1 H), 7.17–7.80 (m, 5 H); IR (CCl_4) 1661, 1628 (w), 1600, 1580 (w) cm^{-1}.

2-((Benzylthio)methyl)cyclooctanone (Table II, Entry 4). Following the alkylation procedure outlined for Table II, entry 3, 379 mg of cyclooctanone gave 403 mg (51%) of sulfide after preparative TLC: ^1H NMR (CCl_4, 100 MHz) δ 1.1–2.1 (m, 10 H), 2.1–2.8 (m, 5 H), 3.59 (br s, 2 H), 7.22 (br s, 5 H); IR 1703, 1600 (w) cm^{-1}; MS, M^+, 262.1393 (calcd for $C_{16}H_{22}OS$, 262.1370).

2-Methylenecyclooctanone. Following the oxidation (4.5 h) and elimination (3.5 h) procedures outlined for Table II, entry 1, 262 mg (1 mmol) of 2-((benzylthio)methyl)cyclooctanone gave 85 mg (62%) of 2-methylenecyclooctanone[21] after preparative TLC: ^1H NMR (CCl_4, 100 MHz) δ 1.4–1.9 (m, 8 H), 2.4–2.7 (m, 4 H), 5.12 (m, 1 H), 5.76 (d, J = 2.5 Hz, 1 H); IR 1701, 1605 (w) cm^{-1}.

Acknowledgment. We thank the National Institutes of Health (NIADDK) for financial support of this work. Dr. S. L. Peake and Dr. C. A. Hoeger carried out preliminary experiments. We thank them for their contribution and Professor D. H. Rich for helpful discussions.

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Nitrogen Bridgehead Compounds. 63.[1] Ring–Chain Tautomerism of [(α-Azaarylamino)methylene]malononitriles

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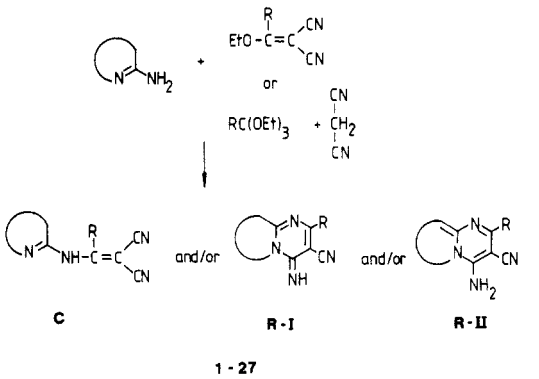
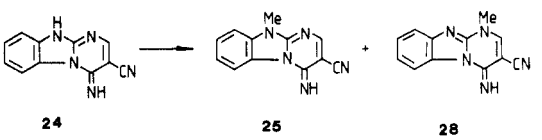
Twenty-one α-amino aza heterocycles were reacted with (ethoxymethylene)malononitrile. UV and ^1H and ^{13}C NMR studies indicated that in solution the structures of the condensation products can be described as chain and ring tautomers. Investigations were also made of the solvent and temperature dependence of the position of equilibrium of the ring and chain tautomer forms and the effect of protonation on the ring–chain tautomerism of the 2-aminopyridine derivative. The proportion of the ring form is increased by the presence of a substituent in position 2 of the pyridopyrimidine skeleton type ring tautomer and also by electron-donating substituents in position 7 or 8, while electron-accepting groups increase the content of the chain tautomer. A substituent in position 6 sterically favors the chain form, while substituent in position 9 influences the equilibrium between the ring and chain tautomer forms through its electronic and steric properties and its hydrogen bond forming ability. The 1-aminoisoquinoline derivative is present in ring form in both $CDCl_3$ and Me_2SO-d_6. The derivatives of 2-aminoquinoline, 3-aminoisoquinoline, 2-aminopyrimidine, and 2-aminopyrazine predominantly exist as chain tautomers. The derivatives of π-excess five-membered heterocycles—of 2-aminothiazole, 3-aminopyrazole, 2-aminobenzthiazole, and 2-aminobenzimidazoles—favor the ring form. In the case of 3-aminopyrazole, the chain and ring forms could be separated.

(Ethoxymethylene)malononitrile is a versatile reagent for the preparation of heterocyclic ring systems.[2] Its reaction with aromatic α-amino aza heterocycles affords antiallergic[3] and bactericidal[4] agents and also intermediates for the preparation of antiallergenics,[5,6] bronchodilators,[6] and vasodialtors.[5] The structures of these products have been reported to be chain form **C**[3-13] or ring forms **R**-I[14] or **R**-II[15] (see Scheme I). For the sake of clarity the numbering used for certain open-chain heterocycles follows from the ring-closed form (e.g., **1R**-I → **1C**). Although investigated by UV and ^1H and ^{13}C NMR,[6,11,14,16] these forms have often proved to be incorrectly assigned.

