming addition complexes with nucleophiles at the highly electron-deficient position 6 indicate that a 1,6-dihydro compound, *e.g.* **5** in the reaction with the anion of diethyl malonate, is a reasonable step to initiate the ring transformation. When the methylene proton is sufficiently acidic to form the carbanion **6**, ring opening can easily occur, yielding a non-isolable open-chain product **7**. Ring closure by an intramolecular nucleophilic attack of the nitrogen at the ethoxycarbonyl-group gave **8**. Degradation of the amidine side-chain in **8** can be easily envisaged in this basic medium by the way indicated.

In the cases, where the anion of malonodinitrile or ethyl cyanoacetate reacts with 1-methyl-4-phenylpyrimidinium iodide, as intermediates are proposed **10** (X=CN or $CO_2C_2H_5$). The ring closure can now easily take place by addition of nitrogen across the C≡N group. The question, why, in the intermediate **11**, which is proposed in the reaction of the 5-phenyl derivative **1c** with the anion of ethyl cyanoacetate, the ring cyclisation takes place mainly by loss of an ethoxide anion and not by addition across the C≡N group, is not quite clear at the moment.

10

11

Scheme 4

When this work was nearly completed several papers[4,5,6] appeared in the literature describing conversions of pteridine and 8-azapurine into pyridopyrazine and triazolopyridine derivatives, respectively, by the action of active methylene compounds, thus without the use of a basic catalyst. Both molecules are characterised by a strong tendency for addition of nucleophiles; across the N_3-C_4 bond in pteridine and across the N_1-C_6 bond in 8-azapurine.

The transformation of pyrimidine and 4-methylpyrimidine into the corresponding pyridine derivatives during the reaction with malonodinitrile in the absence of a catalyst, was also mentioned. We have observed that ethyl cyanoacetate and diethyl malonate do not react with *non*-quaternised pyrimidines even in the presence of sodium ethoxide. So, our method of activating pyrimidines by quaternisation and then reacting them with active methylene compounds in basic media seems to provide us with a useful extension of methods for converting pyrimidines into pyridines.

Experimental part

Melting points are uncorrected.

The PMR spectra were recorded on a Jeol JNM-C60 spectrometer, using tetramethylsilane (TMS) or 3-(trimethylsilyl)propanesulfonate as internal standard.

The IR spectra were recorded with a Perkin Elmer-spectrometer (model 237).

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[4] *A. Albert* and *H. Mizuno*, J. Chem. Soc. Perkin I, **1973**, 1615.

[5] *A. Albert* and *W. Pendergast*, J. Chem. Soc. Perkin I, **1973**, 1794.

[6] *A. Albert* and *H. Mizumo*, J. Chem. Soc. Perkin I, **1973**, 1974.

[7] *H. Bredereck, R. Gompper* and *G. Morlock*, Chem. Ber. **90**, 942 (1957).

[8] *H. Bredereck, R. Gompper* und *H. Herlinger*, Chem. Ber. **91**, 2832 (1958).

[9] *W. H. Davies* and *H. A. Piggott*, J. Chem. Soc. **1945**, 349.

[10] *A. Dornow* and *P. Karlson*, Chem. Ber. **73**, 542 (1940).

[11] *M. Julia, H. Pinhas* and *J. Igolen*, Bull, Soc. Chim. France **1966** (7), 2387.

1) Preparation of the starting materials

a) Pyrimidine[7], methyl 1-methylpyrimidinium sulfate[8] and 4-phenylpyrimidine[8] were synthesized as described in the literature.

b) *1-Methyl-4-phenylpyrimidinium iodide*

2.0 g (1.3×10^{-2} mol) of 4-phenylpyrimidine were heated under reflux with 8 ml of methyl iodide for 3-4 hrs; a precipitate was obtained, which was collected and dried. Yield: 2.6 g (67 %). M.p. 167–168°C (dec.) (recrystallized from ethanol).
Analysis: $C_{11}H_{11}IN_2$ (298.13); calc. C 44.31, H 3.72; found: C 44.59, H 3.78.

c) *4-Hydrazino-5-phenylpyrimidine*

A solution of 6.3 g (3.3×10^{-2} mole) of 4-chloro-5-phenylpyrimidine[9] and 8 ml of hydrazine hydrate in 50 ml of absolute ethyl alcohol was heated under reflux for 3 hrs. The solvent was distilled off. The resulting solid residue was washed with water and dried. Yield: 5.2 g (85 %). M.p. 141–143°C (recrystallized from ethanol).
Analysis: $C_{10}H_{10}N_4$ (186.21); calc. C 64.50, H 5.41; found: C 64.71, H 5.41.

d) *1-Methyl-5-phenylpyrimidinium iodide*

To a suspension of 4.2 g (2.3×10^{-2} mole) of 4-hydrazino-5-phenylpyrimidine in 85 ml of water were added, portionwise, 20.0 g of silver acetate. After addition the whole mixture was heated under reflux for 3 hrs. The precipitate was removed by filtration. After extracting the filtrate with chloroform, the extracts were dried over $MgSO_4$. Evaporation of the chloroform gave 2.2 g of crude 5-phenylpyrimidine. 1.0 g of this crude product was heated under reflux with 8 ml of methyl iodide for 6 h, 1.2 g of a precipitate were formed which was collected and recrystallised from ethanol. M.p. 194–196° (with decomposition).
Analysis: $C_{11}H_{11}IN_2$ (298,13); calc. C 44.31, H 3.72; found: C 44.06, H 3.80.

2) Reactions of the *N*-methylpyrimidinium salts with the active methylene compounds diethyl malonate, ethyl cyanoacetate and malonodinitrile

A solution of 1.0 g of the *N*-methylpyrimidinium salt, the methylene compound (1 equiv.) and sodium ethoxide (2 equivs.) in 30 ml of ethanol (abs) was heated to 90–110° during 3–4 hrs. In the case when ethyl cyanoacetate or malonodinitrile was used as active methylene compound, after the reaction, 30–40 ml of water were added to the reaction mixture; upon cooling a voluminous precipitate was formed, which was collected, recrystallized and dried. In the reaction of 1-methyl-5-phenylpyrimidinium iodide with ethyl cyanoacetate the precipitate was formed after the addition of 30–40 ml of 6*N*-HCl. The reaction mixtures obtained from the *N*-methylpyrimidinium salts and diethyl malonate were basified with 30–40 ml of concentrated potassium hydroxide solution (100 g/l); this solution was heated to 110–120° during $\frac{1}{2}$ h. Acidification of the resulting reaction mixture with concentrated hydrochloric acid gave a precipitate which was collected, recrystallized and dried.

The yields obtained in the several reactions and the physical data of all products formed are summarized in Table I; the elemental analyses of these products are given in Table II.

Table II Elemental analyses of the pyridine derivatives

Compound	Empirical formula	Mol. weight	Calculated		Found	
			C	H	C	H
2a	$C_6H_5NO_3$	139.11	52.00	3.62	51.80	3.59
2b	$C_{12}H_9NO_3$	215.20	66.97	4.22	66.40*	4.21
2c	$C_{12}H_9NO_3$	215.20	66.97	4.22	66.51	4.46
3a	$C_{12}H_9N_3$	195.22	73.83	4.65	73.92	4.62
3b	$C_{14}H_{14}N_2O_2$	242.28	69.40	5.82	69.53	5.92
4	$C_{12}H_8N_2O$	196.21	73.46	4.11	73.18	4.22

* This compound easily loses carbon dioxide, giving 1,2-dihydro-2-oxo-6-phenylpyridine; this explains why the carbon analyses are somewhat over error limit.

Acknowledgement

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We are indebted to Mr. *A. van Veldhuizen* for measuring PMR- and IR-spectra and to Mr. *W. P. Combé* for carrying out the microanalyses.

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Ring transformations in reactions of heterocyclic compounds with nucleophiles (XIII)[1]

Degenerate ring transformations of *N*-methylpyrimidinium salts into 2-substituted pyrimidines[2]

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Abstract. On treatment of the quaternary pyrimidinium salts *i.e.* 1-methyl-4-phenylpyrimidinium iodide and 1-methyl-5-phenylpyrimidinium iodide with cyanamide, *O*-methylisouronium chloride or bis[*S*-methylisothiouronium] sulfate in basic media, 2-amino-4-phenylpyrimidine and 2-amino-5-phenylpyrimidine are formed respectively. A ring transformation is involved in which the two-atom fragment N(1)–C(2) of the pyrimidine ring is replaced by an N–C fragment of the reagent. On reacting 1-methylpyrimidinium iodide with benzamidinium chloride or pivalamidinium chloride in a solution of sodium ethoxide in ethanol, 2-phenylpyrimidine and 2-*tert*-butylpyrimidine are formed respectively.

It is proved by ^{15}N-labelling that this nucleophilic substitution occurs *via* a ring transformation in which the N(1)–C(2)–N(3) fragment of the pyrimidine is replaced by the N–C–N fragment of the amidine. These reactions are new examples of a nucleophilic substitution occurring according to an S_N(ANRORC) mechanism.

Introduction

The dominant characteristic of the chemistry of pyrimidine is the susceptibility of the ring system to addition reactions by nucleophiles. Among such nucleophilic reagents the strong nucleophilic amide ion has received considerable attention[3-8]. We observed that activation of the pyrimidine ring by quaternisation enables addition of carbanionic reagents[9] and of the weak nucleophiles, ammonia[10], hydrazine[11] and hydroxylamine[12] under very mild conditions. The addition takes place to the strongly polarised N(1)–C(6) bond. After addition ring opening can occur affording an open-chain intermediate, which gives, after recyclisation and aromatisation, a heterocycle in which the atoms of the ring skeleton are different from those present in the starting substance.

The ring transformations of pyrimidinium salts with ammonia have led to the concept of so-called degenerate ring transformations. It is proved, for example, by ^{15}N-labelling that the *N*-demethylation which occurs on reaction of methylpyrimidinium salts with liquid ammonia[10], acts in such a way that the $\equiv N^+-CH_3$ moiety of the pyrimidinium salt is replaced by the N atom of the ammonia. Thus, though the starting substance and product have the same ring system, in fact a ring transformation is involved. We refer to this type of ring transformation as degenerate ring transformation.

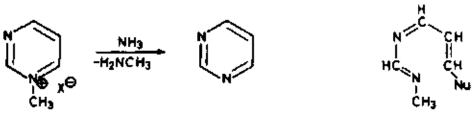

Fig. 1

In this demethylation reaction it is evident that the ring opening, which takes place by fission of the N(1)–C(6) bond in the adduct, must give a formamidine derivative as open-chain intermediate. It occurred to us that if amidines were used as nucleophiles, instead of ammonia or amide ions, the addition to C(6) of these nucleophiles would also occur readily. After the ring opening a diamidine derivative would be obtained which could recyclise into a 2-substituted pyrimidine. Examples of similar degenerate ring transformations had already been found[13] with *s*-triazine and proved to be an excellent synthetic route to the preparation of substituted *s*-triazines.

Results and Discussion

The reaction of *N*-methylpyrimidinium iodide (**1**) with a solution of benzamidine in basic medium has been found to yield 2-phenylpyrimidine (**6a**, R = C_6H_5) (45%) (see Table I). The reaction of **1** 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, a small yield (10%) of 2-*t*-butylpyrimidine (**6a**, R = *t*-Bu) could be isolated.

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[1] See for part XII in these series: *E. A. Oostveen* and *H. C. van der Plas*, Recl. Trav. Chim. (Pays-Bas) **95**, 104 (1976). For a general review on this subject see: *H. C. van der Plas*, Ring Transformations of Heterocycles, vol. 1 and 2, Academic Press, London and New York, 1973.

[2] Part LIV on Pyrimidines from this laboratory; Part LIII: see reference 1.

[3] *J. A. Zoltewicz* and *L. S. Helmich*, J. Amer. Chem. Soc. **94**, 682 (1972).

[4] *A. P. Kroon* and *H. C. van der Plas*, Recl. Trav. Chim. (Pays-Bas) **93**, 227 (1974).

[5] *A. P. Kroon, H. C. van der Plas* and *G. van Garderen*, Recl. Trav. Chim. (Pays-Bas) **93**, 325 (1974).

[6] *J. P. Geerts, C. A. H. Rasmussen, H. C. van der Plas* and *A. van Veldhuizen*, Recl. Trav. Chim. (Pays-Bas) **93**, 231 (1974).

[7] *J. P. Geerts, H. C. van der Plas* and *A. van Veldhuizen*, Recl. Trav. Chim. (Pays-Bas) **92**, 1232 (1973).

[8] *J. P. Geerts, H. C. van der Plas* and *A. van Veldhuizen*, Org. Magn. Reson. **7**, 86 (1975).

[9] *E. A. Oostveen* and *H. C. van der Plas*, Recl. Trav. Chim. (Pays-Bas) **93**, 233 (1974).

[10] *E. A. Oostveen, H. C. van der Plas* and *H. Jongejan*, Recl. Trav. Chim. (Pays-Bas) **93**, 114 (1974).

[11] *H. C. van der Plas* and *H. Jongejan*, Tetrahedron Letters **44**, 4385 (1967).

[12] *H. C. van der Plas*, Miss *M. C. Vollering, H. Jongejan* and *B. Zuurdeeg*, Recl. Trav. Chim. (Pays-Bas **93**, 225 (1974).

[13] *F. C. Schaefer* and *G. A. Peters*, J. Amer. Chem. Soc. **81**, 1470 (1959).

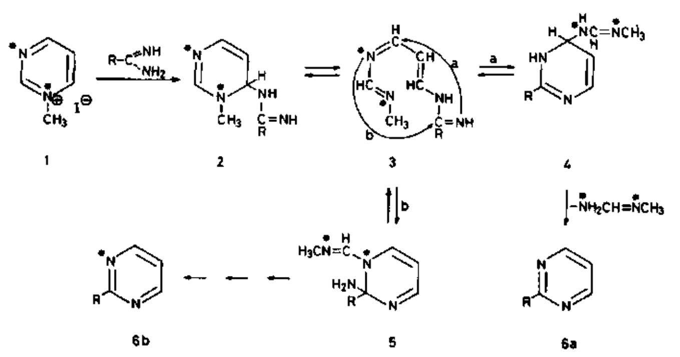
Table I Reaction of N*-methylpyrimidinium salts with amidines, isouronium- and isothiouronium salts and cyanamide.*

Pyrimidinium salt	Equiv. of Reagent	Base	Reaction time h	Reaction temp. °C	Product	Yield %
1	4 equiv. D[a]	4 equiv. I[b]	5	110–120	**6a** (R = C_6H_5)	45
1	5 equiv. E[a]	12 equiv. I[b]	1	210	**6a** (R = *t*-Bu)	10
9	1.3 equiv. A[a]	2.2 equiv. II[b]	3	110–120	**11**	60
10	1.3 equiv. A[a]	2.2 equiv. II[b]	3	110–120	**12**	35
9	2.0 equiv. B[a]	10 equiv. I[b]	6	110–120	**11**	35
10	2.0 equiv. B[a]	10 equiv. I[b]	6	110–120	**12**	15
9	2.0 equiv. C[a]	10 equiv. I[b]	3	110–120	**11**	70
10	2.0 equiv. C[a]	10 equiv. I[b]	3	110–120	**12**	40

[a] A: cyanamide; B: *O*-methylisouronium chloride; C: bis[*S*-methylisothiouronium] sulfate; D: benzamidinium chloride; E: pivalamidinium chloride.

[b] I: sodium ethoxide; II: potassium hydroxide.

The following mechanism (shown in Scheme 1), involving a degenerate ring transformation, is advanced for this reaction, which may also, in fact, be regarded as a nucleophilic substitution at C(2) of the pyrimidine ring.



Scheme 1

The transient intermediate (**2**) formed by attack of the nucleophilic nitrogen of the amidine at C(6) is in a tautomeric ring-chain equilibrium with **3**. This can revert either to **2** or cyclise to the dihydropyrimidines **4** (route a) or **5** (route b). Aromatisation into the 2-substituted pyrimidine (**6**) takes place, by a base-catalysed loss of *N*-methylformamidine.

In order to decide between the two possible reaction paths, a and b, we synthesized the ^{15}N-labelled *N*-methyl-[1,3-^{15}N]-pyrimidinium iodide[12], containing an excess of ^{15}N (5%). We observed that after the reaction with benzamidinium hydrochloride *unlabelled* 2-phenylpyrimidine is obtained. From this result we have to conclude that this degenerate ring transformation proceeds *via* the pathway involving the reaction intermediates **2**, **3** and **4**. In the conversion of **1** into **6a** (R = C_6H_5) we have thus encountered the first example of a nucleophilic substitution in which the N–C–N fragment of the nucleophilic amidine replaces a *three*-atom N(1)–C(2)–N(3) fragment of the pyrimidine ring. This nucleophilic substitution reaction represents an interesting new variation of the S_N(ANRORC) mechanism, which is already well-documented to occur in the amination of halogenopyrimidines[14,15] and halogenopyrazines[16] with potassium amide in liquid ammonia, but only involves the replacement of *one* of the ring nitrogens by the nitrogen of the amide ion *e.g.* **7** → **8**.

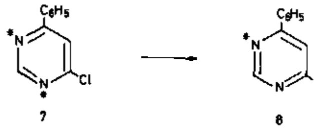
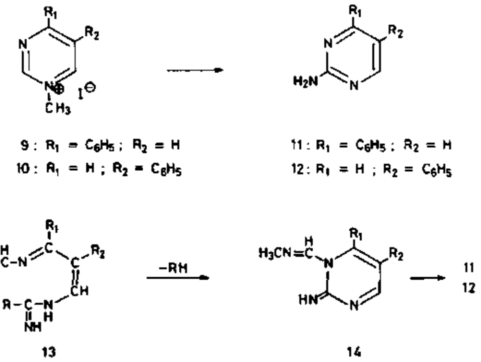


Fig. 2

Compounds in which an amidino group is attached to an element other than carbon have also been investigated. We observed that **1**, when reacted with *O*-methylisourea or with *S*-methylisothiourea in basic medium, does *not* give a substituted pyrimidine. Reaction of 1-methyl-4-phenylpyrimidinium iodide (**9**) and 1-methyl-5-phenylpyrimidinium iodide (**10**) with *O*-methylisourea leads to a complicated reaction mixture from which we were able to isolate as main product 2-amino-4-phenylpyrimidine (**11**) (35%) and 2-amino-5-phenylpyrimidine (**12**) (15%), respectively (see Table I). The corresponding reaction of **9** and **10** with *S*-methylisothiourea also gives **11** and **12**, respectively; the yields, however, were much higher (70% and 40%). Careful investigation of the reaction mixtures obtained after the reaction of **1** and **9** with *O*-methylisourea or *S*-methylisothiourea indicate that no detectable amounts of 2-methoxy- or 2-(methylthio)pyrimidines were present.

It is evident that both amino compounds are formed by a displacement of the *two*-carbon C(2)–N(1) fragment of the pyrimidinium salt by the N–C fragment of the nucleophile; again a new variant of the S_N(ANRORC) mechanism. It is



Scheme 2

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[14] *J. de Valk* and *H. C. van der Plas*, Recl. Trav. Chim. (Pays-Bas) **91**, 1414 (1972).

[15] *J. de Valk, H. C. van der Plas* and *J. W. A. de Bode*, Recl. Trav. Chim. (Pays-Bas) **92**, 442 (1973).

[16] *P. J. Lont, H. C. van der Plas* and *A. J. Verbeek*, Recl. Trav. Chim. (Pays-Bas) **91**, 949 (1972).

convenient to consider the formation of both amino products **11** and **12** by a ring closure of the diamidine **13** (R = OCH_3, SCH_3), due to loss of a methoxide or thiomethoxide ion into the 2-imino-1,2-dihydropyrimidine (**14**) which loses the N(1) side-chain by a base-catalysed fragmentation of the N(1)—C bond. Attempts to prepare **11** or **12** by reaction of **9** and **10** with guanidine failed. With cyanamide however reasonable yields of **11** and **12** were obtained (60% and 35% respectively).

The above-mentioned results are quite different from those obtained when *s*-triazine is reacted with *O*-methylisourea and *S*-methylisothiourea and guanidine. Three *different* products *i.e.* 2-methoxy-, 2-(methylthio)- and 2-amino-*s*-triazine are formed respectively. Why in these reactions the intermediate **11** (replace CR_2 by N) always recyclizes by loss of NH_3 is unclear at this moment.

Experimental part

Melting points are uncorrected.
The PMR spectra were recorded on a Jeol JNM-C 60 spectrometer using tetramethylsilane (T.M.S.) as internal standard. The ^{15}N contents were measured on an A.E.I. MS 902 mass spectrometer.

1. *Preparation of the starting materials*

a) 1-Methyl-4-phenylpyrimidinium iodide[9] (**9**) and 1-methyl-5-phenylpyrimidinium iodide[9] (**10**) were synthesized as described previously in the literature.
b) 1-Methyl-[1,3-^{15}N]-pyrimidinium iodide (**1**).
2.0 g (25 mmoles) of [1,3-^{15}N]-pyrimidine[10] containing 5% ^{15}N in excess, were heated under reflux with 10 ml of methyl iodide for 8 h; a precipitate was obtained, which was collected and dried. Yield 4.5 g (81%). M.p. 135–136° (dec.) (recrystallized from ethanol). Analysis: $C_5H_7IN_2$ (222.04); calc. C 27.04, H 3.18; found C 26.83, H 3.14.

2. *General procedure for the reaction of the* N-*methylpyrimidinium salts* **1**, **9** *and* **10** *with benzamidinium chloride, pivalamidinium chloride,* O-*methylisouronium chloride, bis[*S-*methylisothiouronium] sulfate and cyanamide in basic solution*

1.0 g of the quaternary salt were heated in 40–50 ml of a solution of the above-mentioned nucleophilic reagent and base in abs. ethanol. In Table I are summarized the number of equivalents of the nucleophile and base used, the reaction time, the reaction temperature and the yields of the product obtained after the reaction. The work-up was usually performed as follows: the solvent was removed *in vacuo* and to the residue obtained, 60–70 ml of water were added. This solution was extracted with chloroform. After drying the chloroform extracts with $MgSO_4$ the solvent was distilled off. From the residue obtained, the desired product was isolated either by column chromatography (using silica gel and ethyl acetate as eluent) – such as 2-phenylpyrimidine (**6a**, R = C_6H_5) or 2-*tert*-butylpyrimidine (**6a**, R = *t*-Bu) – or by crystallisation – 2-amino-4-phenylpyrimidine (**11**) and 2-amino-5-phenylpyrimidine (**12**) – in abs. ethanol.

a) 2-Amino-4-phenylpyrimidine (**11**). M.p. 163–164° (Lit.[17]: 164–165°); mixed melting point determination with an authentic specimen gave no depression.

b) 2-Amino-5-phenylpyrimidine (**12**). M.p. 162–163° (Lit.[18]: 161–163°); ^{1}H-NMR ($CDCl_3$): δ 5.4 (N–H broad), δ 7.40 (C_6H_5, s), δ 8.47 ($H_{4,6}$, s).

