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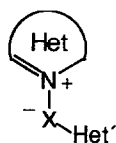
Azinium-N-(2'-azinyl)aminides: Synthesis, Structure and Reactivity

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Abstract: Several azinium-N-(2'-azinyl)aminides are reported. The structure of pyridinium-N-(2'-pyridyl)aminide has been studied, both in solution and in crystalline state, and results have been compared. In non-polar solvents, the aminides present a planar conformation stabilized by an intramolecular hydrogen bond. The reactivity toward electrophiles confirms the structural data, producing either N- or C- substitutions under mild conditions.

As the body of knowledge about the reactivity of azinium *N*-ylides expands,¹⁻³ the interest in such compounds as building blocks for the synthesis of heterocyclic derivatives continuously increases. Some of our work in this field has been concerned with the synthesis of heteroaryl-stabilized cycloiminium ylides **Ia** as a way of producing highly stable dipoles with heterocyclic moieties of unusual reactivity.⁴ While N-(heteroarylmethyl)azinium ylides **Ia** are in general unstable species⁵ which should be trapped with electrophiles, aminides **Ib** are more stable and easy to isolate.^{3,6}



Ia: X=CH

Ib: X=N

In this paper we report the results obtained in the synthesis and structural study of some aminides **Ib** (Het = pyridinium or isoquinolinium; Het' = pyridine, quinoline and diazines).

RESULTS AND DISCUSSION

Synthesis. The preparation of compound **3** was performed using Zincke salts⁷ as starting materials, through an ANRORC mechanism, as reported by Beyer,⁸ (Scheme 1). The reaction of the pyridinium salts **1** with 2-hidrazinoazines, produced the hydrazones **2**, which were cyclized by heating in acetic acid, to yield the azinium salts **3a-f**. The alternative cyclization in dioxane, as described by Knaus,⁹ produced lower yields, and was thus abandoned. Finally, the salts **3** were converted into the aminides **4** by treatment with potassium carbonate. Yields are described in Table 1.

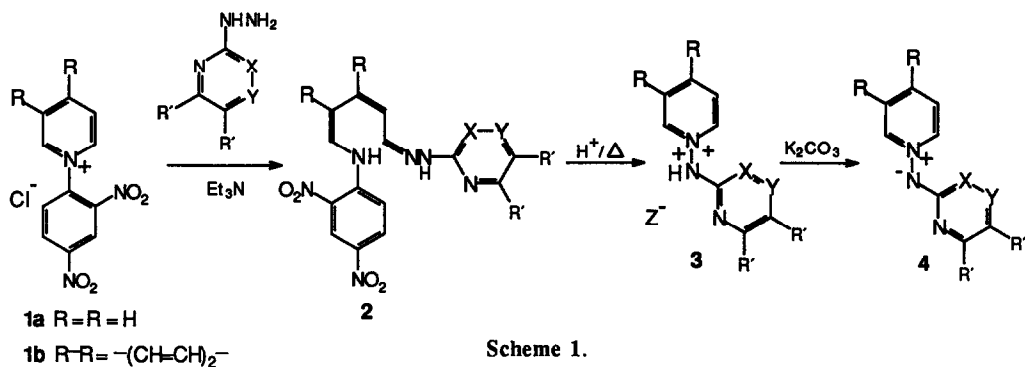


Table 1. Physical data of *N*-(2'-heteroarylamino)azinium salts **3** and the corresponding *N*-aminides **4**.

R	R R'	R' X Y	Comp.	Yield ^a (%)	mp ^b (°C)	Comp.	Yield ^a (%)	mp (°C)
H	H H	H CH CH	3a^c	70	223-4	4a	90	115-6 ^d
H	H	-(CH=CH) ₂ - CH CH	3b^c	82	235-6	4b	96	92-4 ^e
H	H H	H N CH	3c	74	231-3	4c	97	150-2 ^e
H	H H	H CH N	3d	67	198-9	4d	96	157-9 ^e
-(CH=CH) ₂ -	H	H CH CH	3e^c	66	205-6	4e^c	90	106-7 ^b
-(CH=CH) ₂ -	-(CH=CH) ₂ -	CH CH	3f	78	161-2	4f	92	111-3 ^e

^aYields were not optimized. ^b From abs. ethanol. ^c Described in ref. 8. ^d From hexane. ^e From ethyl acetate.

NMR Data. ¹H NMR spectra of the *N*-(2'-azinylamino)pyridinium and isoquinolinium salts **3**, presented two clearly differentiated sets of signals, one low-field resonance due to the cationic moiety (9.1-8.2 ppm for derivatives **3a-d** and 10.2-8.5 ppm for the isoquinolinium compounds **3e,f**) and another, more shielded resonance from the 2-azinylamino fragment (6.8-8.5 ppm). ¹H NMR data of compounds **3** and **4** are described in Tables 2, 3. As expected, when betaines **4** were obtained, chemical shifts (in DMSO-*d*₆) of most of the azinium protons moved upfield with respect to their precursors **3**. The effect, however, was not observed for H2(6) in the pyridinium series, and for H1 in the isoquinolinium derivatives. These protons were only slightly shifted upfield or, in some cases, appeared at even lower fields than in the precursors **3**. Chemical shifts of these *alpha*-protons were also affected by the solvent as is shown in Table

Table 2.- ¹H NMR spectral data of *N*-(2'-azinylamino)pyridinium salts **3a-d** and the aminides **4a-d** (DMSO-*d*₆)

Comp.	H2(6)	H4	H3(5)	Others
3a	9.14 (d, 5.7)	8.69 (t, 7.8)	8.27 (t, 7.3)	6.8-6.9(m, 2H, H3'+H5'); 7.78(brt, 1H, J=7.5, H4'), 7.97(d, 1H, J=4.9, H6')
3b	9.03 (d, 5.7)	8.54 (t, 7.7)	8.21 (t, 7.2)	6.5-6.6(m, 1H, H3'); 7.26(brt, 1H, J=7.9, H6') 7.5-7.6(m, 2H, H7', H8'); 7.73(d, 1H, J=7.7, H5'), 8.0(d, 1H, J=9.6, H4')
3c	9.12 (brd, 5.5)	8.64 (brt, 7.7)	8.21 (brt, 6.5)	6.96(t, 1H, J=5.0, H5'); 8.47(d, 2H, J=5.0, H4', H6')
3d	9.18 (brd, 5.6)	8.76 (brt, 7.8)	8.1-8.5 (m)*	8.1-8.5(m, 5H, H3(5), H3', H5', H6')*
4a	8.98-9.03 (m)	7.6-7.7 (m)	7.6-7.7 (m)	6.28(dd, 1H, J=6.3 and 5.4, H5'); 6.34(dd, 1H, J=8.3 and 1.0, H3'); 7.25(ddd, 1H, J=8.3, 6.8 and 2.0, H4'), 7.70(ddd, 1H, J=5.0, 1.9 and 0.8, H6')
4b	9.2-9.4 (m)	8.29 (t, 7.6)	8.05 (t, 7.1)	6.61(d, 1H, J=9.4, H3'); 7.16(t, 1H, J=7.3, H6'), 7.40 (d, 1H, J=8.2, H8'); 7.49(t, 1H, J=7.6, H7'), 7.64(d, 1H, J=7.5, H5'); 7.88(d, 1H, J=9.4, H4')
4c	8.75 (d, 6.5)	8.07 (t, 7.5)*	7.82 (t, 7.0)	6.26(t, 1H, J=4.6, H5'); 8.04(d, 2H, J=4.6, H4', H6')*
4d	8.95 (d, 6.0)	7.93 (t, 7.4)	7.77 (t, 6.7)*	7.35(d, 1H, J=2.9, H6'); 7.53(dd, 1H, J=2.9 and 1.5, H5'), 6.74(d, 1H, J=1.5, H3')*