Scheme I



Scheme II



We have recently focused our interest on the factors that determine the structures of these products. Our studies included 2-aminopyridine and its methyl, ethoxycarbonyl,

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0022-3263/86/1951-2988$01.50/0

Table I. [(α-Azaarylamino)methylene]malononitriles 1-27

aminoheterocycle	method	scale, mmol	EtOH, mL	reacn conditions		product						
				temp, °C	time, h	cmpd	R	yield, %	recrystn solv	mp, °C	lit. mp, °C	lit.
2-aminopyridine	A	10	10	25	0.5	1	H	68.3	EtOH	175–176	175	11, 13
	B	10				2	Me	70.6	PrOH	202–203	196–198	13
	C	10				2	Me	34.8	PrOH	199–200		
	C	10				3	Et	40.4	EtOH	123–124	122–123	13
	C	10				4	Pr	49.0	EtOH	98–100		
	B	10				5	Ph	40.6	PrOH	212–214		
2-amino-3-methylpyridine	A	10	10	25	0.5	6	H	51.7	EtOH	164–166	162	11
2-amino-4-methylpyridine	A	10	10	25	0.5	7	H	69.0	EtOH	205–206	203–204	11
											201–203	13
	C	10				7	H	78.0	EtOH	202–204		
2-amino-5-methylpyridine	A	10	10	25	0.5	8	H	74.0	EtOH	185	184–185	11
	C	10				8	H	76.0	EtOH	184		
2-amino-6-methylpyridine	A	10	10	25	24.0	9	H	77.0	EtOH	181–183	181–183	11, 14
	B	10				10	Me	75.0	EtOH	166–167	164–166	13
ethyl 2-amino-3-pyridinecarboxylate	A	2.5	25	80	6	11	H	*a*		175–174		
ethyl 2-amino-4-pyridinecarboxylate	A	5	25	25	72	12	H	58.6	MeCN	175–177		
ethyl 2-amino-5-pyridinecarboxylate	A	5	20	25	72	13	H	29.5	MeCN	223–224		
ethyl 2-amino-6-pyridinecarboxylate	A	5	20	25	72	14	H	56.9	EtOH	218–219		
2-amino-5-chloropyridine	A	10	20	25	5	15	H	58.6	EtOH	225–226		
2-amino-5-bromopyridine	A	5	20	25	24	16	H	72.3	EtOH	230–231		
2-aminoquinoline	A	5	20	25	24	17	H	90.8	EtOH	242–244	227	11
1-aminoisoquinoline	A	5	30	25	24	18	H	81.7	MeCN	222–224		
3-aminoisoquinoline	A	1	10	25	3	19	H	66	EtOH[b]	230		
2-aminopyrimidine	A	10	25	25	24	20	H	14.7	EtOH	230	200	11, 13
	C	30				20	H	89.5	EtOH	245–247		
2-aminopyrazine	A	10	20	25	24	21	H	27.5	EtOH	245–246	208	11, 13
	C	30				21	H	62.4	EtOH	245–246		
2-aminothiazole	A	10	25	25	24	22	H	82.1	EtOH	175–176	168–169	11
2-aminobenzthiazole	A	10	25	25	24	23	H	81.7	EtOH	189–190	183–184	11
											186–187	6
2-aminobenzimidazole	A	10	15	25	0.5	24	H	83.2	DMF	350		
2-amino-1-methylbenzimidazole	A	1.2	5	25	18	25	H	71.8	MeCN	241–242		
3-aminopyrazole	A	10	20	−10	15	26	H	73.2		*c*		
	A	10	20	80	15	27	H	85.3	EtOH	306–308		

[a] Isolated by means of thin-layer chromatography (see Experimental Section) on a Kieselgel plate. Eluent: benzene–methanol (4:1). [b] Refluxed in the solvent given. [c] Cyclized to **27** on melting.

5-chloro, and 5-bromo derivatives, 1- and 3-aminoisoquinolines, the 2-amino derivatives of quinoline, pyrimidine, pyrazine, thiazole, benzthiazole, benzimidazole, and 1-methylbenzimidazole, and 3-aminopyrazole.

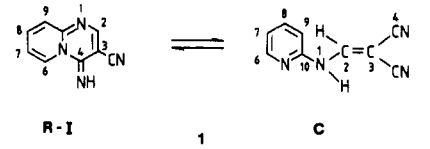
Chemistry. Aromatic α-amino aza heterocyles were reacted with (ethoxymethylene)malononitrile, either in ethanol at −10 °C and ambient temperature or in the melt at 120 °C. A "one-pot" procedure was sometimes applied, starting from amines, malononitrile, and ortho esters (see Scheme I). Besides (ethoxymethylene)malononitrile, its methyl, ethyl, propyl, and phenyl derivatives (R) were also used for 2-aminopyridine and 2-amino-6-methylpyridine. The products are characterized in Table I.

The treatment of pyrimido[1,2-*a*]benzimidazole **24** with methyl iodide in the presence of potassium carbonate in dimethylformamide gave a ca. 1:1 isomeric mixture of N-methylated derivatives **25** and **28** (Scheme II). Compound **28** was separated on a preparative TLC plate. Compound **25** was also prepared from 2-amino-1-methylbenzimidazole with (ethoxymethylene)malononitrile.

Results and Discussion

Structure of the Product 1 Formed from 2-Aminopyridine with (Ethoxymethylene)malononitrile. The 2-aminopyridine derivative **1** was described as a monocyclic structure (**1C**) by Okamoto et al.[11] and by Junek and Schmidt.[13]

When we recorded the UV spectrum of compound **1**, we observed that, besides the maxima reported by Okamoto et al.,[11] it exhibited a maximum beyond 390 nm (Table II). Since it has been shown for similar systems[17] that the appearance of an UV maximum beyond 350 nm is characteristic of the pyrido[1,2-*a*]pyrimidine skeleton, the bicyclic form **R-I** also has to be considered as concerns the structure of this compound. Further, the UV spectrum of **1** exhibited a considerable solvent dependence (Table II). Again, when taken at different time intervals, the spectra varied through an isosbestic point. All of these results indicated that **1** should be described as a ring–chain tautomer system involving forms **C** and **R-I**.



