Reaction of Arylglyoxals with 2-Amino Heterocycles[1]

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The reaction of some arylglyoxals with a variety of 2-amino heterocycles, including pyridine, diazine, and azole derivatives, has been studied, with or without BF_3·Et_2O complex as catalyst. On the basis of the isolation of different intermediate carbinolamines and of some crossover cyclization experiments, a reasonable mechanism has been proposed for all these processes. In addition, some structural features of the resulting bicyclic imidazo[1,2-*a*] derivatives having a potential hydroxyl group in position 3 are discussed.

Introduction

The reaction of some glyoxal derivatives with different 2-amino heterocycles in acidic media has been investigated previously by several authors. Thus, Goto et al.[2] have reported the synthesis of compounds **1** and **2** (Chart I), the model compounds of *Cypridina luciferine*,[3] by heating 2-aminopyridine or aminopyrazines with both phenylglyoxal and pyruvaldehyde in aqueous acid solution. Later, Barlin et al.[4] described the synthesis of compounds **2** (R^1 = Ph, R^2 = H) and **3** by reacting phenylglyoxal with 2-aminopyrazine and 3-aminopyridazines, respectively, in ethanolic solution and in the presence of concentrated hydrochloric acid. In all these cases the observed regiochemistry is accounted for through an intermediate α-ketimine aldehyde arising from initial condensation of the amino group with the keto group of the α-keto aldehyde (Scheme I). On the other hand, in early reports no tautomeric studies have been made to provide some evidence for the assigned structures.

As part of our systematic study on the reactions of α-dicarbonyl compounds with heterocyclic amines we have explored the reaction of some arylglyoxals with various 2-amino heterocycles. In a preliminary communication[1] we reported the reaction of phenylglyoxal with 2-aminopyridine in benzene and, on the basis of UV data, the structure 2-phenyl-1*H*-imidazo[1,2-*a*]pyridinium-3-olate (**4a**, NH meso-ionic tautomer) instead of the structure **1** (R = Ph) of hydroxy tautomer[2,5] was proposed. On the other hand, isolation and characterization of the intermediate carbinolamine **5a** and identification of the final structure as **4a** allowed us to propose tentatively the reaction pathway shown in Scheme II for this reaction.

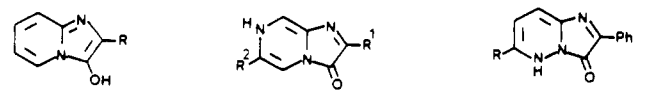
In this paper we have extended the above reaction to other arylglyoxals and to a series of representative 2-amino heterocycles with the aim of studying its scope and generality for the synthesis of bicyclic meso-ionic imidazo-[1,2-*a*] derivatives and, if possible, to elucidate the reaction course for all these processes.

Results and Discussion

We began this investigation by examining the reaction between several para-substituted phenylglyoxals[6] and a series of representative C-substituted 2-aminopyridines. By reacting equimolar amounts of the arylglyoxal and the 2-aminopyridine in benzene or methylene chloride at room temperature and in the absence of any catalyst, we obtained in fair to excellent yields either carbinolamines **5** or imidazo[1,2-*a*]pyridinium-3-olates **4a–f**, depending on the nature of the substituents on both aromatic rings. On the other hand, compounds **4** were the only isolated products when the reaction was carried out in the presence of a catalytic amount of BF_3·Et_2O. Carbinolamines **5** in turn cyclized to the related **4** with yields identical with those obtained from the reagents in the presence of the same catalyst, with the only exception being compound **5k**, which did not react even after prolonged reaction time. Table I shows physical data and reaction conditions for compounds **4**, along with those for compounds **10** and **11**.

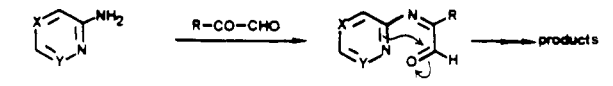
Compounds **4** were obtained as hydrates, and the corresponding anhydrous products, generally orange or red powdery solids, were sparingly soluble in most usual organic solvents and could not be recrystallized as such.

Chart I

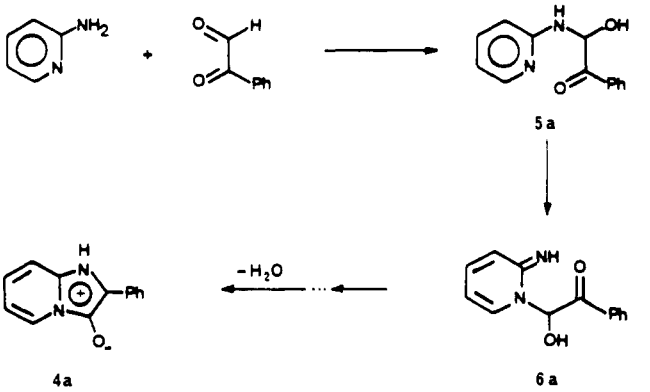


1, R = Me, Ph 2, R^1 = Me, Ph; R^2 = H, Ph, Me 3, R = H, Cl

Scheme I



Scheme II



(1) For a preliminary communication see: Alcaide, B.; Pérez-Ossorio, R.; Plumet, J.; Sierra, M. A. *Tetrahedron Lett.* **1986**, *27*, 1627.