Table 3.- ¹H NMR spectral data of *N*-(2'-azinylamino)isoquinolinium salts **3e,f** and the aminides **4e,f** (DMSO-*d*₆)

Comp.	H1	H3	H4	H8	H5	H6	H7	Others
3e	10.24 (brs)	8.81 (dd)	8.69 (d)	8.57 (d)	8.42 (d)	8.30 (t)	8.10 (t)	6.92(t,1H,J=6.4,H5'), 7.00(d,1H,J=7.8 H3'), 7.78(ddd,1H, J=8.1,7.3 and 1.6 H4'), 7.95(brd, 1H, J=4.4, H6')
3f	10.05 (brs)	8.81 (dd)	8.65 (d)	8.45 (d)	8.38 (d)	8.20 (t)	8.04 (t)*	6.7-6.8(m,1H,H3'), 7.2-7.3(m,1H, H6'), 7.5-7.6(m,2H,H7'+H8'), 7.73 (d, 1H,J=7.8,H5'); 7.99(d,1H,J=9.3,H4')*
4e	10.56 (brs)	8.39 (dd)	7.98 (d)*	8.02 (d)*	7.99 (d)*	7.7-7.75 (m)	7.7-7.75 (m)	6.41(ddd,1H,J=6.7,5.2 and 1.3,H5') 6.51(d,1H,J=8.5,H3'); 7.34(ddd, 1H, J=8.6,6.8 and 1.9,H4'); 7.87(dd,1H, J=5.1 and 1.9, H6')
4f	11.05 (brs)	8.53 (dd)	8.10 (d)	8.21 (dd)	8.07 (d)	7.8-7.9 (m)	7.8-7.9 (m)	6.76(d,1H,J=9.0,H3'); 7.04(ddd,1H, J=7.9,5.3 and 2.6,H6'); 7.35-7.4(m, 2H,H7'+H8'), 7.53(d,1H,J=7.6,H5'); 7.75 (d,1H,J=9.0, H4')

(*) Partially overlapped signals.

4 for 4a. When CD₃OD was used, H2(6) resonances appeared at higher fields ($\Delta\delta \approx 0.3$ ppm) than in CDCl₃ or DMSO-d₆ solutions. The effect was more dramatic in the isoquinolinium betaine 4e, where H1 resonance was shifted towards an even higher field in CD₃OD compared with DMSO-d₆ ($\Delta\delta = 1.0$ ppm).

Table 4. Solvent effects of the ¹H-NMR Spectral Data of Pyridinium N-(2'-Pyridyl)aminide 4a.

Solvent	H2(6)	H4	H3(5)	H6'	H4'	H3'	H5'
DMSO-d ₆	9.00	7.65*	7.65*	7.70	7.25	6.34	6.28
DCCl ₃	9.09	7.35*	7.35*	7.90	7.35*	6.60	6.46
CD ₃ OD	8.70	8.00	7.77	7.63	7.35	6.49	6.37

(*) Partially overlapped signals.

When a solution of 4a in CD₃OD was allowed to stand at 20 °C for two months (Fig. 1), nearly complete exchange of H2(6) protons of the pyridinium ring was observed. Similar results were seen with 4e, where the H1 singlet disappeared after 15 days. No deuterium exchange was detected in the salts 3a and 3e.

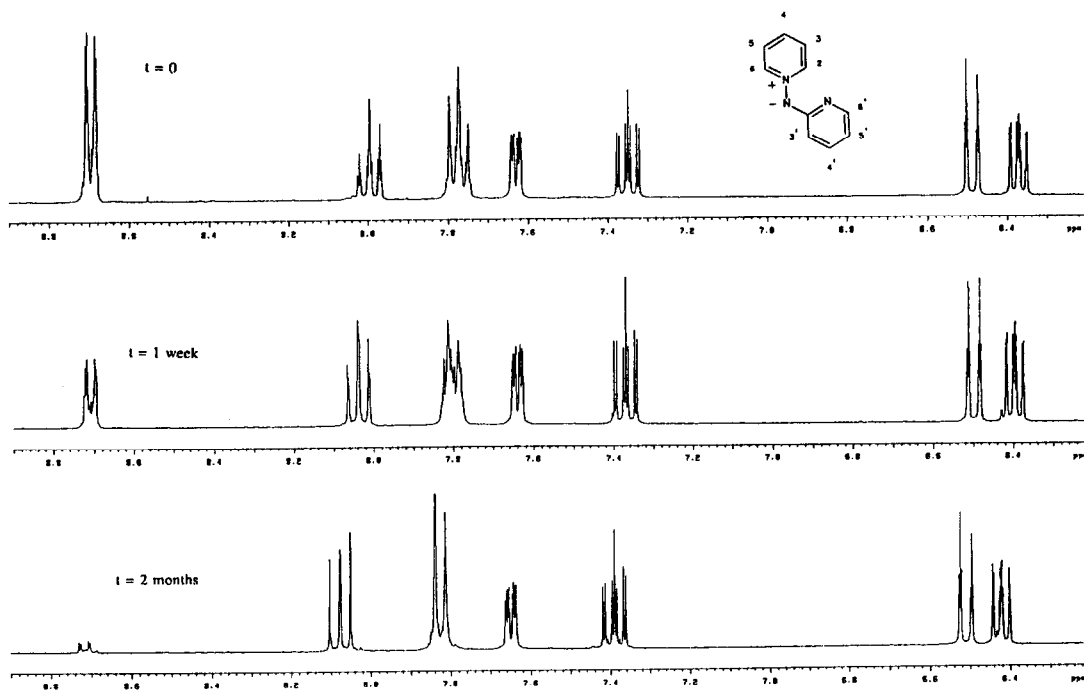
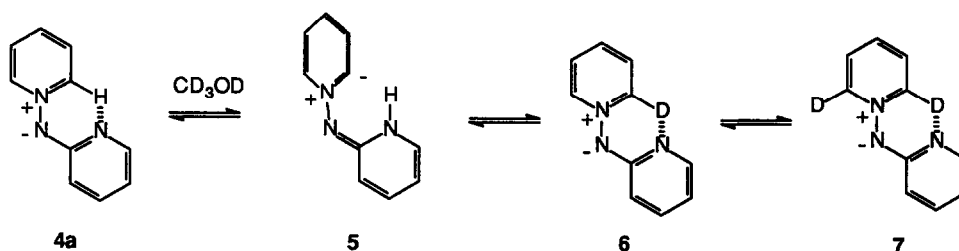


Figure 1. Time dependent ¹H NMR CD₃OD spectra of 4a

These spectroscopic observations suggested the existence of a hydrogen bond between the proton in the *alpha*-position of the pyridinium ring, the more acidic hydrogen, and the nitrogen of the 2'-pyridylimino moiety, as indicated in Scheme 2. The deuteration process can be rationalized from the ylide structure 5, which is likely to be produced in a protic solvent such as methanol. A similar type of hydrogen bond has recently been reported¹⁰ for pyridinium derivatives. These results suggest planar structures for compounds 4 in aprotic solvent solutions.