*c) 2-*tert*-Butylpyrimidine* (**6a**, R = *t-Bu*). ^{1}H-NMR ($CDCl_3$): δ 1.43 (*t*-Bu, s), δ 7.04 (H_5, t), δ 8.65 ($H_{4,6}$, d); mass spectrum, *m/e* 136 (M^+), 121 ($M^+ - CH_3$), 57 (t-$C_4H_9^+$).
M.p. of 2-*tert*-butylpyrimidine chloroaurate: 146–147° (from aqueous ethanol). Analysis: $C_8H_{13}AuCl_4N_2$ (476.23): calc. C 20.18, H 2.75, Au 41.41; found C 20.45, H 2.84, Au 41.34.

d) 2-Phenylpyrimidine (**6a**, *R = C_6H_5*). ^{1}H-NMR ($CDCl_3$): δ 7.10 (H_5, t), δ 7.52 (3 × H C_6H_5, m), δ 8.52 (2 × H C_6H_5, m), δ 8.78 ($H_{4,6}$, d); mass spectrum: *m/e* 156 (M^+), 129 ($M^+ - HCN$), 103 ($C_6H_5CN^+$), 76 ($C_6H_5CN^+ - HCN$).

Acknowledgement

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[17] *W. K. Detweiler* and *E. D. Amstutz*, J. Amer. Chem. Soc. **73**, 5451 (1951).

[18] *T. V. Protopopova, V. T. Klimko* and *A. P. Skoldinov*, Khim. Nauka i Prom. 4, 805 (1959).

On the *N*-ethylation of 4-alkoxy- and 4,6-dialkoxypyrimidines with triethyloxonium tetrafluoroborate[1]

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Abstract. Reaction of 4-alkoxy-(**1–4**) or 4,6-dialkoxypyrimidines (**5–9**) with 1 equivalent of triethyloxonium tetrafluoroborate yields 4-alkoxy-*N*-ethyl (**13–15**) or 4,6-dialkoxy-*N*-ethylpyrimidinium salts (**10–12**), respectively. With two or more equivalents of this reagent, rearrangement of *N*-ethylalkoxypyrimidinium salts into 1-ethyl-3-alkyl-1,4(3,4)-dihydro-4-oxopyrimidinium salts (**16–22**) takes place. These rearrangements can also be performed by heating. The mechanism of these rearrangement reactions is discussed.

In connection with our studies on ring transformations of *N*-alkyl-, *C*-methyl- or *C*-phenylpyrimidinium salts with nucleophiles[2–6], we became interested in the preparation of *N*-alkylated pyrimidinium salts derived from 4-alkoxy- and 4,6-dialkoxypyrimidines. There are only a few reports[7,8,9] in the literature dealing with the *N*-alkylation of these alkoxypyrimidines. This is in contrast to the *N*-alkylation of 2-alkoxy- and 2,4-dialkoxypyrimidines, which has been studied in more detail due to its potential use as a synthetic tool for the preparation of various 1,2-dihydro-2-oxopyrimidine nucleosides, when protected glycosyl halides are used as quaternisation reagents (Hilbert-Johnson procedure)[10,11,12]. In these reactions, initially alkylation of the nitrogen atom *N*(1) takes place. Since the alkoxy group in 2-alkoxypyrimidinium salts is generally unstable at room temperature, conversion into 1-alkyl-1,2-dihydro-2-oxopyrimidines takes place readily. *N*-Alkyl derivatives of 2-oxo- and 4-oxopyrimidines, respectively, can be formed also by rearrangements of 2-alkoxy- or 4-alkoxypyrimidines in the presence of organic bases, functioning as catalysts[13,14,15]. However, in these base-catalysed rearrangements it is the alkyl group attached to the oxygen atom which migrates to the neighbouring nitrogen atom. In our study we chose as alkylating agent Meerwein's triethyloxonium tetrafluoroborate (TOF)[16]. This reagent has already been applied to the alkylation of pyrimidine and 4,6-dimethylpyrimidine and was found to give *di*-quaternary pyrimidinium salts when two or more equivalents of TOF are used[17].

1 : $R^1 = C_2H_5$; $R^2 = R^3 = H$
2 : $R^1 = CH_3$; $R^2 = R^3 = H$
3 : $R^1 = C_2H_5$; $R^2 = H$; $R^3 = C_6H_5$
4 : $R^1 = C_2H_5$; $R^2 = C_6H_5$; $R^3 = H$

5 : $R^1 = C_2H_5$; $R^2 = H$
6 : $R^1 = C_2H_5$; $R^2 = CH_3$
7 : $R^1 = C_2H_5$; $R^2 = C_6H_5$
8 : $R^1 = CH_3$; $R^2 = CH_3$
9 : $R^1 = CH_3$; $R^2 = C_6H_5$

Figure 1

In this paper we report on the reaction of several 4-ethoxypyrimidines (**1**, **3**, **4**), 4-methoxypyrimidine (**2**), the 4,6-diethoxypyrimidines (**5–7**) and 4,6-dimethoxypyrimidines (**8**, **9**) with one and with two or more equivalents of TOF.

4,6-Dialkoxypyrimidines (5–9)

We will discuss first the alkylation of **5**, since this reaction has been investigated in detail, the structures of the products obtained have been unequivocally established by X-ray analysis and the results are applicable to the other compounds investigated.

Reaction of **5** with *one* equivalent of TOF in the solvent dichloroethane gave a product A, m.p. 97–98° (yield 74%) and treatment of **5** with *two* equivalents of the same reagent gave product B, m.p. 181–182° (yield 55%). Elemental analyses showed that both A and B have the molecular formula $C_{10}H_{17}BF_4N_2O_2$. Product A could be converted into B by treatment with one or more equivalents of TOF or by heating for a few minutes at 230°. In the IR spectrum of B a strong absorption is present at 1730 cm^{-1}, probably due to the presence of a CO group, which is absent in A.

The ^{1}H-NMR spectra were as follows: compound A δ 9.05 (s), δ 6.92 (s), δ 4.3–4.9 (m), δ 1.3–1.8 (m); compound B δ 9.50 (s), δ 6.14 (s), δ 4.0–4.7 (m), δ 1.3–1.8 (m). These data indicate that A and B are pyrimidinium salts containing three different ethyl groups, but unfortunately they did not enable us to make a *conclusive* structure assignment. In order to establish the structures firmly an X-ray study was undertaken, showing that compound A is 4,6-diethoxy-1-ethyl-

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[1] Part LVIII on pyrimidines from this laboratory; See for Part LVII *F. Roeterdink* and *H. C. van der Plas*, Recl. Trav. Chim. (Pays-Bas) **95**, 282 (1976).

[2] *H. C. van der Plas* and *H. Jongejan*, Tetrahedron Letters **44**, 4385 (1967).

[3] *H. C. van der Plas*, Miss *M. C. Vollering*, *H. Jongejan* and *B. Zuurdeeg*, Recl. Trav. Chim. (Pays-Bas) **93**, 225 (1974).

[4] *E. A. Oostveen*, *H. C. van der Plas* and *H. Jongejan*, Recl. Trav. Chim. (Pays-Bas) **93**, 114 (1974).

[5] *E. A. Oostveen* and *H. C. van der Plas*, Recl. Trav. Chim. (Pays-Bas) **93**, 233 (1974).

[6] *E. A. Oostveen* and *H. C. van der Plas*, Recl. Trav. Chim. (Pays-Bas) **95**, 209 (1976).

[7] *D. J. Brown* and *T. Teitei*, Australian J. Chem. **17**, 567 (1964).

[8] *M. Prystas*, Collection Czechoslov. Chem. Comm. **32**, 1298 (1967).

[9] *M. Prystas*, Collection Czechoslov. Chem. Comm. **32**, 4241 (1967).

[10] *J. Priml* and *M. Prystas*, Advan. Heterocyclic Chem. **8**, 115 (1967).

[11] *T. Ueda* and *H. Nishino*, J. Amer. Chem. Soc. **90**, 1678 (1968).

[12] *T. Ueda* and *H. Ohtsuka*, Chem. Pharm. Bull of Japan **21**, 1451 (1973).

[13] *D. J. Brown* and *R. V. Foster*, J. Chem. Soc. **1965**, 4911.

[14] *D. J. Brown* and *R. V. Foster*, Australian J. Chem. **19**, 1487 (1966).

[15] *D. J. Brown* and *T. C. Lee*, Australian J. Chem. **21**, 243 (1968).

[16] *H. Meerwein*, Org. Synth. **46**, 113 (1966).

[17] *T. J. Curphey*, J. Amer. Chem. Soc. **87**, 2063 (1965); *T. J. Curphey* and *A. S. Prasad*, J. Org. Chem. **37**, 2259 (1972).

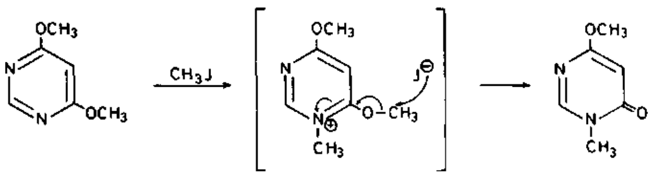
pyrimidinium tetrafluoroborate (**10**) and compound B 1,3-diethyl-1,4(3,4)-dihydro-6-ethoxy-4-oxopyrimidinium tetrafluoroborate (**16**). A detailed description of these structure assignments will be published elsewhere[18].

10) R^1=C$_2$H$_5$, R^2=H, R^3=OC$_2$H$_5$
11) R^1=CH$_3$, R^2=CH$_3$, R^3=OCH$_3$
12) R^1=CH$_3$, R^2=C$_6$H$_5$, R^3=OCH$_3$
13) R^1=C$_2$H$_5$, R^2=R^3=H
14) R^1=CH$_3$, R^2=R^3=H
15) R^1=C$_2$H$_5$, R^2=C$_6$H$_5$, R^3=H

16) R^1=C$_2$H$_5$, R^2=H, R^3=OC$_2$H$_5$
17) R^1=C$_2$H$_5$, R^2=CH$_3$, R^3=OC$_2$H$_5$
18) R^1=C$_2$H$_5$, R^2=C$_6$H$_5$, R^3=OC$_2$H$_5$
19) R^1=C$_2$H$_5$, R^2=R^3=H
20) R^1=CH$_3$, R^2=R^3=H
21) R^1=C$_2$H$_5$, R^2=C$_6$H$_5$, R^3=H
22) R^1=C$_2$H$_5$, R^2=H, R^3=C$_6$H$_5$

Figure 2

The above mentioned results are quite different from those obtained when 4,6-dimethoxypyrimidine (**23**) is reacted with methyl iodide[7,9] (Scheme 1). The 1-methyl-4,6-dimethoxypyrimidinium iodide (**24**) is formed initially but is further demethylated by the iodide ion to 1,6-dihydro-4-methoxy-1-methyl-6-oxopyrimidine (**25**). That **10** is stable is due to the less nucleophilicity of the BF_4^- ion.



23 24 25

Scheme 1

Similarly, reaction of 4,6-dimethoxy-2-methylpyrimidine (**8**) and 4,6-dimethoxy-2-phenylpyrimidine (**9**) with one equivalent of TOF in dichloroethane gave 4,6-dimethoxy-1-ethyl-2-methylpyrimidinium tetrafluoroborate (**11**) and 4,6-dimethoxy-1-ethyl-2-phenylpyrimidinium tetrafluoroborate (**12**), respectively. The structural evidence of both compounds is based on microanalytical data, the absence of a CO absorption around 1720 cm^{-1} (ruling out the possibility of an isomeric 4-oxo structure) and on the ^{1}H-NMR data (see Table I). The 4-oxopyrimidinium derivatives **17** and **18** were prepared directly from the 4,6-diethoxypyrimidines **6** and **7**, respectively, on melting with the TOF reagent. Both compounds show the characteristic CO stretching vibration at 1710–1730 cm^{-1}.

4-Alkoxypyrimidines (1–4)

Interaction of **1** with one equivalent of TOF in dichloroethane, leads to ethylation at N(1), yielding 4-ethoxy-1-ethylpyrimidinium tetrafluoroborate (**13**). The structure assignment is based on the ^{1}H-NMR data (see Table I). Essential in this assignment is the argument that the H(2) and H(6) hydrogen atoms are coupled ($J_{2,6}$ 2.2 Hz), indicating that they are located adjacent to a positive nitrogen. A similar coupling has been observed in aromatic *N*-oxides and quaternary salts derived from pyrimidines; it was usefully applied for structure identification[19]. The occurrence of this small coupling constant rules out the possibility that the isomeric 6-ethoxy-1-ethylpyrimidinium tetrafluoroborate is formed in the ethylation of **1**. Also ethylation of 4-ethoxy-2-phenylpyrimidine (**4**) gives substitution at N(1), the pyrimidinium salt **15** being obtained. Surprisingly, ethylation of 4-ethoxy-6-phenylpyrimidine (**3**) occurs mainly at N(3), 6-ethoxy-1-ethyl-4-phenylpyrimidinium salt (**26**, R^2 = H; R^3 = C$_6$H$_5$) being formed. The structure assignment of **26** was made on the observation that the methylene protons of the ethoxy group appear at a lower field (about 0.3 ppm) than those in the compounds **13** and **15** (see Table I). We ascribe this difference to the fact that in **26** the positive charge at the N(1) atom has a deshielding effect on the neighbouring ethoxy group.

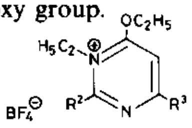


Figure 3

26

Table I Chemical shifts (ppm) and coupling constants (Hz) of **10–15** *and* **26**.

Compound*	H(5)	R^2	R^3	H(a) N$^+$CHCH$_3$	H(a) OCHCH$_3$	H(b) N$^+$CH$_2$CH$_2$	H(b) OCH$_2$CH$_2$	OCH$_3$	$J_{5,6}$	$J_{2,6}$
13	7.45	9.36	8.90	4.65	4.75	1.50	1.65	–	7.2	2.2
14	7.47	9.36	8.90	4.63	–	1.64	–	4.28	6.8	1.8
15	7.44	7.77 (m)	8.90	4.46	4.68	1.48	1.50	–	7.5	–
26	8.20	9.36	8.3–8.5 (2H) 7.5–7.8 (3H)	4.63	5.00	1.64	1.68	–	–	–
11	6.84	2.95	4.35	4.45	–	1.46	–	4.16	–	–
12	7.05	7.7 (m)	4.45	4.3	–	1.41	–	4.18	–	–
10	6.92	9.05	–	4.3–4.9		1.3–1.8		–	–	–

* Compounds **10** and **12–14** were measured in acetone-d_6; compounds **11**, **15** and **26** in a mixture of acetone-d_6 and D$_2$O.

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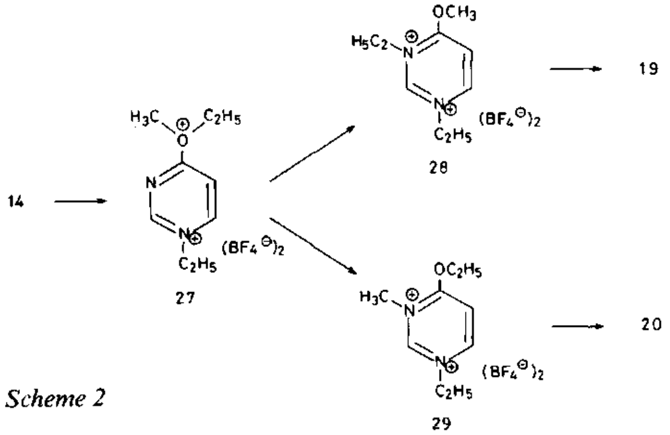
[18] *D. Heijdenrijk, C. H. Stam, H. C. van der Plas* and *E. A. Oostveen*, Recl. Trav. Chim. (Pays-Bas), submitted.

[19] *M. Ogata, H. Wtanabe* and *K. Tori*, Tetrahedron Lett. **1964**, 19; *K. Tori, M. Ogata* and *H. Kano*, Chem. Pharm. Bull of Japan **11**, 681 (1963); *S. Castellano* and *R. Rostelnik*, J. Amer. Chem. Soc. **90**, 141 (1968); *R. A. Abramovitch* and *J. B. Davis*, J. Chem. Soc. B **1966**, 1137; *R. Peereboom, H. C. van der Plas* and *A. Koudijs*, Recl. Trav. Chim. (Pays-Bas) **93**, 58 (1974).

Treatment of the 1-ethyl-4-ethoxypyrimidinium salt **13** with TOF leads to the 4-oxopyrimidinium salt **19**. This reaction can proceed along two pathways: a) initial ethylation at N(3) followed by loss of the ethyl group of the ethoxy group adjacent to N(3) (Hilbert-Johnson mechanism), b) initial addition at oxygen, leading to an oxonium type intermediate which changes into **19** by a migration of one of the ethyl groups to position N(3), followed by loss of a second ethyl group, from the C(4) oxygen in a Hilbert-Johnson fashion. A similar mechanism is proposed for the acid-catalysed rearrangement of 3,6-dimethoxypyridazine into 1-methyl-3-methoxypyridazin-6-one[20]. In order to distinguish between these two mechanisms, 1-ethyl-4-methoxypyrimidinium tetrafluoroborate (**14**) was prepared and treated with TOF. A mixture of pyrimidinium salts was obtained, consisting, according to the ^{1}H-NMR spectrum, of 80% of 1,4(3,4)-dihydro-1-ethyl-3-methyl-4-oxopyrimidinium tetrafluoroborate (**20**) – also prepared from 3,4-dihydro-3-methyl-4-oxopyrimidine and triethyloxonium tetrafluoborate – and 20% of 1,3-diethyl-1,4(3,4)-dihydro-4-oxopyrimidinium tetrafluoroborate (**19**). On refluxing 4-methoxypyrimidine with two equivalents of TOF in dichloroethane, a mixture of **19**/**20** in a 40/60 ratio was obtained. From these results we can conclude that alkylation of **14** proceeds *via* **27** and **28** (Scheme 2). This interesting difference with the Hilbert-Johnson mechanism can be explained by the fact that TOF is a much harder alkylating agent than those used in the Hilbert-Johnson conversions and therefore reacts more easily with the harder centre *i.e.* the oxygen atom. It was of interest to observe that on heating **14** at 270–280° for a few minutes *only* **20** is formed. It is apparent that in this thermally-induced rearrangement the reaction takes a different course; the alkyl group attached to oxygen migrates to the neighbouring nitrogen atom. The same thermal behaviour is observed with **15** yielding the corresponding 4-oxopyrimidinium salt **21** and with **26** giving **22**, together with compound **3**.



Scheme 2

Experimental part

Melting points are uncorrected. The PMR spectra were recorded on a Jeol JNM-C60 spectrometer using tetramethylsilane (TMS) or 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as internal standard. The IR spectra were recorded with a Perkin Elmer-spectrometer (model 237).

1) Preparation of the starting materials

a) 4-ethoxypyrimidine (**1**)[21] 4-methoxypyrimidine (**2**)[22], 4,6-diethoxypyrimidine (**5**)[23], 4,6-diethoxy-2-methylpyrimidine (**6**)[23], 4,6-diethoxy-2-phenylpyrimidine (**7**)[23], 4,6-dimethoxy-2-methylpyrimidine (**8**)[25], 4,6-dimethoxy-2-phenylpyrimidine (**9**)[24] and 3,4-dihydro-3-methyl-4-oxopyrimidine[26] were synthesized as described previously.

b) *4-Ethoxy-6-phenylpyrimidine* (**3**)

To a solution of 4.3 g (187 mmol) of sodium in 80 ml of absolute ethanol a solution of 7.0 g (36.8 mmol) of 4-chloro-6-phenylpyrimidine [27] in 50 ml of absolute ethanol was added portionwise. After additional refluxing for 3 hrs the solvent was removed *in vacuo*. The residue was dissolved in water and this solution was extracted with chloroform. After drying the extracts over $MgSO_4$, the solvent was distilled off. The residue was distilled *in vacuo* yielding 5.3 g (72%) of **3** (B.p. 172–173°C/23 mm). M.p. picrate of **3**: 145–146°C (from ethanol). Analysis: $C_{18}H_{15}N_5O_8$ (429.34) calc.: C 50.35, H 3.52; found C 50.50, H 3.58.

c) *4-Ethoxy-2-phenylpyrimidine* (**4**)

The synthesis of this compound was similar to that of **3**, see section 1b. From 9.9 g (52 mmol) of 4-chloro-2-phenylpyrimidine[28] we obtained 6.8 g (65%) of **4** (B.p. 163–164°/20 mm). M.p. picrate of **4**: 197–198° (from ethanol). Analysis: $C_{18}H_{15}N_5O_8$ (429.34) calc.: C 50.35, H 3.52; found C 50.42, H 3.62.

2) Reactions of the 4-alkoxy- and 4,6-dialkoxypyrimidines with triethyloxonium tetrafluoroborate (TOF)

For conversion into the corresponding 1-ethylpyrimidinium salts 1 equiv. of TOF was used, for the formation of the 1,3-diethyl-4-oxopyrimidinium salts 2.2 equivs. were employed.

2.1. The compounds **10–16** and **19–20** were prepared by treatment of the pyrimidines in dichloroethane solution for the appropriate length of time. After the reaction, the solvent was distilled off under reduced pressure. If possible the residue was crystallised twice from absolute ethanol and washed with absolute ether. The reaction conditions, yields, melting points, IR data and elemental analyses are summarized in Table II.

1,3-Diethyl-1,4(3,4)-dihydro-6-ethoxy-4-oxopyrimidinium tetrafluoroborate (**16**)

This compound has been obtained also from 4,6-diethoxy-1-ethylpyrimidinium tetrafluoroborate (**10**) by heating at 230°/20 mm for 3 minutes (yield 60%) and by treatment of **10** with 2.0 equivs. of the Meerwein reagent in dichloroethane for 1 h (yield 80%). ^{1}H-NMR (acetone-d_6): δ 4.0–4.7 (m), δ 1.3–1.8 (m). (See for ring protons, Table III.)

1,3-Diethyl-1,4(3,4)-dihydro-4-oxopyrimidinium tetrafluoroborate (**19**)

This compound was also obtained by heating 4-ethoxy-1-ethylpyrimidinium tetrafluoroborate (**13**) for 3 min at 275°/20 mm; yield 85%; and further by treatment of **13** with 1.5 equivs. of triethyloxonium tetrafluoroborate for 2 h in refluxing dichloroethane. Yield 80%. ^{1}H-NMR (acetone-d_6): δ 4.36 (q), δ 4.18 (q), δ 1.57 (t), δ 1.45 (t); see for the ring protons Table III.

2.2. The following compounds were prepared by melting together the pyrimidine and the Meerwein reagent at a temperature of 100–110°; in the reaction of **6** additional heating at about 250° was

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[20] *K. Eichenbergen, A. Staehelin* and *J. Druey*, Helv. Chim. Acta **37**, 837 (1954).

[21] *H. C. van der Plas* and *H. Jongejan*, Recl. Trav. Chim. (Pays-Bas) **91**, 336 (1972).

[22] *D. J. Brown* and *L. N. Short*, J. Chem. Soc. **1953**, 331.

[23] *H. C. van der Plas* and *H. Jongejan*, Recl. Trav. Chim. (Pays-Bas) **89**, 680 (1970).

[24] *M. P. L. Caton, M. S. Grant, D. L. Pain* and *R. Slack*, J. Chem. Soc. **1965**, 5467.

[25] *D. Pfleiderer* and *H. Mosthaf*, Ber. **90**, 728 (1957).

[26] *S. Hünig* and *K. H. Oette*, Ann. Chem. **640**, 98 (1961).

[27] *H. C. van der Plas* and *G. Geurtsen*, Tetrahedron Lett. 1964, 2093.

[28] *S. Rukeman* and *A. S. Hemmy*, Ber. **30**, 2029 (1897).