R-I 1 C

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Table II. UV Data on Compounds 1 and 9

compd	solv	ϵ_1/ϵ_2	λ_{max}, nm (ϵ_1)	λ_{max}, nm (ϵ_2)	ref
1	water			324 (5580), 271 (3060), 262 (3670)	11
	water	1.41	391 (12030)	321 (8510), 269 (4430), 261 (4770)	
	EtOH	0.24	397 (4600)	323 (19300), 272 (7800), 266 (7300)	
9	water			324 (12200), 273 (7680), 267 (6580)	11
	water[a]			320 (35300), 271 (13000), 266 sh (11400)	
	EtOH			326 (28780), 273 (11600), 266 sh (10190)	14
	EtOH			326 (33110), 273 (12580), 267 (10960)	

[a] Contains 10% of ethanol.

Table III. Characteristic NMR Data (δ; J, Hz) on Compound 1 in Me_2SO-d_6

tautomer	$\delta_{2\text{-H}}$	$\delta_{6\text{-H}}$	$\delta_{9\text{-H}}$	δ_{NH}	$J_{6,7}$	$J_{CH=NH}$	$\delta_{C\text{-}3}$	$\delta_{C\text{-}4}$	$\delta_{C\text{-}6}$	$\delta_{C\text{-}9}$	δ_{CN}
R-I	8.27	9.30	7.61	8.00	7.0		89.8[a]	153.0[a]	129.1	126.3	117.3
C	8.77	8.37	7.32	11.65	4.9	12.0[a]	54.5	116.0	148.4	113.0	113.7

[a] Measured in $CDCl_3$.

Table IV. Equilibrium Ring-Chain Tautomer Ratio for Compound 1 at 30 °C in Different Solvents

tautomer	ratio of tautomer, % $CDCl_2CDCl_2$	D_2O	$CDCl_3$	CD_3NO_2	CD_3CN	CD_3OD	CD_3COCD_3	Me_2SO-d_6
R-I	96	95	80	80	62	40	28	5
C	4	5	20	20	38	60	72	95

Our assumption was supported by ^1H and ^{13}C NMR studies. In various solvents two series of signals appear, which can be assigned to the chain **1C** and ring **1R**-I tautomers (Table III); the ratio of the signals varies with time until the equilibrium ratio characteristic of the given solvent is established (Table IV).

In the ^1H NMR spectrum of the ring tautomer (**R**-I), protons 6-H and 9-H are shifted downfield as compared with the corresponding signals of the chain tautomer (**1C**);[18] due to the anisotropic effect of the adjacent C=N double bonds. The coupling constants $J_{6,7}$ are also characteristically different for the two tautomers, which reflects the change in electron distribution in the bicyclic form. In the chain tautomer (**1C**), a coupling of 12 Hz can be observed in certain solvents for the N(1)H–C(2)H protons, indicating an antiperiplanar arrangement of these protons. In Me_2SO-d_6, the C(4)=NH proton absorbs at around 8 ppm in the ring tautomer (**1R**-I), while for the chain form (**1C**) the N(1)H signal appears at 11.65 ppm due to hydrogen bonding with the solvent. In $CDCl_3$, the NH proton signal for the chain form appears at 9.5 ppm, whereas for the ring form it is at 7.5 ppm.

In the ^{13}C NMR spectrum of 1 in Me_2SO-d_6, Sterk and Schmidt detected[16] only one set of signals, which were assigned to the chain tautomer on the basis of two signals in the nitrile carbon range (112.2 and 115.0 ppm). However, in the same solvent, we observed a second set of weaker signals, which we attribute to the bicyclic form.

Equilibrium ratios in different solvents, established after 1 day and determined from the integrated ^1H NMR spectra, are shown in Table IV. The equilibrium ratios seem to be primarily influenced by the hydrogen-acceptor properties of the solvent.

The temperature dependence of the equilibrium ratio was studied in $CDCl_2CDCl_2$. The equilibrium ratios and the molar free energy differences (ΔG_m) of the tautomers are compiled in Table V.

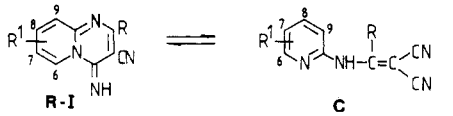
Disregarding the temperature dependence of the molar enthalpy differences, an analysis of the temperature dependence of the molar free enthalpy indicated that the entropy of the chain tautomer was higher by 50 eu, which explains its increasing proportion on elevation of the temperature.

(18) For the sake of uniformity, both tautomers have been numbered identically.

