52. ^{15}N-NMR. Studies of Aminopyridines, Aminopyrimidines and of Some Diazine N-Oxides[1])

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Summary

^{15}N-NMR. spectra of mono- and diaminopyridines, and mono-, di- and triaminopyrimidines including trimethoprim and other dihydrofolate reductase inhibitors have been studied in neutral and acidic media. Complete chemical shift assignments are given. Ring-nitrogen shifts are discussed in terms of β-, χ- and δ-substituent effects of amino and alkyl groups. Protonation states in TFA- and FSO_3H-solution and protonation increments for the ^{15}N-shifts of ring and amino N-atoms are determined. A linear correlation is observed between amino substituent effects ($\Delta\delta$ (^{15}N)) on the ring N-atom in aminopyridines and corresponding $\Delta\delta$ (^{13}C) values in aminobenzenes and, similarly, between $\Delta\delta$ (^{15}N) values in aminopyrimidines and $\Delta\delta$ (^{13}C) values in aminopyridines. Assignment of the ^{15}N-NMR. spectra of pyrimidine *N*-oxides, pyrazine *N*-oxides and pyridazine *N*-oxides is achieved by comparison with ^{14}N-NMR. data and with the aid of Yb(fod)$_3$-induced shifts. One-bond ^{15}N, ^{1}H-coupling constants are reported for aminopyridines and aminopyrimidines and discussed in terms of conjugative interaction between NH_2-group and ring system.

Introduction. – The aminopyrimidine system is an important structural unit in a number of natural products of biological importance, such as purines, nucleosides and nucleotides, as well as pteridines, including folic acid and its derivatives. Furthermore, there is a large class of pharmacologically important, substituted aminopyrimidines which act as dihydrofolate reductase (DHFR) inhibitors. Typical representatives are 2,4-diamino-5-(3,4,5-trimethoxybenzyl)-pyrimidine (trimethoprim, TMP[3])), 2,4-diamino-5-(4-chlorophenyl)-6-ethylpyrimidine (pyrimethamine)[4]), and methotrexate (MTX) with a modified folic acid structure. The binding

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mechanism of TMP and MTX to DHFR from different sources is at present the subject of extensive investigations [2]. On the other hand, there is a particular interest in the structure of the drug metabolites some of which are known to be mono-*N*-oxides [3].

Since the biological activity of substrate and inhibitor appears to be closely associated with the N-atoms of the pyrimidine entity [2b] nitrogen NMR. promises to constitute a valuable tool for the study of the structure of these compounds and their binding to the enzyme. Two isotopes of nitrogen (^{14}N, 99.6%, $I=1$ and ^{15}N, 0.4%, $I=\frac{1}{2}$) are available for such studies. The large experimental line-width associated with the ^{14}N-nucleus, however, is a handicap in resolving the individual N-resonances in di- and triaminopyrimidines. On the other hand, NMR. of the much less sensitive ^{15}N-isotope has made considerable progress in recent years. In addition, there are at least two properties which make the ^{15}N-isotope the preferred nucleus. Firstly, ^{15}N-resonance lines are usually very sharp and, secondly, a large NOE factor ($\eta=-4.93$) enhances the signal intensities of protonated N-atoms under proton noise-decoupling conditions. The long relaxation times of tertiary (ring) N-atoms can be shortened by the addition of paramagnetic relaxation reagents, such as $Cr(acac)_3$, and small unfavourable NOE factors can be eliminated by a suitable decoupler gating technique.

Previous investigations of substituted pyridines and pyrimidines by ^{14}N-NMR. are covered by two reviews [4] [5]. More recently, ^{15}N-NMR. data have been published for substituted pyridines [6], monoaminopyridines [7] [8b], purines [8], and pteridines [1]. Very few data on ^{14}N-NMR. of amino-substituted pyrimidines are available [9]. In order to explore the potential of nitrogen NMR. in this field, we have initiated a systematic study of ^{15}N-chemical shifts in mono-, di- and triaminopyrimidines and their protonated forms. In addition, some pyrimidine mono-*N*-oxides and other diazine oxides have been investigated.

Results. – Since amino-substituted aza-aromatic compounds contain two types of N-atoms with very different spectroscopic properties, it is essential to select optimum instrumental conditions for the observation of the ring and amino group N-atoms. In general, the N-resonances have been investigated under proton-noise-decoupled conditions, fully proton-coupled conditions and with a gated noise-decoupling technique including the addition of the relaxation reagent $Cr(acac)_3$. Whereas the first two conditions yield mainly information about the chemical shifts and N,H-coupling constants of the amino groups, the gated decoupling procedure allows the measurement of both amino and ring nitrogen chemical shifts in the same spectrum. The resonances of the ring N-atoms in the parent compounds **1**, **9**, **31** and **38** lie in the typical range of azine N-atoms (+20 to −90 ppm, relative to external, neat CH_3NO_2 [4]). They experience substantial shifts to lower frequencies upon amino substitution of the respective ring systems. In aminopyridines and aminopyrimidines the ring N-atoms are found between −60 and −195 ppm. On the other hand, the amino resonances are observed at much lower frequencies, corresponding to higher negative δ values (−290 to −360 ppm). Also in this case, shielding increases with the number of amino groups present. An unambiguous assignment of the resonance lines within the two regions

is sometimes difficult. For the ring N-atoms, substituent effects of amino and alkyl groups and two-bond N,H-coupling constants are particularly useful, whereas amino groups can be differentiated with the aid of one-bond N,H-coupling constants and, in some cases, relative signal intensities. In addition, selective protonation and complexation by paramagnetic reagents can be useful.

The chemical shifts of the ring N-atoms of the aminopyridines **2**, **3** and **4** illustrate that the shielding effect of the NH_2-substituent is largest in the 2-position ($\Delta\delta = -50$ ppm), followed by the 4-position ($\Delta\delta = -40$ ppm), whereas an amino group in the 3-position has essentially no effect. It turns out that these effects also hold in the case of amino-substituted pyrimidines and constitute an important assignment criterion. Even in the presence of several amino groups the chemical shifts of the ring N-atoms can be estimated in an additive way from the corresponding increments in the pyrimidine series. The extent of conjugation between amino group and ring N-atoms is also reflected in the one-bond N,H-coupling constants, for example in 2- and 4-aminopyridine *versus* 3-aminopyridine, and hence, this effect provides an assignment criterion for amino groups. If a ring N-atom is protonated, the strongest interaction is observed with an amino group in 4-position ($\Delta\delta = +20 \pm 5$ ppm). The corresponding effects with amino groups in 2- and 3-position are small ($\Delta\delta = \pm 2$ to 5 ppm).

Mono-*N*-oxidation in diazines usually leads to low frequency shifts (increased shielding) of both N-atoms, which complicates the assignment. In this case, selective complexation by a suitable lanthanide ion at the *N*-oxide O-atom allows an unambiguous assignment of the *N*-oxide N-atom.