Table II Reaction conditions for the formation of **10–16**, **19–20** *and some of their physical properties.*

Compound	Reaction conditions		Yield (%)	M.p. (°C)	IR spectra (cm^{-1}) (KBr)	Empirical formula	Mol. weight	Analysis (%)			
								Calculated		Found	
	Time	Temperature						C	H	C	H
10[1]	1 h	reflux	74	97–98	$C{=}N^+$– 1640 (s)	$C_{10}H_{17}BF_4N_2O_2$	284.07	42.28	6.03	42.11	5.92
11	0.5 h	ambient	70	173–174	$C{=}N^+$– 1635 (s)	$C_9H_{15}BF_4N_2O_2$	270.05	40.03	5.60	40.21	5.71
12	1 h	reflux	38	130–131	1630 (s) 1655 (s)	$C_{14}H_{17}BF_4N_2O_2$	332.11	50.63	5.16	50.75	5.15
13[2]	15 min	ambient	90	oil	$C{=}N^+$– 1645 (s)	$C_8H_{13}BF_4N_2O$	240.02	40.03	5.46	40.18	5.70
14	0.5 h	ambient	84	77–79	$C{=}N^+$– 1640 (s)	$C_7H_{11}BF_4N_2O$	225.99	37.20	4.91	36.91	5.14
15	0.5 h	ambient	67	89–90	$C{=}N^+$– 1645 (s)	$C_{14}H_{17}BF_4N_2O$	316.11	53.19	5.42	53.21	5.16
16[3]	1 h	reflux	55	181–182	C=O 1730 (s)	$C_{10}H_{17}BF_4N_2O_2$	284.07	42.28	6.03	42.61	6.10
19	1 h	reflux	70	116–117	C=O 1710–1730 (s)	$C_8H_{13}BF_4N_2O$	240.02	40.03	5.46	40.21	5.35
20[4]	15 min	ambient	85	101–102	C=O 1720–1730 (s)	$C_7H_{11}BF_4N_2O$	225.99	37.20	4.91	36.92	5.23

1) % N: calc. 9.86; found 9.78.
2) The colourless oily residue obtained after distilling off the solvent was washed with dry distilled ether.
3) % N: calc. 9.86; found 9.88.
4) This compound was obtained on treating 3,4-dihydro-3-methyl-4-oxopyrimidine with 1 equiv. of TOF.

necessary. After cooling the mixture was dissolved in absolute ethanol. After a few minutes crystals separated. In some cases it appeared to be necessary to add some absolute ether to start crystallisation. The crystals were collected, recrystallised from absolute ethanol and washed with absolute ether.

1,3-Diethyl-1,4(3,4)-dihydro-6-ethoxy-2-methyl-4-oxopyrimidinium tetrafluoroborate (**17**)

4,6-Diethoxy-2-methylpyrimidine (**6**) was melted together with 2.1 equivs. of triethyloxonium tetrafluoroborate for 0.5 h at 120°. The resultant reaction mixture was heated for 5 min at 255°/20 mm. Yield: 22%. M.p. 227–228°. ^{1}H-NMR (acetone-d_6/D_2O): δ 4.0–4.6 (m), δ 1.2–1.7 (m). (See for the ring protons Table III.) IR-spectrum (KBr): 1705–1730 cm^{-1} (s) (C=O). Analysis: $C_{11}H_{19}BF_4N_2O_2$ (298.10): calc. C 44.32, H 6.42; found C 44.29, H 6.29.

1,3-Diethyl-1,4(3,4)-dihydro-6-ethoxy-4-oxo-2-phenylpyrimidinium tetrafluoroborate (**18**)

Reaction time 1.5 h. Yield 40%. M.p. 169–170°.
^{1}H-NMR (acetone-d_6): δ 4.50 (q), δ 3.97 (q), δ 3.84 (q), δ 1.53 (t), δ 1.15 (t). (See for the other protons Table III.) IR spectrum (KBr): 1710 cm^{-1} (s) (C=O). Analysis: $C_{16}H_{21}BF_4N_2O_2$ (360.16): calc. C 53.55, H 5.88; found C 53.33, H 6.04.

6-Ethoxy-1-ethyl-4-phenylpyrimidinium tetrafluoroborate (**26**)

Reaction time: 20 min. Yield 44%. M.p. 178–179°. IR spectrum (KBr): 1630 cm^{-1} (s) ($C{=}\overset{\oplus}{N}$). Analysis: $C_{14}H_{17}BF_4N_2O_2$ (316.11): calc. C 53.19, H 5.42; found C 52.90, H 5.18.

Table III Chemical shifts (ppm) and coupling constants (Hz) of **16–22**.

Compound	R^3	R^2	H(5)	$J_{5,6}$	$J_{2,6}$
16[2]	–	9.50	6.14	–	–
17[2]	–	3.08	6.07	–	–
18[2]	–	7.6–8.1 (m)	6.20	–	–
19[2]	8.20	9.50	6.80	7.8	2.2
20[3]	8.24	9.49	6.83	7.8	2.2
21[2]	7.66 (s)	9.99	6.70	–	–
22[2]	8.30	7.88 (s)	6.92	7.8	–

1) Most compounds were measured in the solvent acetone-d_6; in the case of **17** and **22** a mixture of acetone-d_6 and D_2O was used.
2) The absorptions originating from $N^+CH_2CH_3$ and OCH_2CH_3 could not be unequivocally assigned; they are mentioned in the experimental section with the individual compounds.
3) δ 3.71 (s, CH_3), δ 4.34 (q, $N^+\overset{\overset{\text{H(a)}}{|}}{C}HCH_3$), δ 1.57 (t, $N^+CH_2\overset{\overset{\text{H(b)}}{|}}{C}H_2$).

3) Thermal rearrangement of 1-ethylpyrimidinium salts

1,3-Diethyl-1,4(3,4)-dihydro-2-phenyl-4-oxopyrimidinium tetrafluoroborate (**21**)

By heating of **15** for 5 min at 300°/20 mm. Yield: 63%. M.p. 190–191°.
^{1}H-NMR (acetone-d_6/D_2O): δ 3.95 (q), δ 3.88 (q), δ 1.36 (t), δ 1.18 (t). (See for the other protons, Table III.) IR spectrum (KBr): 1720 cm^{-1} (s) (C=O). Analysis: $C_{14}H_{17}BF_4N_2O$ (316.21): calc. C 53.19, H 5.42; C 53.47, H 5.31.

1,3-Diethyl-1,4(3,4)-dihydro-6-phenyl-4-oxopyrimidinium tetrafluoroborate (**22**)

By heating of **26** for 5 min at 290°/20 mm. Yield: 50%. M.p. 111–112°.
^{1}H-NMR (acetone-d_6): δ 4.25 (q), δ 4.21 (q), δ 1.47 (t), δ 1.29 (t). (See for the other protons, Table III.) IR spectrum 1730 cm^{-1} (s) (C=O). Analysis: $C_{14}H_{17}BF_4N_2O$ (316. 1): calc. C 53.19, H 5.42; found C 53.26, H 5.70.

Acknowledgement

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Recueil, Journal of the Royal Netherlands Chemical Society, in the press

The crystal and molecular structures of 1-ethyl-4,6-diethoxypyrimidinium tetrafluoroborate and 1,3-diethyl-1,4(3,4)-dihydro-6-ethoxy-4-oxopyrimidinium tetrafluoroborate, two isomeric reaction products of 4,6-diethoxypyrimidine with Meerwein reagent

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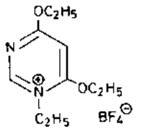
Abstract The crystal and molecular structures of two isomeric compounds, 1-ethyl-4,6-diethoxypyrimidinium tetrafluoroborate and 1,3-diethyl-1,4(3,4)-dihydro-6-ethoxy-4-oxopyrimidinium tetrafluoroborate, reaction products of 4,6-diethoxypyrimidine with Meerwein reagent $\left[O(C_2H_5)_3{}^+BF_4{}^-\right]$, have been determined by means of X-ray diffraction. 1-Ethyl-4,6-diethoxypyrimidinium tetrafluoroborate is monoclinic a=10.794, b=13.361, c=10.892 Å, β=112.6°, space group $P2_1/n$, four molecules per unit cell.
1,3-Diethyl-1,4(3,4)-dihydro-6-ethoxy-4-oxopyrimidinium tetrafluoroborate is monoclinic, a=17.637, b=14.054, C=11.501 Å, β=101.7°, space group C2/c, eight molecules per unit cell.

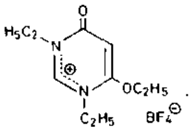
In both structures the fluoroborate ions are disordered. The bond distances in the π-electron systems are reasonably well described in terms of a small number of resonance structures.

Introduction

Reaction of 4,6-diethoxypyrimidine with one equivalent Meerwein reagent (triethyloxonium tetrafluoroborate) yields a tetrafluoroborate of composition $C_{10}H_{17}N_2O_2 \cdot BF_4$ and melting point 97-98°C. Further treatment with Meerwein reagent or heat treatment results in an isomeric compound of melting point 181-182°C[1]. Since conclusive structure assignments of the two compounds could not be made with the usual spectroscopic techniques, crystal structure determinations of both compounds were undertaken. The lower melting compound turned out to be 1-ethyl-4,6-diethoxypyrimidinium tetrafluoroborate (I); the higher melting compound is 1,3-diethyl-1,4(3,4)-dihydro-6-ethoxy-4-oxopyrimidinium tetrafluoroborate (II).



I



II

Experimental

Compound I.

The crystals are monoclinic with cell constants: a=10.794(2), b=13.361(3), c=10.892(4) Å and β=112.61(3)°. The space group is $P2_1/n$ (extinctions: h0l for h+l odd, 0k0 for k odd) with four formula units per unit cell (d_{calc}= 1.301 gcm^{-3}). 1038 independent reflexions (I >2σ (I)) were collected by means of a NONIUS CAD4 automatic diffractometer, using graphite monochromated Cu Kα radiation. No absorption correction was applied (μ= 12.2 cm^{-1}, crystal dimensions 0.35x0.45x0.05 mm).

Compound II.

The crystals are monoclinic with cell constants: a=17.637(4), b=14.054(6), c=11.501(5) Å and β=101.69(3)°. The space group is C2/c (extinctions: hkl for h+k odd, h0l for l odd) with eight formula

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1. E.A.Oostveen and H.C.van der Plas, to be published, Recl.Trav.Chim.Pays-Bas, 96, 64 (1977).

Table 1

Final parameters for compound I

The anisotropic temperature factors are expressed as $\exp(-2\pi^2(h^2a^{*2}U_{11}+k^2b^{*2}U_{22}+l^2c^{*2}U_{33}+2hka^*c^*U_{12}+2hla^*c^*U_{13}+2klb^*c^*U_{23})$. The standard deviations are given in parentheses. pp = population parameter.

	x/a	y/b	z/c	pp	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	.2606(10)	-.0526(8)	.1030(9)		.073(7)	.058(7)	.064(7)	.003(6)	.027(6)	.010(6)
C(2)	.3960(10)	.0759(8)	.1954(11)		.068(8)	.052(7)	.103(9)	.009(6)	.042(7)	.016(7)
C(3)	.3718(10)	.0716(8)	.3124(9)		.062(7)	.064(7)	.069(7)	-.004(7)	.028(6)	-.002(6)
C(4)	.2813(10)	-.0007(8)	.3151(10)		.059(7)	.064(7)	.068(7)	.023(7)	.023(5)	.005(6)
C(5)	.1290(10)	-.1437(8)	.2064(10)		.075(8)	.060(7)	.071(7)	-.015(7)	.026(6)	.000(6)
C(6)	-.0103(11)	-.1022(10)	.1692(11)		.058(8)	.129(11)	.092(9)	-.008(8)	.024(7)	-.003(8)
C(7)	.5019(16)	.1649(11)	.0632(16)		.225(17)	.130(14)	.217(16)	-.096(13)	.199(15)	-.083(13)
C(81)	.4082(24)	.2384(18)	-.0212(20)	.52(2)	.188(20)	.149(18)	.098(14)	.052(16)	.082(15)	.053(14)
C(82)	.5723(26)	.2390(21)	.0746(23)	.48	.198(24)	.181(22)	.132(18)	-.043(19)	.124(19)	-.034(16)
C(9)	.2851(11)	.0518(9)	.5255(10)		.085(9)	.087(9)	.065(7)	.001(7)	.028(7)	-.014(7)
C(10)	.2255(13)	.0092(12)	.6199(12)		.121(11)	.168(14)	.079(9)	-.009(11)	.054(9)	-.021(9)
N(1)	.2250(8)	-.0646(6)	.2073(7)		.064(6)	.045(5)	.061(6)	.004(5)	.026(5)	-.005(5)
N(2)	.3416(9)	.0135(6)	.0910(8)		.095(7)	.056(6)	.069(6)	-.012(5)	.045(6)	-.015(5)
O(1)	.4811(8)	.1478(6)	.1918(8)		.101(7)	.063(5)	.106(7)	-.015(5)	.059(5)	-.016(5)
O(2)	.2391(7)	-.0182(5)	.4113(6)		.076(5)	.066(5)	.065(5)	.001(4)	.034(4)	-.005(4)
B	.025(2)	.230(2)	.170(2)		.070(7)	.154(13)	.084(9)	.002(9)	.003(7)	.004(8)
F(11)	.039(3)	.294(3)	.081(3)	.61(1)	.149(16)	.090(9)	.107(12)	.025(10)	.037(10)	.050(9)
F(12)	.072(5)	.283(4)	.083(4)	.39	.141(21)	.306(42)	.095(19)	-.111(24)	.042(15)	.059(20)
F(21)	-.108(3)	.226(2)	.143(2)	.61	.103(10)	.133(12)	.140(12)	.018(10)	.038(10)	.009(12)
F(22)	-.094(4)	.195(3)	.121(4)	.39	.119(23)	.244(24)	.220(27)	-.098(23)	.058(18)	-.186(25)
F(31)	.110(2)	.245(2)	.298(2)	.61	.125(9)	.158(11)	.069(6)	-.058(9)	.015(6)	-.185(7)
F(32)	.093(3)	.177(3)	.252(3)	.39	.131(17)	.174(21)	.135(18)	.066(16)	-.015(13)	.017(16)
F(41)	.062(2)	.132(1)	.137(2)	.61	.187(10)	.092(7)	.147(9)	.043(8)	.023(9)	-.007(7)
F(42)	.008(2)	.322(2)	.251(2)	.39	.157(14)	.086(9)	.080(9)	-.032(9)	.023(9)	-.031(8)

units per unit cell (d_{calc}= 1.351 gcm^{-1}). 1185 independent reflexions were collected in the same way as with compound I. Again no absorption correction was applied (μ =12.7 cm^{-1}, crystal dimensions: 0.45x0.25x0.04 mm).

Structure determination and refinement

Compound I

From the peaks surrounding the origin in an E^2-Patterson synthesis the orientation of the six-membered ring could be derived. A sixfold Patterson minimum function, based on the relative positions of the ring atoms thus obtained, resulted in several possibilities for the position of the ring relative to the symmetry elements. One of these led via Fourier and difference Fourier calculations to a solution for the structure. In this solution disorder had to be postulated for the BF_4 ion in the form of two partial-weight BF_4 tetrahedra with a common B atom. Additional disorder was found in one of the ethyl groups, with two positions for the terminal atom C(8) (see fig.1 for the numbering of the atoms).

Refinement was carried out by means of diagonal least-squares calculations. Towards the end of the refinement a difference Fourier synthesis indicated the hydrogen atoms except those at C(7), C(81) and C(82) which are involved in the disorder of the ethyl group at O(1). The indicated hydrogen atoms

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2. D.W.J.Cruickshank, in Computing Methods and the Phase Problem in X-Ray Crystal Analysis, p.41. Oxford, Pergamon Press, 1961.

Table 2

Final parameters for compound II

The anisotropic temperature factors are expressed as $\exp(-2\pi^2(h^2a^{*2}U_{11}+k^2b^{*2}U_{22}+l^2c^{*2}U_{33}+2hka^*c^*U_{12}+2hla^*c^*U_{13}+2klb^*c^*U_{23})$. The standard deviations are given in parentheses. pp = population parameter.

	x/a	y/b	z/c	pp	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	-.0017(3)	.6887(4)	-.0003(5)		.066(3)	.050(3)	.048(3)	-.006(3)	.012(3)	-.003(3)
C(2)	-.0714(3)	.8081(4)	.0809(5)		.066(4)	.084(4)	.054(3)	.000(3)	.020(3)	.005(3)
C(3)	-.0013(3)	.8616(4)	.1046(4)		.066(4)	.058(4)	.050(3)	-.008(3)	.013(3)	-.012(3)
C(4)	.0633(3)	.8275(4)	.0755(4)		.067(4)	.049(4)	.041(3)	-.005(3)	.004(3)	-.003(3)
C(5)	.1363(4)	.6966(4)	-.0033(6)		.084(4)	.051(3)	.091(5)	-.009(3)	.032(4)	-.025(4)
C(6)	.1880(4)	.6572(5)	.1027(7)		.068(4)	.092(6)	.121(6)	.010(4)	-.003(4)	.008(5)
C(7)	-.1368(4)	.6594(5)	-.0067(6)		.081(4)	.086(5)	.098(5)	-.028(3)	.019(4)	-.004(4)
C(8)	-.1819(4)	.6816(7)	-.1262(7)		.069(5)	.160(8)	.119(6)	-.033(4)	-.004(4)	-.010(6)
C(9)	.1381(4)	.9659(4)	.1328(5)		.084(4)	.048(4)	.076(4)	-.013(3)	.006(3)	-.015(3)
C(10)	.2151(4)	1.0025(5)	.1201(7)		.096(5)	.069(5)	.132(6)	-.028(4)	.008(5)	-.004(4)
N(1)	.0635(3)	.7373(3)	.0236(4)		.054(3)	.048(3)	.050(3)	-.007(2)	.012(2)	-.001(2)
N(2)	-.0658(3)	.7181(3)	.0244(4)		.063(3)	.054(3)	.053(3)	-.015(3)	.010(2)	-.002(3)
O(1)	-.1325(3)	.8317(4)	.1054(5)		.078(3)	.113(4)	.119(4)	-.007(3)	.041(3)	-.031(4)
O(2)	.1319(2)	.8686(3)	.0887(3)		.064(3)	.054(2)	.061(3)	-.012(2)	.010(2)	-.012(2)
B(1)	.0126(8)	.5242(7)	.2503(15)	.5	.053(3)					
B(2)	.4833(7)	.6405(7)	.2456(13)	.5	.056(4)					
F(1)	.0166(20)	.6172(5)	.2442(38)	.5	.232(31)	.062(4)	.076(7)	-.049(11)	.001(16)	.011(10)
F(2)	.0740(6)	.4810(9)	.2838(12)	.5	.107(6)	.171(10)	.239(12)	.055(7)	.021(7)	.055(9)
F(3)	-.0308(6)	.4894(6)	.1484(7)	.5	.208(9)	.071(6)	.099(6)	.019(6)	-.011(6)	-.035(5)
F(4)	-.0305(7)	.5031(7)	.3424(9)	.5	.211(10)	.131(8)	.144(8)	.003(7)	.120(8)	.027(7)
F(5)	.4526(6)	.5917(7)	.1618(8)	.5	.208(10)	.112(7)	.083(5)	-.079(7)	.018(6)	-.008(5)
F(6)	.4342(6)	.6655(7)	.3058(9)	.5	.168(8)	.112(7)	.135(8)	.015(6)	.061(7)	-.018(6)
F(7)	.5261(6)	.7234(6)	.2320(11)	.5	.187(14)	.113(7)	.129(10)	-.062(7)	-.017(9)	.064(8)
F(8)	.5263(7)	.5885(6)	.3423(6)	.5	.242(10)	.104(6)	.051(4)	-.075(7)	.003(5)	.039(4)

were introduced at their calculated positions with isotropic temperature parameters equal to the averaged anisotropic temperature parameters of the atoms to which they are attached. Their parameters were kept constant during the final cycles of refinement which converged to an R-index of 9.5% for the 1038 observed structure factors. Cruickshank weighting[2] was applied. The final parameters are listed in table 1.

Compound II.

The same procedure as used for compound I was applied in deriving the structure of compound II. Some difficulty was encountered in placing the BF_4 ions. In the model eventually arrived at, two independent BF_4 groups are centered at twofold axes at X=0, Z=¼ and X=½, Z=¼, both groups exhibiting disorder. A difference Fourier synthesis towards the end of the diagonal least-squares refinement revealed all of the 17 hydrogen atoms of the cation. Since the boron atoms, which up till now had been in special positions at twofold axes, has become strongly anisotropic, it was considered more realistic to replace each of them by two half-weight isotropic atoms in general position. After introducing isotropic hydrogen atoms at calculated positions with fixed parameters and removing the strongest reflexion (200), which apparently suffered from extinction, refinement converged to an R-index of 6.6% for the 1185 observed structure factors. Cruickshank weighting[2] was applied. The final parameters are listed in table 2.

Discussion

Compound I

The BF_4 ion.

From the thermal parameters of table 1 and the bond distances and angles of table 3 it is clear that the model used to account for the disorder in the BF_4 group is rather defective, although it reasonably represents the observed electron density. Since our interest was primarily in the structure and geometry of the pyrimidinium ion, no further effort has been made to obtain a physically more acceptable model for the BF_4 ion.

Table 3

Bond distances and interbond angles in compound I

N(1)-C(1)	1.34(2) Å	C(4)N(1)C(1)	118(2)°
C(1)-N(2)	1.28(2)	C(1)N(1)C(5)	121(2)
N(2)-C(2)	1.35(2)	C(4)N(1)C(5)	122(2)
C(2)-C(3)	1.40(2)	N(1)C(1)N(2)	127(2)
C(3)-C(4)	1.38(2)	C(1)N(2)C(2)	116(2)
C(4)-N(1)	1.39(2)	N(2)C(2)C(3)	125(2)
N(1)-C(5)	1.48(2)	N(2)C(2)O(1)	120(2)
C(5)-C(6)	150(2)	C(3)C(2)O(1)	115(2)
C(2)-O(1)	1.34(2)	C(2)C(3)C(4)	115(2)
O(1)-C(7)	1.52(2)	C(3)C(4)N(1)	120(2)
C(7)-C(81)	1.46(4)	C(3)C(4)O(2)	127(2)
C(7)-C(82)	1.22(4)	N(1)C(5)C(6)	111(2)
C(4)-O(2)	1.31(2)	C(2)O(1)C(7)	119(2)
O(2)-C(9)	1.48(2)	O(1)C(7)C(81)	111(3)
C(9)-C(10)	1.52(2)	O(1)C(7)C(82)	108(3)
B-F(11)	1.34	C(4)O(2)C(9)	117(3)
B-F(21)	1.35	O(2)C(9)C(10)	104(3)
B-F(31)	1.36	F(11)BF(21)	106
B-F(41)	1.46	F(11)BF(31)	116
B-F(12)	1.42	F(11)BF(41)	106
B-F(22)	1.28	F(21)BF(31)	118
B-F(32)	1.16	F(21)BF(41)	106
B-F(42)	1.57	F(31)BF(41)	104
		F(12)BF(22)	118
		F(12)BF(32)	122
		F(12)BF(42)	98
		F(22)BF(32)	109
		F(22)BF(42)	102
		F(32)BF(42)	103

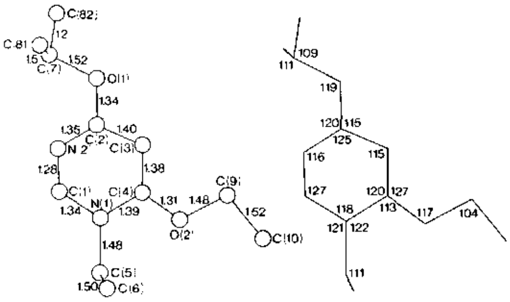

Fig.1 Bond distances and interbond angles for the cation of compound I. C(81) and C(82) are two alternatives for the disordered terminal atom C(8)

The cation.