Table V. Equilibrium Ring-Chain Tautomer Ratio in $CDCl_2CDCl_2$ at Different Temperatures for Compound 1

	temp, K 307	337	367	397
ring/chain	96/4	92/7	86/14	78/22
K_T	0.04	0.08	0.16	0.28
ΔG_m, kJ/mol	8.1	7.2	5.5	4.2

Table VI. Equilibrium Tautomer Ratios for 2-Aminopyridine Derivatives 1–16 at 30 °C



compd	R	R^1	in $CDCl_3$ **R**-I, %	in $CDCl_3$ C, %	in Me_2SO-d_6 **R**-I, %	in Me_2SO-d_6 C, %
1	H	H	80	20	5	95
2	Me	H	100		100	
3	Et	H	100		100	
4	Pr	H	100		100	
5	Ph	H	100		100	
6	H	9-Me	100		70	30
7	H	8-Me	100		25	75
8	H	7-Me	95	5	5	95
9	H	6-Me		100		100
10	Me	6-Me		100		100
11	H	9-COOEt		100		100
12	H	8-COOEt	70	30		100
13	H	7-COOEt	70	30		100
14	H	6-COOEt		100		100
15	H	7-Cl	20	80		100
16	H	7-Br	5	95		100

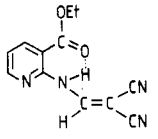
The Structures of Other 2-Aminopyridine Derivatives (2–16). Detailed UV and ^1H and ^{13}C NMR data on compounds **2–16** are to be found in the supplementary material. Equilibrium tautomeric ratios in $CDCl_3$ and Me_2SO-d_6 are listed in Table VI. It can be observed that the position of the equilibrium is influenced not only by interactions with the solvent but also by both the electronic and steric effects of the substituents.

With 6-substituted 2-aminopyridines **9**, **10**, and **14**, the equilibrium is very much in favor of the chain form, due

to an unfavorable steric interaction between the substituent at C-6 and the neighboring 4-imino group in the cyclic tautomer.[19,20]

In derivatives substituted at positions 7 and 8 (**7**, **8**, **12**, **13**, **15**, and **16**), electron-donating substituents (methyl group) increase the proportion of the ring tautomer (**R**-I), while electron-accepting groups (COOEt, halogen) increase that of the chain form (**C**). Electron-donating substituents increase and electron-attracting ones decrease the nucleophilic power of the pyridine nitrogen and thereby the ratio of the ring tautomer.

The simultaneous influence of electronic and steric effects can be observed in the 9-substituted compounds **6** and **11**. In the 9-methyl derivative, the ring tautomer predominates, even in Me_2SO-d_6. This may be attributed to the facts that in the ring form there is much less crowding than in the chain tautomer and that in the chain tautomer the closely situated methyl group interferes with hydrogen bonding involving the solvent. In contrast, in the case of the 9-ester **11**, even in $CDCl_3$, only the signals of the chain form can be detected, since this form is stabilized by an internal hydrogen bond between the ester carbonyl and the NH group. This is evidenced by the chemical shift of the NH signal (11.75 ppm) in the ^1H NMR spectrum.



11

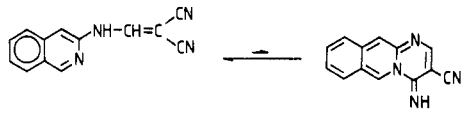
For the 2-alkyl and 2-phenyl derivatives **2**–**5**, in the solvents examined, the only detectable tautomer was the ring form. Apart from the electronic effect of the 2-substituent stabilizing the ring form,[21] the interference of this substituent with hydrogen bonding between the adjacent NH group and the solvent in the chain form can again be invoked as an explanation. In the case of the 2-methyl and 2-phenyl derivatives **2** and **5**, no signals of the chain tautomer could be detected even at 100 °C in $CDCl_2CDCl_2$.

The intense yellow color of the 6-unsubstituted derivatives **1**–**8**, **12**, **13**, **15** and **16** indicates that these compounds exist as ring tautomers in the solid state, while the white 6-substituted derivatives **9**, **10**, and **14** are present as chain tautomers.

The Structures of Further α-Amino Aza Heterocyclic Derivatives (17–28). Our studies on ring–chain tautomerism were extended to a series of products (**17**–**27**) obtained from aromatic α-amino aza heterocycles and (ethoxymethylene)malononitrile (see Table I). Detailed UV and ^1H and ^{13}C NMR data are reported in the supplementary material. Some characteristic ^1H and ^{13}C NMR data recorded in Me_2SO-d_6 are given in Table VII.

The 2-aminoquinoline derivative **17**, which can be regarded as a 6-substituted 2-aminopyridine derivative, exists predominantly in the chain form (**17C**) both in $CDCl_3$ and Me_2SO-d_6, while the 1-aminoisoquinoline derivative **18**, formally a 3-substituted 2-aminopyridine derivative, exists exclusively in the ring form (**18R**-I), even in Me_2SO-d_6.

In the 3-aminoisoquinoline derivative **19**, the equilibrium between the ring and chain forms is strongly in favor of the chain tautomer (**19C**) both in $CDCl_3$ and in Me_2SO-d_6. A possible interpretation of this phenomenon is the



19

"annelation effect",[22] which is an extension of Clar's principle[23] to polyfused heteroaromatic systems. Clar's theorem states that the stability in a series of isomers increases with the number of aromatic sextets. The chain form of **19** contains such a sextet, indicated by a circle, while the ring form does not, and therefore the heteroaromatic stability of the former must be higher.