(2) (a) Inoue, S.; Sugiura, S.; Kakoi, H.; Goto, T. *Tetrahedron Lett.* **1969**, 1609. (b) Sugiura, S.; Kakoi, H.; Inoue, S.; Goto, T. *Yakugaku Zasshi*, **1970**, *90*, 441.

(3) Yamaguchi, I. *Biochem. J.* **1975**, *151*, 9.

(4) Barlin, G. B.; Brown, D. J.; Kadunc, Z.; Petric, A.; Stanovnik, B.; Tisler, M. *Aust. J. Chem.* **1983**, *36*, 1215.

(5) The synthesis of **4a** and some derivatives by reaction of phenacyl bromides with 2-aminopyridine 1-oxide has been also described. See: (a) Deady, L. W.; Stanborough, M. S. *J. Heterocycl. Chem.* **1979**, *16*, 187. (b) Deady, L. W.; Stanborough, M. S. *Aust. J. Chem.* **1981**, *34*, 1295.

(6) The arylglyoxals were used in all cases as hydrates given their greater stability and easier handling. The results obtained with free arylglyoxals were identical in the cases for which both forms were tested.

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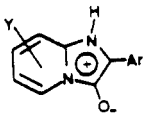
Table I. Reaction Conditions and Relevant Physical Data for Compounds 4, 10, and 11



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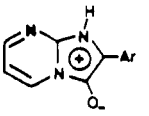
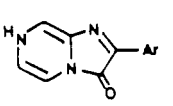


10



11

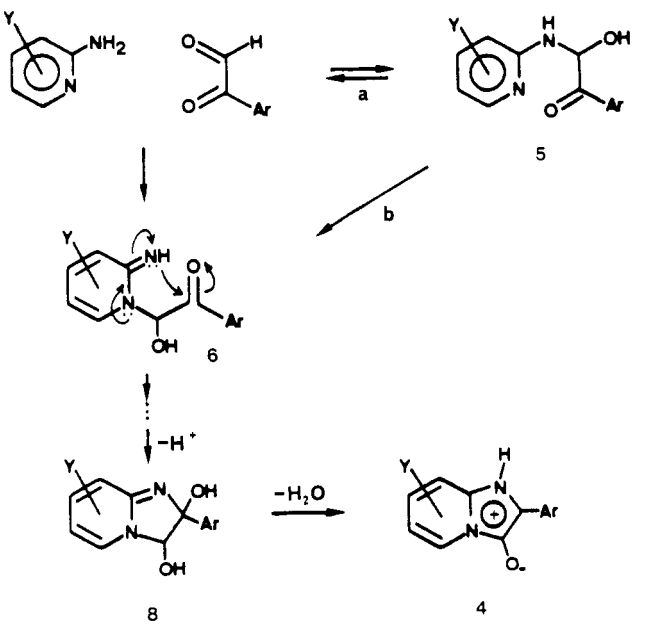
						^{1}H NMR[c,d]										
						δ, ppm				J, Hz						
compd	Ar	Y	method[a]	t, h	yield,[b] %	H-5	H-6	H-7	H-8	$J_{5,6}$	$J_{5,7}$	$J_{6,7}$	$J_{6,8}$	$J_{7,8}$	λ_{max} (log ϵ)[e]	ν,[f] cm^{-1}
4a	Ph	H	A	48	100	8.16	6.93	7.31	7.34	6.53		6.14		8.10	400 (3.97)	1645
4b	Ph	8-OMe	A	22	78										376 (4.01)	1640
4c	Ph	5-Me	A	40	60		6.76	7.36	7.43			5.93		8.56	402 (4.02)	1650
4d	Ph	6-Me	A	48	81	8.18		7.35	7.44		1.04			8.55	402 (4.14)	1645
4e	Ph	7-Me	A	30	90	8.12	6.70		7.61	8.53			1.98		393 (3.94)	1650
4f	Ph	8-Me	A	28	94	8.23	7.05	7.30		6.87		6.84			388 (4.11)	1630
4g	Ph	6-Cl	B	120	35										419 (4.02)	1640
4h	p-MeOC$_6$H$_4$	H	B	29	60	8.13	6.94	7.22	7.32	6.53	0.86	6.59	0.90	8.70	407 (4.15)	1640
4i	p-MeC$_6$H$_4$	H	B	7	73										403 (4.23)	1650
4j	p-ClC$_6$H$_4$	H	B	24	75	8.16	6.92	7.31	7.32	6.91	0.73	6.83		8.65	401 (4.10)	1640
4k	p-NO$_2$C$_6$H$_4$	H	B	113	80	8.24	6.97	7.47	7.37	6.68		6.83		8.33	461 (4.68)	1640
4l	p-MeC$_6$H$_4$	6-Me	B	18	60										403 (4.12)	1600
4m	p-ClC$_6$H$_4$	6-Me	B	22	60										401 (4.13)	1645
4n	p-NO$_2$C$_6$H$_4$	6-Me	B	42	100										459 (4.56)	1625
10a	Ph		B	168	45										461 (3.88)	1625
10b	p-ClC$_6$H$_4$		B	168	72										456 (3.97)	1625
10c	p-MeC$_6$H$_4$		B	264	40										460 (3.93)	1625
11a	Ph		B	168	100	6.81	7.28		7.99	5.93					486 (2.99)	1665
11b	p-MeOC$_6$H$_4$		B	192	53	6.93	7.43		8.15	5.74					465 (3.08)	1670
11c	p-ClC$_6$H$_4$		B	264	100	7.01	7.58		8.21	5.62					470 (3.10)	1660