Scheme 2. Proposed deuterium-exchange mechanism of 4a

X-Ray Data. The molecular structure of pyridinium *N*-(2'-pyridyl)aminide 4a was determined by single crystal X-ray diffraction analysis. Figure 2 shows the perspective diagram of the product with the corresponding atomic numbering. The torsion angle C5-N1-N3-C6 between both pyridine moieties (65.7°) is a relevant structural parameter (further details are provided in Tables 5-8), showing that the proposed hydrogen bond does not exist in the crystalline state. The unit cell (Fig. 3) shows a head-to-tail interaction between molecules.

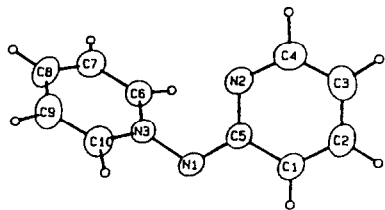


Figure 2. X-ray structure of *N*-(2'-pyridylimino)-pyridinium aminide (4a) with atomic numbering.

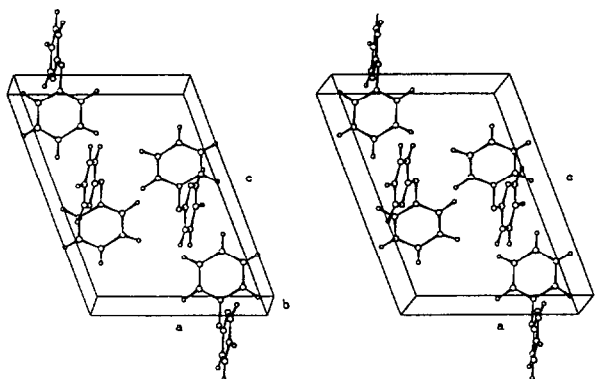


Figure 3. Crystal packing of neighbour molecules of 4a in the unit cell. For clarity only four molecules have been depicted.

Table 5. Structure of compound 4a. Positional Parameters and $B_{eq}(\text{Å}^2)$ values.

Atom	x	y	z	B
N1	0.7013(3)	0.1001(4)	-0.0534(2)	3.75(6)
N2	0.7980(3)	-0.1686(4)	0.0303(2)	3.79(6)
N3	0.7577(3)	0.1632(3)	0.0557(2)	2.99(5)
C1	0.7013(3)	-0.1468(5)	-0.1669(2)	3.27(7)
C2	0.6904(4)	-0.3209(5)	-0.1790(3)	4.04(8)
C3	0.7608(5)	-0.4216(5)	-0.0862(3)	5.30(1)
C4	0.8110(5)	-0.3396(5)	0.0143(3)	5.30(1)
C5	0.7279(3)	-0.0713(4)	-0.0599(2)	2.79(6)
C6	0.9070(3)	0.1679(5)	0.1128(3)	3.34(7)
C7	0.9577(4)	0.2368(5)	0.2177(3)	3.63(7)
C8	0.8589(4)	0.3040(5)	0.2643(3)	3.89(8)
C9	0.7079(4)	0.3008(5)	0.2043(3)	4.34(8)
C10	0.6586(3)	0.2306(5)	0.0998(3)	3.79(7)
H1	0.619 (3)	-0.078 (4)	-0.229 (2)	1.7 (7)
H2	0.650 (3)	-0.371 (5)	-0.255 (2)	2.0 (8)
H3	0.790 (4)	-0.546 (5)	-0.090 (3)	4.0 (1)
H4	0.881 (4)	-0.403 (5)	0.084 (3)	4.0 (1)
H6	0.975 (3)	0.120 (4)	0.072 (2)	1.5 (7)
H7	1.055 (3)	0.235 (4)	0.254 (2)	1.6 (7)
H8	0.897 (3)	0.347 (4)	0.338 (2)	1.3 (7)
H9	0.631 (3)	0.348 (5)	0.232 (3)	2.1 (8)
H10	0.548 (3)	0.222 (4)	0.051 (2)	1.4 (7)

Hydrogen atoms were refined isotropically. Anisotropically refined atoms are given in the form of isotropic equivalent displacement parameter defined as:
 $B = (4/3)[a^2B(1,1)+b^2B(2,2)+c^2B(3,3)+ab(\cos\gamma)B(1,2)+ac(\cos\beta)B(1,3)+bc(\cos\alpha)B(2,3)]$.

Table 6. Structure of Compound 4a. Bond distances (Å).

N1 - N3	1.405(3)	C4 - H4	1.031(3)
N1 - C5	1.354(4)	N2 - C5	1.351(4)
C1 - C2	1.367(5)	C6 - C7	1.374(4)
C1 - C5	1.419(4)	C6 - H6	1.022(4)
C1 - H1	0.964(3)	C7 - C8	1.369(5)
N3 - C6	1.357(4)	C7 - H7	0.881(3)
N3 - C10	1.352(5)	C8 - C9	1.377(4)
C2 - C3	1.390(5)	C8 - H8	0.952(3)
C2 - H2	1.000(3)	C9 - C10	1.373(5)
C3 - C4	1.368(5)	C9 - H9	0.983(4)
C3 - H3	1.012(4)	C10 - H10	1.021(3)
C4 - N2	1.348(5)		

Table 7. Structure of compound 4a. Torsion Angles (°).

C5-N1-N3-C6	65.7(4)	C6-N3-C10-C9	-1.7(5)
C5-N1-N2-C10	-118.8(3)	C1-C2-C3-C4	-0.1(6)
N3-N1-C5-C1	179.6(3)	C2-C3-C4-N2	-0.2(7)
N3-N1-C5-N2	1.7(4)	C3-C4-N2-C5	1.0(7)
C5-C1-C2-C3	-0.4(5)	C4-N2-C5-N1	176.5(4)
C2-C1-C5-N1	-176.8(3)	C4-N2-C5-C1	-1.5(5)
C2-C1-C5-N2	1.3(5)	N3-C6-C7-C8	-1.3(5)
N1-N3-C6-C7	177.5(3)	C6-C7-C8-C9	0.2(5)
C10-N3-C6-C7	2.1(5)	N1-N3-C10-C9	-177.3(3)
C7-C8-C9-C10	0.2(6)	C8-C9-C10-N3	0.5(6)

Table 8. Structure of Compound 4a. Bond Angles (°).

N3 - N1 - C5	112.5(2)	N1 - C5 - H3	122.6(3)
C2 - C1 - C5	119.7(2)	C1 - C5 - N2	120.8(3)
C2 - C1 - H1	120.0(2)	N3 - C6 - C7	119.8(4)
C5 - C1 - H1	120.0(2)	N3 - C6 - H6	116.0(1)
N1 - N3 - C6	121.7(2)	C7 - C6 - H6	124.0(1)
N1 - N3 - C10	117.6(2)	C6 - C7 - C8	120.5(3)
C6 - N3 - C10	120.5(3)	C6 - C7 - H7	118.0(2)
C1 - C2 - C3	119.5(3)	C8 - C7 - H7	121.0(2)
C1 - C2 - H2	118.0(2)	C7 - C8 - C9	118.9(3)
C3 - C2 - H2	122.0(2)	C7 - C8 - H8	118.0(2)
C2 - C3 - C4	117.5(3)	C9 - C8 - H8	123.0(2)
C2 - C3 - H3	124.0(2)	C8 - C9 - C10	120.1(4)
C4 - C3 - H3	118.0(2)	C8 - C9 - H9	123.0(2)
C3 - C4 - N2	125.1(3)	C10 - C9 - H9	117.0(2)
C3 - C4 - H4	121.0(2)	N3 - C10 - C9	120.2(3)
N2 - C4 - H4	113.0(2)	N3 - C10 - H10	115.0(2)
C4 - N2 - C5	117.3(3)	C9 - C10 - H10	124.0(2)
N1 - C5 - C1	116.5(2)		

Theoretical study. The semiempirical molecular orbital program MOPAC (version 6.0,¹¹) was used with AM1¹² parametrization to optimize all the geometrical variables of the X-ray structure of 4a, which were specified in internal coordinates. The eigenvector following routine¹³ (keyword EF) and a step-size of 0.05 (Å or radians) allowed full geometry optimization to a gradient norm of 0.01 kcal/mole. The main geometrical difference between the crystal structure and the optimized one is the dihedral angle around the N1-N3 bond. It was found to be $\pm 65.7^\circ$ in the crystal, and nearly 0° in the MOPAC optimized structure.