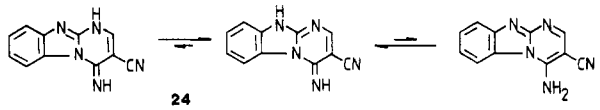
In Me_2SO-d_6, the 2-aminopyrimidine and 2-aminopyrazine derivatives **20** and **21** exist as the chain tautomers, similarly to the 2-aminopyridine derivatives containing an electron-acceptor substituent (**12**, **13**, **15**, and **16**).[24] Compounds **20** and **21** do not dissolve in $CDCl_3$.

With products obtained from five-membered heteroaromatic amines, the equilibrium favors the ring form, probably because of the decreased aromaticity of the five-membered rings[25] as compared to that of six-membered rings in the chain form.

Even in Me_2SO-d_6, the percentage of the ring tautomer (**R**-I) was 100% for **22** and **25** and 70% for **23**.

When the parent heterocyclic amine contains a further mobile hydrogen atom in addition to those in the amino group, then more than one form of the ring tautomer can be envisaged.

Thus, besides the chain form, three tautomeric ring forms can be considered for the structure of the product **24** obtained from 2-aminobenzimidazole. The ^1H and ^{13}C NMR spectra contained only one set of signals, and, among others, the chemical shift (151.1 ppm) of C(4) indicated that either one of the ring forms or a mixture of the rings forms giving a fast prototropic equilibrium is present.



R-III **24** **R**-I **R**-II

A comparison of the chemical shift of C(2) in compound **24** with those in the fixed tautomers **25** and **28** and also the identical data for 6,7,8,9- and 1,6,7,8-tetrahydropyrido[1,2-*a*]pyrimidin-4-ones[26] containing similar moieties in the pyrimidine ring suggested that the main tautomeric form of **24** is **R**-I. The predominance of this tautomeric form was earlier found for ethyl 4-oxo-4,10-dihydropyrimido[1,2-*a*]benzimidazole-3-carboxylate.[27] Compounds **24** and **25** also gave very similar UV spectra,[28] but the different intensities of the maxima at 310 and 299 nm, which were absent from the spectra of **25**, indicated that

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(21) Adams, R.; Pachter, I. J. *J. Am. Chem. Soc.* **1952**, *74*, 5491.
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(23) Clar, E. *Aromatic Sextet*; Wiley: New York, 1972.
(24) In the equilibrium mixture the proportion of the ring tautomer (**R**-I) decreases with decreasing pK_a value of the parent amine. pK_a values: 2-aminopyridine, 6.86; ethyl 2-aminopyridine-4-carboxylate, 4.73; 2-amino-5-chloropyridine, 4.83; 2-aminopyrimidine, 3.45; 2-aminopyrazine, 3.07. Perrin, D. D. In *Dissociation Constants of Organic Bases in Aqueous Solution*; Butterworths: London, 1965.
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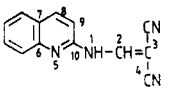
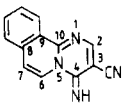
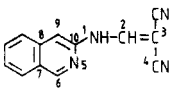
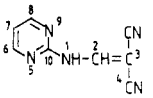
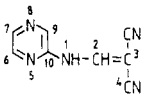
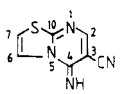
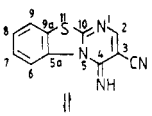
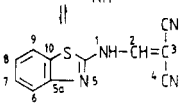
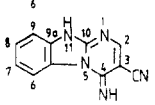
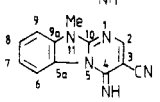
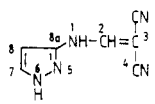
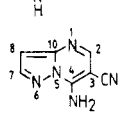
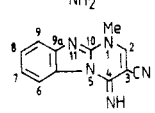
(27) Dunwell, D. W.; Ewans, D. *J. Chem. Soc., Perkin Trans. 1*, **1973**, 1588.
(28) UV (EtOH) (in nm). **24**: γ_{max} 368 (ε 5000), 350 (7700), 310 (6500), 299 (6700), 256 (30800). **25**: 370 (14000), 358 (18900), 256 (14000). **28**: 335 (9200), 275 (5200), 247 (10600).

Table VII. Characteristic NMR Data on 17–28 in Me_2SO-d_6 and Equilibrium Ring–Chain Tautomer Ratios at 30 °C

									tautomer ratio, %			
					δ				in $CDCl_3$		in Me_2SO-d_6	
cmpd	structure	2-H	6-H	NH	C-2	C-3	C-4	CN	R	C	R	C
17		8.93		11.93	153.3	56.0	115.9	113.5		100		100
18		8.41	9.02	7.95	154.2	93.3	152.2	115.9	100		100	
19		8.88	9.23	11.40	153.3	53.0	116.2	113.9		100		100
20		8.72	8.75	12.23	154.0	57.2	115.5	112.6	*a*			100
21		8.76	8.48	11.95	153.3	57.2	115.4	113.3	*a*			100
22		8.12	8.25	8.00	154.7	90.1	149.5	116.2	100		100	
23		8.14	9.38	8.20	153.6	94.1	153.4	115.4	100		70	
	⇌ 	8.57	7.96	*b*	158.1	59.8	115.4	113.4		0		30
24		8.52	8.58	8.92	156.6	*c*	151.1	116.2	*a*		100	
25		8.20	8.76	7.63	156.0	86.7	152.3	116.4	100		100	
26		8.33	12.68	11.32[d]	155.2	51.4	116.4	113.0	*a*			*e*
27		8.36		8.95	151.1	73.2	150.2	116.0	*a*		100	
28		8.51	8.58	8.27	147.1	83.1	150.6	115.2	100		100	

[a] Insoluble. [b] In exchange. [c] Could not be observed because of low intensity. [d] $J_{2\text{-H,NH}}$ = 13.7 Hz. [e] At ambient temperature the chain form is gradually converted to the ring form.

the tautomeric form **R-II** is also present as a minor component in the equilibrium mixture of **24**. As a consequence of protonation,[29] **24** and **25** gave very similar UV spectra.