The chemical shift data presented in this paper are summarized as follows: amino- and diaminopyridines *(Table 1)*, mono-, di- and triaminopyrimidines *(Table 2)*, pyridazine, cinnoline and phthalazine, pyrimidine and quinazoline, pyrazine and quinoxaline *(Table 3)*. *Table 3* also contains the chemical shifts of mono-*N*-oxidized 1,2-, 1,3- and 1,4-diazines. All compounds were measured as neutral species in dimethyl sulfoxide (DMSO). Whenever possible, monocations (in trifluoroacetic acid, TFA) and dications or higher protonated species (in fluorosulfonic acid, FSO_3H) were also investigated. One-bond N,H-coupling constants ($^1J(N,H)$) and some long-range coupling constants ($^2J(N,H)$ and $^3J(N,H)$) of aminopyridines and -pyrimidines are collected in *Table 5*.

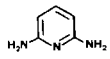
Discussion. – 1. *Chemical Shifts.* 1.1. *Ring N-atoms.* For a discussion of substituent effects in aminopyrimidines it is essential to know the chemical shifts of the parent compounds obtained under experimental conditions which apply throughout the whole series. Although this information is already partly available from ^{14}N-chemical shift measurements in various solvents and, more recently, from ^{15}N-studies, one has to consider that chemical shifts of sp^2 hybridized N-atoms can be strongly dependent upon effects arising from the medium, such as variations in solvent and concentration [6b]. For this reason, all substituent effects discussed further below will be based on the chemical shifts of pyridine and pyrimidine given in *Table 1* and *Table 2*, respectively.

The amino group exhibits the largest shielding increment of all the ordinary substituents in pyridines and pyrimidines [9], and, as expected, the value depends

upon the relative orientation of amino substituent and ring N-atoms. The amino group as a β-, γ- and δ-substituent[5]) on pyridine causes shielding increments of -50.8, -0.9 and -40.7 ppm, respectively. The fact that an amino group in 3-position (γ) gives only a small perturbation of the pyridine system is confirmed by the shielding increments of the γ-amino group in 2,3-diaminopyridine (**5**) and in 3,4-diaminopyridine (**7**) (-0.7 and $+4.4$ ppm, respectively). Analogous increments of an amino group, although somewhat smaller, are also observed in the pyrimidine series, with large effects as β- (-45 ppm) and δ-substituent (-38 ppm). The increment of a γ-amino group is again comparably small as illustrated in the pair 4,5,6-triaminopyrimidine (**30**) and 4,6-diaminopyrimidine (**22**) ($\Delta\delta$N(1) $= -3.3$ ppm).

The shielding increments of an amino group, however, also depend on the number of amino groups already present in the molecule. Thus, a third amino

Table 1. *^{15}N-Chemical shifts*[a]) *of aminopyridines*

Compound		N(1)	NH_2(2)	NH_2(3)	NH_2(4)	NH_2(6)	Solvent
1		– 63.0					DMSO
		– 182.5					TFA
		– 186.9					FSO_3H
2		– 113.8	– 307.3				DMSO
		– 226.0	– 305.6				TFA
		– 229.5	– 292.6	(monocation)			FSO_3H
		– 192.4	– 330.6	(dication)			FSO_3H
3		– 63.9		– 325.3			DMSO
		– 184.7		– 325.2			TFA
		– 181.1		– 334.8	(monocation)		FSO_3H
		– 181.1		– 345.4	(dication)		FSO_3H
4		– 103.7			– 312.0		DMSO
		– 220.7			– 293.0		TFA
		– 210.8			– 295.1	(monocation)	FSO_3H
		– 181.6			– 330.2	(dication)	FSO_3H
5		– 114.5	– 313.5	– 330.4			DMSO
		– 219.4	– 305.0	– 337.0			TFA
		– 219.5	– 305.0	– 339.5			FSO_3H
6		– 149.0	– 309.1			– 309.1	DMSO
		– 239.3	– 312.3			– 312.3	TFA
7		– 99.3		– 336.9	– 322.0		DMSO
		– 216.9		– 339.0	– 290.4		TFA
8		– 179.1[b])					DMSO

[a]) δ [ppm] relative to external, neat CH_3NO_2.
[b]) From [13].

[5]) This nomenclature is consistent with the designation of substituents in ^{13}C-NMR. but does not correspond to the classical notation in heterocyclic chemistry.

Table 2. *^{15}N-Chemical shifts*[a]) *of aminopyrimidines*

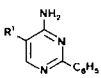
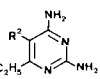
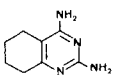
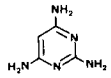
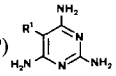
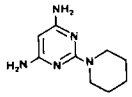
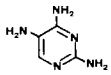
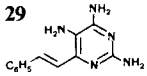
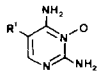
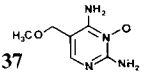
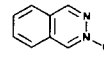
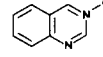
Compound		N(1)	N(3)	NH_2(2)	NH_2(4)	NH_2(5)	NH_2(6)	Solvent
9		– 84.8	– 84.8					DMSO
		– 134.8	– 134.8					TFA
		– 182.6	– 182.6					FSO_3H
10		– 129.9	– 129.9	– 297.9				DMSO
		– 178.8	– 178.8	– 294.3				TFA
		– 220.0	– 220.0	– 286.7				FSO_3H
11		– 132.0	– 132.0	– 311.9	($-N(CH_3)_2$)			DMSO
12		– 246.9	– 98.6	– 194.4	(=NH)			DMSO
13		– 229.2	– 115.7	– 283.3				DMSO
14		– 88.2	– 88.2					DMSO
15[b])		– 120.9	– 132.7		– 298.4			DMSO
		– 217.9[c])	– 218.6[c])		– 278.3			TFA
16[b])		– 127.8	– 141.3		– 297.8			DMSO
		– 227.6	– 227.6		– 281.2			TFA
		– 224.2	– 230.9		– 270.8			FSO_3H
17		– 164.5	– 173.4	– 301.6	– 299.6			DMSO
		– 253.5	– 231.6	– 296.4	– 276.2			TFA
		– 253.6[c])	– 254.3[c])	– 293.1	– 271.4			FSO_3H
18[b])		– 163.0	– 174.4	– 304.6	– 302.3			DMSO
		– 253.3	– 226.3	– 299.0	– 279.0			TFA
		– 252.1[c])	– 254.3[c])	– 293.1	– 271.4			FSO_3H
19[d])		– 176.3	– 176.3	– 300.9[c])	– 299.4[c])			DMSO[e])
		– 247.5	– 247.5	– 294.5	– 274.9			TFA
		– 249.9[c])	– 250.7[c])	– 295.8	– 274.5			FSO_3H
20		– 174.1	– 174.1	– 305.1	– 302.6			DMSO
		– 247.1[c])	– 245.1[c])	– 296.4	– 278.7			TFA
		– 248.4[c])	– 255.2[c])	– 297.8	– 278.0			FSO_3H
21		– 166.1	– 178.7	– 297.7	– 296.6			DMSO
		– 227.4[c])	– 229.1[c])	– 297.9	– 283.5			TFA
		– 248.0	– 257.0	– 292.1	– 271.8			FSO_3H

Table 2 (cont.)