In order to account for this discrepancy, the dependence of both the intramolecular energy and the dipole moment on the rotation about the N1-N3 bond of compound 4a was studied. The dihedral space for this torsional angle was divided into 10° intervals and the remaining geometrical variables were fully optimized as before. As indicated by the energy diagram in Figure 4, the planar structure is energetically favoured over all others, either in vacuum or in solution, and specially in non polar solvents. The change

in dipole moment parallels the calculated change in energy¹¹.

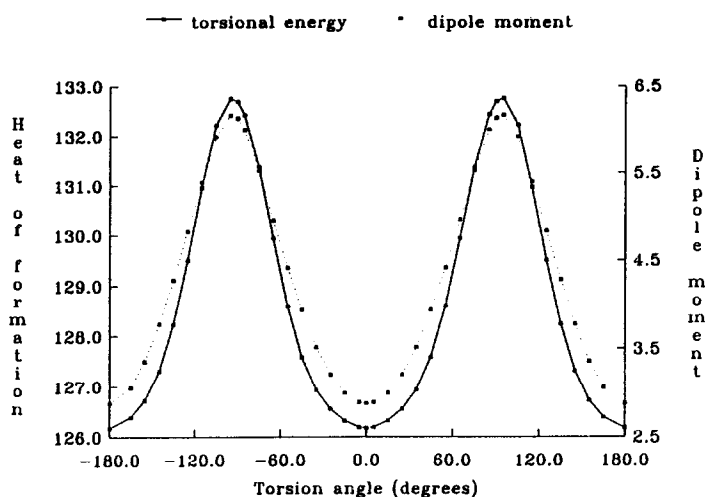


Figure 4. AM1 heat of formation and dipole moment of 4a

In the crystal packing arrangement (Figure 3), clear head-to-tail interactions are present between the pyridinium and pyridine rings of two neighbouring molecules of 4a in the solid state. Superimposition of the corresponding calculated dipole moment vectors on two interacting molecules provides a visual

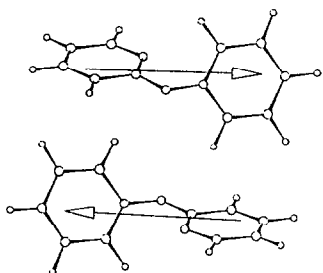


Figure 5. Schematic representation of the dipole moment vectors of two adjacent molecules of 4a, as seen in the crystal structure.

explanation of why the preferred conformation in the crystal is not the planar structure predicted by the calculations and implied by experimental observations in solution: rotation of the 2'-pyridylimino moiety around the N1-N3 bond from 0° to 65.7°, costing about 4 kcal/mole, is accompanied by an increase in dipole moment of more than 2 D (Figure 4), giving rise to a highly favourable dipole-dipole interaction between adjacent molecules in the crystal (Figure 5). Thus, in the crystalline state, the gain in intermolecular association energy apparently offsets the loss of intramolecular stabilization represented by the out of plane conformation of

the pyridine rings. In isolated molecules, the coplanar structure, in addition to having a more efficient intramolecular interaction between the two oppositely charged π systems, has a hydrogen bond between C6-H (*alpha* to the pyridinium N atom) and the 2-pyridyl nitrogen. The semiempirical calculations described yield a bond order for C6-H of 0.9076 vs. 0.9279 for the equivalent C10-H bond. This is

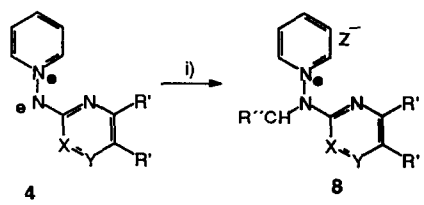
reflected in a longer bond length (1.1084 vs. 1.1063 Å). The magnitude of this hydrogen bond can be measured as the sum of electronic and nuclear energies between the two atoms (-0.0502 eV).

Reactivity.

The structural conclusions above described suggested an interesting reactivity of the aminides **4** against electrophiles in two alternative ways: by substitution of the aminide nitrogen, which would be regioselective by the partial blockage of the azine nitrogen via hydrogen bond, or by substitution of the azine ring which would behave as an electron-rich system, thus giving C-substitution under mild conditions.

C-Electrophiles. The alkylation of *N*'-substituted iminoazinium betaines is highly dependent on the *N*-substituent.¹ The alkylation of aminides **4** could take place in both imino or azine nitrogens. However, when the process was performed on **4** with methyl iodide or benzyl chloride, only the *N*-amino pyridinium salts **8** were obtained (Table 9). To test the regioselectivity of the alkylation process, the alternative **4a** regioisomer as *N*-methylpyridyl **9** was obtained by reaction of *N*-aminopyridinium iodide with 2-chloro-1-

Table 9. *N*'-substituted azinium salts **8**

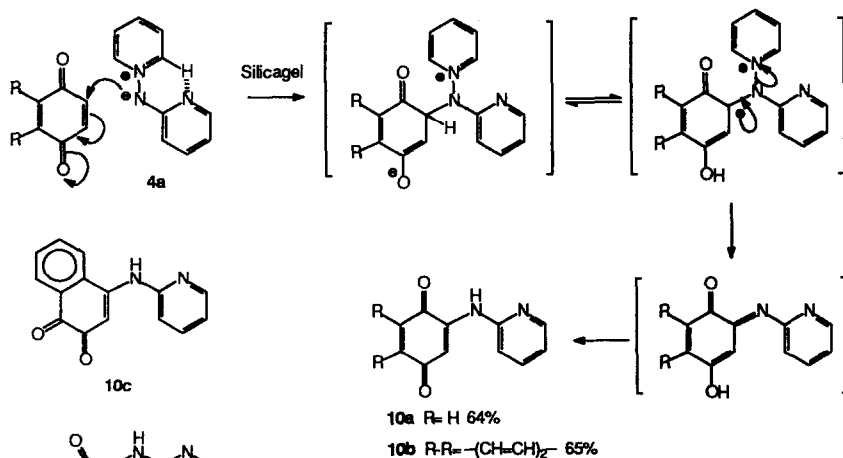


Comp	R'	R'	X	Y	R''	Yield(%)	Mp(°C)
8a	H	H	CH	CH	H	75	146-8
8b	-(CH=CH) ₂ -	CH	CH	H	H	71	177-9
8c	H	H	N	CH	H	60	152-4
8d	H	H	CH	N	H	60	148-9
8e	H	H	CH	CH	Ph	82	132-3

i) For compounds **8a-d**: MeI / acetone, r.t.
For compound **8e**: PhCH₂Cl / Toluene, Δ

methylpyridinium iodide in the presence of base. When **8a** was obtained, no traces of **9** were detected.