The bond distances and interbond angles of the pyrimidinium ion are indicated in fig.1 and are listed in table 3 together with their calculated standard deviations. Fig. 1 also gives the shape of the cation as projected onto the plane of the ring.

Although the rather poor model for the BF_4 ion will have affected the experimental bond lengths and angles in the cation, the fact that most of the hydrogen atoms were represented in a difference Fourier synthesis suggests that the effect cannot be very dramatic. As a further check a simple resonance calculation has been carried out. In the pyrimidinium ion resonance might be expected between the four structures of fig.2. Pauling's relation[3] $R = R_1-(R_1-R_2) \cdot 3x/(2x+1)$ between the double bond character, x, and the bond length, R, using single-bond values, R_1, of 1.54, 1.48 and 1.42 Å and double-bond values, R_2, of 1.33, 1.24

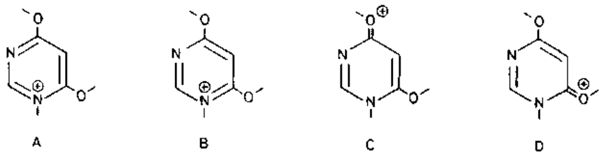

Fig.2 Resonance structures for the cation of compound I

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3. L.Pauling, The Nature of the Chemical Bond, Ithaca, Cornell University Press, 1940.

Table 4

Comparison of calculated (r_c) and observed bond lengths (r_o) for compound I

	r_o	r_c
N(1)-C(1)	1.34 Å	1.34 Å
C(1)-N(2)	1.28	1.28
N(2)-C(2)	1.35	1.33
C(2)-C(3)	1.40	1.37
C(3)-C(4)	1.38	1.35
C(4)-N(1)	1.39	1.38
C(2)-O(1)	1.34	1.32
C(4)-O(2)	1.31	1.30

and 1.20 Å for C-C, C-N and C-O respectively, leads to contributions A: 35%, B: 20%, C: 20% and D: 25%. This result, although not much more than qualitative, is satisfactory, approximately equal contributions of the four most obvious resonance structures reasonably accounting for the experimental bond lengths (see table 4). So it may be assumed that the actual accuracy is about that indicated in table 3 for the atoms involved in the disorder of the ethyl group attached to O(1). The calculated e.s.d.'s of C(7), C(81) and C(82) are considerably higher than those of the other atoms in the cation, but from the distance C(7)-C(82) of 1.22 Å it is clear that the actual accuracy for these atoms is probably worse.

The six-membered ring is planar within the limits of accuracy (largest deviation from the best plane 0.013 Å). The nearest neighbours O(1), O(2) and C(5) are coplanar with the ring (deviations 0.03, 0.03 and 0.01 Å respectively). Of the next nearest neighbours, C(7) and C(9) are near the plane of the ring (deviations 0.20 and 0.15 respectively), in agreement with the relatively large contributions of resonance structures C and D, implying O(1)-C(7) and O(2)-C(9) to be coplanar with the ring. C(6) is at 1.40 Å from the plane of the ring, the plane of N(1)C(5)C(6) being almost perpendicular to the ring. The ethoxy groups involving C(10) and C(82) are practically coplanar with the ring (deviations 0.08 and 0.32 Å respectively). For steric reasons the ethyl groups then have to be directed away from the ring. The plane of the ethoxy group involving C(81) is nearly perpendicular to the ring.

Compound II.

The BF_4 ions.

From the results for the BF_4 groups (tables 2 and 5) it is evident that not much value can be attached to the parameters for B and F, especially the thermal parameters. As with compound I no attempts were made to improve the models.

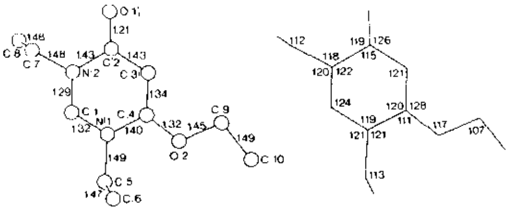

Fig.3 Bond distances and interbond angles for the cation of compound II

Table 5

Bond distances and interbond angles in compound II

N(1)-C(1)	1.318(7)	C(4)N(1)C(1)	118.7(7)°
C(1)-N(2)	1.288(7)	C(1)N(1)C(5)	120.6(7)
N(2)-C(2)	1.435(7)	C(4)N(1)C(5)	120.7(7)
C(2)-C(3)	1.425(8)	N(1)C(1)N(2)	123.7(7)
C(3)-C(4)	1.340(7)	C(1)N(2)C(2)	121.8(7)
C(4)-N(1)	1.402(7)	C(1)N(2)C(7)	120.3(8)
N(1)-C(5)	1.494(8)	C(2)N(2)C(7)	117.9(8)
C(5)-C(6)	1.474(10)	N(2)C(2)C(3)	114.5(7)
C(2)-O(1)	1.214(8)	N(2)C(2)O(1)	119.5(7)
N(2)-C(7)	1.482(8)	C(3)C(2)O(1)	126.0(7)
C(7)-C(8)	1.475(11)	C(2)C(3)C(4)	120.8(7)
C(4)-O(2)	1.321(6)	C(3)C(4)N(1)	120.4(7)
O(2)-C(9)	1.455(7)	C(3)C(4)O(2)	128.3(7)
C(9)-C(10)	1.487(10)	N(1)C(4)O(2)	111.3(7)
B(1)-F(1)	1.31	N(1)C(5)C(6)	112.7(7)
B(1)-F(2)	1.23	N(2)C(7)C(8)	112.1(8)
B(1)-F(3)	1.35	C(4)O(2)C(9)	117.0(7)
B(1)-F(4)	1.45	O(2)C(9)C(10)	107.3(7)
B(2)-F(5)	1.22	F(1)B(1)F(2)	117
B(2)-F(6)	1.26	F(1)B(1)F(3)	110
B(2)-F(7)	1.41	F(1)B(1)F(4)	106
B(2)-F(8)	1.42	F(2)B(1)F(3)	114
		F(2)B(1)F(4)	103
		F(3)B(1)F(4)	106
		F(5)B(2)F(6)	110
		F(5)B(2)F(7)	123
		F(5)B(2)F(8)	114
		F(6)B(2)F(7)	106
		F(6)B(2)F(8)	92
		F(7)B(2)F(8)	107

The cation

The bond distances and interbond angles in the cation are indicated in fig.3 and are listed in table 5 together with the calculated standard deviations. Fig. 3 is also depicting the shape of the cation as projected onto the plane of the ring.

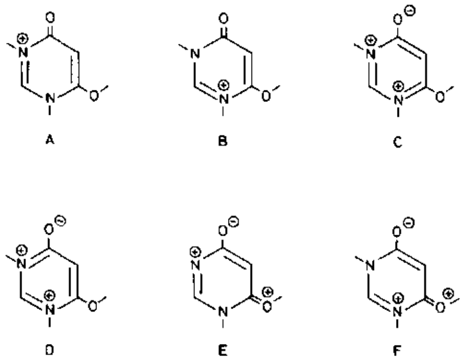

Fig.4 Resonance structures for the cation of compound II

A simple resonance calculation as indicated above has also been carried out for compound II. From the relatively short distances C(1)-N(1), C(1)-N(2) and C(3)-C(4) it is clear that in the resonance picture the main contribution has to come from structures A and B of fig.4. However, in order to account for the shortening of N(2)-C(2), C(2)-C(3) and C(4)-O(2), polar structures like C, D, E and F will also have to contribute. The calculation yields contributions of 75% for A+B, 10% for C+D and 15% for E+F. Again the results are satisfactory (see table 6), implying reasonable consistency among the set of bond lengths involved.

Table 6

Comparison of calculated (r_c) and observed bond lengths (r_o) for compound II

	r_o	r_c
N(1)-C(1)	1.32 Å	1.29 Å
C(1)-N(2)	1.29	1.29
N(2)-C(2)	1.43	1.47
C(2)-C(3)	1.43	1.45
C(3)-C(4)	1.34	1.35
C(4)-N(1)	1.40	1.44
C(2)-O(1)	1.21	1.22
C(4)-O(2)	1.32	1.35

The six-membered ring is planar within 0.014 Å. The nearest neighbours O(1), O(2), C(5) and C(7) are at 0.04, 0.05, 0.07 and 0.04 Å respectively from the plane of the ring. The ethoxy group has the same configuration as its counterpart in compound I with C(9) and C(10) at 0.19 and 0.45 Å from the plane of the ring. The N-ethyl groups have configurations similar to the one in compound I with C(6) and C(8) at opposite sides of the ring at distances of 1.43 and 1.42 Å.

Ring transformations of heterocyclic compounds with nucleophiles[1]. Part XVI. Degenerate ring transformations of 1,3-diethyl-1,4(3,4)-dihydro-4-oxopyrimidinium tetrafluoroborates with ammonia[2]

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Abstract. Treatment of 1,3-diethyl-1,4(3,4)-dihydro-4-oxopyrimidinium tetrafluoroborate and its 2-phenyl, 6-phenyl, 6-methyl and 6-ethoxy derivatives with aqueous ammonia resulted in the formation of a mixture of open-chain compounds *i.e.* *N*-formyl(acetyl,benzoyl)-*N*-ethyl-3-(ethylamino)-acrylamides and *N*-ethyl-3-[formyl(acetyl,benzoyl)ethylamino]-acrylamides. They are formed by cleavage of the pyrimidine ring between the N(1)—C(2) and N(3)—C(2) bond, respectively. In liquid ammonia the same ring cleavage generally occurs; however, in the case where a 6-ethoxy group is present, recyclisation can take place, leading to 6-(ethylamino)pyrimidine derivatives. This degenerate ring transformation has been observed also with the 2-methyl and 2-phenyl derivative of 1,3-diethyl-1,4(3,4)-dihydro-6-ethoxy-4-oxopyrimidinium tetrafluoroborate. Evidence is presented by means of ^{1}H-NMR and ^{13}C-NMR spectroscopy that all these reactions are iniated by attack of NH_3 at the C(2)-position. Some of the above-mentioned open-chain compounds underwent a ring closure to the initially used 1,3-diethyl-1,4(3,4)-dihydro-4-oxopyrimidinium tetrafluoroborates on treating them with hydrofluoroboric acid in absolute ethanol.

Ring cleavage reactions of pyrimidines under the influence of nucleophiles are the subject of extensive study in this laboratory[1b,3–7] and in others[8–11]. Ring cleavage normally occurs in the dihydropyrimidine derivatives (or their conjugated bases) formed by addition of the nucleophile to the N—C bond. Electron withdrawing groups tend to favour addition and to decrease the resistance of the dihydropyrimidine ring to cleavage. This can be exemplified in the facile ring opening of 5-nitropyrimidines[8,9,11] and of pyrimidine-5-carbaldehydes[10]. The intermediary open-chain compounds obtained as a result of the ring opening can undergo further conversions. Depending on the substituents and the nature of the entering nucleophile either stable functionalized aliphatic compounds are formed or recyclisation occurs leading again to a pyrimidine derivative or to another heterocyclic ring system.

Recently[3] we found that *N*-methylpyrimidinium salts undergo demethylation into pyrimidine derivatives with liquid ammonia under very mild conditions (−33°). It has been proved by use of ^{15}N-labelled pyrimidinium salts and application of ^{1}H-NMR spectroscopy that this demethylation reaction involves an Addition-Nucleophile-Ring-Opening-Ring-Closure mechanism leading to an *N*-demethylated pyrimidine derivative. Since one of the nitrogen atoms of the pyrimidine ring is exchanged with the nitrogen of the ammonia during the demethylation we refer to these reactions as degenerate ring transformations. As an extension we report in this paper on the reaction of some other pyrimidinium salts, *i.e.* the 1,3-diethyl-1,4(3,4)-dihydro-4-oxopyrimidinium tetrafluoroborates (**1**–**7**) with aqueous ammonia or with liquid ammonia.

First we shall discuss in detail the reaction of **1** with aqueous ammonia, since the results obtained are typical for the behaviour of these 4-oxo compounds. In contrast to the *N*-demethylation of pyrimidinium salts by action of liquid ammonia just-mentioned, it was found that with concentrated aqueous ammonia at room temperature **1** gives a mixture of three isomeric open-chain compounds: one pair of the geometrical *Z* and *E* isomers of *N*-ethyl-*N*-formyl-3-(ethylamino)acrylamide (**8**) (formed by cleavage of the N(1)—C(2) bond) and the *Z* isomer of *N*-ethyl-3-(formylethylamino)acrylamide (**12**) (formed by fission of the N(3)—C(2) bond).

The structural evidence of these geometrical isomers **8** and compound **12** is based on microanalytical data and mass spectra, but mainly on the ^{1}H-NMR data (see Table I) and IR spectra. From the ^{1}H-NMR data it is apparent that the *Z* and *E* isomers of **8** differ essentially from **12** in showing that *one* of the ethylenic protons appears as a double doublet [due to coupling with H(5) and with the hydrogen at N(1)] and the *other* as a doublet, while in **12** *both* ethylenic protons appear as doublets. In the *Z* and *E* isomers of **8** the coupling constants $J_{1,6}$ are 13.5 and 9.0 Hz respectively. We ascribe the somewhat higher $J_{1,6}$ in the *Z* isomer to the formation of an intramolecular hydrogen bridge (structure A) which results in a *trans*-configuration of the proton on N(1) and C(6). It was further observed that when the ^{1}H-NMR spectrum of **8** is measured in D_2O at 50°, the

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[1a] See for part XV in these series: *F. Roeterdink* and *H. C. van der Plas*, Recl. Trav. Chim. Pays-Bas, **95**, 282 (1976).

[b] For a general review on this subject see: *H. C. van der Plas*, Ring Transformations of Heterocycles, Vol. **1** and **2**, Academic Press, London and New York, 1973.

[2] Part LIX on Pyrimidines from this laboratory; Part LVIII, *E. A. Oostveen* and *H. C. van der Plas*, Recl. Trav. Chim. Pays-Bas, **96**, 64 (1977).

[3] *E. A. Oostveen, H. C. van der Plas* and *H. Jongejan*, Recl. Trav. Chim Pays-Bas **93**, 114 (1974).

[4] *H. C. van der Plas*, Miss *M. C. Vollering, H. Jongejan* and *B. Zuurdeeg*, Recl. Trav. Chim. Pays-Bas **93**, 225 (1974).

[5] *E. A. Oostveen* and *H. C. van der Plas*, Recl. Trav. Chim. Pays-Bas **93**, 233 (1974).

[6] *E. A. Oostveen* and *H. C. van der Plas*, Recl. Trav. Chim. Pays-Bas **95**, 104 (1976).

[7] *E. A. Oostveen, H. C. van der Plas* and *H. Jongejan*, Recl. Trav. Chim. Pays-Bas **95**, 209 (1976).

[8] *J. Clark, I. Gelling* and *G. Neath*, Chem. Comm. **1967**, 859.

[9] *J. Clark, I. Gelling, I. W. Southon* and *M. S. Morton*, J. Chem. Soc. (C) **1970**, 494.

[10] *J. Clark, B. Parvizi* and *I. W. Southon*, J. Chem. Soc. Perkin I **1976**, 125.

[11] *J. Clark, B. Parvizi* and *R. Colman*, J. Chem. Soc. Perkin I **1976**, 1004.

Table I Chemical shifts (ppm) and coupling constants (Hz) of the H atoms in the compounds* **8–17****.

Compound	R^1	R^2	H(5)	NH	H(1a)	H(1b)	H(3a)	H(3b)	$J_{5,6}$	$J_{1,6}$
8 (Z)***	6.90	9.20	4.84	9.0	3.34	1.19	3.73	1.27	7.5	13.5
8 (E)***	7.86	9.28	5.15	6.0	3.3	1.2	3.7	1.3	12.7	9.0
9	2.08	9.29	4.78	9.9	3.35	1.17	3.68	1.29	–	–
10	CH_2 = 4.10 CH_3 = 1.42	9.31	4.45	9.6	3.33	1.19	3.70	1.22	–	–
11	CH_2 = 3.92 CH_3 = 1.3	7.2–7.7 (m)	4.04	9.28	3.22	1.2	3.52	1.2	–	–
12	6.33	8.60	5.57	7.5	3.73	1.18	3.3	1.18	9.8	–
13	2.07	8.12	5.83	7.3	3.62	1.1	3.27	1.2	–	–
14	6.34	7.2–7.6 (m)	5.18	6.5	3.94	1.18	3.20	1.07	9.8	–
15	7.45 (s)	8.26	6.13	6.8	3.46	1.16	3.32	1.06	–	–
16	CH_2 = 3.85 CH_3 = 1.40	2.08	5.14	6.6	3.55	1.17	3.22	1.14	–	–
17	CH_3 = 3.6 CH_3 = 1.20	7.1–7.5 (m)	4.72	6.1	3.5	1.12	3.07	0.97	–	–

* Solvent $CDCl_3$.

** The numbering in **8–17** refers to the position of the atoms in the pyrimidine ring.

*** The ratio between both geometrical isomers was determined to be Z/E = 60/40, based on the area of the peaks at δ 4.84 and δ 5.15.

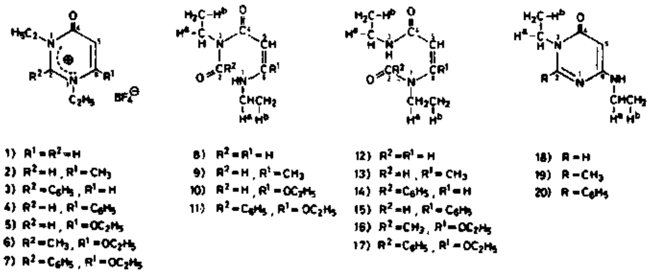
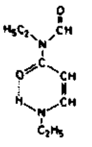


Fig. 1

coupling between H(6) and the hydrogen at N(1) has disappeared.



A

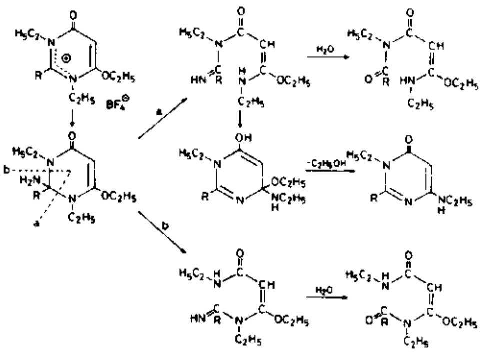
The ^{1}H-NMR spectra of the two geometrical isomers **8** also differ from that of **12** in showing that the chemical shift of the proton of the formyl group appears about 0.6 ppm at a lower field in **8** than in **12**. In the IR spectrum the isomers **8** *(Z)* and **8** *(E)* show two separate strong absorption frequencies in the 1600–1700 cm^{-1} region *i.e.* at 1640 cm^{-1} at 1690 cm^{-1} while on the other hand, **12** shows a broad absorption band between 1600 cm^{-1} and 1720 cm^{-1} with a maximum at 1655 cm^{-1}.

Liquid ammonia at −33°, instead of aqueous ammonia at room temperature, was found to give the same products **8** and **12** in much lower yields however.

The differences between the isomers **8** and **12** in the multiplicity of H(6), the chemical shift of the hydrogen of the formyl group and the differences in absorption frequencies in the 1600–1720 cm^{-1} region gave us a diagnostic tool for the structure assignment of the products obtained from the other derivatives **2**–**7**. The 6-methyl derivative **2** reacts with aqueous ammonia in the same way as **1**, giving **9** and **13**. The IR spectrum of **13** shows the broad absorption band between 1600 cm^{-1} and 1700 cm^{-1} and **9** gives two separate absorption maxima at 1610 cm^{-1} and 1690 cm^{-1}. The hydrogen atom of the formyl group in **9** resonates at a lower field than that of **13** (δ 9.29 and δ 8.12, respectively, Table I). The reaction of the 2-phenyl derivative **3** and the 6-phenyl derivative **4** with aqueous ammonia takes a somewhat different course since only products **14** and **15** could be identified; apparently only ring cleavage between C(2)–N(3) has taken place. Both compounds show the broad absorption between 1600 cm^{-1} and 1700 cm^{-1} in the IR spectrum and the ^{1}H-NMR spectrum of the compound obtained after the reaction of **3** showed two doublets for the ethylenic protons at δ 6.34 ($J_{5,6}$ 9.3 Hz) and at δ 5.18 with *no* additional coupling of H(6) with a NH proton.

Attempts were made to improve the yield of the products **9** and **13**–**15** by reacting **2**, **3** and **4** with liquid ammonia. It was observed that all three compounds gave a very complicated reaction mixture which was not investigated further.

We were surprised to observe that in the reaction of 1,3-diethyl-1,4(3,4)-dihydro-6-ethoxy-4-oxopyrimidinium tetrafluoroborate (**5**) with aqueous ammonia only isomer **10** is formed, but that in liquid ammonia only 1,6-dihydro-1-ethyl-4-(ethylamino)-6-oxopyrimidine (**18**) could be isolated as reaction product. A degenerate ring transformation has taken place. In order to establish whether the presence of a 6-ethoxy substituent is a structural requirement for the occurrence of ring transformations in liquid ammonia with these 4-oxopyrimidinium salts, the 2-methyl derivative **6** was also investigated in both aqueous and liquid ammonia.



Scheme 1

With aqueous ammonia only the open-chain compound **16** could be isolated (IR spectrum shows a broad absorption band between 1600 cm^{-1} and 1700 cm^{-1}), but with liquid ammonia the 4-(ethylamino)pyrimidine derivative **19** was obtained besides **16**. It is evident that in the liquid ammonia open-chain intermediates which are formed by cleavage of the N(1)–C(2) bond, can easily undergo ring closure to **18** and **19**, respectively. Both open-chain compounds **11** and **17** and the pyrimidine **20** are formed during the reaction of the 2-phenyl-6-ethoxy derivative (**7**) with aqueous ammonia as well as with liquid ammonia.

Some of the open-chain compounds *e.g.* **9**, **10**, **13–15** could be recyclised on treating them with a solution of hydrofluoroboric acid in absolute ethanol, obtained by dissolving the Meerwein reagent in ethanol. The starting materials, 1,3-diethyl-1,4(3,4)-dihydro-4-oxopyrimidinium tetrafluoroborates, were produced *via* a ring closure by an intramolecular attack of the N(1) in **9–10** or N(3) in **13–15** at the O=C(2) group and aromatisation by loss of H_2O; thus, from **9**, **10**, **13**, **14** and **15** the corresponding tetrafluoroborates were obtained in yields of 85, 60, 41, 14 and 55%, respectively.

Why the other open-chain compounds **8**, **11**, **12**, **16** and **17**, under the same reaction conditions, did not recyclise into the corresponding tetrafluoroborates is not clear at this moment.