[a] See Experimental Section. [b] In pure, isolated product (as dihydrate for compounds **4a–f** and **11a**, monohydrate for compounds **4h–n** and **11b,c**, and anhydrous for **4g**), with correct analytical data. All compounds except **11a** (mp 115 °C) decompose before melting. [c] In DMSO-d_6 solution. Spectra were recorded at 360 MHz except for **4h**, **4j**, and **11a–c** (300 MHz). [d] Compounds **10** were insoluble in common NMR solvents. [e] In MeOH solution. [f] As a KBr pellet.

Oxidative degradation and other reactions described below favor structure **4** over its regioisomer **7**, which was compared with an authentic sample prepared recently by Robert in an alternative way.[7] The UV spectra of compounds **4** were particularly important in structural assignments; generally, three absorption maxima, at λ close to 400, 275, and 205 nm, respectively, were encountered in methanolic solution. The band at higher wavelength undergoes a strong hypsochromic shift (77 nm for compound **4a**) when the spectrum is measured in methanol in the presence of hydrochloric acid. This effect has allowed for the assignment of a meso-ionic tautomeric structure (NH) for these compounds, as we have previously reported for compound **4a**.[1] The band at about 400 nm is associated to the meso-ionic structure of these products. In their IR spectra, the most characteristic absorption appears between 1650 and 1620 cm^{-1}; some authors[8] attribute this band, in related products, to the C–O$^-$ group stretch, but it could as well be assigned to the C=N group. It should be considered, for example, that this band appears approximately at the same frequency for **4a** and for its corresponding hydrochloride, **4a** (HCl, 1645 and 1650 cm^{-1}, respectively). The chemical shifts and coupling constants are generally in good agreement with those described for imidazo[1,2-*a*]pyridines.[9]

We have previously proposed the mechanism shown in Scheme II to account for the formation of compounds **4**, the rearrangement of intermediate carbinolamine **5a** to pyridone imine **6a** (a Chapman-like isomerization process[10]) being the key step in the process. However, formation of the intermediate **6a** could also arise through a mechanism implying previous equilibration of carbinolamine **5** with the reagents, which would then lead to pyridone imine **6a** (Scheme III).

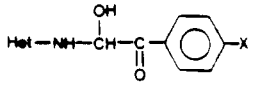
Scheme III



To shed some light on this problem, we have carried out some crossover experiments with different carbinolamines.

(7) Guinamant, J. L.; Robert, A. *Tetrahedron* **1986**, *42*, 1169.
(8) Potts, K. T.; Chen, S. J.; Kane, J.; Mashall, J. L. *J. Org. Chem.* **1977**, *42*, 1633.
(9) See: Blewitt, H. L. In *Specials Topics in Heterocyclic Chemistry*; Weissberger, A., Taylor, E. C., Eds.; Wiley: New York, 1977; Chapter II, pp 126.
(10) See, for example: Stevens, T. S.; Watts, W. E. In *Selected Molecular Rearrangements*; Van Nostrand Reinhold: New York, 1973, pp 67.

Table II. Reaction Conditions and Selected Physical Data for Compounds 5 and 9



compd	het	X	method[a]	t, h	yield,[b] %	mp, °C	δ (^{4}H)[c] CHNH (J, Hz)	δ (^{13}C)[d] CHOH	δ (^{13}C)[d] C=O	$\nu_{C=O}$,[e] cm^{-1}
5a	2-pyridyl	H	A	0.25	80[f]					1680
5g	5-chloro-2-pyridyl	H	B	2	90	118		73.9	195.4	1690
5h	2-pyridyl	OMe	A	1	85	80–82	6.55 (7.10)	73.5	194.2	1680
5i	2-pyridyl	Me	A	3	80	90–94	6.63 (7.20)	73.7	195.2	1680
5j	2-pyridyl	Cl	A	0.5	85	96–100	6.62			1700
5k	2-pyridyl	NO_2	A	6	100[f]					1710
5l	5-methyl-2-pyridyl	Me	A	1	80	92–94	6.60 (6.59)			1680
5m	5-methyl-2-pyridyl	Cl	A	0.5	85	120–122	6.56	74.2	194.8	1695
5n	5-nitro-2-pyridyl	H	A	5	90	142	5.98			1685
9a	2-pyrimidinyl	H	B	1.5	90	110–112	6.71 (8.43)	74.4	195.4	1695
9b	2-pyrazinyl	H	B	0.5	90	121–122	6.56 (8.05)	73.5	195.2	1690
9c	2-thiazolyl	H	B	1.5	90	114	6.47	76.8	194.7	1690