The reaction of heteroaromatic *N*-imines with α,β -unsaturated carbonyl derivatives is a common



Scheme 3

process usually yielding cycloaddition products.³ Typical dipolarophiles were tested toward N-(2'-pyridyl-imino)pyridinium betaine **4a** with no success, probably due to the stability of the dipole. By contrast, an alternative Michael process, similar to the one described by Sasaki *et al.*¹⁴ was successfully applied, using silica gel as acid catalyst, and producing in one step, the substituted 2-aminopyridines **10a-b** (Scheme 3). Reaction with 1,2-naphthoquinone and N-phenylmaleimide produced, in a similar way, **10c** and **11**.

X-Electrophiles

Nitration: Electrophilic aromatic nitration of N-(*o*- or *p*-nitrophenylimino)pyridinium betaines has been reported¹⁵ to produce, depending on the reaction conditions, different polynitro derivatives. When pyridinium N-(2'-pyridyl)aminide **4a** was nitrated with a mixture (1:1 v/v) of concentrated nitric and sulfuric acids, a mixture of pyridinium N-[2'-(5'-nitropyridyl)] and N-[2'-(3',5'-dinitropyridyl)]aminides **12a** and **13a** was obtained (after neutralization), the former being the main product (25%) (Table 10).

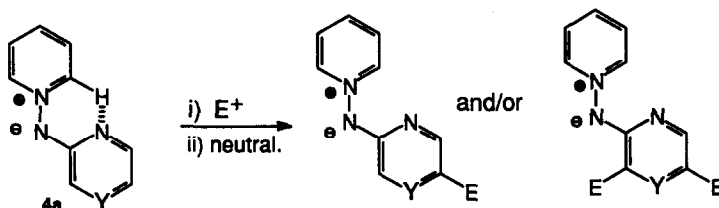


Table 10. Physical data of C-substituted Pyridinium N-(2'-heteroaryl)aminides **12** and **13**

Y	E	Comp. ^a	Yield ^b (%)	mp(°C)	Comp. ^a	Yield ^b (%)	mp(°C)
CH	NO ₂	12a ^c	25	216-8	13a ^c	20	190-2
CH	Br	12b ^d	50	125-8	13b ^{d,e}	14(75)	140-2
CH	I	12c ^d	61	132-5	13c ^e	70	110-11
CH	PhN ₂	12d ^c	50	134-6			
N	PhN ₂	12e ^c	45	173-5			

^aSatisfactory analytical data ($\pm 0.4\%$ for C, H, N) were obtained for all new compounds.

^bYields were not optimized. ^c For nitration: Conc. H₂SO₄ and HNO₃, r.t. For diazo coupling: PhN₂⁺, Cl⁻/HCl, 5 °C ^d Equimolar amount of bromine or iodine in Cl₂CH₂, r.t. ^e Three molar excess of bromine or iodine, K₂CO₃ (excess), Cl₂CH₂, r.t.

Halogenation: When the pyridinium N-(2'-pyridyl)aminide **4a** was treated with an equimolar amount of bromine, in dichloromethane at room temperature, electrophilic aromatic substitution took place and a

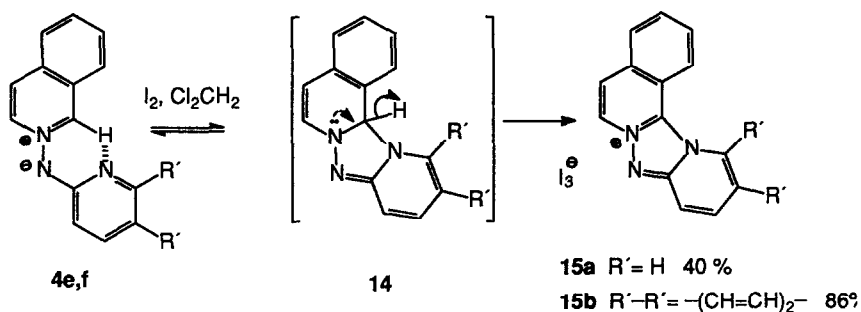
Table 11.- ¹H NMR spectral data of *N*-(2'-azinylamino)pyridinium derivatives 8-13 (DMSO-d₆)

Comp.	H2(6)	H4	H3(5)	Others
8a	9.37 (dd, 6.8,1.3)	8.80 (tt, 7.8,1.3)	8.34 (dd, 7.8,6.8)	3.75(s, 3H, Me); 7.09(dd, 1H, J=7.3 and 4.3, H5'), 7.18(d, 1H, J=8.3, H3'); 7.89 (ddd, 1H, J=7.9, 7.1 and 1.7 H4'); 8.11(ddd, 1H, J=5.0, 1.8 and 0.9, H6')
8b	9.45 (dd, 7.3,1.3)	8.87 (tt, 7.8,1.3)	8.46 (dd, 7.3,6.7)	3.91 (s, 3H, Me); 7.42 (d, 1H, J=9.0, H3'); 7.4-7.5 (m, 2H, H6', H8'); 7.63(ddd, 1H, J=7.0, 7.0 and 1.5, H7'); 7.93 (dd, 1H, J=8.1 and 1.6, H5'); 8.16(d, 1H, J=8.8, H4')
8c	9.41 (dd, 6.7,1.4)	8.85 (tt, 7.8,1.3)	8.59 (dd, 7.6,6.8)	3.84(s, 3H, Me); 7.16(t, 1H, J=4.8, H5'); 8.37(d, 2H, J=4.8, H4'+H6')
8d	9.40 (dd, 6.8,1.4)	8.83 (tt, 7.8,1.3)	8.38 (dd, 7.6,6.8)	3.85(s, 3H, Me); 8.17(dd, 1H, J=2.7 and 1.5, H'); 8.34(d, 1H, J=2.7, H6'); 8.68(d, 1H, J=1.6, H3')
8e	9.36 (dd, 6.7,1.3)	8.71 (tt, 7.8,1.3)	8.23 (dd, 7.8,6.7)	5.41(s, 2H, CH ₂ Ph), 7.14(dd, 1H, J=7.3 and 4.9, H5'); 7.27(d, J=8.5, H3'); 7.3-7.35(m, 3H, Ph); 7.35-7.4(m, 2H, Ph); 7.90(ddd, 1H, J=7.7,6.7 and 1.7, H4'); 8.17(ddd, 1H, J=4.9,1.8 and 0.6, H6')
12a	8.76 (dd, 6.8,1.3)	8.23 (tt, 7.7,1.3)	7.94 (dd, 7.7,6.8)	6.28(d, 1H, J=9.6, H3'); 7.84(dd, 1H, J=9.6 and 2.8, H4'), 8.56(d, 1H, J=2.8, H6')
12b	8.87 (brd, 6.9)	7.79 (brt, 7.6)	7.5-7.65* (m)	6.28(d, 1H, J=9.0, H3'); 7.30 (dd, 1H, J=9.0 and 2.2, H4'), 7.5-7.65(m, 1H, H6')
12c	9.12 (brd, 6.0)	8.69 (brt, 7.6)	8.0-8.3* (m)	6.87(d, 1H, J=8.7, H3'); 8.0-8.3(m, 2H, H4'+H6')
12d	8.86 (dd, 6.8,1.1)	8.13 (tt, 7.7,1.1)	7.89 (dd, 7.6,6.9)	6.44(d, 1H, J=9.4, H3'); 7.33(tt, 1H, J=7.2, and 1.1, H4'') 7.45(brt, 2H, J=7.6, H3''+H5''); 7.67(brd, 2H, H=7.5, H2''+H6''); 7.78(dd, 1H, J= 9.3, 2.5, H4'); 8.23 (d, 1H, J=2.6, H6')
12e	8.90 (brd, 5.9)	8.20 (brt, 7.7)	7.94 (brt, 7.4)	7.38(brt, 1H, J=7.3, H4''), 7.48(brd, 2H, J= 7.5, H3''+H5''); 7.72(brd, 2H, J=7.4, H4''+H6''); 7.81(s, 1H, H6'); 8.16(s, 1H, H3')
13a	8.80 (dd, 6.7,1.3)	8.34 (tt, 7.8,1.3)	8.03 (dd, 7.8,6.7)	8.69 (d, 1H, J=2.6, H4'); 8.73(d, 1H, J=2.6, H6')
13b	8.73 (dd,7.2,1.3)	8.03 (tt,7.7,1.2)	7.80 (brt, 7.1)	7.59(d,1H, J=2.2, H6'); 7.68(d, 1H, J=2.2, H4')
13c	8.80 (brd, 5.9)	8.17 (brt, 7.6)	7.89 (brt, 7.1)	7.78(d, 1H, J=2.1,H4'); 8.04(d, 1H, J=2.0).