In the case of the compound derived from 3-aminopyrazole, the lower solubility of the chain tautomer meant that it was possible to isolate both the chain form **26** and the ring form of type **R-II 27**, the latter containing an amino group (see Table I). On standing in Me_2SO-d_6 solution at room temperature, the chain tautomer **26** gradually transformed to the ring tautomer **27**. This cyclization followed first-order kinetics. The free energy of activation of cyclization was ΔG^*_{295} = 26.2 kcal/mol, as calculated from the rate constant $k_1 = 1.1 \times 10^{-7}$ s^{-1}. The chain form **26** also cyclized to give the ring form **27** on attempted crystallization from ethanol or during melting. The structure of the ring form was supported by comparison of the ^{13}C shifts with the literature data[30] and by the observation that the doublet–triplet signal of C(3) in the proton coupled spectrum ($^2J_{C(3),2\text{-H}}$ = 9.7 Hz and $^3J_{C(3),4\text{-NH}_2}$ = 4.5 Hz) collapsed to a doublet on addition of D_2O.

The Effects of Protonation on the Ring–Chain Tautomerism of Compounds 1, 2, and 9. In the UV

(29) UV (EtOH + 0.1 N HCl) (in nm). **24**: γ_{max} 348 sh (ε 10000), 338 (11300), 286 (4600), 256 (28000), 253 sh (27400), 229 (22000). **25**: 354 sh (8100), 344 (9400), 282 (4600), 259 (19000), 254 (18600), 230 (16200).

(30) Gonzalez, E.; Faure, R.; Vincent, E. J.; Espada, M.; Elquero, J. *Org. Magn. Reson.* **1979**, *12*, 587.

Table VIII. UV Data on Compounds 1, 2, 9, 29, and 30 in EtOH and 0.1 N HCl

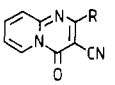
cmpd	solv	λ_{max}, nm (ϵ)
1	0.1 N HCl	358 (15100), 352 (13700), 310 (6000), 302 (5400), 252 sh (10100)
2	EtOH	394 (11840), 328 (7630), 274.5 (5720), 266 (6050)
	0.1 N HCl	355 (12900), 347 sh (11800), 309 (5000), 297 (4500), 260 (13000), 253 sh (10900)
9	0.1 N HCl	319 (12600), 312 sh (12200), 271 (5000), 266 sh (4200), 229 (5600)
29	EtOH	365 (15900), 359 sh (15500), 311 (3600), 301 sh (3400), 254 (8400), 247 (8200)
	0.1 N HCl	358 (16300), 350 sh (14900), 306 (4100), 297 sh (4000), 252 (9800), 247 sh (9200)
30	EtOH	356 (15200), 312 (8050), 299 sh (7300), 258 (10700), 251 (10000)
	0.1 N HCl	353 sh (3970), 331 (10900), 295 (5900), 287 sh (5200), 253 (9300), 247 sh (8110)

Table IX. Characteristic Chemical Shift Differences between Unprotonated (in $CDCl_3$) and Protonated Forms (in $CDCl_3$ + CF_3COOD) of Ring Tautomers[a]

cmpd	$\Delta\delta_{H-2}$	$\Delta\delta_{H-6}$	$\Delta\delta_{H-7}$	$\Delta\delta_{H-8}$	$\Delta\delta_{H-9}$
1	1.01	−0.24	0.84	0.70	0.81
2		−0.33	0.81	0.65	0.92

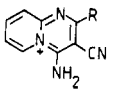
[a] $\Delta\delta = \delta_{CDCl_3 + CF_3COOD} - \delta_{CDCl_3}$.

spectra of the 4-imino-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbonitriles 1 and 2 in 0.1 N HCl, a hyperchromic effect and a hypsochromic shift of about 39 nm of the longest wavelength maximum can be observed relative to the spectra recorded in ethanol (see Tables II and VIII). Since shifts of this magnitude are unlikely to be caused by protonation at N(1),[31] it must be assumed that protonation affects the imino group. In the spectra of the 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbonitriles **29** and **30**,[13] the



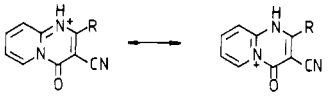
29 R = H
30 R = Me

same maximum is shifted by only 7 nm (see Table VIII). The 4-imino derivatives 1 and 2 are transformed by protonation to the 4-amino-3-cyanopyrido[1,2-*a*]pyrimidinum cation **31**, with an aromatic character.