Compound	N(1)	N(3)	$NH_2(2)$	$NH_2(4)$	$NH_2(5)$	$NH_2(6)$	Solvent
22 	−149.4	−149.4		−309.1		−309.1	DMSO
	−210.3	−210.3		−289.0		−289.0	TFA
	−233.9	−233.9		−289.1		−289.1	FSO_3H
23[f] 	−151.8	−151.8		−304.5		−304.5	DMSO
	−209.9	−209.9		−297.2		−297.2	TFA
	−230.7	−230.7		−289.6		−289.6	FSO_3H
24 	−132.6[c])	−133.5[c])		−305.9	−338.0		DMSO
	−215.1	−215.1		−282.3	−335.8		TFA
	−216.7[c])	−220.2[c])		−261.6	−340.9		FSO_3H
25 	−189.5	−189.5	−304.0	−306.0		−306.0	DMSO
	−261.7	−261.7	−291.3	−291.3		−291.3	TFA
	−260.0	−260.0	−281.4	−264.5		−264.5	FSO_3H
26[b]) 	−191.6	−191.6	−305.5	−306.4		−306.4	DMSO
	−261.5	−261.5	−297.5	−295.9		−295.9	TFA
	−261.8	−261.8	−293.6	−264.4		−264.4	FSO_3H
27 			(piperidyl)				
	−190.2	−190.2	−308.2	−306.2		−306.2	DMSO
	−266.1	−266.1	−295.8	−293.3		−293.3	TFA
	−261.1	−261.1	−283.9	−261.1		−261.1	FSO_3H
28 	g)	g)	−311.2	−316.3	−357.3		DMSO[h])
	−218.8	−218.8	−310.1[c])	−309.0[c])	−357.3		DMSO + 0.2 equiv. HCl[i])
29 	−173.0	−180.2	−303.4	−311.5	−345.9		DMSO[h])
	−260.8	−260.8	−303.1	−279.4	−336.1		DMSO + 1.0 equiv. HCl[k])
30 	−152.7	−152.7		−309.8	−346.9	−309.8	DMSO[h])
	−181.7	−181.7		−301.5	−343.2	−301.5	DMSO + 0.2 equiv. HCl[i])

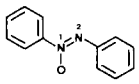
[a]) δ [ppm] relative to external, neat CH_3NO_2.
[b]) R^1 = 3,4,5-trimethoxybenzyl.
[c]) Assignment arbitrary.
[d]) R^2 = 4-chlorophenyl.
[e]) At 60°.
[f]) R^3 = 3,4-dimethoxybenzyl.
[g]) Not observed due to insufficient solubility.
[h]) Dissolved as hydrochloride; 1 mol. equivalent of 4N NaOH added.
[i]) *N*(1)-hydrochloride, dissolved with the aid of 0.8 mol.-equivalents of 4N NaOH.
[k]) Dissolved as hydrochloride.

Table 3. *^{15}N-Chemical shifts[a]) of diazines and some mono-N-oxides*

Compound		N(1)	N(2)	N(3)	N(4)	NH_2	Solvent
31		+ 20.3	+20.3				DMSO
32		− 55.1 − 54.7	−33.6 −32.8				DMSO $CHCl_3$
9		− 84.8		− 84.8			DMSO
33		− 90.0 − 89.9		− 80.3 − 79.5			DMSO $CHCl_3$
34		−134.0 −231.5		−130.1 −146.3		−304.8 −305.5	DMSO H_2O
35		−166.8		−167.8		−306.2; −307.4	DMSO
36[b])		−164.9		−168.8		−308.6; −309.5	DMSO
37		−164.8		−169.2		−308.1; −311.1	DMSO
38		− 46.3			−46.3		DMSO
39		− 75.7 − 75.2			−70.4 −69.1		DMSO $CHCl_3$
40		+ 44.6[c])	+41.3[c])				DMSO
41			−10.3	− 10.3			DMSO
42			−68.9	− 53.2			DMSO
43		− 85.5[c])		− 96.9[c])			DMSO
44		− 89.5		− 89.5			DMSO
45		− 49.8			−49.8		DMSO
46		− 80.7[d])			−76.8[d])		DMSO

[a]) δ [ppm] relative to external, neat CH_3NO_2.
[b]) See footnote[b]) in *Table 2.*
[c]) Assignment see text.
[d]) Arbitrary assignment.

Table 4. *Yb(fod)$_3$ induced ^{15}N shifts $\Delta\delta$ [ppm] of some diazine* N*-oxides*[a])

Compounds		N(1)	N(2)	N(3)	N(4)
	32	+119.3	+86.0		
	33	+ 31.6		−4.7	
	39	+ 85.6			+76.2
47[b])		+ 44.5	+28.5		

[a]) $\Delta\delta$ values (in $CHCl_3$) extrapolated to a 1:1 molar ratio of substrate and reagent. Positive numbers denote high-frequency shifts.
[b]) Doubly labelled with ^{15}N (95%).

Table 5a. *One-bond N,H coupling constants (Hz) of aminopyridines and aminopyrimidines*[a])

Compound	$NH_2(2)$	$NH_2(3)$	$NH_2(4)$	$NH_2(5)$	$NH_2(6)$
2	85.2±0.5				
3		80.5±0.5			
4			87.6±0.5		
5	81.8	77.4			
6	82.9				82.9
7		78.0	84.0		
10	88.5±0.5				
13	91.7				
15			87.1		
16			87.5		
17	86.8±0.5		88.2±0.5		
18	87.5±0.5		88.6±0.5		
21	88.6		89.6		
24			88.2	80.9	
25	85.6		86.7		86.7
26	87.1		87.1		87.1
27			86.6		86.6
34	91.8				
35	90.2; 91.3 (not assigned)				
36	90.3±0.3; 90.7±0.3 (not assigned)				

[a]) Measured in DMSO; absolute values ±2 Hz unless specified.

Table 5b. *Two- and three-bond N,H coupling constants (Hz) of N(1)*[a])

Compound	^2J(N,H)	^3J(N,H)
17	2.3±0.3	1.5±0.3
18	7.9±0.3	
36	5.5±0.3	

[a]) In DMSO.

group introduced into the 6-position of a diaminopyrimidine system affects the ring-N(1) by only -20 to -25 ppm and the ring-N(3) by -16 to -20 ppm, which may be compared with the effects of the first amino group (-45 and -38 ppm, respectively). On the other hand, an amino group introduced at C(2) always has a strong shielding effect on N(1) and N(3) (-40 to -45 ppm), independent of the number of NH_2 substituents already present. This is indicative of a strong conjugation of an NH_2 group at C(2) with the neighbouring ring N-atoms leading to a guanidine type system.

The NH_2-increments are useful for an estimation of the ring N-atom shifts of di- and triaminopyrimidines. For example, the calculated[6]) data for 2,4-diaminopyrimidine (**17**) show a very satisfactory agreement with the experimental data, N(1): -167.8 ppm (calc.), -164.5 ppm (exper.); N(3): -174.8 ppm (calc.), -173.4 ppm (exper.). In triaminopyrimidines, however, the attenuation of the β- and δ-increments as mentioned above, must be considered.

It is remarkable that the shielding increments of an NH_2-group on the two N-atoms of a pyrimidine ring is only slightly smaller than on the single N-atom of a pyridine ring. This seems to indicate a more effective conjugation in the aminopyrimidine systems. It is also reflected in the $^1J(N,H)$ coupling constant which increases from 85.2 ± 0.5 Hz in 2-aminopyridine (**2**) to 88.5 ± 0.5 Hz in 2-aminopyrimidine (**10**), a trend which may also be observed for other structural pairs from *Table 5a* (discussion see Section 2).