* Partially overlapped signals

mixture of the 5'-bromo and 3',5'-dibromo aminides **12b** and **13b** (4:1) was obtained, after neutralization. The same process in the presence of base, and with a three molar excess of bromine, produced the aminide **13b** as the only product (75 %).

Iodination was also tested, and using equimolar amounts of iodine and the aminide **4a**, in dichloromethane at room temperature, the pyridinium N-[2'-(5'-iodopyridyl)]aminide **12c** was obtained. When the reaction was carried out in the presence of base, and using a three molar excess of iodine, further substitution took place and, the 3,5'-diiodo aminide **13c** was obtained (70 %). However, when iodination was tested on the isoquinolinium N-(2'-pyridyl)aminide **4e**, the tetracyclic periodide **15a** (Scheme 4) was the only isolated product, showing that iodine preferentially produces the oxidation of the cyclic tautomer **14a**, which should coexist in solution with the betaine **4e**. This cyclic form is not detected by NMR in **4a** samples, so only a small percentage should be responsible for the process, the equilibrium being shifted to **15a** in the presence of the oxidant. In pyridinium derivatives **4a-d**, the presence of cyclic tautomers should be smaller than that required to allow the oxidation process, so only the substitution is observed. A similar behaviour was observed with the isoquinolinium aminide **4f**.



Scheme 4

Diazonium salts: Coupling with benzenediazonium chloride was performed on the pyridinium betaines **4a** and **4d**. The 2-azinyli moiety was selectively attacked on the 5-position, yielding the diazo derivatives **12d** and **12e**.

EXPERIMENTAL.

Melting points were determined on a Büchi SMP-20 and are uncorrected. IR spectra (KBr) were recorded using a Perkin-Elmer 700 or 1310 spectrophotometer. ¹H NMR spectra were obtained on a Bruker AC 200P (200 MHz) or Varian Unity (300 MHz) spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane (Tables 2, 3 and 11). Selectively ¹H decoupled spectra as well as 2D homonuclear ¹H-¹H (COSY-45) shift correlation experiments were applied where necessary. Elemental analyses were carried out on a Heraeus

Table 12. Microanalyses of all new derivatives.

Comp.	Mol.formula	Calcd(%)			Found(%)		
		C	H	N	C	H	N
3c	C ₉ H ₁₀ N ₄ Br ₂	32.54	3.04	16.87	32.29	3.05	16.78
3d	C ₉ H ₁₀ N ₄ Br ₂	32.54	3.04	16.87	32.19	3.28	16.60
3f	C ₁₈ H ₁₅ N ₃ Cl ₂	62.96	4.41	12.25	62.99	4.58	12.58
4a	C ₁₀ H ₉ N ₃	70.14	5.30	24.56	69.89	5.37	24.80
4b	C ₁₄ H ₁₁ N ₃	75.99	5.01	19.00	76.33	5.21	19.11
4c	C ₉ H ₈ N ₄	62.76	4.69	32.55	62.39	4.72	32.66
4d	C ₉ H ₈ N ₄	62.76	4.69	32.55	62.50	4.93	32.36
4f	C ₁₈ H ₁₃ N ₃	79.67	4.83	15.50	79.45	4.68	15.30
8a	C ₁₁ H ₁₂ N ₃ I	42.17	3.86	13.42	42.45	3.82	13.42
8b	C ₁₅ H ₁₄ N ₃ I	49.58	3.89	11.57	49.46	4.01	11.79
8c	C ₁₀ H ₁₁ N ₄ I	38.22	3.53	17.84	38.12	3.62	17.53
8d	C ₁₀ H ₁₁ N ₄ I	38.22	3.53	17.84	38.52	3.71	17.88
8e	C ₁₇ H ₁₆ ClN ₃	68.66	5.43	14.14	68.30	5.34	14.31
9	C ₁₁ H ₁₂ N ₃ I	42.17	3.86	13.42	42.20	3.68	13.18
10a	C ₁₁ H ₈ N ₂ O ₂	65.98	4.03	14.00	66.05	3.85	13.89
10b	C ₁₅ H ₁₀ N ₂ O ₂	71.98	4.03	11.20	71.98	3.95	10.98
10c	C ₁₅ H ₁₀ N ₂ O ₂	71.98	4.03	11.20	71.78	3.94	10.87
11	C ₁₅ H ₁₁ N ₃ O ₂	67.90	4.18	15.85	67.75	4.50	16.03
12a	C ₁₀ H ₈ N ₄ O ₂	55.54	3.73	25.92	55.93	3.40	25.94
12b	C ₁₀ H ₈ BrN ₃	48.19	3.24	16.87	47.90	3.30	16.67
12c	C ₁₀ H ₈ IN ₃	40.41	2.71	14.15	40.63	2.57	14.33
12d	C ₁₆ H ₁₃ N ₅	69.79	4.76	25.45	69.70	4.96	25.41
12e	C ₁₅ H ₁₂ N ₆	65.19	4.38	30.43	65.17	4.60	30.07
13a	C ₁₀ H ₇ N ₅ O ₄	45.97	2.70	26.82	45.71	2.32	26.55
13b	C ₁₀ H ₇ Br ₂ N ₃	36.71	2.16	12.85	36.48	2.14	12.59
13c	C ₁₀ H ₇ I ₂ N ₃	28.38	1.67	9.93	28.26	1.93	9.70
15a	C ₁₄ H ₁₀ I ₃ N ₃	27.96	1.68	6.99	28.10	1.58	7.10
15b	C ₁₈ H ₁₂ I ₃ N ₃	33.19	1.86	6.45	32.98	2.02	6.80

Rapid CHN analyzer and are within 0.4% of the theoretical value for all new compounds described (Table 12). MOPAC was implemented on a CYBER 910B-480 workstation.

Preparation of N-(2'-azinylamino)pyridinium bromide hydrobromides 3a-d (Table 1)

To a solution of N-(2',4'-dinitrophenyl)pyridinium chloride (2.8 g, 0.01 mol) in ethanol (15 ml), was added the corresponding α -hydrazinoazine (0.01 mol) in ethanol (5 ml) followed by triethylamine (1.5 ml). The reaction mixture was stirred at room temperature for 15 minutes. The precipitate was washed with 10% hydrochloric acid (until the filtrate reached pH 5-6), then with methanol (30 ml) and finally with ether (30 ml). The crude hydrazone 2 obtained was suspended in glacial acetic acid (25 ml) and refluxed for 30 minutes until a clear solution was obtained. The mixture was then concentrated to dryness. The residue was stirred in water and the insoluble material removed by filtration. The filtrate was decolorized with charcoal, acidified with 47% hydrobromic acid (0.02 mol), then concentrated to dryness and the residue recrystallized from absolute ethanol.