[a] See Experimental Section. [b] No analytical data were taken for compounds **5a–n** due to their instability. Compounds **9a–c** gave correct analyses. [c] In $DCCl_3$ solution. Spectra were recorded at 300 MHz except for **5n** and **9b** (360 MHz). Signals appeared as broad doublets in those cases for which *J* are given and as broad singlets for the rest. [d] In DMSO-d_6 solution. Spectra were recorded at 20.15 MHz except for **5n**, **5l**, and **5j** (75 MHz). Compounds **5a** and **5k** decompose instantaneously in DMSO-d_6. [e] In KBr pellet. [f] Decomposes before melting.

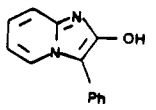
If carbinolamine **5** followed an intramolecular reaction course (route b), only the normal cyclization products would be expected. On the other hand, an intermolecular reaction pathway (route a) would also lead to the mixed cyclization products. From the reaction of carbinolamines **5i** and **5h**, four different cyclization products were obtained, **4i**, **4j**, **4l**, and **4m**, as deduced by comparison of the mass spectrum of the reaction mixture and the mass spectra of the pure products. This and other similar crossover experiments with different carbinolamines suggest a mechanism implying a previous equilibration of carbinolamine **5** with the reagents which then leads to pyridone imine **6**, the actual intermediate in the cyclization to **4**. The above experiments rule out the previously proposed intramolecular migration of the α-hydroxyphenacyl group in a Chapman-like isomerization process (route b).[1]

In conclusion, it may be stated that the reaction between arylglyoxals and 2-aminopyridines to give 2-arylimidazo[1,2-*a*]pyridinium-3-olates, **4**, takes place with initial formation of carbinolamines **5**, which are the kinetic products. Compounds **5** then lead to pyridone imines **6**, by reversion to the reagents and subsequent recombination, which cyclize rapidly to the corresponding dihydroxyimidazolines **8**, which have not been isolated in any case. Compounds **8** give the reaction products **4** by dehydration.

The results obtained in the reaction of phenylglyoxal with the 2-aminopyridines considered, in benzene and without catalyst, may be easily justified as a function of the relative nucleophilicity of the aminoheterocycle. The more nucleophilic heterocycles (Y = MeO, Me, H) cyclize directly to the corresponding compounds **4** while the less nucleophilic heterocycles (Y = 5-Cl, 5-NO_2) produce the corresponding carbinolamines, and addition of BF_3·Et_2O is necessary to effect the cyclization. In contrast with this, the results obtained for other para-substituted arylglyoxals (X = MeO, Me, Cl, NO_2) in the same conditions cannot be easily rationalized since upon reaction with 2-aminopyridines (Y = Me, H) they produced, in all cases studied, the corresponding carbinolamines instead of the cyclization products; the latter were obtained only in the presence of the catalyst.

The reactions of arylglyoxals with other 2-amino heterocycles, including 2-aminopyrimidines, 2-aminopyrazine, and 2-aminothiazole, were also investigated. Either carbinolamines **9** (Table II) or imidazo[1,2-*a*]diazine derivatives, **10** and **11**, were obtained in fair to excellent yields depending on the amino heterocycle and on whether or not BF_3·Et_2O was present as catalyst. Carbinolamines **9** were the only products when the reaction was carried out without BF_3·Et_2O, in all cases. In the presence of catalyst, only the 2-aminodiazines afforded the corresponding imidazo[1,2-*a*]diazines, **10** and **11**, whereas the reaction fails with 2-aminothiazole. In comparison with compounds **4**, the reaction times required for the synthesis of both **10** and **11** were remarkably longer as expected on account of their lower nucleophilicity and assuming a similar reaction pathway (see Scheme III).

Chart II



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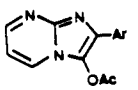
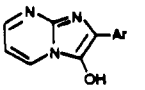


12, Ar = *p*-ClC_6H_4



13, Ar = *p*-BrC_6H_4

Carbinolamines **9** and **5** (except **5a**) are compounds stable at room temperature; however, they decompose upon heating in a variety of solvents. The assignment of the structure of these compounds was based mainly on spectroscopic and analytical data. The relative stability of these carbinolamines[11] is noteworthy; this could be due to two main factors: the electronic deficiency of the heterocyclic nuclei, which disfavors their dehydration,[12] and the possibility of chelation, as can be deduced from the proton coupling in the CHNH moiety observed in most cases in their corresponding ^{1}H NMR spectra.[11a]

On the basis of UV data the meso-ionic bicyclic structure **10** should be assigned to these products. Thus, the UV spectrum in methanol of **10b** was compared with that of the *O*-acetyl derivative **12** (Chart II), a spectral model for the hydroxy tautomer **10b** (OH, Figure 1). This comparison showed that the compound does not exist in the hydroxy form and should have the meso-ionic (NH) structure. Furthermore, when a drop of concentrated HCl

(11) For other related carbinolamines derived from α-keto aldehydes, see: (a) Alcaide, B.; Escobar, G.; Pérez-Ossorio, R.; Plumet, J.; Sanz, D. *J. Chem. Res., Synop.* **1984**, 144; **1984**, 1466; (b) Malassa, I; Matthies, D. *Liebigs Ann. Chem.* **1986**, 1133.