Although substituent effects of alkyl and aryl groups are of secondary importance as compared with the amino group, such increments will be briefly discussed because they are useful for assignment purposes. In general, sp^2 and sp^3 C-substituents cause a moderate shielding of the ring N-resonance [10] [6a]. In the aminopyrimidines, the largest value (-10 ± 4 ppm) is observed for a β-substituent as shown for the chemical shift of N(1) in the structurally related pairs **19/18** and **16/15**. γ- and δ-substituents have only small effects on the ring N-atoms (0 ± 2 ppm).

The observation of N,H-coupling constants in the amino groups of aminopyridines and aminopyrimidines proves the non-dynamic nature of the potentially tautomeric structures in DMSO solution. Furthermore, the number of resonance lines and the chemical shift values are in full agreement with the presence of the aminopyridine and aminopyrimidine forms only. The chemical shift data for 2-aminopyrimidine (**10**) are in very good agreement with those of the *N,N*-dimethylamino derivative **11**, if α- and γ-substituent increments of the methyl groups are taken into account. On the other hand, a blocked tautomeric form **12** with an imino group at C(2) yields chemical shift data which are atypical for the present series. The absence of such imino forms has previously been deduced from ^{14}N- and ^{13}C-chemical shifts (in acetone solution) as well as N-atoms charge density calculations [10] [11].

Protonation of pyridine produces a large shielding effect (low frequency shift) of -118 ppm [4] [6a]. Therefore, it can be expected that chemical shifts obtained in TFA and FSO_3H solution will yield information about the site and extent of

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[6]) Calculated using a β-effect of -45 ppm and a δ-effect of -38 ppm.

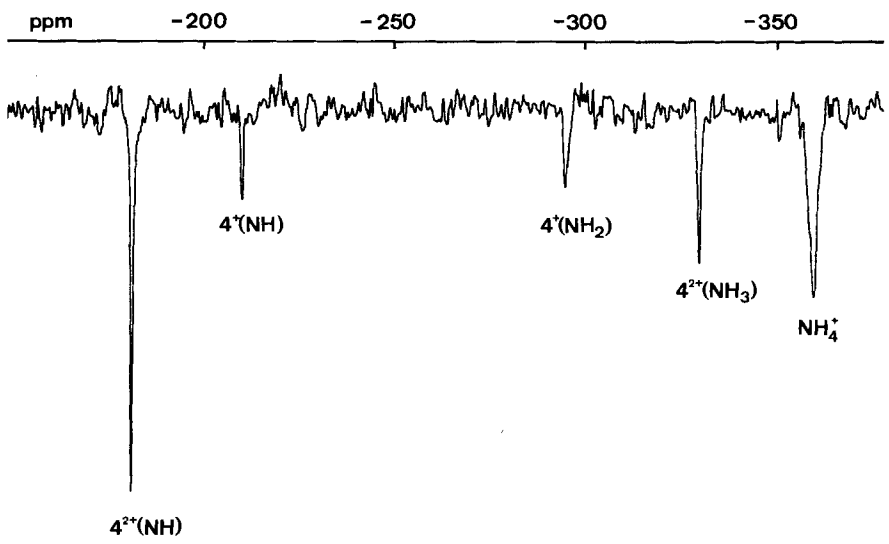
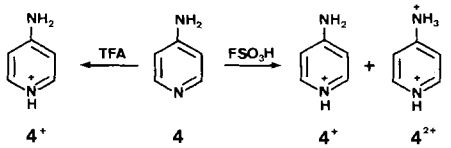


Fig. 1. *^{15}N-NMR. spectrum of 4-aminopyridine* (**4**) *in FSO_3H at 40° with signals assigned to the mono- and dication* (NH_4^+ = reference signal).

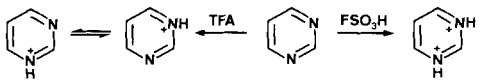
protonation of aminopyrimidines. Previous studies have used ^1H- and ^{13}C-nuclei to obtain the same information in an indirect way [12]. The ^{15}N-NMR. spectra of the monoaminopyridines **2**, **3** and **4** in TFA solution yield protonation increments of $\Delta\delta = -112$ to -121 ppm in agreement with the value observed for pyridine. In all these cases full protonation of the ring N-atom is achieved. A similar low-frequency shift effect (-116 ppm) has been reported for *N*-methylpyridinium iodide [13]. For the diaminopyridines the protonation increment is somewhat smaller (-107 to -90 ppm) and depends on the position of the amino groups with respect to the ring N-atom. In FSO_3H, 4-aminopyridine (**4**) yields a mixture of the mono and dication *(Fig. 1, Scheme 1)*, *i.e.* 4 resonance lines which can be assigned *(Table 1)* with the aid of the resonances of the monocation in TFA and those of the pyridinium ion and the anilinium ion [14]. Indicative for the protonation of an aromatic amino group is a low-frequency shift increment leading to a resonance position of about -330 ppm. At the same time the ring N-atom resonance in the dication approaches the value for the pyridinium ion. 3-Aminopyridine shows the same protonation behaviour whereby the ring N-atom resonances of the mono- and dication coalesce. In the spectrum of 2-aminopyridine (**2**) in FSO_3H diprotonation appears to be more complete since the two lines of the monocation are barely visible.

Scheme 1



In the pyrimidine series the protonation increment can be obtained from the spectrum of pyrimidine in FSO_3H which effects complete diprotonation [12a]. The experimental value *(Table 2)* of $\Delta\delta = -98$ ppm, however, is roughly 20% smaller than in pyridine. In TFA, monoprotonation occurs with a rapid prototropic equilibrium *(Scheme 2)* and the observed protonation increment is -50 ppm. Very similar protonation increments result for 2-aminopyrimidine (**10**), -49 ppm for monoprotonation and -90 ppm for diprotonation. The 1-methyl-2-aminopyrimidinium iodide (**13**) is a good model for monoprotonation and allows the influence of a quaternary N-atom (N(1)) on the chemical shift of the second ring N-atom (N(3)) to be determined. The resonance of N(3) suffers a high-frequency shift (deshielding effect) of $+14$ ppm if **13** and **10** are compared. Thus, if a deshielding effect on N(3) is considered for monoprotonated pyrimidine the average calculated protonation shift for monoprotonated pyrimidine is -52 ppm which compares well with the experimental value of -50 ppm.

Scheme 2



	9$^+$	**9**	**9**$^{2+}$
$\Delta\delta_{obs.}$ N(1,3)	-50		-98 [ppm]
$\Delta\delta_{calc.}$ N(1)	-118	$+14$	$-118+14$
N(3)	$+14$	-118	$-118+14$
$\Delta\delta_{calc.}$ N(1,3)	-52		-104

Similarly, the calculated protonation increment for diprotonated pyrimidine is -104 ppm and the experimental value -98 ppm. Also the protonation shifts for 2-aminopyrimidine (**10**) (-49 ppm and -90 ppm) clearly indicate the stepwise protonation of the two ring N-atoms, and the chemical shift of the NH_2-group in FSO_3H excludes the presence of an ammonium form.