Preparation of N-(2'-azinylamino)isoquinolinium chloride hydrochlorides 3e,f (Table 1)

To a solution of N-(2',4'-dinitrophenyl)isoquinolinium chloride (3.3 g, 0.01 mol) in ethanol (70 ml), was added the α -hydrazinoazine (0.01 mol) in ethanol (5 ml) followed by triethylamine (1.5 ml). The mixture was refluxed for 1 h. The precipitate formed was filtered and washed with 10% hydrochloric acid (until the filtrate reached pH 5-6), and then with ethanol (30 ml). The crude hydrazone was suspended in a mixture of ethanol (45 ml) and 35% hydrochloric acid (15 ml) and refluxed until a clear solution was obtained (1h). The dinitroaniline was precipitated by addition of water (120 ml) and filtered off. The filtrate was concentrated to about 10 ml and then treated with charcoal, and filtered. The oily residue obtained on concentration was triturated with acetone and the solid was recrystallized from absolute ethanol.

Preparation of N-(2'-azinylimino)azinium betaines 4 (Table 1)

To a vigorously stirred solution of the corresponding salt 3 (10 mmol) in acetone (45 ml), potassium carbonate (20 mmol) was added. After 3 h of stirring at room temperature the inorganic salts were filtered, and the filtrate evaporated to dryness. The residue was recrystallized as indicated in Table 1.

Reaction of aminides 4 with electrophiles.

a) **Reaction with alkyl halides.** (Table 9) To a solution of the aminide 4 (10 mmol) in acetone (30 ml, for 4a-d) or toluene (25 ml, for 4e), the alkyl halide (12 mmol) was added, and the mixture was stirred at room temperature for 2 h (for 4e reflux for 6 h was necessary). The precipitate formed was isolated by filtration (for 4e as the chloride was hygroscopic it was necessary to do an halogen interchange to iodide). Recrystallization from abs. ethanol gave the salts 8.

N-[2'-(1'-methyl-1'H,2'H-pyridyl)imino]pyridinium iodide (9). A solution of 2-chloro-1-methylpyridinium iodide (0.2 g, 0.78 mmol) and 1-aminopyridinium iodide (0.19 g, 0.86 mmol) in acetonitrile (25 ml) was vigorously stirred with potassium carbonate (0.36 g, 2.6 mmol) at room temperature for 12 days. The inorganic salt was removed by filtration and the filtrate evaporated in vacuo, the residue so obtained was scratched with ether to yield a solid which was recrystallized from abs. ethanol, yielding 0.165 g (67%), mp 215-216 °C ¹H NMR (DMSO-d₆) δ 3.67 (s, 3 H, CH₃), 6.04 (d, 1 H, J = 8.8 Hz, H3'), 6.42 (t, 1 H, J = 6.7 Hz, H5'), 7.45 (ddd, 1 H, J = 8.1, 7.1 and 1.7 Hz, H4'), 7.96 (d, 1 H, J = 6.4 Hz, H6'), 8.14 (t, 2 H, J = 6.8 Hz, H3 and H5), 8.46 (t, 1 H, J = 7.8 Hz, H4), 8.86 (d, 2 H, J = 5.9 Hz, H2 and H6).

b) Reaction with α , β -unsaturated carbonyl derivatives. General procedure. A mixture of pyridinium *N*-(2'-pyridyl)aminide **4a** (0.34 g, 2 mmol), the corresponding α , β -unsaturated carbonyl derivative (2 mmol) and silica gel (2 g) in acetonitrile (10 ml), was stirred at room temperature until no starting material was detected by TLC. The silica was removed by filtration and the solvent evaporated under vacuo to give a solid which was recrystallized from the suitable solvent.

2-[*N*-(2'-pyridylamino)]-1,4-benzoquinone (10a). Yield 64 %, mp 102-104 °C (from ethanol)

¹H NMR (DMSO-*d*₆) δ 6.53 (brs, 1 H, H3), 6.74 (dd, 1 H, J = 10.0 and 2.6 Hz, H5), 6.86 (d, 1 H, J = 10.0 Hz, H6), 7.02 (dd, 1 H, J = 7.7 and 5.0 Hz, H5'), 7.51 (d, 1 H, J = 8.3 Hz, H3'), 7.75-7.8(m, 1 H, H4'), 8.85 (dd, 1 H, J = 5.1 and 2.0 Hz, H6'), 9.16 (brs, 1 H, NH).

2-[*N*-(2'-pyridylamino)]-1,4-naphthoquinone (10b). Yield 65 %, mp 198-200 °C (from ethanol)

¹H NMR (DMSO-*d*₆) 7.05 (dd, 1 H, J = 7.1 and 4.7 Hz, H5'), 7.57 (d, 1 H, J = 8.5 Hz, H3'), 7.76 (ddd, 1 H, J = 8.1, 7.2 and 2.0 Hz, H4'), 7.80 (ddd, 1 H, J = 7.3, 7.2 and 1.7 Hz, H7), 7.86 (ddd, 1 H, J = 7.3, 7.0 and 1.6 Hz, H6), 7.96 (dd, 1 H, J = 7.5 and 1.7 Hz, H5), 8.05 (s, 1 H, H3), 8.07 (dd, 1 H, J = 7.3 and 1.6 Hz, H8), 8.40 (dd, 1 H, J = 5.1 and 2.1 Hz, H6'), 9.45 (brs, 1 H, NH).

2-[*N*-(2'-pyridylamino)]-1,2-naphthoquinone (10c). Yield 60 %, mp 220-222 °C (from ethanol)

¹H NMR (DMSO-*d*₆) 7.18 (dd, 1 H, J = 7.3 and 4.8 Hz, H5'), 7.45-7.5 (m, 1 H, H3'), 7.8-7.9 (m, 3 H, H3, H7 and H4'), 8.03 (d, 1 H, J = 7.8 Hz, H5), 8.32 (d, 1 H, J = 8.1 Hz, H8), 8.47 (brd, 1 H, J = 4.9 Hz, H6'), 10.00 (brs, 1 H, NH).

***N*-phenyl-3-(2'-pyridylamino)maleimide (11).** Yield: 90 %, mp 216-217 °C (from ethyl acetate) ¹H NMR (DMSO-*d*₆) δ 6.58 (s, 1 H, H4), 7.05 (dd, 1 H, J = 7.3 and 5.0 Hz, H5'), 7.3-7.4 (m, 3 H, H2'', H4'' and H6'), 7.4-7.5 (m, 3 H, H3', H3'' and H5'), 7.76 (ddd, 1 H, J = 8.2, 7.3 and 2.0 Hz, H4'), 8.38 (dd, 1 H, J = 5.1 and 2.0 Hz, H6'), 10.37 (s, 1 H, NH).

c) Electrophilic aromatic substitution.

c.1) Nitration. To a precooled solution (2 °C) of the pyridinium *N*-(2'-pyridyl)aminide **4a** (200 mg, 1.17 mmol) in concentrated sulfuric acid (1 ml), a mixture of concentrated nitric (0.3 ml) and sulfuric acids (0.3 ml) were slowly added. The reaction mixture was vigorously stirred at room temperature for 1 h. Neutralization with potassium carbonate in water, afforded an orange solid, which was chromatographed on neutral alumina (Brockmann grade 1) suspended in ethyl acetate. By elution with ethyl acetate/ethanol (7:3 v/v) two products were isolated, identified as the pyridinium *N*-[2'-(5'-nitropyridyl)]aminide (**12a**) (R_f = 0.4) in 25 % yield, mp 216-218 °C (ethanol), and the pyridinium *N*-[2'-(3',5'-dinitropyridyl)]aminide (**13a**) (R_f = 0.7) in 20 %, mp 190-192 °C (ethanol).

c.2) Halogenation. General procedures: Method A: To a stirred solution of the corresponding aminide **4a** (1 mmol) in dichloromethane (5 ml), a solution of the halogen (iodine or bromine) (1 mmol) in dichloromethane (5 ml) was dropwise added. Stirring was continued at room temperature for the time indicated. The reaction mixture was neutralized with sodium carbonate and then concentrated to dryness. The residue was chromatographed through a column with neutral alumina (Brockmann grade 1) prepacked with ethyl acetate. By elution with ethyl acetate/ethanol (9:1, v/v), the corresponding compounds were isolated and recrystallized from acetone.