(12) All attempts to effect dehydration of carbinolamines **9** in different experimental conditions were fruitless; complex mixtures of products of undetermined nature and composition were obtained.

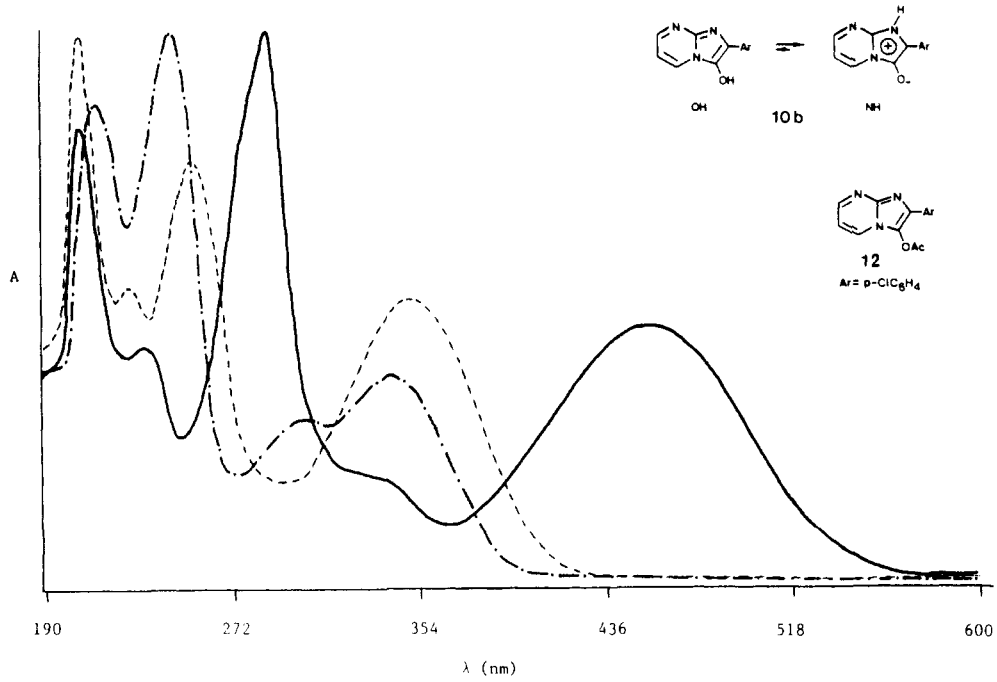
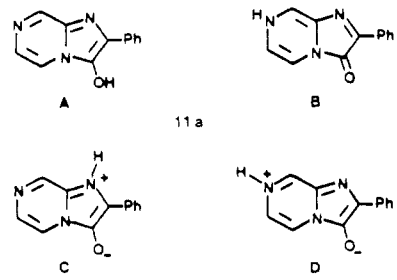


Figure 1. UV spectra of compounds **10b** in methanol (—) and in methanol/HCl (---) and **12** (-·-) in methanol.

Chart III

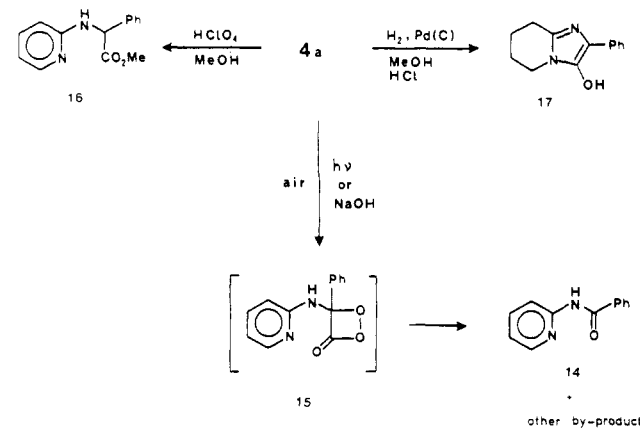


was added to the solution of **10b** in methanol, its color faded out quickly and the UV spectrum of the resulting solution became rather similar to that of *O*-acetyl derivative. Thus, in neutral solution (orange–red) the chromophore of compound **10b** is different from that in acidic solution (colorless). The band at 450–460 nm in compounds **10** undergoes a strong hypsochromic effect (100–110 nm) in the presence of hydrochloric acid and is probably related to the meso-ionic structure of these compounds. Therefore, these compounds exist primarily as 2-aryl-1*H*-imidazo[1,2-*a*]pyrimidinium-3-olates, in methanolic solution. The only synthetic precedent for compounds **10** is by Deady and Stanborough,[5b] who reported the synthesis of the hydrobromide of **13**. These authors, who did not obtain the free base, have not carried out any tautomeric studies on that compound.