31

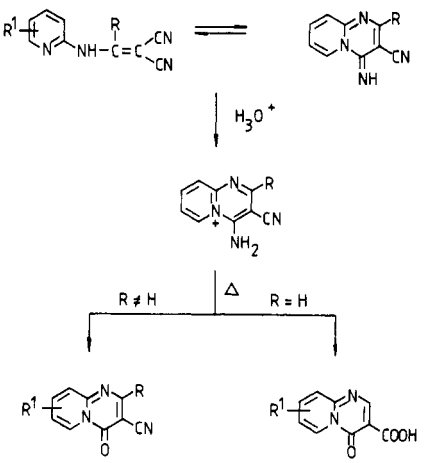
As with pyridine itself,[32] addition of TFA to the solution led to substantial paramagnetic shifts of the β and γ protons of the pyridine moiety in the ^1H NMR spectra of the 4-imino derivatives 1 and 2 (Table IX), which indicated that, on protonation at the imino group, the positive charge becomes localized on the N(5) atom. On protonation at N(1) in turn, the positive charge is distributed between N(1) and N(5).[33]



As a result of the combined action of protonation and transformation of the imino group to an amino group, the signal of the adjacent 6-H suffers a small upfield shift.

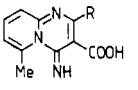
On protonation, the ring–chain equilibrium for compound 1 is shifted toward the ring form **31** (R = H), because this involves the formation of a pyrido[1,2-*a*]pyrimidinium cation with an aromatic character. Under similar conditions, the 6-methyl compound **9** still exists exclusively as the chain tautomer, owing to hindrance by the 6-methyl group.

Scheme III

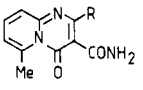


Thus, the cyclization of the 2-aminopyridine derivatives 1–8 in hydrochloric acid[13] may be interpreted in terms of the formation, on protonation, of the 4-aminopyrido[1,2-*a*]pyrimidinium form; on heating, hydrolysis of the 4-amino group gives rise to 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (Scheme III).

In compounds unsubstituted in position 2 (e.g., **1**), hydrolysis of the amino group is accompanied by hydrolysis of the 3-cyano function to a carboxyl group.[11,13] The 6-methyl derivatives, such as **9** and **10**, can be converted to pyrido[1,2-*a*]pyrimidines only under more energetic conditions, e.g., by heating in polyphosphoric acid;[13,34] in contrast to earlier data in the literature,[13] 4-imino-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acids (**32**) were not obtained, but the isomeric 4-oxo carboxamides **33** and **34** were. The products did not dissolve in alkali and could



32



33 R = H
34 R = Me

not be esterified with diazomethane. Compound **33**, obtained by cyclization of **9** in polyphosphoric acid, could be identified via the mixed melting point and the UV, IR, and ^1H NMR spectra with an amide prepared[35] from 6-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimdine-3-carboxylate with concentrated aqueous ammonia.

Experimental Section

Melting points were measured in capillaries and are uncorrected. Combustion analyses for C, H, and N gave results within 0.4% of theory. UV spectra were recorded on a UNICAM Sp-800 spectrophotometer. NMR spectra were recorded in the Fourier

(31) Horváth, G.; Kiss, Á. I.; Mészáros, Z.; Hermecz, I. *Acta Chim. Acad. Sci. Hung.* **1974**, *83*, 15.
(32) Jackman, L. M.; Sternhall, S. In *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*; Pergamon: Oxford, 1972; p 208.
(33) (a) Sasvári, K.; Csonka-Horvai, J.; Simon, K. *Acta Crystallogr., Sect B* **1972**, *28B*, 2405. (b) Sasvári, K.; Simon, K.; Mészáros Z.; Horváth, G.; Dvortsák, P. *Cryst. Struct. Commun.* **1976**, *5*, 611.
(34) Toyofuku, H.; Tachibana, K. Japan Kokai 77-48962, 1977; *Chem. Abstr.* **1977**, *87*, 1178954.
(35) Náray-Szabó, G.; Hermecz, I.; Mészáros, Z. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1753.

transform mode on a Bruker WP-80 spectrometer, with $SiMe_4$ as internal standard.

Ethyl 2-amino-3-pyridinecarboxylate,[36] ethyl 2-amino-4-pyridinecarboxylate,[37] ethyl 2-amino-5-pyridinecarboxylate,[38] ethyl 2-amino-6-pyridinecarboxylate,[39] 2-aminoquinoline,[40] 1-aminoisoquinoline,[40] 3-aminoisoquinoline,[41] 2-amino-1-methylbenzimidazole,[42] (ethoxymethylene)malononitrile,[43] (1-ethoxyethylidene)malonitrile,[43] and (1-ethoxybenzylidine)malonitrile[43] were prepared by the literature methods.

Method A. The heteroaromatic amine was allowed to react with 1 mol equiv of (ethoxymethylene)malononitrile in ethanol. Reaction temperatures and times are given in Table I. The precipitated product was filtered off and washed with ethanol. Solvents for recrystallization, yields, and melting points are given in Table I.

Starting from ethyl 2-amino-3-pyridinecarboxylate, a crystalline precipitate was obtained in 14% yield, from which compound **11** was isolated by means of preparative thin-layer chromatography using Kieselgel PF_{254} plates (Merck) and benzene–methanol (4:1) as eluent. Compound **13** was also purified by preparative TLC as for compound **11**.

Method B. 2-Aminopyridine or 2-amino-6-methylpyridine (10 mmol) was reacted with (1-ethoxyethylidene)- or (*1*-ethoxybenzylidene)malononitrile (10 mmol) at 120 °C for 10 min. The reaction mixture was then treated with ethanol (20 mL). After cooling to 0 °C, the precipitated product was filtered off and recrystallized (see Table I).