As evidenced by the formation of the open-chain products **8–11**, **12–17**, the 1,3-diethyl-1,4(3,4)-dihydro-4-oxopyrimidinium salts undergo ring opening by cleavage of the N(1)–C(2) as well as the N(3)–C(4) bond. This indicates that the first step in the reaction is an attack by the NH_3 molecule at the strongly π-deficient 2-position of the pyrimidine ring. There is no indication from ^{1}H- and ^{13}C-NMR spectroscopy (see further on) for addition of the nucleophile to the CO group. This addition at the 2-position of **1–7** contrasts with the behaviour of 1-methylpyrimidinium salts, in which addition at the 6-position is strongly favoured, even in the case where the 6-position is blocked by the methyl group[3]. After addition, ring cleavage indicated by a and b (Scheme I) occurs, yielding one or two open-chain products. They can undergo ring closure or react further with water (present in the ammonia or during the work-up).

To substantiate our proposal we carried out ^{1}H- and ^{13}C-NMR measurements of solutions of **1** and **5** in liquid ammonia in order to obtain further proof for the initial addition of the NH_3 molecule at C(2). Application of this technique has been applied successfully by us[3,12,13] and others[14,15] in the study on adduct formation in liquid ammonia.

The ^{1}H-NMR spectrum of **1** in liquid NH_3 showed that the ring protons resonate at a higher field than in the solvent acetone-d_6. The upfield shift is most pronounced for H(2) (see Table III), ascribed to a rehybridisation of C(2) ($sp^2 \rightarrow sp^3$), due to formation of a covalent adduct at C(2). Also, the ^{13}C-NMR data of **1** confirm this addition pattern at C(2). The chemical shift difference Δδ for C(2) in acetone-d_6 and liquid ammonia is 77.3 ppm; the ^1J[C(2)H] changes from 210 Hz (acetone-d_6) to 152 Hz (NH_3), which can be

Table II Chemical shifts (ppm) and coupling constants (Hz) of the H atoms in compounds **18–20**.

Compound	R	H(5)	NH	H(6a)	H(6b)	H(3a)	H(3b)
18	7.79	5.22	5.3	3.11 (m)	1.25	3.87 (q)	1.34
19	2.45	5.18	4.9	3.10 (m)	1.22	3.98 (q)	1.28
20	7.50 (s)	5.30	5.0	3.10 (m)	1.16	3.86 (q)	1.22

Table III Chemical shifts (ppm) and coupling constants (Hz) of the ring hydrogen and carbon atoms of* **1** *and* **5** *in acetone-d_6 and liquid ammonia respectively.*

Compound	Solvent	H(2)	H(5)	H(6)	$J_{2,6}$	$J_{5,6}$	C(2)	C(4)	C(5)	C(6)	^1J[C(2)H]	^1J[C(5)H]	^1J[C(6)H]
1	acetone-d_6	9.50	6.80	8.20	2.2	7.8	155.8	158.5	117.6	145.1	210	180	192
1	NH_3	5.25	4.50	6.85	1.7	7.2	78.5	164.3	89.8	145.7	152	170	172
5	acetone-d_6	9.50	6.14	–	–	–	154.7	161	91.8	161	214	174	–
5	NH_3	5.20	4.12	–	–	–	79.1	166.1**	69.8	161.8**	160	170	–

* The spectral assignment of the ^{13}C-resonances has been performed by measuring the proton decoupled as well as the proton coupled ^{13}C spectra.

** These assignments are based on the upfield shifts in the σ-complex formation between **1** and NH_3.

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[12] *J. P. Geerts, C. A. H. Rasmussen, H. C. van der Plas* and *A. v. Veldhuizen*, Recl. Trav. Chim. Pays-Bas **93**, 231 (1974).

[13] *J. P. Geerts, H. C. van der Plas* and *A. van Veldhuizen*, Org. Magn. Reson. **7**, 86 (1975).

[14] *J. A. Zoltewicz, T. M. Oestreich, J. K. O'Halloran* and *L. S. Helmick*, J. Org. Chem. **38**, 1949 (1973).

[15] *J. A. Zoltewicz, L. S. Helmick, T. M. Oestreich, R. W. King* and *P. E. Kandetzki*, J. Org. Chem. **38**, 1947 (1973).

explained only by the formation of a tetrahedral C(2) in liquid ammonia.

The ^{1}H- and ^{13}C-NMR spectra of **5** in acetone-d_6 and in liquid ammonia gave similar results and fully support the C(2) addition.

Experimental

Melting points are uncorrected. The ^{1}H-NMR spectra were recorded on a Jeol JNM C-60 spectrometer and the carbon spectra were measured on a Varian XL 100-15 spectrometer operating at 25.2 MHz, equipped with a pulse unit and a 620 L-16K on line computer system.

The spectra were taken in $CDCl_3$ or acetone-d_6, using TMS ($\delta = 0$) as internal standard; in liquid ammonia, $(CH_3)_3N$ was used as internal standard and the chemical shifts measured from trimethylamine were converted to the TMS scale by adding, in the ^{1}H-NMR, 2.13 ppm and in the ^{13}C-NMR spectra, 47.5 ppm. The probe temperature when measuring in liquid ammonia was $-50°$. The IR spectra were recorded with a Perkin Elmer spectrometer (model 237).

I. Preparation of the starting materials

a) The compounds **1**, **3–7** were prepared as described earlier[2].

b) 1,3-diethyl-1,4(3,4)-dihydro-6-methyl-4-oxopyrimidinium tetrafluoroborate (**2**).

To a solution of 4.0 g (28.8 mmoles) of 4-ethoxy-6-methylpyrimidine in 50 ml of dichloroethane were added 11.0 g (2.0 equiv.) of Meerwein's triethyloxonium tetrafluoroborate[16]. This solution was heated under reflux for 1 h. Thereupon the solvent was distilled off. The residue was recrystallized twice from absolute ethanol and washed with absolute ether. Yield: 6.3 g (63%). M.p. 125–126°. ^{1}H-NMR (acetone-d_6): δ,9.53 (s), δ 6.75 (s), δ 4.40 (q), δ 4.21 (q), δ 2.64 (s), δ 1.60 (t), δ 1.46 (t). IR spectrum (KBr): 1720–1730 cm^{-1} (s) (C=O). Analysis: calc. for $C_9H_{15}BF_4N_2O$ (254.05): C 42.55, H 5.95; found C 42.74, H 5.85.

II. Reactions

1) General procedure for conversions with ammonia

A solution of 1.0 g of the pyrimidinium salt in 20–50 ml of concentrated ammonia was allowed to react for 15 min at room temperature. Thereupon the solution was extracted (or continuously extracted in the case of the reaction product of **1**) with chloroform. After drying the chloroform extracts the solvent was distilled off. From the residue obtained the oily products were isolated by column or thick-layer chromatography, using silica gel and ethyl acetate as eluent. A mixture of ethyl acetate and methanol (9/1) was used when the reaction products of **1** or **2** were isolated.

Compound **8**

Yield: 39%.
IR spectrum ($CHCl_3$): 1590 cm^{-1} (s), 1640 cm^{-1} (s), 1690 cm^{-1} (s), 3300 cm^{-1} (br), 3430 cm^{-1} (sp). Mass spectrum: *m/e* 170 (M^+). Analysis: $C_8H_{14}N_2O_2$ (170.21) calc. C 56.45, H 8.29; found C 56.61, H 8.41.

Compound **9**

Yield: 26%.
IR spectrum ($CHCl_3$): 1580 cm^{-1} (s), 1610 cm^{-1} (s), 1680 cm^{-1} (s). Mass spectrum: *m/e* 184 (M^+). Analysis: $C_9H_{16}N_2O_2$ (184.23) calc. C 58.67, H 8.75; found C 58.94, H 8.54.

Compound **10**

Yield: 42%.
IR spectrum ($CHCl_3$): 1580 cm^{-1} (s), 1625 cm^{-1} (s), 1680 cm^{-1} (m). Mass spectrum: *m/e* 214 (M^+). Analysis $C_{10}H_{18}N_2O_3$ (214.26): calc. C 56.05, H 8.47; found C 55.87, H 8.61.

Compound **11**

Yield: 17%.
IR spectrum ($CHCl_3$) 1580 cm^{-1} (s), 1610 cm^{-1} (s), 1730 cm^{-1} (m). Mass spectrum: *m/e* 290 (M^+). Analysis: $C_{16}H_{22}N_2O_3$ (290.35): calc. C 66.18, H 7.64; found C 66.31, H 7.50.

Compound **12**

Yield: 11%.
IR spectrum ($CHCl_3$): 1590 cm^{-1} (m), 1600–1700 cm^{-1} with a maximum at 1665 cm^{-1} (s), 3330 cm^{-1} (br), 3430 cm^{-1} (sp). Mass spectrum: *m/e* 170 (M^+). Analysis $C_8H_{14}N_2O_2$ (170.21): calc. C 56.45, H 8.29; found C 56.32, H 8.58.

Compound **13**

Yield: 41%.
IR spectrum ($CHCl_3$): 1600–1710 cm^{-1} with a maximum at 1660 cm^{-1} (s), 3360 cm^{-1} (br), 3460 cm^{-1} (sp). Mass spectrum: *m/e* 184 (M^+). Since **13** could not be completely purified by column chromatography, we prepared a picrate. It appeared that the picrate obtained, m.p. 138–139° (from ethanol), is not that of **13** but of **2** (replace BF_4^- by a picrate anion). Apparently under the influence of picric acid ring closure has occurred. Analysis $C_{15}H_{19}N_5O_9$ (413.34): calc. C 45.57, H 4.33; found C 45.48, H 4.36.

Compound **14**

Yield: 45%.
IR spectrum ($CHCl_3$): 1590–1700 cm^{-1} with maxima at 1610 cm^{-1} (s) and 1655 cm^{-1} (s), 3350 cm^{-1} (br), 3455 cm^{-1} (sp). Mass spectrum: *m/e* 246 (M^+). Analysis: $C_{14}H_{18}N_2O_2$ (246.30): calc. C 68.27, H 7.37; found C 68.00, H 7.44.

Compound **15**

Yield: 80%.
IR spectrum ($CHCl_3$): 1600–1700 cm^{-1} with maxima at 1630 cm^{-1} (m) and 1670 cm^{-1} (s), 3380 cm^{-1} (br), 3480 cm^{-1} (sp). Mass spectrum: *m/e* 246 (M^+). Since **15** could not be completely purified by column chromatography, we prepared a picrate, m.p. 189–190° (from ethanol). As with **13** this appeared to be **4** (replace BF_4^- by a picrate anion). Anal. $C_{20}H_{21}N_5O_9$ (475.41): calc. C 52.51, H 4.19; found C 52.45, H 4.37.

Compound **16**

Yield: 66%.
IR spectrum ($CHCl_3$): 1600–1700 cm^{-1} with a maximum at 1650 cm^{-1} (s), 3400 cm^{-1} (br), 3480 cm^{-1} (sp). Mass spectrum: *m/e* 228 (M^+). Anal. $C_{11}H_{20}N_2O_3$ (228.29): calc. C 57.87, H 8.83; found C 57.62, H 8.86.

Compound **17**

Yield: 30%.
IR spectrum ($CHCl_3$) 1580–1700 cm^{-1} with a maximum at 1655 cm^{-1} (s), 3370 cm^{-1} (br), 3470 cm^{-1} (sp). Mass spectrum: *m/e* 290 (M^+). Anal. $C_{16}H_{22}N_2O_3$ (290.35): calc. C. 66.18, H 7.64; found C 66.27, H 7.82.

Compound **20**

Yield: 7%.
IR spectrum ($CHCl_3$): 1650 cm^{-1} (s), ca. 3400 cm^{-1} (br), 3440 cm^{-1} (sp). Mass spectrum: *m/e* 243 (M^+). Anal. $C_{14}H_{17}N_3O$ (243.30): calc. C 69.11, H 7.04; found C 68.88, H 7.27.

2) General procedure for conversions with liquid ammonia

A solution of 1.0 g of the pyrimidinium salt in ~50 ml of liquid ammonia was allowed to react for 1 h at $-33°$. Subsequently the ammonia was allowed to evaporate and 40 ml of water were added. Isolation of products was as described under *1)*. The yields of the compounds obtained was as follows: **8**: 8%; **11**: 48%; **12**: 5%; **16**: 25%; **17**: 28%; **20**: 11%.

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[16] *H. Meerwein*, Org. Synth. **46**, 113 (1966).

a) Compound **18**

Yield: 28%.

IR spectrum ($CHCl_3$): 1670 cm^{-1} (s), 3400 cm^{-1} (br), 3460 cm^{-1} (sp). Mass spectrum: *m/e* 167 (M^+). M.p. 139–140°. Anal. $C_8H_{13}N_2O$ (167.21): calc. C 57.46, H 7.84; found C 57.56, H 7.91.

b) Compound **19**

The reaction product obtained from **6** was separated by means of thick-layer chromatography, yielding a mixture of **19** and **16**. ^{1}H-NMR analysis showed that **19** and **16** were formed in yields of 23 and 25%, respectively. Compound **19** was isolated by heating the mixture with an excess of aqueous sodium hydroxide (25%) for ten minutes (to decompose compound **16**) and extracting this alkaline solution with chloroform. Purification by thick-layer chromatography, using silica gel and ethyl acetate as eluent, gave **19**.
IR spectrum ($CHCl_3$): 1650 cm^{-1} (s), 3400 cm^{-1} (br), 3450 cm^{-1} (sp). Mass spectrum: *m/e* 181 (M^+). M.p. picrate of **19**: 154–155°. Anal. $C_{15}H_{18}N_6O_8$ (410.34): calc. C 43.90, H 4.42; found C 43.76, H 4.54.

3) General procedure for the conversion of **9**, **10**, **13–15** *with hydrofluoroboric acid into the corresponding salts*

To a solution of 0.5 g of the open-chain compound in 5 ml of absolute ethanol were added 5 ml of a solution of 2 equivs. of triethyloxonium tetrafluoroborate[16] in absolute ethanol. The resulting solution was refluxed for 5 min. By evaporating the solvent the solution was concentrated as far as possible. After cooling, crystals separated, which were collected and washed with absolute ether. The products were identified by mixed melting point determination with the tetrafluoroborates, synthesized as described in a previous paper[2].

Acknowledgement

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Ring transformations in reactions of heterocyclic compounds with nucleophiles[1]

Reactions of 4(6)-alkoxy-1-ethyl- and 4,6-dialkoxy-1-ethylpyrimidinium tetrafluoroborates with liquid ammonia[2]

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Abstract On treatment with liquid ammonia at -33° the quaternary pyrimidinium salts i.e. 4-ethoxy-1-ethyl- (1) and 4,6-diethoxy-1-ethylpyrimidinium tetrafluoroborate (3) undergo amino-de-ethoxylation, yielding 1,4-dihydro-1-ethyl-4-iminopyrimidine hydrogen tetrafluoroborate (7) and a mixture of 1,4-dihydro-6-ethoxy-1-ethyl-4-imino- (9) and 1,6-dihydro-4-ethoxy-1-ethyl-6-iminopyrimidine hydrogen tetrafluoroborate (11), respectively. ^{1}H-NMR and ^{13}C-NMR spectroscopic evidence is presented for the fact that compounds 1 and 3 easily give σ-adducts at position 2. Using ^{15}N-labelled ammonia it was shown that in these amino-de-ethoxylation reactions the substitution at C(4) or C(6) does not involve ring opening but probably occurs via an $S_N(AE_n)$ process. Reaction of 4-ethoxy-1-ethyl-2-phenyl- (2), 6-ethoxy-1-ethyl-4-phenyl- (4), 4,6-dimethoxy-1-ethyl-2-phenyl- (5) and 4,6-dimethoxy-1-ethyl-2-methylpyrimidinium tetrafluoroborate (6) with liquid ammonia gives besides the amino-de-ethoxylation product degenerate ring transformations leading to the N-de-ethylated products 14-16 and 4(6)-ethylaminopyrimidines 17-19. The salt 11 and 1,6-dihydro-1-ethyl-6-imino-4-phenylpyrimidine hydrogen tetrafluoroborate (12) undergo, with potassium hydroxide, a Dimroth rearrangement to pyrimidines 20 and 17, respectively.

1. Introduction

The study of ring transformations, of N-alkylpyrimidinium salts upon treatment with nucleophiles (hydrazine[3], hydroxylamine[4], ammonia[5,6], carbanions[7], cyanamide[8] and amidines[8]) has our continuing interest.

In a previous paper[5] we have reported that N-methylpyrimidinium methyl sulfate and its C-methyl derivatives on treatment with liquid ammonia at -33° undergo demethylation via a ring opening/ring closure sequence. The initial step in this mechanism, the addition of the nucleophile at position 6, was proved unequivocally by ^{1}H-NMR spectroscopy. In order to investigate the scope of these degenerate ring transformations, we have examined the reaction of alkoxypyrimidinium salts (1-6)[9] with liquid ammonia at -33°.

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[1] a. For part XVII in these series see: H.C.van der Plas, M.Wóźniak and A.van Veldhuizen, Recl. Trav.Chim.Pays-Bas, in the press. b. For a general review on this subject see: H.C.van der Plas, Ring transformations of Heterocycles, vol.1 and 2, Academic Press, London and New York, 1973.

[2] Part LXI on Pyrimidines from this laboratory, see for part LX F.Roeterdink and H.C.van der Plas, Recl.Trav.Chim.Pays-Bas, in the press. Part XIV on NMR-studies on σ-adducts in heterocyclic systems with nucleophiles. See for Part XIII, H.C.van der Plas, M.Wóźniak and A.van Veldhuizen, Recl.Trav.Chim.Pays-Bas, 1977, in the press.

[3] H.C.van der Plas and H.Jongejan, Tetrahedron Lett. 44, 4385 (1967).

[4] H.C.van der Plas, M.C.Vollering, H.Jongejan and B.Zuurdeeg, Recl.Trav.Chim.Pays-Bas 93, 225 (1974).

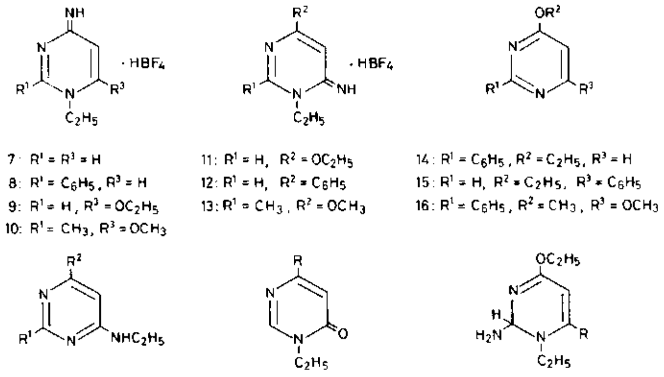
1: $R^1 = H$
2: $R^1 = C_6H_5$

3: $R^1 = H$, $R^2 = OC_2H_5$, $R^3 = C_2H_5$
4: $R^1 = H$, $R^2 = C_6H_5$, $R^3 = C_2H_5$
5: $R^1 = C_6H_5$, $R^2 = OCH_3$, $R^3 = CH_3$
6: $R^1 = CH_3$, $R^2 = OCH_3$, $R^3 = CH_3$

Fig. I

2. Results and Discussion

On reacting 4-ethoxy-1-ethylpyrimidinium tetrafluoroborate (1) with liquid ammonia, amino-de-ethoxylation occurs yielding 1,4-dihydro-1-ethyl-4-iminopyrimidine hydrogen tetrafluoroborate (7, 68%). Reaction of 4,6-diethoxy-1-ethylpyrimidinium tetrafluoroborate (3) with liquid ammonia gives amino-de-ethoxylation at position 4 or 6, as indicated by the formation of the two isomeric compounds i.e. 1,4-dihydro-6-ethoxy-1-ethyl-4-iminopyrimidine hydrogen tetrafluoroborate (9, 55%) and 1,6-dihydro-4-ethoxy-1-ethyl-6-iminopyrimidine hydrogen tetrafluoroborate (11). The structure evidence was based on chemical transformations. Structure 9 was established by the formation of 4-amino-1,6-dihydro-1-ethyl-6-oxopyrimidine (21) on treatment of 9 with aqueous potassium hydroxide or with concentrated hydrochloric acid, structure 11 by the fact that with a large excess of aqueous potassium hydroxide, 4-ethoxy-6-ethylaminopyrimidine (20) was obtained. The latter compound is formed via a Dimroth rearrangement[10] proving that the imino group and the N-ethyl group in 11 are in adjacent positions[11].



7: $R^1 = R^3 = H$
8: $R^1 = C_6H_5$, $R^3 = H$
9: $R^1 = H$, $R^3 = OC_2H_5$
10: $R^1 = CH_3$, $R^3 = OCH_3$

11: $R^1 = H$, $R^2 = OC_2H_5$
12: $R^1 = H$, $R^2 = C_6H_5$
13: $R^1 = CH_3$, $R^2 = OCH_3$

14: $R^1 = C_6H_5$, $R^2 = C_2H_5$, $R^3 = H$
15: $R^1 = H$, $R^2 = C_2H_5$, $R^3 = C_6H_5$
16: $R^1 = C_6H_5$, $R^2 = CH_3$, $R^3 = OCH_3$

17: $R^1 = H$, $R^2 = C_6H_5$
18: $R^1 = C_6H_5$, $R^2 = OCH_3$
19: $R^1 = CH_3$, $R^2 = OCH_3$
20: $R^1 = H$, $R^2 = OC_2H_5$

21: $R = NH_2$
22: $R = F$

23: $R = H$
24: $R = OC_2H_5$

Fig. II

4-Ethoxy-1-ethyl-2-phenylpyrimidinium tetrafluoroborate (2) shows a somewhat different behaviour towards liquid ammonia than 1 and 3.
Besides amino-de-ethoxylation into 1,4-dihydro-1-ethyl-4-imino-2-phenylpyrimidine hydrogen tetrafluoroborate (8, 66%), N-de-ethylation occurs yielding 4-ethoxy-2-phenylpyrimidine (14, 10%).