With increasing basicity of the ring N-atoms (pyrimidine, $pk_a^1 = 1.3$; 2-aminopyrimidine, $pk_a^1 = 3.5$; 4-aminopyrimidine, $pk_a^1 = 5.7$; 2,4-diaminopyrimidine, $pk_a^1 = 7.3$ [15]) diprotonation may already occur in TFA. An example is the 4-aminopyrimidine **15** which shows protonation shifts in TFA of -97 ppm for N(1), -86 ppm for N(3) and $+20$ ppm for the NH_2-group. These data are only consistent with a large extent of N(1),N(3) diprotonation, as is evident in a comparison with the corresponding protonation shifts obtained from a FSO_3H solution of the aminopyrimidine **16**. The occurence of only one signal each for ring and amino N-atoms in the TFA spectrum of **16** indicates fast exchange between the mono- and dications. The ring N-atom chemical shifts for 2,4-diaminopyrimidine **17** in DMSO, TFA and FSO_3H can also be rationalized in terms of complete protonation of N(1) and partial N(3) protonation to form a dication (about 60%) in TFA, and complete N(1),N(3) diprotonation in FSO_3H. Since the NH_2-groups do not experience low-frequency shifts of the order of -20 ppm but rather high-frequency shifts of the same order of magnitude, the formation of ammonium ions can be excluded (*cf.* Section 1.2). The equilibrium between mono- and diprotonated species depends

on the presence of other substituents as in the case of the 6-chloro derivative **21** which shows less diprotonation in TFA.

Upon introduction of a third NH_2-group into a pyrimidine, the shift increment for complete protonation of a ring N-atom further decreases (−70 ppm) and there is no significant difference for the N(1),N(3) chemical shifts in TFA or FSO_3H. This leads to the conclusion that 2,4,6-triaminopyrimidines are fully diprotonated already in TFA.

1.2. *Amino groups.* In the mono- and diaminopyridines the resonance positions of NH_2-groups at C(2), C(4) and C(6) (−307 to −322 ppm) can be clearly differentiated from the more highly shielded NH_2-group at C(3) or C(5) (−325 to −337 ppm). Furthermore, the more conjugated NH_2-group at C(4) (*cf.* Section 2) experiencies rather large high-frequency shifts upon protonation of the ring N-atom (NH_2(4): +20 to +30 ppm) whereas the NH_2-groups at C(2,6) and C(3,5) exhibit smaller shift effects of −2 to +8 ppm and 0 to −7 ppm, respectively. In the aminopyrimidines the resonances of the NH_2-groups are shifted to higher frequencies, but as in the pyridine series increasing substitution of the ring by NH_2-groups results in an increased shielding. As shown in the 2,4-diaminopyrimidine (**17**) and its N(1),N(3) dication the NH_2-group at C(4) again suffers a larger protonation shift (+28 ppm) than the NH_2-group at C(2) (+9 ppm) and, hence, these effects are useful for the otherwise difficult assignment of the NH_2-resonances. A further criterion can be found in the ^1J(N,H) coupling constants (*cf.* Section 2). Protonation of a NH_2-group to form an ammonium species would be indicated by a low-frequency shift of *ca.* −20 ppm as discussed above.

In di- and tri-aminopyrimidines an NH_2-group at C(5) can be clearly distinguished from one at C(2,4 and 6) by virtue of its high shielding value (−338 to −357 ppm). If another mode of conjugation is available for the NH_2-group at C(5) as in the triaminopyrimidine **29** a corresponding high-frequency shift can be observed.

1.3. N-*Oxides.* The shift effects observed upon mono-*N*-oxidation of pyridazine (**31**), pyrimidine (**9**) and pyrazine (**38**) are illustrated in *Figure 2* which also contains the corresponding data for pyridine-*N*-oxide [13] [6a]. With these parent compounds, *N*-oxidation leads to low-frequency shifts for the oxidized and non-oxidized N-atoms, with the exception of pyrimidine (and quinazoline (**43**)) in which N(3) is shifted to higher frequency. This behaviour of the ^{15}N-resonances creates an assignment problem. In the first step the ^{14}N-shifts of the oxidized N-atoms can be consulted for which a similar assignment problem does not exist [16]. Owing to the much reduced electric field gradient at the oxidized N-atom, ^{14}N-line widths are rather small whereas resonances of the non-oxidized N-atom are very broad, and accurate chemical shift values are not easily obtained. In fact, a comparison of our data with the ^{14}N-data yields very satisfactory agreement (±4 ppm) for the *N*-oxide N-atom, whereas the chemical shift values reported by *Stefaniak* [16a] for the non-oxidized N-atom do not agree with our data. The good agreement between the ^{15}N- and ^{14}N-shifts for the *N*-oxide N-atoms is also apparent when the linear correlation [16a] between diazine and diazine *N*-oxide shifts is used for our ^{15}N-data (see below). Furthermore, the lanthanide-induced shifts (see below)

observed for the oxidized and non-oxidized ring N-atoms confirm the correct assignment of the *N*-oxide resonance lines. The poor agreement between the ^{15}N- and ^{14}N-shifts for the non-oxidized N-atoms is certainly due to the ^{14}N-line-width problem resulting in an overlap of the two ^{14}N-lines.

For an estimate of the ^{15}N-chemical shifts of 2,4-diaminopyrimidine 1-oxide and its 5-alkyl substituted derivatives, compounds of very low solubility and, therefore unsuitable for ^{15}N-NMR., shielding increments of the NH_2-groups can be extracted from the data of compounds **33**, **34** and **35** *(Table 3)*. A NH_2-group at C(2) exerts a shielding effect of -47 ± 3 ppm on the oxidized and non-oxidized β-N-atoms. Introduction of a second NH_2-group as in **35** results in a restricted β-effect on the *N*-oxide N-atom (-34 ppm) and in a δ-effect of -37 ppm on the

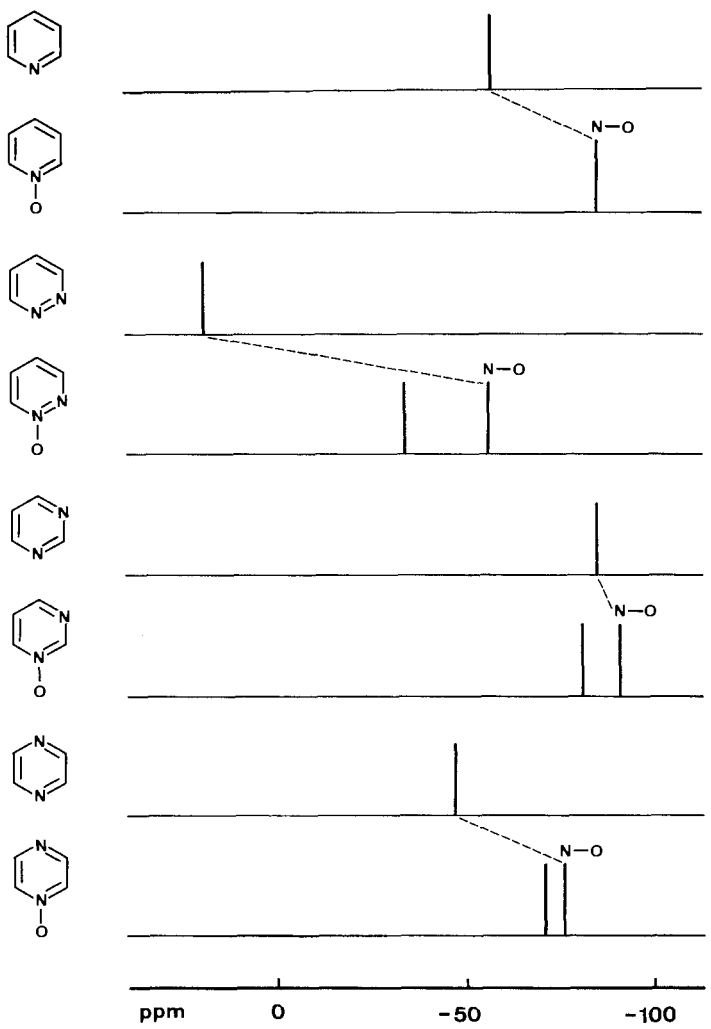


Fig. 2. *Schematic ^{15}N-NMR. spectra of diazines and the corresponding mono-*N*-oxides*