Method C. A mixture of the aminoheterocycle (10 mmol), malononitrile (10 mmol), and triethyl orthoformate, triethyl orthoacetate, triethyl orthopropionate, or triethyl orthobutyrate (11 mmol) was heated at 110 °C for 10 min. After cooling to ambient temperature, the reaction mixture was treated with ethanol (20 mL), and the crystals were filtered off and recrystallized (see Table I).

1-Methyl-4-imino-4*H*-pyrimido[1,2-*a*]benzimidazole-3-carbonitrile (28). To a suspension of 4-imino-4*H*-pyrimido[1,2-*a*]benzimidazole-3-carbonitrile (**24**) (1 g, 4.6 mmol) and potassium carbonate (2.0 g) in dimethylformamide (80 mL) was added methyl iodide (10 mL). The reaction mixture was stirred at ambient temperature for 1 h. The clear reaction solution was then evaporated to dryness in vacuo. The residue was treated with ethanol. The filtered crystals were recrystallized from propanol to give 0.7 g (65.5%) of a ca. 1:1 mixture of compounds **25** and **28**. Compound **28** was isolated by means of preparative thin-layer chromatography using Kieselgel PF_{254} plates (Merck) and chloroform–carbon tetrachloride–methanol (40:25:5) as eluent.

4-Oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbonitrile (29). 4-Oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide (7 g, 37 mmol), prepared from ethyl 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate[44] with 1:1 aqueous ammonium hydroxide and ethanol in a yield of 73%, mp 268–269 °C (DMF), was dehydrated with phosphoryl chloride (7 mL) in dimethylformamide by heating at 60 °C for 1 h and at 100 °C for 1 h. The cooled reaction mixture was poured onto crushed ice, and the pH of the aqueous phase was adjusted to 8 with 10% Na_2CO_3 solution. The precipitated crystals were filtered off and recrystallized from ethanol to give **29**, yield 16.6%, mp 216–218 °C.

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Registry No. **1C**, 51991-83-4; **1R-I**, 51991-96-9; **2R-I**, 102781-15-7; **3R-I**, 102781-16-8; **4R-I**, 102781-17-9; **5R-I**, 102781-18-0; **6R-I**, 102781-19-1; **7R-I**, 102781-20-4; **8C**, 51991-86-7; **8R-I**, 102781-21-5; **9C**, 51991-87-8; **10C**, 64500-78-3; **11C**, 102781-22-6; **12C**, 102781-33-9; **12R-I**, 102781-23-7; **13C**, 102781-34-0; **13R-I**, 102781-24-8; **14C**, 102807-70-5; **15C**, 102781-25-9; **15R-I**, 102781-35-1; **16C**, 102781-26-0; **16R-I**, 102781-36-2; **17**, 51991-91-4; **18**, 102781-27-1; **19**, 102781-28-2; **20**, 51991-88-9; **21**, 51991-89-0; **22**, 102781-29-3; **23**, 21787-04-2; **24**, 102781-30-6; **25**, 102781-31-7; **26**, 102781-32-8; **27**, 89975-57-5; **28**, 102781-37-3; **29**, 69372-04-9; 2-aminopyridine, 504-29-0; 2-amino-3-methylpyridine, 1603-40-3; 2-amino-4-methylpyridine, 695-34-1; 2-amino-5-methylpyridine, 1603-41-4; 2-amino-6-methylpyridine, 1824-81-3; ethyl 2-amino-3-pyridinecarboxylate, 13362-26-0; ethyl 2-amino-4-pyridinecarboxylate, 13362-30-6; ethyl 2-amino-5-pyridinecarboxylate, 39658-41-8; ethyl 2-amino-6-pyridinecarboxylate, 69142-64-9; 2-amino-5-chloropyridine, 1072-98-6; 2-amino-5-bromopyridine, 1072-97-5; 2-aminoquinoline, 580-22-3; 1-aminoisoquinoline, 1532-84-9; 3-aminoisoquinoline, 25475-67-6; 2-aminopyrimidine, 109-12-6; 2-aminopyrazine, 5049-61-6; 2-aminothiazole, 96-50-4; 2-aminobenzthiazole, 136-95-8; 2-aminobenzimidazole, 934-32-7; 2-amino-1-methylbenzimidazole, 1622-57-7; 3-aminopyrazole, 1820-80-0; (ethoxymethylene)-malononitrile, 123-06-8; (1-ethoxyethylidene)malononitrile, 5417-82-3; (1-ethoxybenzylidene)malononitrile, 60776-91-2; 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide, 33359-76-1; ethyl 4-oxo-pyrido[1,2-*a*]pyrimidine-3-carboxylate, 32092-18-5.

Supplementary Material Available: A detailed description of UV data in EtOH, $CHCl_3$, and Me_2SO (Table X), ^1H NMR data in $CDCl_3$ and Me_2SO-d_6 (Tables XI and XII), coupling constants (Table XIII), and ^{13}C NMR data in $CDCl_3$ and Me_2SO-d_6 (Tables XIV and XV) for compounds 1–28 and analytical data for all new compounds (Table XVI) (12 pages). Ordering information is given on any current masthead page.

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