From 6-ethoxy-1-ethyl-4-phenylpyrimidinium tetrafluoroborate (4) besides 1,6-dihydro-1-ethyl-6-imino-4-phenylpyrimidine hydrogen tetrafluoroborate (12, 50%) and 4-ethoxy-6-phenylpyrimidine (15, 16%), 4-ethylamino-6-phenylpyrimidine (17, 10%) was isolated. Compound 17 is not formed from 12, since 12 is stable in liquid ammonia at -33^{o} and only undergoes a Dimroth rearrangement into 17 by treatment with aqueous potassium hydroxide. The formation of 14, 15 and 17 presents new examples of degenerate ring transformations; they are initiated by an attack of NH_3 at the C(2) position of the pyrimidine ring (see Section 4). Reacting 4,6-dimethoxy-1-ethyl-2-phenylpyrimidinium tetrafluoroborate (5) with liquid ammonia gives N-de-ethylation into 4,6-dimethoxy-2-phenylpyrimidine (16) and formation of 4-ethylamino-6-methoxy-2-phenylpyrimidine (18) in yields of 53 and 37% respectively. The ^{1}H-NMR spectrum of the crude reaction mixture obtained after the evaporation of the ammonia shows the

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5. E.A.Oostveen, H.C.van der Plas and H.Jongejan, Recl.Trav.Chim.Pays-Bas 93, 114 (1974).
6. E.A.Oostveen and H.C.van der Plas, Recl.Trav. Chim.Pays-Bas 96, 64 (1977).
7. E.A.Oostveen and H.C.van der Plas, Recl.Trav. Chim.Pays-Bas 93, 233 (1974).
8. E.A.Oostveen, H.C.van der Plas and H.Jongejan, Recl.Trav.Chim.Pays-Bas 95, 209 (1976).
9. E.A.Oostveen and H.C.van der Plas, Recl.Trav. Chim.Pays-Bas 96, 68 (1977).
10. D.J.Brown in Mechanisms of Molecular Migrations, Vol. 1, Interscience Publishers, New York, London, Sydney and Toronto 1968, p.209.
11. An analogous conversion has been reported to occur on treatment of 1,6-dihydro-6-imino-4-methoxy-1-methylpyrimidinium hydroiodide with base, yielding 4-methoxy-6-methylaminopyrimidine. See: D.J.Brown and T.Teitei, J.Chem.Soc. 1963, 3535.

presence of 4- and/or 6-iminopyrimidine hydrogen tetrafluoroborate in very small amounts, if any. Reaction of 4,6-dimethoxy-1-ethyl-2-methylpyrimidinium tetrafluoroborate (6) with liquid ammonia gives 1,4-dihydro-1-ethyl-4-imino-6-methoxy-2-methylpyrimidine hydrogen tetrafluoroborate (10) as main product (yield 55%). That this product was not the isomeric 1,6-dihydro-1-ethyl-6-imino-4-methoxy-2-methylpyrimidine hydrogen tetrafluoroborate (13) has been established by the non-occurrence of a Dimroth rearrangement into an ethylaminopyrimidine derivative, when 10 is reacted with aqueous potassium hydroxide; under these circumstances 10 decomposed. Furthermore, we could isolate by means of column chromatography, 4-ethylamino-6-methoxy-2-methylpyrimidine (19, 11%). A higher yield (22%) of compound 19 could be obtained when, before isolation, the residue of the reaction mixture of 6 with liquid ammonia was treated with aqueous base. It indicates that besides 10 the isomeric salt 13 was probably formed. The several reactions which are found to occur are summarized in Table I.

Table I: Observed conversions

$1 \rightarrow 7$

$2 \rightarrow 8 + 14$

$3 \rightarrow 9 + 11$

$4 \rightarrow 12 + 15 + 17$

$5 \rightarrow 16 + 18$

$6 \rightarrow 10 + 13 + 19$

3. On the mechanism of the amino-dealkoxylations

In order to get some insight into the mechanism(s) of the above-mentioned amino-dealkoxylation reactions we investigated first whether N-ethylpyrimidinium salts form covalent σ-adducts with liquid ammonia by measuring the ^{1}H-NMR and ^{13}C-NMR spectra of solutions of some of the compounds, i.e. 1 and 3, in acetone-d_6 at room temperature and in liquid ammonia at -50°. The measurements in liquid ammonia were carried out immediately after dissolving the compounds. The results are summarized in Table II.

NMR spectra of 1 and 3 in the solvent liquid ammonia show that the absorptions of the ring hydrogen and ring carbon atoms lie at a much higher field than in acetone-d_6; these upfield shifts are the most pronounced for the C(2) and H(2) atoms. These data combined with the considerable decrease in the magnitude of the $^{1}J\left[C(2)H\right]$ coupling constants (see Table II) led us to the conclusion that in liquid ammonia not the parent compounds 1 and 3 but the covalent σ-adducts 23 and 24, respectively, are present. These adducts are stable at -50° since the spectra do not change on standing.

In order to decide whether or not the replacement of the 4-ethoxy group in 3 by an imino group takes place by a degenerate ring transformation $\left[S_N\text{(ANRORC) mechanism}\right]$ we studied the conversion of 3 into 9 with $\left[^{15}N\right]$ ammonia (∼ 7% of excess). In the 4-iminopyrimidine hydrogen tetrafluoroborate (9) the ^{15}N content could not be

Table II: Chemical shifts (ppm) and coupling constants (Hz) of the ring hydrogen and ring carbon atoms of 1 and 3 in acetone-d_6 and liquid ammonia respectively[1]

Compound	Solvent	H(2)	H(5)	H(6)	$J_{2,6}$	$J_{5,6}$	C(2)	C(4)	C(5)	C(6)	$^{1}J\left[C(2)H\right]$	$^{1}J\left[C(5)H\right]$	$^{1}J\left[C(6)H\right]$
1	acetone-d_6	9.36	7.45	8.90	2.2	7.2	156.2	172.8	111.9	151.4	210	180	192
1	NH_3	5.37	4.57	6.84	1.5	7.2	78.3	162.1	83.1	144.4	165	170	172
3	acetone-d_6	9.05	6.92	--	--	--	154.9	174.7[2]	91.2	165.2[2]	216	178	--
3	NH_3	5.26	4.10	--	--	--	81.0	164.2[3]	62.8	160.8[3]	163	170	--

[1] The spectral assignments of the ^{13}C resonances have been performed by measuring the proton decoupled as well as the proton coupled spectra.

[2] These assignments are based on the substituent effects of a 6-ethoxy group at C(4) and C(6), calculated from the difference in chemical shifts of the ^{13}C resonances of 1,3-diethyl-1,4(3,4)-dihydro-4-oxo- and 1,3-diethyl-1,4(3,4)-dihydro-6-ethoxy-4-oxopyrimidinium tetrafluoroborate.

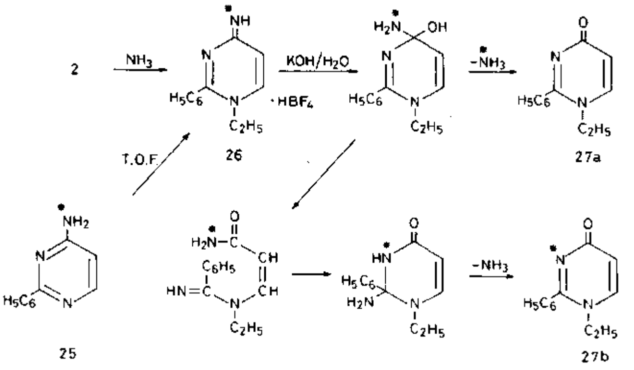
[3] These assignments are based on the upfield shifts of the C(4) and C(6) atoms in the σ-complex formation between 1 and NH_3.

measured by mass spectrometry. Therefore it was converted into 21 by treatment with acid; 21 contained an excess of 7.5 (7.5)*% ^{15}N. For the determination of the ^{15}N excess in the ring nitrogen atoms $[^{15}N]$ 21 was diazotized by sodium nitrite in an aqueous solution of hydrofluoroboric acid (40%) and so converted into the 1,6-dihydro-1-ethyl-4-fluoro-6-oxopyrimidine (22). This was found to be unlabelled!

From this result it is very evident, that the conversion of 3 into 9 does not proceed by an S_N(ANRORC) mechanism. An addition/elimination reaction [$S_N(AE)_n$ mechanism] is probably operative. Whether this replacement occurs in the substrate 3 or in its σ-adduct 24 is unknown and cannot be determined from the data so far available.

The mechanism of the amino-de-ethoxylation of 2 into 8 [S_N(ANRORC) or $S_N(AE)_n$] was also investigated with $[^{15}N]$ammonia (containing an excess of 6.0 (6.7)* % ^{15}N). In order to remove the 4-imino group in the salt 26, it was converted into 1,4-dihydro-1-ethyl-4-oxo-2-phenylpyrimidine (27) by refluxing in aqueous potassium hydroxide. Compound 27 contained an excess of 2.3 (2.6)*% ^{15}N. This result seems to indicate that a ring opening/ring closure sequence is involved in the amino-de-ethoxylation of 2 into 26. This result is, however, in sharp contrast to the results obtained with 3. We could prove, however, that the presence of ^{15}N in 27 must be explained by a rearrangement of an exocyclic nitrogen to a ring nitrogen during the treatment of 26 with base. This proof was based on the following:

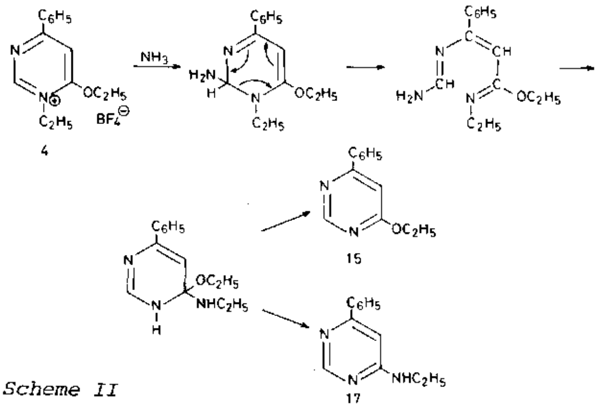
We synthesized 4-$[^{15}N]$-amino-2-phenylpyrimidine (25) by heating 4-chloro-2-phenylpyrimidine with an ethanolic solution of ^{15}N-labelled ammonia (6.7% of ^{15}N excess). That the amino compound 25 formed was exclusively ^{15}N-labelled in the amino group, was established by an acid hydrolysis of 25 with hydrochloric acid, yielding unlabelled 2-phenyl-4-pyrimidone. On treating 25 with triethyloxonium tetrafluoroborate (TOF) ^{15}N-labelled 26 was formed. The latter salt gave, after refluxing in aqueous potassium hydroxide 27 , containing an excess of 2.5 (2.7)*% ^{15}N. Thus the hydrolysis of the amino group in 26 proceeds apparently in two ways: via an addition/elimination reaction leading to 27a and simultaneously by a degenerate ring transformation into 27b (Scheme I). Both ^{15}N studies on the amino-de-ethoxylation (2 → 8, 3 → 9) lead to the conclusion that the amination of 4-alkoxy-N-ethylpyrimidinium salts by liquid ammonia does not involve ring opening.



Scheme I

4. On the mechanism of the N-de-ethylation and the formation of the 4(6)-ethylaminopyrimidines

We have investigated the de-ethylation of 2 with $[^{15}N]$ ammonia, containing 6.0 (6.7)*% of ^{15}N excess following the method as described previously for the N-demethylation of N-methylpyrimidinium salts. Compound 14 contained about the same ^{15}N enrichment 6.0 (6.2)*% as the $[^{15}N]$ammonia. This proves that like the N-demethylation of N-methylpyrimidinium methylsulfate the N-de-ethylation reaction proceeds via a ring opening/ring closure sequence. Since in our experiments N-de-ethylation is often accompanied by the formation of 4(6)-ethylaminopyrimidine derivatives we assume that both processes take place via a common intermediate formed by an initial addition of ammonia at C(2). This is exemplified in the formation of 15 and 17 from 4, as shown in Scheme II.



Scheme II

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* The number between the backets refers to duplicate experiments

Experimental part

Melting points are uncorrected. The ^{1}H-NMR spectra were recorded on a Jeol JNM C-60 spectrometer and the carbon spectra were measured on a Varian XL 100-15 spectrometer operating at 25.2 MHz, equipped with a pulse unit and a 620 L-16K on line computer system.

The spectra were taken in $CDCl_3$ or acetone-d_6, using TMS (δ= 0) as internal standard; in liquid ammonia Me_3N was used as internal standard and the chemical shifts measured from trimethylamine were converted to the TMS scale by adding in the ^{1}H-NMR 2.13 ppm and in the ^{13}C-NMR spectra 47.5 ppm. The probe temperature when measuring in liquid ammonia was -50°.

The IR spectra were recorded with a Perkin Elmer spectrometer (model 237).

The ^{15}N contents were measured on an AEI-MS 902 mass spectrometer.

I. Preparations of starting materials and reference compounds

a. The alkoxy-1-ethylpyrimidinium tetrafluoroborates (1-6)[9], 4-ethoxy-2-phenyl- (14)[6], 4-ethoxy-6-phenyl- (15)[6] and 4,6-dimethoxy-2-phenylpyrimidine (16)[12] were synthesized as described previously.

b. 1,4-Dihydro-1-ethyl-4-imino-2-phenylpyrimidine hydrogen tetrafluoroborate (8)

1.0 g (5.8 mmoles) of 4-chloro-2-phenylpyrimidine[13] were added to 20 ml of absolute ethanol saturated at 0° with ammonia. This solution was heated at 140° in a sealed tube for 10 h. After the reaction, the solvent was removed under diminished pressure. The residue was dissolved in ~10 ml of conc.HCl. 4-Amino-2-phenylpyrimidine was precipitated by addition of an excess of a KOH solution (25%). The crystals were collected and recrystallized from a mixture of ethanol and water (2/1). After drying, 0.6 g of impure 4-amino-2-phenylpyrimidine was

Table III: Yields, melting points and elemental analyses of the compounds 7-10, 12, 17-20

Compound	Yield %	M.p. (°C)	Empirical formula	mol. weight	Analyses			
					Calculated		Found	
					C	H	C	H
7	68	127-128	$C_6H_{10}BF_4N_3$	210.98	34.15	4.78	34.39	4.82
8	66	181-182*	$C_{12}H_{14}BF_4N_3$	287.08	50.20	4.92	50.03	4.75
9	55	197-198	$C_8H_{14}BF_4N_3O$	255.04	37.67	5.53	37.69	5.52
10	54	208-209	$C_8H_{14}BF_4N_3O$	255.04	37.67	5.53	37.61	5.40
12	50	158-159	$C_{12}H_{14}BF_4N_3$	287.08	50.20	4.92	50.24	4.72
17	10	oil	$C_{12}H_{13}N_3$	199.25	72.33	6.58	72.11	6.69
18	37	50-52	$C_{13}H_{15}N_3O$	229.27	68.10	6.59	67.83	6.83
19	10	oil	$C_8H_{13}N_3O$	167.21	57.64	7.84	57.52	8.00
20	31	88-89	$C_8H_{13}N_3O$	167.21	57.64	7.84	57.20	7.92

*It was identified by comparison with an authentic specimen, prepared from 4-amino-2-phenylpyrimidine and triethyloxonium tetrafluoroborate.

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[12] M.Pl.Caton, M.S.Grant, D.L.Pain and R.Slack, J.Chem.Soc. 1965, 5467.

[13] S.Ruheman and A.S.Hemmy, Ber. 30, 2029 (1897).

Table IV: Chemical shifts (ppm) and coupling constants (Hz) of the compounds 7-12 and 17-20*

Compound	R^1	R^2	R^3	H(5)	H(a) $NCHCH_3$	H(b) NCH_2CH_2	$J_{2,6}$	$J_{5,6}$
7	8.92	--	8.45	7.07	4.38	1.57	1.8	7.5
8	7.7(s)	--	8.45	7.05	4.24	1.41	--	7.5
9	8.63	--	CH_2: 4.53 CH_3: 1.53	6.48	4.30	1.47	--	--
10	2.73	--	4.19	6.45	4.29	1.41	--	--
11	8.71	CH_2: 4.4 CH_3: 1.5	--	6.48	4.4	1.5	--	--
12	8.87	7.4-7.7(3H) 8.0-8.3(2H)	--	7.72	4.47	1.55	--	--
17	8.62	7.3-7.6(3H) 7.8-8.1(2H)	--	6.64	3.37	1.28	--	--
18	7.3-7.6(3H) 8.3-8.5(2H)	4.03	--	5.55	3.28	1.23	--	--
19	2.40	3.90	--	5.47	3.18	1.20	--	--
20	8.20	CH_2: 4.31 CH_3: 1.36	--	5.59	3.21	1.36	--	--

*The compounds 7-12 were measured in acetone-d_6, the compounds 17-20 in $CDCl_3$

obtained. This product (0.6 g) was heated under reflux with a solution of 1.4 g of triethyloxonium tetrafluoroborate in 20 ml of dichloroethane. The solvent was then distilled off and the residue was crystallized twice from absolute ethanol. Yield 0.53 g of 8 (31%). M.p. 181-182°. For the analysis and the spectroscopic data, see Tables III and IV, respectively.

For the determination of the ^{15}N content in labelled 4-[^{15}N]-amino-2-phenylpyrimidine (25), obtained from 4-chloro-2-phenylpyrimidine with [^{15}N]-ammonia a little of the "crude" product was further purified by preparative gas chromatography on a Becker gas chromatograph (Delft, The Netherlands) using a stainless steel column (length 100 cm, internal diameter 0.3 cm), containing OV-17 on anachrom ABS Q 70-80 mesh, weight ratio 20:80.

II. Reactions

a. General procedure for the reaction of the alkoxy-1-ethylpyrimidinium tetrafluoroborates (1-6) with liquid ammonia; isolation and characterisation of products

A solution of 1.0 g of the pyrimidinium salt in $\sim$ 50 ml of liquid ammonia was allowed to react for 0.5 h at -33°, after which the ammonia was allowed to evaporate. The residue obtained was crystallized from absolute ethanol and washed with absolute ether. The mother liquor was concentrated by evaporation of the solvent and the non-crystalline products were isolated if possible by column chromatography, using silica gel and ethyl acetate as eluent. Chloroform was preferred to ethyl acetate as eluent when the reaction products of 5 were isolated. The yields of the isolated 1-ethyl-4(6)-iminopyrimidine hydrogen tetrafluoroborates (7-10, 12) and 4(6)-ethylaminopyrimidines (17-20), their melting points and elemental analyses are brought together in Table III, the ^{1}H-NMR data of the compounds 7-12 and 17-19 are given in Table IV. The mass spectra of 17-20 and the IR spectra of 7-12 and 17-20 are in excellent agreement with the proposed structures. The products 14-16 were identified by comparing their IR and ^{1}H-NMR spectra with the spectra of the authentic specimens (see I.a).

1,6-Dihydro-4-ethoxy-1-ethyl-6-iminopyrimidine hydrogen tetrafluoroborate (11) obtained from 3 could not be satisfactorily purified. It was characterized by formation of 4-ethoxy-6-ethylaminopyrimidine (20) when impure 11 was refluxed with an aqueous solution of an eighty-fold excess of KOH for 15 min. 4-Ethoxy-6-ethylaminopyrimidine (20) was isolated by extraction of the solution with chloroform and purified further by column chromatography, using silica gel and ethyl acetate as eluent. Yield 31% (based on 3). For analysis and ^{1}H-NMR data see Tables III and IV, respectively.

b. Conversion of 1,6-dihydro-1-ethyl-6-imino-4-phenylpyrimidine hydrogen tetrafluoroborate (12) into 4-ethylamino-6-phenylpyrimidine (17)

This Dimroth rearrangement was carried out by the same procedure as described above for the conversion of 11 into 20. Yield 65%.

c. Conversion of 1,4-dihydro-1-ethyl-4-imino-2-phenylpyrimidine hydrogen tetrafluoroborate (8) into 1,4-dihydro-1-ethyl-4-oxo-2-phenylpyrimidine (27)

A solution of 0.44 g (1.5 mmoles) of 8 in 30 ml of water, containing 0.18 g (2.0 equiv.) of KOH was heated under reflux for 0.5 h. After the solvent had been distilled off under diminished pressure, 27a was isolated from the residue obtained by means of column chromatography, using silica gel and a mixture of ethyl acetate and methanol (1/1) as eluent. Yield: 55%. ^{1}H-NMR ($CDCl_3$):δ 7.54 [H(6), d],δ 7.50 (C_6H_5, s),δ 6.23 [H(5), d] , δ 3.85 (CH_2, q),δ 1.24 (CH_3, t). IR spectrum: 1640-1650 cm^{-1} (s) C=O stretching vibration. Mass spectrum: m/e 200 (M^+). This compound was converted into 1,3-diethyl-1,4(3,4)-dihydro-4-oxo-2-phenylpyrimidinium tetrafluoroborate by a reaction with triethyloxonium tetrafluoroborate, following the procedure already described[9]. M.p. 189-190°. Mixed melting point determination with an authentic specimen[9] gave no depression.

d. Conversion of 1,4-dihydro-6-ethoxy-1-ethyl-4-iminopyrimidine hydrogen tetrafluoroborate (9) into 4-amino-1,6-dihydro-1-ethyl-6-oxopyrimidine (21)

A solution of 0.4 g (1.6 mmoles) of 9 in 30 ml of conc. HCl was refluxed for 0.5 h. The water was then distilled off almost completely under diminished pressure. After the residual solution was neutralized with $NaHCO_3$ solution, the water was again removed under diminished pressure and the remaining solid was extracted with chloroform. The solvent was distilled off from the chloroform solution and 21 was isolated from the residue obtained by column chromatography, using silica gel and a mixture of ethyl acetate and methanol (1/1) as eluent. Yield: 50%. ^{1}H-NMR (acetone-d_6):δ 8.04 [H(2), s],δ 5.31 [H(5), s],δ 3.90 (CH_2, q), δ 1.27 (CH_3, t),δ 6.0 (NH_2, broad). IR spectrum 3450 cm^{-1} (sp), 3360 cm^{-1}(br), 1660 cm^{-1} (C=O stretching vibration, s). Mass spectrum: m/e 139 (M^+). M.p. picrate of 21: 176-177° (from ethanol).
Analysis: $C_{12}H_{12}N_6O_8$ (386.26): calc. C 39.13, H 3.28; found C 39.43, H 3.44. The conversion of 9 into 21 could also be performed in aqueous potassium hydroxide, using the same procedure as described for the conversion of 8 into 27a. In this case, however, 1.5 equivalents of KOH were used. Yield: 70-75%.

e. Conversion of 4-amino-1,6-dihydro-1-ethyl-6-oxopyrimidine (21) into 1,6-dihydro-1-ethyl-4-fluoro-6-oxopyrimidine (22)

140 mg of 4-amino-1,6-dihydro-1-ethyl-6-oxopyrimidine (21) (1.0 mmoles) were dissolved in 3 ml of an aqueous solution of hydrofluoroboric acid (40%). While stirring, a solution of 760 mg of sodium nitrite (11.0 mmoles) in 3 ml of water was added drop by drop over a period of 20 min., keeping the temperature of the mixture at -10°. The reaction mixture was stirred for two h during which the temperature was allowed to rise to room temperature. The reaction mixture was then neutralized with $NaHCO_3$. The residue obtained after the evaporation of the solvent was extracted with chloroform. The

extracts were dried over $MgSO_4$. The chloroform was distilled off and from the oily residue compound 22 was isolated by column chromatography, using silica gel and ethyl acetate as eluent. Yield: 20%. M.p. 86-88°. ^1H-NMR ($CDCl_3$): δ 8.10 [H(2), s,] δ 6.02 [H(5), s], δ 4.05 (CH_2, q), δ 1.45 (CH_3, t). IR spectrum 1670-1690 cm^{-1} (s), C=O stretching vibration. Mass spectrum m/e 142 (M^+). Analysis: $C_6H_7FN_2O$ (142.13): calc. C 50.70, H 4.96; found C 50.35, H 5.25.

Acknowledgement

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). We are indebted to Mr.A.van Veldhuizen and Dr.P.Smit for their help during the PMR measurements, to Drs.C.A.Landheer and Mr.W.P. Combé for mass spectrometric data, to Mr.H.Jongejan for performing the microanalyses and to Ir.A.L.H. Daemen for carrying out some of the experiments.