Barlin and co-workers[4] have proposed dipolar structure D (Chart III) for compound **11a** based upon ^{1}H NMR studies on 7-quaternized imidazo[1,2-*a*]pyrazines. However, all four forms considered by Barlin are in fact three, since B and D are two canonical forms of the same molecular species.

In our case, it has not been possible to obtain any model compound, since both acetylation and methylation, in different reaction media and reaction conditions, were fruitless. However, the strong carbonylic absorption observed between 1670 and 1660 cm^{-1} in their IR spectra appears to indicate that at least in the solid state, these compounds exist as quinoid tautomers B rather than as hydroxylic (A) or dipolar (C) tautomers. The UV spectra

Scheme IV



in methanol show, among others, an absorption maximum around 470 nm responsible for the red color of these compounds. Addition of HCl induces a splitting of this band to λ close to 500 and 400 nm (Figure 2), which could be attributed to the effect of protonation on their nitrogen atoms N(1) and/or N(7), rather than to a tautomeric change. The ^{13}C NMR spectrum of **11a** in DMSO-d_6 presents resonances at 150.7 and 140.0 ppm which may be assigned to the C=O and C=N groups, respectively. These data seem to indicate that compounds **11** exist as quinoid tautomers (B in Chart III) in solution as well.

We have also investigated some reactions of compound **4a** which have furnished chemical evidence for the assigned structures. These include the oxidative degradation to *N*-(2-pyridyl)benzamide, the opening of the imidazole ring with methanol in perchloric acid, and, finally, the catalytic hydrogenation of the pyridine ring (Scheme IV). It has been observed that solutions of **4** in methanol, DMF, and other solvents are stable only in the absence of visible light or when total exclusion of air is secured. Thus, when a methanolic solution of **4a** is exposed to air and sunlight, photooxidation takes place, yielding a mixture of products. From this mixture *N*-(2-pyridyl)benzamide (**14**, major product, 40%), methyl phenylglyoxalate (15%), and 2-

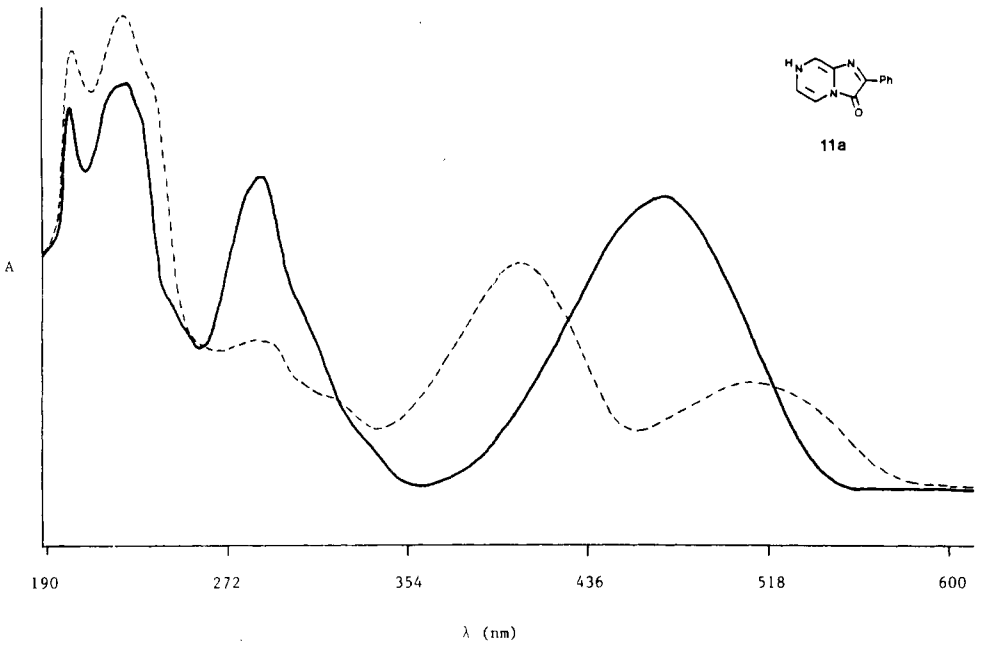


Figure 2. UV spectra of compound **11a** in methanol (—) and in methanol/HCl (---).

aminopyridine were isolated and characterized. With 30% aqueous NaOH in the presence of air a similar reaction occurs, yielding **14** (67%), 2-aminopyridine, and phenylglyoxilic acid, the latter isolated as benzoic acid (25%). Formation of these products can be accounted for through the intermediate dioxetanone **15**, in a process similar to that proposed for oxidation in *Cypridina luciferine* and related compounds.[13] By reaction of compound **4a** with perchloric acid in boiling methanol the corresponding α-amino ester **16** was obtained in 70% yield. Finally, the catalytic hydrogenation of compound **4a** was easily achieved at room temperature with palladium on charcoal (10%) catalyst in methanol–concentrated hydrochloric acid solution, to give, after neutralization with sodium carbonate, the tetrahydro derivative **17**.