azine N-atom. Thus, the shielding increments are very similar to those in the aminopyrimidines (see p. 506ff). As expected, the benzyl and methoxymethylene groups at C(5) have no significant effect on the shift of the oxidized N-atom. For 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine-1-oxide, one of the TMP metabolites, it is therefore possible to predict the following chemical shifts, N(1) *ca.* −160 ppm, N(3) *ca.* −175 ppm.

Apart from the monocyclic diazine mono-*N*-oxides we have also determined the chemical shifts of the bicyclic diazines **40**, **41**, **43** and **45**, and of the corresponding mono-*N*-oxides **42**, **44** and **46** *(Table 3)*. Assignment problems arise for the unsymmetrical molecules cinnoline (**40**), quinazoline (**43**), and for *N*-oxides with a very small chemical shift difference for the two N-atoms, such as **46**. The assignment for phthalazine 1-oxide (**42**) is supported by the ^{14}N-chemical shift of the *N*-oxide N-atom as reported by *Stefaniak* [16a]. The N-screening constants of cinnoline (**40**) and quinazoline (**43**) were calculated by CNDO-methods [17] with the result that N(1) is less shielded than N(2) or N(3). Our assignment given in *Table 3* is based on these calculations, but there is no experimental support.

1.4. *Lanthanide-induced ^{15}N-shifts.* The ^{15}N-chemical shift data of some diazine mono-*N*-oxides require an independent method for unambiguous assignment. For this reason, we have tested the possibility of applying paramagnetic shift reagents in a selective complexation of the diazine oxide system. Since this moiety contains two nucleophilic centres for metal complexation large induced chemical shifts can be expected. Previous studies on the ^{14}N-resonance of pyridine [18a, b] and aliphatic and alicyclic amines [18b, c] using a variety of lanthanide ions have shown that upon direct complexation of the nitrogen-induced shifts of up to several thousand ppm can be observed (extrapolated to a 1:1 molar ratio of substrate and reagent). For the *N*-oxide system preferred complexation at the nucleophilic O-atom can be expected which will lead to considerably smaller shift effects due to the increased distance between metal and N-atom. As a model compound we have studied the behaviour of *trans*-azoxybenzene towards the two reagents Yb(fod)$_3$ and Eu(dpm)$_3$. The LIS results *(Table 4)* are consistent with a preferred complexation at the O-atom, particularly as there are no large induced shifts such as those observed for pyridine (Yb(dpm)$_3$: +425 ppm; Eu(dpm)$_3$: −1500 ppm). Together with the chemical shift effects, complexation by paramagnetic ions leads to a partial quenching of the ^{15}N-{^{1}H}-NOE. Thus, in the case of Eu(dpm)$_3$ the *N*-oxide N-atom showing the larger induced shift also experiences a more extensive NOE quenching than the other N-atom. The preferred complexation at the O-atom is also confirmed by an LIS study on the ^{1}H-NMR. spectra of *p,p'*-disubstituted azoxybenzenes [19].

The Yb(fod)$_3$-induced chemical shifts for the diazine N(1)-oxides **32**, **33** and **39** are listed in *Table 4*. The most striking difference in the LIS values for the two N-resonances is observed in the case of the pyrimidine *N*-oxide (**33**) which allows assignment of the resonance at −89.9 ppm to the *N*-oxide N(1) (LIS: +31.6 ppm) and the resonance at −79.5 ppm to N(3) (LIS: −4.7 ppm). For N(3) a smaller LIS value has to be expected because of the larger distance to the Yb^{3+}, and possibly also due to the angular dependence of the pseudo-contact term. For pyridazine *N*-oxide (**32**) where the reagent is also close to the N(2), large LIS values

for both ^{15}N-resonances have been obtained (+119.3 and +86.0 ppm). In the case of pyrazine *N*-oxide (**39**), quite unexpectedly large LIS effects are measured for both N-atoms (N(1): +85.6 ppm; N(4): +76.2 ppm). This seems to indicate that complexation at the N(4) center must also be taken into account. Since the *N*-oxide group increases the electron density at C(4) and C(2), the same interpretation might also hold for the large LIS observed for N(2) in pyridazine *N*-oxide. In conclusion, the use of lanthanide-induced chemical shifts, which has not previously been explored for ^{15}N-NMR. spectroscopy, appears to be a valuable assignment aid.

1.5. *Correlations between ^{15}N- and ^{13}C-chemical shifts.* The very large substituent effects of amino groups in pyridines and pyrimidines illustrate conjugative interaction between an NH_2-group and the hetero-aromatic ring. Since such effects are also known in amino-substituted benzenes it is obvious to seek a correlation between the substituent effects on the ^{15}N-shifts and the corresponding effects on the ^{13}C-shifts. A correlation for pyridines between $\Delta\delta$(N) and $\Delta\delta$(C) is shown in *Figure 3*. A somewhat less satisfactory plot can also be obtained for the ^{15}N-shift in amino-substituted pyrimidines against the ^{13}C-shifts of the amino-substituted benzenes. The quality of the latter correlation can be improved if the $\Delta\delta$(N) values are plotted versus the $\Delta\delta$(C) values of amino-substituted pyridines *(Fig. 4)*.

The slopes of these linear correlations are approximately 3 (3.2±0.5) which is indicative of a stronger conjugation of an amino group with an aza-aromatic ring as compared with a benzene ring. It also indicates that the ^{15}N-shifts in this class of compounds are governed by the same factors as the ^{13}C-shifts. If such a correlation is extended to a variety of substituents in substituted pyridines and pyrimidines, the slopes of the linear plots remain essentially constant (~3.3). Previous studies have attempted correlation between ^{14}N- [9] [10] [16a] or ^{15}N- [6a] chemical shifts and calculated π-electron densities at the N-atom. Our treatment of the experimental

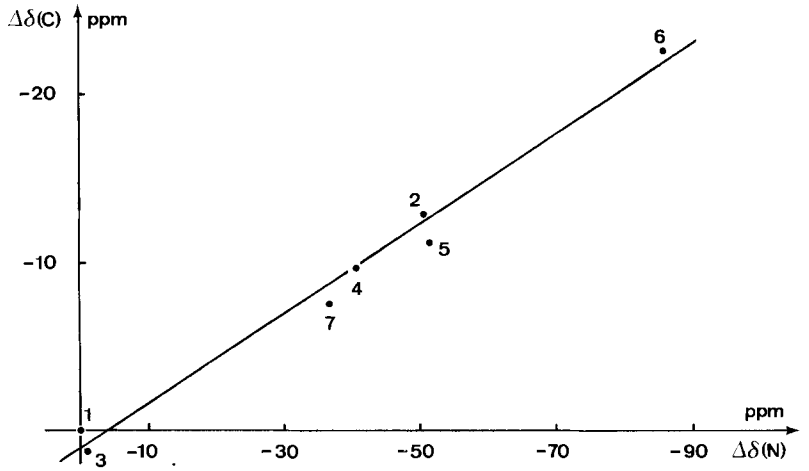


Fig. 3. *Amino substituent effects $\Delta\delta$(N) in aminopyridines plotted against the corresponding $\Delta\delta$(C) values [20] in amino-substituted benzenes.* Linear regression: $\Delta\delta(N) = 3.73 \cdot \Delta\delta(C) - 4.62$ (correlation coefficient: 0.9985).