Ring transformations in reactions of heterocyclic compounds with nucleophiles (XII)[1]

A ^{15}N and ^{14}C study of the conversion of pyrimidine into 5-ethyl-2-methylpyridine[2]

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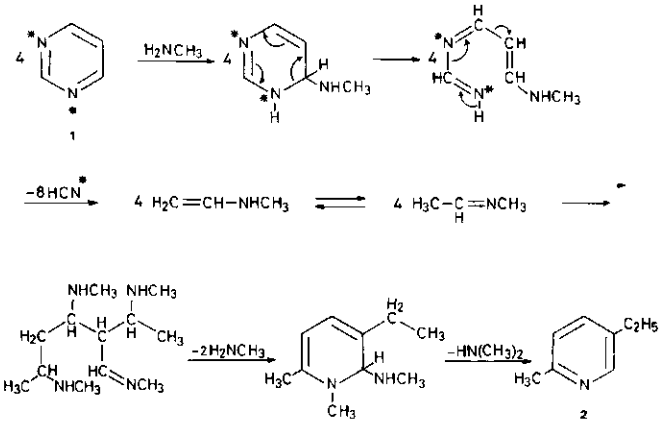
Abstract. The mechanism of the conversion of pyrimidine into 5-ethyl-2-methylpyridine has been investigated. It has been proved, using the labelled compounds [1,3-^{15}N]pyrimidine, [4,6-^{14}C]pyrimidine and [5-^{14}C]pyrimidine, that this reaction proceeds *via* a mechanism, in which the pyrimidine ring is fragmentated into two molecules of HCN and one molecule of *N*-methylacetaldimine. Four molecules of this imine undergo an aldol type condensation leading to 5-ethyl-2-methylpyridine.

In a previous paper[3] we reported on the conversion of pyrimidine into 5-ethyl-2-methylpyrimidine (**2**), when heated with aqueous methylamine at about 190° during five h. At the same time a somewhat similar ring transformation *i.e.* of 5-aryl-2-methoxypyrimidine into 3,5-diarylpyridine was reported[4].

In order to gain some insight into the mechanism of this new ring transformation, we were particularly interested in the problem as to which compound (pyrimidine or methylamine) the nitrogen atom of the pyridine ring originates and which carbon atoms of the pyrimidine [C(2), C(4,6), C(5)] are built into **2**. We therefore investigated the reaction with the labelled compounds [1,3-^{15}N]pyrimidine (**1**), [4,6-^{14}C]-pyrimidine (**3a**) and [5-^{14}C]pyrimidine (**3b**) under the conditions mentioned above.

Starting from **1** containing an excess of 3.9 (3.0)* of ^{15}N we observed the formation of unlabelled 5-ethyl-2-methylpyridine. This result clearly indicates that after fragmentation of the pyrimidine ring the N(1) and N(3) atoms and consequently also the C(2) atom of the pyrimidine nucleus are *not* built into **2**. This has led us to propose the following reaction pathway for the formation of **2** (Scheme 1).



Scheme 1

First an addition of the methylamine to the N(1)–C(6) azomethine bond takes place. There is overwhelming evidence that addition of nitrogen nucleophiles to C(6) of the pyrimidine ring can easily occur[5,6,7]. After ring opening, an open-chain propenylideneformamidine is obtained, which decomposes into two molecules of hydrogen cyanide and one molecule of *N*-methylacetaldimine. In a repeatedly occurring aldol condensation of this intermediary *N*-methylacetaldimine with methylamine, 5-ethyl-2-methylpyridine is formed.

In order to substantiate this mechanism further, the ring transformation of [4,6-^{14}C]pyrimidine (**3a**) and [5-^{14}C]-pyrimidine (**3b**) was studied. From the mechanism proposed in Scheme 1 it may be expected that 5-ethyl-2-methylpyridine (**4a**) obtained from **3a** should have a specific radioactivity twice as large as that of **3a**. In the case of **3b** as starting substance the specific radioactivity in the pyridine derivative must be four times of that of **3b**. The experimental results being presented below in Scheme 2, clearly show a resonable agreement with these expectations and strongly support the proposed mechanism.

Additional evidence for this mechanism was obtained by oxidation of the two ^{14}C-labelled pyridine derivatives **4a** and **4b** – after being diluted to a specific activity of 0.098 µC/mmol and 0.226 µC/mmol – with potassium permanganate. The oxidation products *i.e.* the 6-methylnicotinic acids were esterified in the usual way be treatment with ethanol and

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* This number in brackets refers to a second experiment with a somewhat different excess of ^{15}N.

[1] See for Part XI in these series, *A. Nagel* and *H. C. van der Plas*, Chem. Pharm. Bull. (Japan) **23**, 1975. For a general review on this subject see *H. C. van der Plas*, Ring Transformations of Heterocycles, vol. 1 and 2, Academic Press, London and New York, 1973.

[2] Part LIII on Pyrimidines from this laboratory; part LII *F. Roeterdink* and *H. C. van der Plas*, J. Chem. Soc., Perkin Trans. I, 1976, in press.

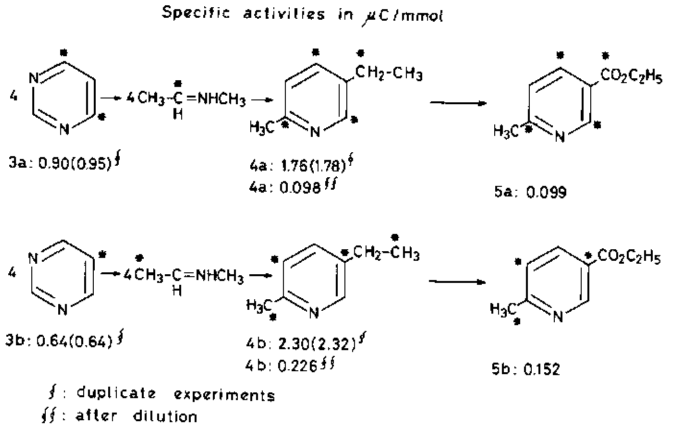
[3] *H. C. van der Plas, H. Jongejan, G. Geurtsen* and Miss *M. C. Vollering*, Recl. Trav. Chim. (Pays-Bas) **90**, 1246 (1971).

[4] *D. J. Brown* and *B. T. England*, Australian J. of Chemistry **23**, 625 (1970).

[5] *J. P. Geerts, H. C. van der Plas* and *A. van Veldhuizen*, Recl. Trav. Chim. (Pays-Bas) **92**, 1232 (1973).

[6] *J. P. Geerts, H. C. van der Plas* and *A. van Veldhuizen*, Org. Magn. Reson. **7**, 86 (1975).

[7] *J. A. Zoltewicz* and *L. S. Helmick*, J. Amer. Chem. Soc. **94**, 682 (1972).



Scheme 2

acid. The ethyl esters **5a** and **5b** were purified by column chromatography and their specific radioactivities were also measured. The specific activity of ester **5b** – derived from [5-^{14}C]pyrimidine (**3b**) – had decreased, whereas the specific activity of ester **5a** – derived from [4,6-^{14}C]pyrimidine (**3a**) – had undergone no considerable change (see Scheme 2).

The above mentioned results unequivocally prove that a C[4(6)]–C(5) fragment is obtained from pyrimidine by thermolysis of pyrimidine with methylamine.

The formation of **2** from this acetaldimine derivative is not unprecedented. It has been reported[8] that acetaldehyde in the presence of ammonia gives **2**. Very likely also in this reaction an acetaldimine is an intermediate.

Experimental part

The ^{15}N contents were measured on an AEI MS 902 mass spectrometer.

a. Preparations

[1,3-^{15}N]pyrimidine (**1**), [4,6-^{14}C]pyrimidine (**3a**) and [5-^{14}C]pyrimidine (**3b**) were prepared by a three-step synthesis as described in the literature for unlabelled pyrimidine[9,10,11]. It comprises the synthesis of barbituric acid by condensation of urea with diethyl malonate, treatment of barbituric acid with phosphoryl chloride and reduction of the resulting 2,4,6-trichloropyrimidine by treatment with hydrogen using a Pd/C catalyst.

b. Reactions

1. *Conversion of pyrimidine into 5-ethyl-2-methylpyridine*

2.0 g (25 mmoles) of pyrimidine, 7 g of 30% aqueous methylamine and 10 ml of water were heated at 190° in a sealed tube for 5 h. The reaction mixture, after being cooled and strongly basified with 25% aqueous KOH solution, was extracted with ether. The ethereal extracts were dried (MgSO$_4$). Evaporation of the solvent gave a residue (0.6 g) which was purified by column chromatography (Silica gel, ethyl acetate as eluent) yielding 0.19 g (25%) of 5-ethyl-2-methylpyridine.

2. *Conversion of 5-ethyl-2-methylpyridine into ethyl 6-methylnicotinate*

The oxidation with potassium permanganate was carried out as described in the literature[12]. The resulting 6-methylnicotinic acid hydrochloride was esterified by a procedure described for nicotinic acid[13].

From 0.52 g (4.25 mmoles) of 5-ethyl-2-methylpyridine we obtained 0.29 g (41%) of ethyl 6-methylnicotinate. M.p. picrate of ethyl 6-methylnicotinate: 165–166° (subl.). Analysis: $C_{15}H_{14}N_4O_9$ (394.29): calc. C 45.69, H 3.58; found C 45.82, H 3.52.

c. Radioactivity measurements

Radioactivity measurements were carried out with a Mark I scintillation counter. The specific activities of the labelled pyrimidines were derived from the specific activities of the corresponding labelled barbituric acids. Thus barbituric acid was dissolved in 10 ml of a scintillation solution, prepared by dissolving 48 g of naphthalene, 9.6 g of PPO and 0.48 g of POPOP in 0.96 l of a cellosolve/dioxane mixture (volume ratio 1 : 5). All the other samples were dissolved in 10 ml of a scintillation solution of 5 g PPO and 0.5 g POPOP in 1 l of ethanol/toluene mixture (volume ratio 1 : 9).

Acknowledgement

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). We are indebted to Drs. *C. A. Landheer* and Mr. *W. P. Combé* for mass spectrometric data and to Mr. *H. Jongejan* for carrying out the microanalyses.

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[8] *F. Brody* and *P. R. Ruby* in "Pyridine and Derivatives" (Ed. *E. Klingsberg*) Part I, pp. 479. Interscience, New York 1960.

[9] *J. B. Dickey* and *A. R. Gay*, Org. Synth. **18**, 8 (1938).

[10] *J. Baddiley* and *A. Topham*, J. Chem. Soc. 1944, 678.

[11] *N. Whittaker*, J. Chem. Soc. 1951, 1565.

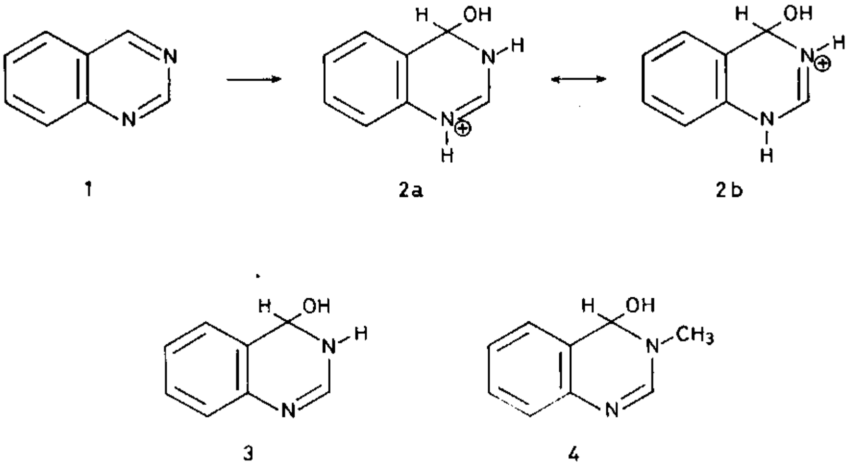
[12] *Pl. A. Plattner*, *W. Keller* and *A. Boller*, Helv. Chim. Acta **37**, 1379 (1954).

[13] *A. I. Vogel*, Practical Organic Chemistry (Ed. Longmans), pp. 849, London, 1959.

Discussion

In this thesis reactions of pyrimidines, featuring the presence of a quaternized nitrogen atom, with nucleophiles are described. Besides displacement reactions, interesting new ring transformations have been found. These ring transformations have in common that they are initiated by an addition of a nucleophile to a polarized azomethine bond. In some cases, i.e. in the reaction of N-alkylpyrimidinium salts with liquid ammonia[1,2,3] the formation of the adducts has been unequivocally established by means of NMR spectroscopy.

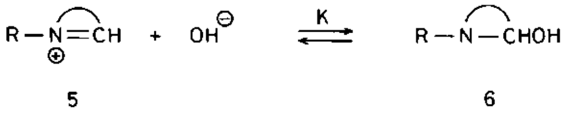
This interesting tendency of heteroaromatics to undergo covalent addition reactions with nucleophiles has been recognised early and studied extensively. The covalent hydration[4-7] especially attracted much attention because of its biochemical implications.
There is an overwhelming amount of literature which proves that the addition of nucleophiles occurs more easily as the number of nitrogen atoms in the heteroaromatic ring is increased[4,6,7]; for example pyridine and pyrimidine do not form covalent hydrates, s-triazine however is easily hydrated[8]. The explanation which is given for the readily occurring covalent addition in polyazaaromatic compounds is based on the fact that the presence of several ring nitrogen atoms depletes the π-electron layer so strongly that the aromatic stability is diminished and consequently addition can take place more easily. It can be expected that heterocycles in which the azaaromatic ring is incorporated in a polycyclic ring system are more inclined to undergo nucleophilic addition than the monocyclic ring systems, since the loss of resonance energy is then less. Thus in contrast to pyrimidine, quinazoline (1) is found to be easily hydrated into 2 in an acidic medium[9]. Besides retaining the aromaticity in the benzene ring, the adduct 2 has additio-



Scheme 1

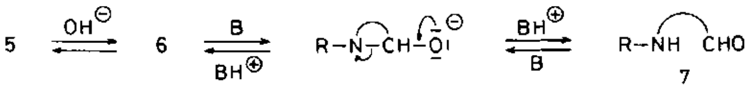
nal stability because of the amidinium resonance 2a ↔ 2b. That this amidinium resonance is an important stabilizing factor in the covalent hydrate appears when the cation is neutralized. A short-lived neutral molecule (3) (half life 9 sec at pH 10) is then obtained which quickly dehydrates into quinazoline[10]. The structure of the unstable neutral molecule (3) was deduced from the similarity of its ultraviolet spectrum with that of the pseudo base (4).

Compound 4 is formed on reacting 3-methylquinazolinium iodide with an aqueous alkaline solution. This reaction shows that positively charged azaaromatics have an enhanced reactivity towards nucleophiles. Other examples of compounds which easily give covalent hydration are the N-methyl derivatives of quinoline, isoquinoline and several diazanaphthalenes (with exception of quinazoline), while the neutral species and cations of these parent compounds do not show covalent hydration to any appreciable extent. J.W.Bunting and W.G.Meathrel[11-17] have extensively studied the influence of the structure of a heterocycle[5] on the equilibrium between the pseudo-base (6) and the N-methyl cations of quinolines, naphthyridines and some three-cyclic azaaromatic compounds in basic medium. In addition they also determined for



Scheme 2

each compound the site of attack for both hydroxide and methoxide ions. It was found that the equilibrium constant (pK) for all the N-methyl-1,X-naphthyridinium cations lies in the range 12.4 - 13.1, indicating that there is only a slight difference in the susceptibilities of the various N-methylnaphthyridinium cations to pseudo-base formation. In contrast the 1-methyl- and 3-methylquinazolinium cations were found to have a considerably enhanced susceptibility to pseudo-base formation. No presence of any appreciable amount of a ring-opened species could be detected. It supports the view of D.Beke[18] - being contrary to the previously widely accepted theory of J.Gademer[19,20] - that in aqueous alkaline solutions of quaternary azaaromatic compounds no mobile equilibrium exists between 5, 6 and the open-chain amino-aldehyde (7).



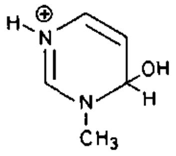
Scheme 3

Similar results have recently been obtained by O.S.Tee et al.[21] in their investigation on pseudo-base formation from 1,3-substituted 1,2-dihydro-2-oxopyrimidinium salts.

No such ring-chain tautomerism has ever been observed during the hydration of non-quaternized polyazaaromatic compounds. The suggestion[22] that such a tautomerism exists during the hydration of pteridine was later proved to be erroneous[23,24].

The pyrimidinium salts which are described in this thesis never form covalent adducts in neutral aqueous solutions. This has been unequivocally proved by means of NMR spectroscopy[1,2,3].

A subject of this thesis is a study on the addition of liquid ammonia to quaternized azaaromatics and the subsequent reactions of the adducts formed[1,2,3]. Based on the results of reactions of i) 1-methylpyrimidinium methylsulfate and the C-alkyl-1-methylpyrimidinium salts[1], ii) 4(6)-alkoxy-1-ethylpyrimidinium and 4,6-dialkoxy-1-ethylpyrimidinium tetrafluoroborates[2] and iii) 1,3-diethyl-1,4(3,4)-dihydro-4-oxopyrimidinium tetrafluoroborates[3] with ammonia we conclude that ammonia adds more easily than water to quaternized pyrimidines (see discussion of results below). The reason why ammonia is more easily added than water has been explained earlier[25] by the fact that in liquid ammonia formation of the covalent 1:1 NH_2-adduct is more favoured than that of the covalent 1:1 OH-adduct since ammonia is less polar than water. This explanation seems however questionable . In case the N-methylpyrimidinium salt reacted with water, the highly polar adduct (8) would be formed. It is evident that the transition state of its formation would, of course, be highly favoured in water. The reason for the occurrence of covalent amination



8

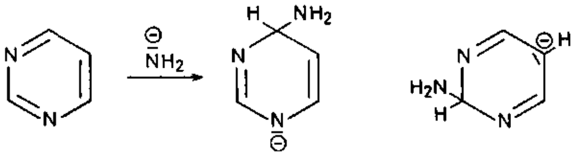
Scheme 4

in ammonia and the non-occurrence of covalent hydration in water is probably related to the higher nucleophilicity of ammonia.

In the following sections we shall not repeat the full discussion which is published in the several papers but concentrate on what can be considered as most essential. New data are added, when of interest.

a) Reaction of 1-methylpyrimidinium methylsulfate, 1,2-dimethyl-, 1,4,6-trimethyl- and 1,2,4,6-tetramethylpyrimidinium iodide with ammonia (paper I)

Because of the presence of a positive charge at the N(1)-nitrogen atom the positions 2 and 6 in these salts are the most suitable sites for an attack of ammonia. By ^{1}H-NMR spectroscopy it was proved that solutions of these salts in liquid ammonia only contained the 1:1 C(6)-σ-adducts. The same site of addition is found when pyrimidine (9)[26] and several of its halogen derivatives[27-29] are reacted with potassium amide in liquid ammonia. The greater reactivity of the C(4,6) position with regard to the C(2) position in pyrimidine has been related with the fact that the paraquinoid mesomeric structure of the C(4) adduct (10) is much more stable than the paraquinoid structure of the C(2) adduct[30,31] (11).



9 10 11

Scheme 5

Another approach for explaining this difference in positions for amide addition is the application of the Frontier Orbital Theory (FOT) of Fukui[32]. According to this theory the reactivity of a certain atom in a molecule depends on the Frontier Orbital Density (Fr^{OD}) at that atom. In the case of a nucleophilic reaction the frontier orbitals are the LUMO of the molecule and the HOMO of the nucleophile. The Fr^{OD} is then a measure for the ease with which the incoming electrons of the nucleophile can be accommodated at a certain position in the molecule. The theory gives no information concerning the transition state, and a high reactivity as determined by the FOT at a certain position does not guarantee that the reaction actually occurs at that position. Application of the FOT requires the reaction to be "Orbital Controlled" in the formalism of Klopman[33]. It can be shown that this is indeed the case for the reactions studied.

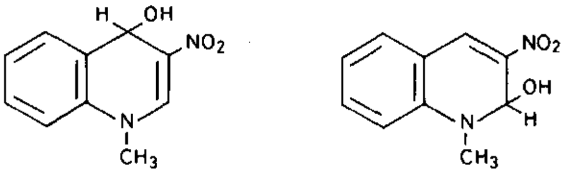
The frontier orbitals were calculated by the SCF-PPP method, using the parameter set of Fisher-Hjalmars et al.[34-44]. These calculations revealed that the frontier orbital densities in the LUMO of pyrimidine are zero at C(2) and C(5)[45]. Therefore the C(2) and C(5) positions are unreactive towards nucleophilic attack. Similar calculations[46] for the covalent amination of 1-methylpyrimidinium salts (i.e. 1,4,6-trimethyl- and 1,2,4,6-tetramethylpyrimidinium iodide) with liquid ammonia showed that the C(4) position is more reactive than the C(2) and C(6) position and that there is only a small difference in reactivity between the C(2) and C(6) positions. That, in contrast to the results of these calculations, the addition of ammonia is experimentally found to take place at C(6) may indicate that the reaction at C(6) is thermodynamically controlled.

It is of interest to note that the adducts of the N-methylpyrimidinium salts with ammonia are stable in solution but on evaporating of the solvent lose a methyl group by a series of reactions, involving a ring closure and aromatization (see paper I)[1]. This is in remarkable contrast to the behaviour of covalent hydrates of azaaromatic compounds, which as has been seen before do not show ring-opening but undergo dehydration.

Covalent amination has also been reported - almost simultaneously with us - by Zoltewicz et al.[25] when N-methylisoquinolinium and N-alkyl-3-substituted pyridinium salts are treated with liquid ammonia at low temperature ($-50^{o}C$). These adducts also lose a methyl group on raising the temperature to $25^{o}C$.
The fact that in all cases described by us[1,2,3] and others[25] the σ-adducts have a considerable life-time leads to the conclusion that the ring cleavage is rate determining in the N-demethylation reaction.

b) Amination of 4(6)-alkoxy-1-ethyl- and 4,6-dialkoxy-1-ethylpyrimidinium tetrafluoroborates with ammonia (paper VII)[2]

As has been established by means of ^{1}H-NMR and ^{13}C-NMR spectroscopy the pyrimidine salts mentioned in the title are present in liquid ammonia as covalent adducts which arise from an attack of NH_3 at the C(2) position. Preliminary results of SCF-PPP calculations[47] combined with the Frontier Orbital Theory, however, indicate that in 1-ethyl-4-ethoxypyrimidinium tetrafluoroborate, like in the 1-methylpyrimidinium salts, position 4 is the most reactive for nucleophilic attack. By means of ^{15}N-labelling it has been proved that the 4(6)-iminopyrimidine hydrogen tetrafluoroborates, which are the main products in most of the reactions, are not formed by an S_N(ANRORC) process but by a displacement of the 4-ethoxy groups via a $S_N(AE_n)$ mechanism. Since only the 1:1 NH_2-adduct could be detected as the sole species present in the liquid ammonia the interesting - but still unsolved - problem arises in which substrate the amino-de-ethoxylation occurs. Is it the 1:1 C(2)-σ-adduct itself or the parent pyrimidinium salt, the latter being present in a small concentration only? Based on the results of the ^{15}N-labelling experiments and preliminary Frontier Orbital calculations, the conclusion seems justified that the formation of the C(2)-σ-adduct is kinetically controlled and that of the C(4)-σ-adduct is thermodynamically controlled. Other examples of reactions showing differences in product formation between the kinetically and thermodynamically controlled nucleophilic addition reactions to quaternary azaaromatic compounds are available in the literature. A kinetic study of the formation and decomposition of the pseudo-base of the 1-methyl-3-nitroquinolinium cation by J.W.Bunting and W.G.Meathrel[13] revealed that 1,4-dihydro-4-hydroxy-1-methyl-3-nitroquinoline (12) is the predominant product at equilibrium. However, the isomeric pseudo-base 1,2-dihydro-2-hydroxy-1-methyl-3-nitroquinoline (13) is the kinetically controlled precursor of 12. Study of the ring-opening of several 1-methoxy-3-carbamoylpyrimidinium salts by liquid ammonia - by means of NMR spectroscopy - shows that at first addition takes place at position 2 but that the ring-opening occurs via the 1:1 NH_2-adduct at position 6[48].