It should be pointed out that the hydrogenation does not take place in the absence of acid. A hydroxylic tautomer structure has been proposed for compound **17** upon consideration of the fact that its UV spectra in methanol and in methanol/hydrochloric acid are practically superimposible.[14] This indicates that the chromophores are similar in both media and suggests the existence of the aforementioned compound as an OH tautomer rather than as an NH tautomer. To state this, we have considered, too, the data mentioned before for compounds **4** and **10** for whom a strong blue shift was observed upon changing the reaction media and going from the NH tautomer to the OH tautomer.

Experimental Section

General Procedures. Melting points were taken on a Buchi 510 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian T-60, on a Varian VXR 300S, and on a Bruker WM spectrometers working at 60, 300, and 360 MHz, respectively. ^{13}C NMR spectra were obtained on Varian FT-80 and Varian VXR 300S spectrometers working at 20.15 and 75 MHz, respectively. Chemical shifts are given in ppm relative to TMS (0 ppm). IR spectra were recorded on a Perkin-Elmer 257 spectrophotometer. Mass spectra were recorded on a Varian MAT-711 spectrometer. Elemental analyses were obtained in the Instituto de Química Bioorgânica (CSIC, Barcelona-Spain).

Materials. All heteroaromatic amines except 2-amino-3-methoxypyridine were obtained from commercial suppliers and used without further purification. 2-Amino-3-methoxypyridine was obtained from commercially available 2-amino-3-hydroxypyridine by reacting with an in situ prepared ethereal solution of diazomethane (generated from alkaline decomposition of Diazald); mp 82–83 °C (lit[15] mp 79–79.5 °C). Arylglyoxals were prepared from commercially available aryl methyl ketones according to the literature procedures.[16]

General Procedures for the Synthesis of Imidazo[1,2-*a*]pyridinium-3-olates (4), Imidazo[1,2-*a*]pyrimidinium-3-olates (10), and Imidazo[1,2-*a*]pyrazin-3-ones (11). Method A. Arylglyoxal hydrate (6.59 mmol) was added in one portion over a solution (or slurry) of heterocyclic amine (6.59 mmol) in benzene (15 mL). The resulting slurry was stirred at room temperature until most of the amine has been consumed. The reaction products were isolated, as dihydrates, by filtration of the thick intensely colored suspension thus obtained.[17] Anhydrous compounds were obtained from the hydrates by azeotropic distillation (benzene) in nearly quantitative yields.

Method B. Arylglyoxal hydrate (1.6 mmol) was added in one portion over a slurry of heterocyclic amine (1.6 mmol) in methylene chloride (10 mL). The resulting suspension was treated with 1 drop of freshly destilled BF_3·Et_2O and stirred until most of the amine has been consumed. The reaction products were isolated as hydrates by filtration of the thick intensely colored reaction mixture.[17] Anhydrous compounds were obtained as described in method A.

Crossover Experiments. Example: Reaction of carbinolamines **5i** and **5m** (0.54 mmol) in methylene chloride (5 mL) under the standard method B conditions for 24 hours gave 0.18 g of a yellow solid. Mass spectral analysis of the reaction mixture showed the presence of compounds **4i**, **4j**, **4l**, and **4m**; mass spectrum, *m/z* (I, compound) 260 (M^+ + 2, 14, **4m**), 258 (M^+, 36, **4m**), 246 (M^+ + 2, 12, **4g**), 244 (M^+, 30, **4g**), 238 (M^+, 20, **4l**), 224 (M^+, 30, **4i**), 195 (28), 180 (18), 93 (88), 92 (44), 79 (100), 78 (56).

3-Acetoxy-2-(*p*-chlorophenyl)imidazo[1,2-*a*]pyrimidine (12). This compound was prepared by stirring at 0 °C a mixture

(13) See, for example: (a) Goto, T.; Inoue, S.; Sugiura, S. *Tetrahedron Lett.* **1968**, 3873. (b) Goto, T.; Iio, H.; Inoue, S.; Kakoi, H. *Ibid.* **1974**, 2321.

(14) For a related tautomerism see: Jacquier, R.; Lacombe, J. M.; Maury, G. *Bull. Soc. Chim. Fr.* **1971**, 1038.

(15) Bernstein, J.; Stearns, B.; Dexter, M.; Scott, W. A. *J. Am. Chem. Soc.* **1947**, *69*, 1147.