^{15}N- and ^{13}C-data offers the possibility of predicting or assigning ^{15}N-resonance frequencies *via* a linear correlation.

Chemical shift correlations between ^{14}N-data of diazines and their corresponding mono-*N*-oxides have also proved useful for assignment purposes [16a] (*cf.* Section 1.3). Since the linear regression derived from the ^{14}N-data ($\delta(N-O) = 0.3117 \cdot \delta(N) - 62.00$) should also be valid for ^{15}N-chemical shift measurements, the experimental shift-data of diazine mono-*N*-oxides can be grouped to fit the linear equation given above. In the case of the *N*-oxides **32**, **33**, **39**, **42** and **46** our assignment (p. 516ff.) of the *N*-oxide N-atom leads to the linear equation $\delta(N-O) = 0.321 \cdot \delta(N) - 63.09$ (correl. coeff. 0.9764) in satisfactory agreement with the equation obtained from the ^{14}N-data.

2. *N, H-Coupling Constants.* As already mentioned in the Results N, H-coupling constants can be a valuable parameter for the assignment of ^{15}N-resonance lines, as for example in the case of NH_2-groups. The $^1J(N,H)$ coupling constants of NH_2-groups can be obtained in DMSO where intermolecular H-exchange is slow. For aminopyridines the values are found in the range from 82 to 88 Hz for amino groups at C(2,4 and 6) whereas they are somewhat smaller for C(3) and C(5) (77–81 Hz, *Table 5a*). Increasing substitution by NH_2-groups results in a slight decrease of this parameter. The positional dependence of the $^1J(N,H)$ coupling constant of NH_2-groups reflects the extent of conjugation between NH_2-group and ring N-atom and constitutes a useful assignment criterion along with the chemical shifts (Section 1). Application of the well-known relationship between $^1J(N,H)$ and the hybridization index of the N-atom [21] to our experimental data yields

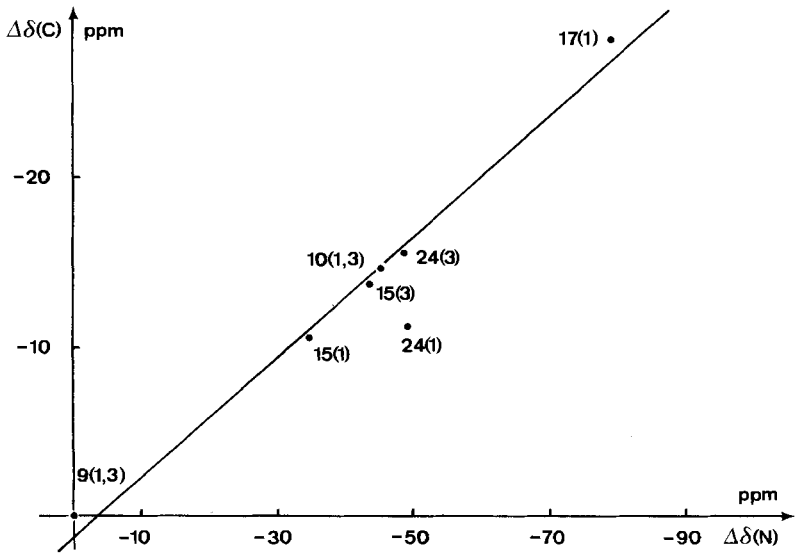


Fig. 4. *Plot of the amino substituent effects $\Delta\delta(N)$ on the ring N-atoms N(1) and N(3) in aminopyrimidines against the corresponding effects on the ^{13}C chemical shifts of aminopyridines.* Linear regression (**24**(1) omitted): $\Delta\delta(N) = 2.78 \cdot \Delta\delta(C) - 3.38$ (correlation coefficient: 0.9904).

values of 31 and 33% *s*-character, respectively, for the NH_2-groups in 2- and 4-aminopyridine, whereas 3-aminopyridine with a value of 29% clearly shows the more pyramidal nature of the amino N-atom in this compound. Also in the diaminopyridines **5**, **6** and **7** the NH_2-group at C(3) appears to be least conjugated with the π-system. Further support for this interpretation of the N,H-coupling constants comes from calculated[7]) free enthalpies of activation for rotation about the N–C-bond in aminopyridines [7]. The reported $\Delta G^{\ddagger}_{301}$ values for 3,4-diaminopyridine are 31.3 kJ/mol and 22.1 kJ/mol for the 4-amino and 3-amino groups, respectively, and a large value (32.2 kJ/mol) is also obtained for 2,6-diaminopyridine.

The small but significant increase of $^1J(N,H)$ in the aminopyrimidines supports the better conjugation in this series as already inferred from ^{15}N-chemical shifts of both the NH_2-group and the ring N-atom. This result may be compared with kinetic data on the rotation of a NH_2-group in 2-aminopyrimidine ($\Delta G^{\ddagger}$: 37.6 kJ/mol [7]). In 2,4-diaminopyrimidine there is a small but significant difference in the N,H-coupling constants in the amino groups. Since kinetic measurements show [22] that a $N(CH_3)_2$ group exhibits stronger conjugation at C(4) than at C(2), we have assigned the larger $^1J(N,H)$ value (88.2 Hz) to the NH_2-group at C(4) and the smaller one (86.8 Hz) to the NH_2-group at C(2). This assignment has been confirmed by ^{15}N-{^1H} off-resonance decoupling experiments.

Two-bond N,H-coupling between a ring N-atom and an *ortho*-proton, although much more difficult to detect, can be useful to differentiate between ring N-atoms. For example, N(1) in TMP-(3)-oxide (**36**) yields a doublet under proton coupled conditions ($^2J(N,H)=5.5$ Hz) whereas the N(3)-resonance remains unchanged. Some data on 2,4-diaminopyrimidines are listed in *Table 5b*.

The authors would like to thank Mr. *F. Stierli* and Mr. *M. Toscan* for the preparation of compounds **20**, **34** and **47**. The spectroscopic equipment was sponsored by the *Swiss National Science Foundation*.