12 13

Scheme 6

It is of interest to note that the products which are obtained from 1-ethyl-4,6-dimethoxy-2-phenylpyrimidinium tetrafluoroborate i.e. 4,6-dimethoxy-2-phenylpyrimidine and 4-ethylamino-6-methoxy-2-phenylpyrimidine can only be explained via a C(2)-σ-adduct as intermediate which undergoes a ring-opening and ring closure reaction. Apparently the presence of the phenyl groups does not prevent addition at that position 2.

It is evident from the results given in the papers I and VII that the problem which factors determine whether a reaction is kinetically or thermodynamically controlled and how they influence the ease of ring cleavage in C(2) or C(4) adducts is still unsolved.

c) <u>Reaction of 1,3-diethyl-1,4(3,4)-dihydro-4-oxopyrimidinium salts with ammonia (paper VI)</u>[3]

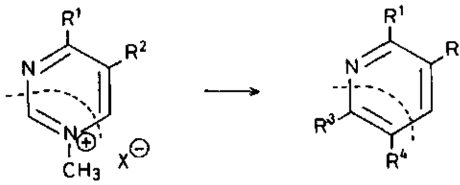
The amination reactions of these salts differ from those discussed above in section b) in two important aspects. i. All the products which are isolated after reaction of the title compounds with liquid ammonia or with aqueous ammonia are open-chain compounds, formed by a process in which a cleavage of the pyrimidine ring is involved. ii. These products require the initial formation of C(2)- σ-adducts.
On reacting with aqueous ammonia the open-chain compounds which are formed by fission of the N(1) - C(2) and/or C(2) - N(3) bond generally react further with the water present to give derivatives of acrylamide. In liquid ammonia this hydrolysis does not take place. The open-chain intermediates which result from a cleavage of the N(1) - C(2) bond in the C(2)-adduct with 4-oxopyrimidinium salts containing a 6-ethoxy group undergo a ring closure into 6-ethylaminopyrimidine derivatives. Apparently the electrophilic character of the C(6) atom in the open-chain compound is enhanced by the presence of the ethoxy group, making a ring cyclisation a favourable process.

In this thesis are also presented the results of investigations dealing with the reactivity of N-methylpyrimidinium salts with other nucleophiles than ammonia (carbanions, amidines, cyanamide, O-methylisourea and S-methylisothiourea). Ring transformations take place with all these reagents and all conversions have an initial attack of the nucleophile at the C(6)-position in common. In our investigations two types of ring modifying processes are discovered.

a) Conversion of pyrimidinium salts (14) into pyridine derivatives (15)(paper II)[49]

The ring transformations are performed by reaction with compounds containing active methylene groups (CH_2XY: $X=Y=CO_2C_2H_5$; X=Y=CN; $X=CO_2C_2H_5$, Y=CN) in alkaline medium. These reagents feature a nucleophilic carbon site as well as a functional group ($CO_2C_2H_5$, CN) to which a nucleophilic addition can easily take place. The overall reaction can be described as a process in which the $C(2) - \overset{\oplus}{N} - CH_3$ moiety of the pyrimidinium salt is replaced by a two carbon fragment of the reagent.

The mechanism of these ring transformations has been extensively discussed in paper II. As has been pointed out the presence of a quaternized nitrogen atom in the pyrimidine ring is in most cases a necessary structural requirement for the occurrence of these ring transformations.

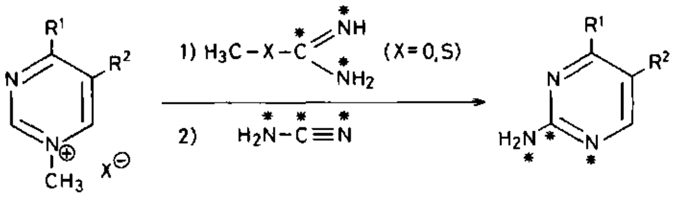


14 15

Scheme 7

b) Ring transformations of pyrimidinium salts into 2-substituted pyrimidines (paper III)[50]

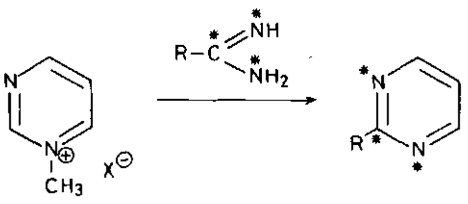
By studying the reaction of N-alkylpyrimidinium salts with the bifunctional nucleophiles cyanamide, O-methylisourea, S-methylisothiourea, benzamidine and pivalamidine a new variant of a nucleophilic substitution according to the S_N(ANRORC) mechanism was discovered. It was shown that 1-methyl-4-phenyl- and 1-methyl-5-phenylpyrimidinium iodide (14) react with cyanamide, O-methylisourea and S-methylisothiourea in such a way that the two atom fragment N(1) - C(2) of the pyrimidinium salt is replaced by an N-C fragment of the nucleophile, a 2-aminopyrimidine derivative (16) being yielded. These reactions present interesting examples of the introduction of an amino group at position 2 of the pyrimidine ring by a ring opening - ring closure mechanism.



14 16

Scheme 8

Somewhat similarly it has been found that N-methylpyrimidinium iodide (17) can be converted into 2-phenyl- (18, $R=C_6H_5$) and 2-t-butylpyrimidine (18, R= t-C_4H_9) on reacting with benzamidine and pivalamidine respectively. ^{15}N-labelling showed, that these ring transformations involve the replacement of a three atom fragment i.e. the N(1) - C(2) - N(3) moiety of the pyrimidinium salt by the N-C-N-fragment



17 18

Scheme 9

of the benzamidine or pivalamidine. These reactions form a useful extension of the nucleophilic substitution being found earlier during amination of 6-chloro-4-phenylpyrimidine with potassium amide into the 6-amino compound (see introduction) in which the replacement of one atom of the ring is involved.

The mechanism of the very remarkable conversion of pyrimidine into 5-ethyl-2-methylpyridine by heating with aqueous methylamine was clarified by studying the reactions of $[1,3-^{15}N]$ pyrimidine, $[4,6-^{14}C]$ pyrimidine and $[5-^{14}C]$ pyrimidine. The results are presented in this thesis (paper VIII[51]). By the distribution of the labelling it is clearly shown that all the carbon atoms of the pyridine derivative originate solely from the C(5) and C(4,6) atoms of the pyrimidine ring and that the nitrogen atom is obtained from the nucleophile. The ring transformation starts by an addition of methylamine to the N(1) - C(6) azomethine bond in the pyrimidine ring; a high reaction temperature is required however, because of the low susceptibility of this bond to nucleophilic attack.

References

1) E.A.Oostveen, H.C.van der Plas and H.Jongejan, Recl.Trav.Chim.Pays-Bas 93, 114 (1974).
2) E.A.Oostveen and H.C.van der Plas, Recl.Trav.Chim.Pays-Bas 96, in the press.
3) E.A.Oostveen and H.C.van der Plas, Recl.Trav.Chim.Pays-Bas 96, 68 (1977).
4) W.L.F.Armarego, Adv.Heterocycl.Chem. 1, 253 (1963).
5) A.Albert and W.L.F.Armarego, Adv.Heterocycl.Chem. 4, 1 (1965).
6) D.D.Perrin, Adv.Heterocycl.Chem. 4, 43 (1965).

7) A.Albert, Angew.Chem.Int.Ed.Engl. 6, 919 (1967).

8) C.Grandmann and A.Kreutzberger, J.Amer.Chem.Soc. 76, 632 (1954).

9) A.Albert, D.J.Brown and H.C.S.Wood, J.Chem.Soc. 1954, 3832.

10) A.Albert, W.L.F.Armarego and F.Spinner, J.Chem.Soc. 1961, 5267.

11) J.W.Bunting and W.G.Meathrel, Can.J.of Chem. 50, 917 (1972).

12) J.W.Bunting and W.G.Meathrel, Can.J.of Chem. 51, 1965 (1973).

13) J.W.Bunting and W.G.Meathrel, Can.J.of Chem. 52, 303 (1974).

14) J.W.Bunting and W.G.Meathrel, Can.J.of Chem. 52, 951 (1974).

15) J.W.Bunting and W.G.Meathrel, Can.J.of Chem. 52, 962 (1974).

16) J.W.Bunting and W.G.Meathrel, Can.J.of Chem. 52, 975 (1974).

17) J.W.Bunting and W.G.Meathrel, Can.J.of Chem. 52, 981 (1974).

18) D.Beke, Adv.Heterocycl.Chem. 1, 167 (1963).

19) J.Gademer, Arch.Pharm. 243, 12 (1905).

20) J.Gademer, J.Prakt.Chem. 84, 817 (1911).

21) O.S.Tee and M.Endo, J.Prakt.Chem. 54, 2681 (1976).

22) D.D.Perrin, J.Chem.Soc. 1962, 645.

23) T.J.Batterham. J.Chem.Soc.(C) 1966, 999.

24) A.Albert, T.J.Batterham and J.J.McCormack, J.Chem.Soc.(B) 1966, 1105.

25) J.A.Zoltewicz, T.M.Oestreich, J.K.O'Halloran and L.S.Helmick, J.Org.Chem. 38, 1949 (1973).

26) J.A.Zoltewicz and L.S.Helmick, J.Amer.Chem.Soc. 94, 682 (1972).

27) J.P.Geerts, H.C.van der Plas and A.van Veldhuizen, Recl.Trav.Chim.Pays-Bas 92, 1232 (1972).

28) J.P.Geerts, H.C.van der Plas and A.van Veldhuizen, Org.Magn.Reson. 7, 86 (1975).

29) J.P.Geerts, C.A.H.Rasmussen and A.van Veldhuizen, Recl.Trav.Chim.Pays-Bas 93, 231 (1974).

30) N.B.Chapman and C.W.Rees, J.Chem.Soc. 1954, 1190.

31) R.G.Shepherd and J.L.Fedrick, Adv.Heterocycl.Chem. 4, 180 (1965).

32) K.Fukui, Theory of Orientation and Stereoselection, Springer Verlag, Heidelberg (1970).

33) G.Klopman, J.Amer.Chem.Soc. 90, 223 (1968).

34) B.Roos and P.N.Skancke, Acta Chem.Scand. 21, 233 (1967).

35) B.Roos, Acta Chem.Scand. 21, 2318 (1967).

36) I.Fischer-Hjalmars and M.Sundbom,Acta Chem.Scand. 22, 607 (1968).

37) a) B.Grabe, Acta Chem.Scand. 22, 2237 (1968).
    b) B.Grabe, Acta Chem.Scand. A 28, 315 (1974).

38) H.Jensen and P.N.Skancke, Acta Chem.Scand. 22, 2899 (1968).

39) G.Höjer, Acta Chem.Scand. 23, 2589 (1969).

40) O.Gropen and P.N.Skancke, Acta Chem.Scand. 23, 2685 (1969).

41) A.Skancke and P.N.Skancke, Acta Chem.Scand. 24, 23 (1970).

42) P.G.Seybold and I.Fischer-Hjalmars, Acta Chem.Scand. 24, 1373 (1970).

43) O.Gropen and P.N.Skancke, Acta Chem.Scand. 24, 1768 (1970).

44) E.M.Farbrot and P.N.Skancke, Acta Chem.Scand. 24, 3645 (1970).

45) R.J.Platenkamp, J.P.Geerts and H.C.van der Plas, unpublished results.

46) R.J.Platenkamp, F.Roeterdink and H.C.van der Plas, unpublished results.

47) R.J.Platenkamp, J.P.Geerts, E.A.Oostveen and H.C.van der Plas, unpublished results.

48) J.A.Zoltewicz, L.S.Helmick and J.K.O'Halloran, J.Org.Chem. 41, 1303 (1976).

49) E.A.Oostveen and H.C.van der Plas, Recl.Trav.Chim.Pays-Bas 93, 233 (1974).

50) E.A.Oostveen, H.C.van der Plas and H.Jongejan, Recl.Trav.Chim.Pays-Bas 95, 209 (1976).

51) E.A.Oostveen and H.C.van der Plas, Recl.Trav.Chim.Pays-Bas 95, 104 (1976).

Samenvatting

In dit proefschrift zijn de resultaten neergelegd van een onderzoek naar het optreden van ringtransformaties tijdens reacties van pyrimidine, N-methylpyrimidiniummethylsulfaat en een aantal N-methyl-C-alkyl(aryl)pyrimidiniumzouten met verschillende typen nucleofielen. Verder is de synthese beschreven van een nieuwe klasse van N-ethylpyrimidiniumzouten nl. die, welke afgeleid zijn van 4-ethoxy-, 4,6-diethoxy- and 1,4(3,4)-dihydro-4-oxopyrimidine. De chemische en fysische eigenschappen van deze nieuwe stoffen zijn onderzocht; met name de reactiviteit t.o.v. ammonia is uitvoerig bestudeerd.

Publikatie I: Tijdens de behandeling van 1-methylpyrimidiniummethylsulfaat, 1,2-dimethylpyrimidiniumjodide, 1,4,6-trimethylpyrimidiniumjodide en 1,2,4,6-tetramethylpyrimidiniumjodide met vloeibare ammoniak bij -33°C treedt N-demethylering op waarbij respectievelijk pyrimidine, 2-methylpyrimidine, 4,6-dimethylpyrimidine en 2,4,6-trimethylpyrimidine worden verkregen. Onder dezelfde omstandigheden wordt [1-methyl- 1,3-^{15}N]pyrimidiniummethylsulfaat omgezet in [1-^{15}N]pyrimidine. Dit betekent dus dat de demethylering verloopt op een wijze, waarbij het stikstofatoom van de ring wordt vervangen door een stikstofatoom van het reagens. Door middel van PMR-spectroscopie kon worden aangetoond, dat de 1,6-azomethineband in deze zouten een covalente additie ondergaat met vloeibare ammoniak. De resultaten van de ^{15}N-experimenten gecombineerd met de PMR-spectroscopische gegevens leiden tot de conclusie dat de N-demethylering verloopt via een Additie-Nucleofiel-Ring-Opening-Ring-Sluitings-mechanisme (ANRORS-mechanisme).

Publikatie II: 1-Methylpyrimidiniummethylsulfaat, 1-methyl-4-fenylpyrimidiniumjodide en 1-methyl-5-fenylpyrimidiniumjodide worden bij behandeling met actieve methyleenverbindingen (malonester, malondinitril, ethylcyaanacetaat) in een oplossing van natriumethanolaat in ethanol omgezet in pyridinederivaten.Deze ringtransformaties worden ingeleid door een additie van het carbanion aan de N(1) - C(6) azomethineband en verlopen zodanig dat het C(2) - N(1) fragment van de pyrimidine ring wordt vervangen door twee koolstofatomen van het nucleofiele reagens.

Publikatie III: De reactie van 1-methyl-4-fenyl- en 1-methyl-5-fenylpyrimidiniumjodide met cyaanamide, O-methylisouroniumchloride of di-S-methylisothiouroniumsulfaat in basisch milieu levert respectievelijk 2-amino-4-fenyl- en 2-amino-5-fenylpyrimidine op. Er vindt dus een ringtransformatie plaats, waarbij het N(1) - C(2) fragment van de pyrimidinering wordt vervangen door een N-C fragment van het reagens. De reactie van 1-methylpyrimidiniumjodide met benzamidiniumchloride of pivalamidiniumchloride in een basisch milieu geeft respectievelijk 2-fenylpyrimidine en 2-*t*-butylpyrimidine. Door middel van ^{15}N-labelling werd vastgesteld dat deze nucleofiele substitutie verloopt via een ringtransformatie, waarin het N(1)-C(2)-N(3) fragment van het pyrimidiniumzout wordt vervangen door het N-C-N-fragment van het amidine. Deze reacties zijn beschreven als nieuwe voorbeelden van een nucleofiele substitutie, die verloopt via een S_N(ANRORS)-mechanisme.

Publikatie IV: Reactie van 4-alkoxy- en 4,6-dialkoxypyrimidinen met 1 equivalent triethyloxoniumtetrafluorboraat geeft respectievelijk 4-alkoxy-N-ethyl- en 4,6-dialkoxy-N-ethylpyrimidiniumzouten. Met twee of meer equivalenten van dit ethyleringsagens ontstaan de 1-ethyl-3-alkyl-1,4(3,4)-dihydro-4-oxopyrimidiniumzouten. Deze 4-oxopyrimidiniumzouten kunnen ook worden verkregen door thermolyse van N-ethylalkoxypyrimidiniumzouten.

Publikatie V: De kristal- en molecuulstructuren van de twee isomeren, die ontstaan bij inwerking van triethyloxoniumtetrafluorboraat op 4,6-diethoxypyrimidine, zijn bepaald met behulp van röntgenanalyse. Vastgesteld werd dat een van de produkten is 1-ethyl-4,6-diethoxypyrimidiniumtetrafluorboraat (monoklien a = 10.794, b = 13.361, C= 10.892 Å, ß = 112.62°, ruimtegroep $P2_1/n$, vier moleculen per eenheidscel) en het andere produkt 1,3-diethyl-1,4(3,4)-dihydro-6-ethoxy-4-oxopyrimidiniumtetrafluorboraat (monoklien, a = 17.637, b = 14.054, C = 11.501 Å, ß = 101.69°, ruimtegroep C2/C, acht moleculen per eenheidscel).
Bij beide verbindingen is de plaats van het fluorboraation niet te bepalen. De gevonden bindingsafstanden in de π-elektronsystemen van de beide verbindingen kunnen redelijk goed worden beschreven door een klein aantal resonantiestructuren.

Publikatie VI: Behandeling van 1,3-diethyl-1,4(3,4)-dihydro-4-oxopyrimidiniumtetrafluorboraat en zijn 2-fenyl-, 6-fenyl-, 6-methyl- en 6-ethoxyderivaten, met ammonia resulteert in de vorming van een mengsel van open-ketenverbindingen, N-formyl(acetyl, benzoyl)-N-ethyl-3-(ethylamino)-acrylamidederivaten en N-ethyl-3-[formyl(acetyl,benzoyl)ethylamino]- acrylamidederivaten. Deze worden gevormd door een verbreking van respectievelijk de N(1) - C(2) en N(3) - C(2) band in het σ-adduct verkregen door additie van ammonia op C(2) van genoemde verbindingen. In het algemeen vindt in vloeibare ammoniak dezelfde ringsplitsing plaats; wanneer echter op de 6-plaats een ethoxygroep aanwezig is, kan een ringsluiting in de open keten acrylamidederivaten optreden; het leidt tot de vorming van 6-ethylaminopyrimidinederivaten. Deze ringtransformatie vindt ook plaats tijdens de reactie met het 2-methyl- en 2-fenylderivaat van 1,3-diethyl-1,4(3,4)-dihydro-6-ethoxy-4-oxopyrimidiniumtetrafluorboraat. Door middel van ^{1}H-NMR- en ^{13}C-NMR-spectroscopie is bewezen dat deze reacties worden geinitieerd door een aanval van NH_3 op de C(2)-plaats.
Enkele van de bovengenoemde open ketenverbindingen kunnen ringsluiten tot de 1,3-diethyl-1,4(3,4)-dihydro-4-oxopyrimidiniumzouten door behandeling met fluorboorwaterstof in absolute ethanol.

Publikatie VII: De quaternaire pyrimidiniumzouten 4-ethoxy-1-ethyl- en 4,6-diethoxy-1-ethylpyrimidiniumtetrafluorboraat ondergaan in vloeibare ammoniak bij -33°C een aminodeëthoxylering, waarbij respectievelijk het HBF_4 zout van 1,4-dihydro-1-ethyl-4-iminopyrimidine en een mengsel van de HBF_4 zouten van 1,4-dihydro-6-ethoxy-1-ethyl-4-imino- en 1,6-dihydro-4-ethoxy-1-ethyl-6-iminopyrimidine worden verkregen.
Met behulp van ^{1}H-NMR- en ^{13}C-NMR-spectroscopie is aangetoond dat de beide tetrafluorboraten gemakkelijk σ-adducten geven op positie 2. Door middel van experimenten met $[^{15}N]$ammoniak is bewezen dat gedurende deze amino-deëthoxyleringsreacties de substitutie op C(4) of C(6) niet gepaard gaat met ringopening, maar dat deze waarschijnlijk verloopt via een $S_N(AE_n)$-proces. De 4-ethoxy-1-ethyl-2-fenyl-, 6-ethoxy-1-ethyl-4-fenyl-, 4,6-dimethoxy-1-ethyl-2-fenyl- en 4,6-dimethoxy-1-ethyl-2-methylpyrimidiniumtetrafluorboraten ondergaan onder invloed van vloeibare ammoniak, naast aminodeëthoxylering, gedegenereerde ringtransformaties, die leiden tot N-gedeëthyleerde produkten en 4(6)-ethylaminopyrimidines.
De Dimroth-omleggingen van de HBF_4 zouten van 1,6-dihydro-4-ethoxy-1-ethyl-6-iminopyrimidine en van 1,6-dihydro-1-ethyl-6-amino-4-phenylpyrimidine in de overeenkomstige 4(6)-ethylaminopyrimidines zijn beschreven.

Publikatie VIII: Het mechanisme van de omzetting van pyrimidine in 5-ethyl-2-methylpyridine is nader onderzocht met behulp van de gelabelde verbindingen $\left[1,3\text{-}^{15}\mathrm{N}\right]$pyrimidine, $\left[4,6\text{-}^{14}\mathrm{C}\right]$ pyrimidine en $\left[5\text{-}^{14}\mathrm{C}\right]$ pyrimidine. Bewezen is dat deze reactie verloopt via een mechanisme, waarin de pyrimidinering wordt afgebroken tot twee moleculen HCN en een molecuul N-methylacetaldimine. Vier moleculen van dit imine ondergaan een aldolcondensatie die uiteindelijk leidt tot 5-ethyl-2-methylpyridine.

Op deze plaats wil ik allen, die op directe of indirecte wijze hebben bijgedragen aan het tot stand komen van dit proefschrift hartelijk danken.

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Curriculum Vitae

Na het behalen van het diploma Gymnasium β aan het St.Bonifatiuslyceum te Utrecht in juni 1965, begon ik in datzelfde jaar met de scheikunde-studie aan de Rijksuniversiteit te Utrecht. Het kandidaatsexamen (S1) werd na een onderbreking van de studie voor het vervullen van de militaire dienstplicht afgelegd in juni 1970. De studie werd voortgezet onder leiding van Prof.Dr.J.F.Arens en Dr.L.Brandsma (hoofdvak: organische chemie) en Prof.Dr.Ir.P.M.Heertjes (bijvak: chemische technologie, Technische Hogeschool Delft). Het doctoraalexamen werd in november 1972 cum laude afgelegd.

Sinds januari 1973 ben ik als wetenschappelijk medewerker verbonden aan het Laboratorium voor Organische Chemie van de Landbouwhogeschool te Wageningen in dienst van de Nederlandse Organisatie voor Zuiver Wetenschappelijk Onderzoek (Z.W.O.).

Het in dit proefschrift beschreven onderzoek werd uitgevoerd onder leiding van Prof.Dr.H.C.van der Plas.