Method B: To a suspension of the corresponding aminide **4a** (1 mmol) and powdered potassium carbonate (2.8 g, 20 mmol) in dichloromethane (10 ml), the chosen halogen (iodine or bromine) (3 mmol) was added. The mixture was

stirred at room temperature until no traces of the starting betaine was detected by thin layer chromatography. The inorganic salts were filtered and washed with dichloromethane (3x15 ml). The solvent was eliminated and the oily residue obtained was purified by column chromatography on neutral alumina (Brockmann grade 1) prepacked with ethyl acetate, using ethyl acetate/ethanol (9:1 v/v) as eluent. Recrystallization from abs. ethanol gave analytical samples of the corresponding dihaloderivatives.

Bromination. Following the Method A, from 4a and after stirring for 10 hours, a mixture was obtained which was separated by column chromatography, using neutral alumina (Brockmann grade 1) and ethyl acetate/ethanol as eluent (1:1 v/v). The pyridinium N-[2'-(3',5'-dibromopyridyl)]aminide (13b) was firstly eluted ($R_f = 0.7$) in 50 % yield after crystallization from acetone, mp 147-149 °C. The second fraction ($R_f = 0.2$) was identified as pyridinium N-[2'-(5'-bromopyridyl)]aminide (12b), and was also crystallized from acetone. Yield = 14 %, mp = 125-128 °C. The pyridinium dibromoaminide 13b was also obtained, using method B, after 10 hours. Yield 75 %, mp 148-149 °C.

Iodinated products:

Pyridinium N-[2'-(5'-iodopyridyl)]aminide (12c). This compound was obtained using Method A, from 4a and after 30 min stirring, in 61 % yield, mp 132-135 °C.

Pyridinium N [(2'-(3',5'-diiodopyridyl)]aminide (13c). The title compound was obtained following Method B from 4a, after stirring for 3 hours, yield: 70 %, mp 110-111 °C.

Pyrido[1,2':3,4][1,2,4]-triazolo[5,1-a]isoquinolin-7-ium Periodide (15a). The title compound was obtained following Method A, from 4e, after stirring for 30 min, in 40 % yield, mp 227-229 °C $^1\text{H NMR}$ (DMSO- d_6) δ 7.67 (t, 1 H, $J = 7.0$ Hz, H10); 8.11 (dd, 1 H, $J = 9.3$ and 7.3 Hz, H9); 8.15-8.2 (m, 2 H, H2 and H4); 8.38 (d, 1 H, $J = 9.3$ Hz, H8); 8.46 (d, 1 H, $J = 7.3$ Hz, H5), 8.5-8.55 (m, 1 H, H1); 9.25-9.3 (m, 1 H, H3), 9.34 (d, 1 H, $J = 7.3$ Hz, H6); 9.87 (d, 1 H, $J = 7.3$ Hz, H11).

Isoquino[2',1':5,1][1,2,4]-triazolo[4,3-a]quinolin-9-ium Periodide (15b). This compound was obtained from 4f according to Method A, and after stirring for 30 min. Yield: 86%, mp 265-266 °C $^1\text{H NMR}$ (DMSO- d_6) δ 7.92 (t, 1 H, $J = 7.3$ Hz, H11); 8.01 (t, 1 H, $J = 7.3$ Hz, H12); 8.10-8.15 (m, 2 H, H2 and H8); 8.22 (t, 1 H, $J = 7.3$ Hz, H3); 8.32 (d, 1 H, $J = 7.3$ Hz, H10), 8.45-8.55 (m, 3 H, H1, H4 and H5); 8.64 (d, 1 H, $J = 8.3$ Hz, H13), 8.91 (d, 1 H, $J = 8.8$ Hz, H9), 9.35 (d, 1 H, $J = 7.3$ Hz, H6).

c.3) Reaction with diazonium salts. General procedure. To a stirred, cool (0 °C) solution of aniline (1 ml, 10 mmol) in 6N HCl (5 ml, 30 mmol), sodium nitrite (0.83 g, 10 mmol) in water (5 ml) was dropwise added. Then, the corresponding aminide 4 (10 mmol) was added, the mixture was stirred at 5 °C and basified with sodium carbonate up to pH = 8.0-8.5, and an orange solid was obtained, which was extracted with dichloromethane (4x 10 ml). The combined organic fractions were washed with water until neutral pH, dried over magnesium sulphate and the solvent removed in vacuo to give a residue which was chromatographed on a neutral alumina (Brockmann grade 1) column prepacked with ethyl acetate. Elution with ethyl acetate/ethanol (1:1 v/v) produced the corresponding coupled products.

Pyridinium N-[2'-(5'-phenylazopyridyl)]aminide (12d). Yield: 50 %, mp 134-136 °C (toluene).

Pyridinium N-[2'-(5'-phenylazopyrazinyl)]aminide (12e). Yield: 45 %, mp 173-175 °C (toluene).

Crystallographic Structural Determination for 4a. Crystal data for compound 4a: $\text{C}_{10}\text{H}_9\text{N}_3$, $M = 171.20$, monoclinic,

space group $P2_1/n$, $a = 9.464$ (4), $b = 7.719$ (3), $c = 12.811$ (8), $\beta = 109.58$ (2), $U = 881.8 \text{ \AA}^3$ (by least-squares refinement on diffractometer angles for 25 automatically centred reflexions), $\lambda = 0.71069 \text{ \AA}$, $Z = 4$, $D_c = 1.29 \text{ gr.cm}^{-3}$. Colourless, $0.20 \times 0.15 \times 0.25 \text{ mm}^{-3}$, $\mu(\text{MoK}\alpha) = 0.759 \text{ cm}^{-1}$, $F(000) = 360$.

All crystallographic measurements were made on a ENRAF-NONIUS CAD-4 diffractometer, ω - 2θ mode with ω scan width = $1.0 + 0.35 \tan \theta$, graphite monochromated MoK α radiation; 2742 unique reflections were measured in the range $[2 \leq \theta \leq 30^\circ, -13 \leq h \leq +13, -10 \leq k \leq 0, -18 \leq l \leq 0]$; 1231 observed reflexions with $I > 3\sigma(I)$. The structure was solved by direct method with MULTAN¹⁴ and DIRDIF¹⁵ programs. All non hydrogen atoms were refined anisotropically by full-matrix least-squares refinement. All the H-atoms were experimentally determined. Final R and R_w values are 0.055 and 0.054 using unit weights for all observed reflections. Anomalous dispersion corrections and atomic scattering factors were taken from international tables¹⁶. The calculations were made with SDP Package¹⁷ in a MICROVAX II computer.

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