Experimental Part

The majority of the ^{15}N-NMR. spectra was measured at 10.1 MHz on a *Varian* XL-100-15 spectrometer equipped with a homebuilt probe head for 20 mm o.d. sample tubes [1b]. Under noise-decoupled conditions the sample temperature was *ca.* 40°, otherwise *ca.* 30°. Some spectra were recorded on a *Varian* XL-200 spectrometer at 20.3 MHz in 10 mm tubes. Chemical shifts (±0.2 ppm) were determined relative to either signal of external aqueous $^{15}NH_4{}^{15}NO_3$ and then converted to the proposed external nitromethane standard [23]. Typical acquisition parameters include a spectral width of 5000 Hz, 0.4 s acquisition time, a flip angle of 50°, and pulse delays of up to 10 s.

The resonances of protonated NH_2-groups and ring N-atoms in TFA and FSO_3H solution were obtained under complete proton-noise-decoupling and required *ca.* 2000 free induction decays for approximately 0.5M solutions. The $^1J(N,H)$ coupling constants were measured with the gated decoupling technique to retain the NOE, whereas the chemical shifts of tertiary N-atoms were detected with an inverse gating and addition of 0.1M $Cr(acac)_3$ to quench an unfavourably small NOE. In 0.5M solutions, the detection of tertiary N-atoms required up to 10,000 free induction decays. The LIS data of *Table 4* were obtained by measuring 4 to 5 points in the concentration range of 0–0.1M in $Yb(fod)_3$ reagent and extrapolation to a 1:1 molar ratio of reagent and substrate.

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7) Calculated using a linear correlation between $\Delta G^{\ddagger}$ and $\delta(^{15}N)$ as obtained from measurements on *N,N*-dimethylaminopyridines.

The following compounds are of commercial origin and were purified when necessary: *Fluka AG*, **1**–**7**, **9**, **10**, **14**, **25**, **31**, **38**, **41**, **43**, **45**; *Aldrich*, **21**, **22**, **24**, **30**; *EGA Chemie*, **40**. The syntheses and purification of **11** [24]; **12**, **13** [25]; **20** [26]; **27** [27]; **29** [28]; **32**–**34** [29]; **36** [30]; **39**, **42**, **44**, **46** [29]; **47** [31] are described in the references.

4-Amino-5-(3,4,5-trimethoxybenzyl)-pyrimidine (**15**). A suspension of 5 g (16 mmol) 4-amino-2-mercapto-5-(3,4,5-trimethoxybenzyl)pyrimidine[8]) and 20 g *Raney* nickel in a mixture of 6 ml 3N NH_4OH and 100 ml water was refluxed for 18 h. Usual work-up yielded after crystallisation from ethyl acetate/petrol ether 1.8 g (40%) **15**, m.p. 153–155°.

$C_{14}H_{17}N_3O_3$ (275.30) Calc. C 61.08 H 6.22 N 15.26% Found C 61.12 H 6.29 N 15.14%

4-Amino-2-phenyl-5-(3,4,5-trimethoxybenzyl)pyrimidine (**16**). A mixture of 0.5 g (1.54 mmol) 3-anilino-2-(3,4,5-trimethoxybenzyl)acrylonitrile[9]) and 0.28 g (2.31 mmol) benzamidine in 20 ml ethanol was refluxed for 100 h. After work-up 0.42 g (77%) **16**, m.p. 123–124°/141–144° (from ethyl acetate/pentane) were obtained.

$C_{20}H_{21}N_3O_3$ (351.41) Calc. C 68.36 H 6.02 N 11.96% Found C 68.45 H 5.90 N 12.12%

4,6-Diamino-5-(3,4-dimethoxybenzyl)pyrimidine (**23**). A solution of 26.3 g (0.1 mol) of 4,6-dichloro-5-(3,4-dimethoxybenzyl)pyrimidine[8]) in ethanolic ammonia solution was heated in an autoclave at 160° for 16 h. The residue after evaporation of the solvent was partitioned between ethyl acetate/water and the ethyl acetate solution extracted with 1N HCl. The aqueous extracts were made alkaline with conc. NH_4OH-solution, the precipitate collected and crystallized from dimethylformamide. Yield 19 g (73%), m.p. 223–224°.

$C_{13}H_{16}N_4O_2$ (260.29) Calc. C 59.95 H 6.20 N 21.53% Found C 59.92 H 6.23 N 21.55%

2,4,6-Triamino-5-(3,4,5-trimethoxybenzyl)pyrimidine (**26**). To a solution obtained by dissolving 0.95 g (41 mmol) Na in 30 ml ethanol, 3.8 g (41 mmol) guanidine hydrochloride and 8.7 g (35 mmol) 2-cyano-(3,4,5-trimethoxy)hydrocinnamonitrile[8]) were added. The mixture was refluxed for 48 h, cooled, crystals collected, washed with cold water and recrystallized from water. Yield 6.5 g (60%), m.p. 240°.

$C_{14}H_{19}N_5O_3$ (305.33) Calc. C 55.07 H 6.27 N 22.94% Found C 54.70 H 6.27 N 22.71%

2,4-Diaminopyrimidine 3-oxide (**35**). A solution of 5.5 g (50 mmol) 2,4-diaminopyrimidine (**17**) and 22 g (0.11 mol) 3-chloroperbenzoic acid in 250 ml dioxane was stirred at RT. for 4 h. The reaction mixture was evaporated to dryness, suspended in CH_2Cl_2 and extracted with 5% $NaHCO_3$-solution. The CH_2Cl_2-phase was dried, evaporated to dryness and the residue subjected to column chromatography (Silicagel 60, *Merck*, eluent CH_2Cl_2/CH_3OH 4:1). 3-Oxide **35** was eluted from the column first. Yield 0.95 g, m.p. 183° (methanol/ether). – ^{1}H-NMR. (DMSO): 7.42 (*d*, J = 8.0 Hz, C(6)–H); 6.10 (*d*, J = 8.0 Hz, C(5)–H); 7.20 and 7.33 (2 *s*, 2 NH_2).

$C_4H_6N_4O$ (126.12) Calc. C 38.09 H 4.80 N 44.42% Found C 38.11 H 4.99 N 44.30%

The 1-oxide was obtained from the later fractions. Yield 0.63 g, m.p. 289° (from methanol/ether). – ^{1}H-NMR. (DMSO): 7.78 (*d*, J = 8.0 Hz, C(6)–H); 5.78 (*d*, J = 8.0 Hz, C(5)–H); 6.65 and 7.12 (2 *s*, 2 NH_2).

2,4-Diamino-5-(methoxymethyl)pyrimidine 3-oxide (**37**). A solution of 15.4 g (0.1 mol) 2,4-diamino-5-methoxymethylpyrimidine[8]) and 44 g (0.44 mol) 3-chloroperbenzoic acid in 500 ml dioxane was stirred at RT. for 4 h. After work-up as for **35** and chromatography (Silicagel 60, *Merck*, eluent: $CHCl_3/C_3H_7OH$/25% ammonia 5:5:0.5) 3-oxide **37** was isolated. Yield 4.6 g, m.p. 240–242°.

$C_6H_{10}N_4O_2$ (170.17) Calc. C 42.35 H 5.92 N 32.92% Found C 42.46 H 6.16 N 32.79%

The 1-oxide was obtained from the later fractions. Yield 4.2 g, m.p. 235–236°.

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[8]) On file at *F. Hoffmann-La Roche* & Co. Ltd., Basel.

[9]) Patent Application (British) CG 11908/69 for the Wellcome Foundation Ltd., London, England.

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