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(17) Most of compounds **4** could be recrystallized from ethanol or ethanol–water mixtures as yellow needles without appreciable modification in their analytical composition.

of **10b** (0.10 g, 0.42 mmol), triethylamine (50 mg, 0.49 mmol), and acetic anhydride (50 mg, 0.50 mmol) in anhydrous acetone (5 mL) during 1.15 h. The red solution thus obtained was quenched on ice yielding **12** (90 mg, 90%) as white needles, mp 166–8 °C (dec). Acetate **12** was thermally unstable and could not be recrystallized; ^{1}H NMR (60 MHz, $DCCl_3$) δ 2.4 (s, 3 H, Me), 6.9 (q, 1 H, J_1 = 7.5 Hz, J_2 = 4.1 Hz, H6), 7.3 (d, 2 H, J = 9.0 Hz, Ar), 7.9 (d, 2 H, J = 9.0 Hz, Ar), 8.0 (q, 1 H, J_1 = 7.5 Hz, J_2 = 2.0 Hz, H5), 8.4 (q, 1 H, J_1 = 4.10 Hz, J_2 = 2.0 Hz, H7); ^{13}C NMR ($DCCl_3$) δ 167.0 (CO), 149.5 (C7), 142.6 (C3), 131.7 (C9), 130.3 (C2), 129.0 (C5), 134.1, 128.7, 128.0, 123.7 (Ar), 108.5 (C6), 20.1 (Me); IR (KBr) ν 1790 (CO), 1615 (C=N) cm^{-1}; UV (MeOH) λ (log ϵ) 340 (3.96), 302 (3.86), 245 (4.39), 212 (4.33).

Synthesis of 1-Aryl-2-hydroxy-2-(2′-heteroarylamino)-ethanones 5 and 9. Method A. Arylglyoxal hydrate (**1g**) was added in one portion over a solution (or slurry) of the equimolecular amount of the corresponding aminopyridine in benzene (15 mL) at room temperature. The resulting suspension was stirred at room temperature until complete reaction. Carbinolamines **5** were isolated by filtration of the reaction mixture and used without subsequent purification. All compounds **5** were white amorphous solids, stable for months at −20 °C but decomposed to generate complex mixtures after a few hours at room temperature.

Method B. 2-Amino heterocycle (2.0 g) was disolved in dry methylene chloride (25 mL), the equimolar amount of arylglyoxal hydrate was added, and the mixture was heated under reflux until complete reaction. Analytically pure carbinolamines **9** crystallized by cooling from the reaction crude and were used without subsequent purification. All compounds **9** were white amorphous solids stable for months at −20 °C.

Oxidation of 4a in Basic Medium. A solution of 0.5 g (2.38 mmol) of **4a** in ethanol (250 mL) and aqueous 30% NaOH (1 mL) was stirred in an open flask for 4 h. After this time the solvent was evaporated under vacuum, and the residual white solid dissolved in water (15 mL). The resulting clear solution was extracted with methylene chloride (3 × 25 mL). The organic layers were dried ($MgSO_4$) and evaporated under vacuum. After chromatography (silica gel, benzene/ethyl acetate 10:1) *N*-(2-pyridyl)benzamide (0.32 g, 67%) was obtained. Benzoic acid (70 mg, 25%) was recovered from the aqueous layer after acidic workup and methylene chloride extraction.

Oxidation of 4a in Neutral Medium. A solution of **4a** (0.5 g, 2.38 mmol) in methanol (125 mL) was irradiated in an open flask under direct sunlight for 15 h on a sunny day in an open vessel. After this time the solution was clear and the former yellow color had disappeared. The solvent was removed under vacuum and the crude material chromatographied (silica gel, benzene/ethyl acetate 10:1). In order of elution, methylphenylglyoxalate (50 mg 15%) and *N*-(2-pyridyl)benzamide (0.19 g, 40%) were obtained.

Reaction of 4a in MeOH/$HClO_4$. Synthesis of the Amino Ester 16. A solution of **4a** (1 g, 4.76 mmol) in methanol (5 mL) and 60% $HClO_4$ (2 mL) was heated under reflux for 24 h. The reaction mixture was cooled at 0 °C and neutralized with saturated sodium carbonate solution. Compound **16** was isolated after methylene chloride extraction and methylene chloride recrystallization in a 65% yield, mp 101–2 °C; ^{1}H NMR (60 MHz, $DCCl_3$) δ 3.7 (s, OMe), 5.6 (s, br, 2 H, CHNH), 6.3–6.7, 7.1–7.6, 8.0–8.2 (m, 9 H, Ar); ^{13}C NMR (DMSO-d_6) δ 172.2 (CO), 157.6, 147.2, 137.5, 136.7, 128.7, 128.1, 127.9, 112.2, 109.6, 58.1 (NHCH), 51.9 (Me); IR (KBr) ν 3240 (br, NH), 1750 (CO). Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.42; H, 5.78; N, 11.57. Found: C, 69.31; H, 5.55; N, 11.34.

Catalytic Hydrogenation of 4a. A solution of 0.5 g (2.38 mmol) of **4a** in methanol (10 mL) and 35% HCl (1 mL) was hydrogenated in the presence of 10% palladium on charcoal (20 mg) under 35 psi of hydrogen. After 2.5 h the catalyst was filtered, and the solvent removed under vacuum. Compound **17** was obtained from the crude hydrochloride by treatment with aqueous sodium carbonate solution followed by recrystallization from methanol; yield 70%; mp (dec) 224–28 °C (MeOH); ^{1}H NMR (60 MHz, DMSO-d_6) δ 1.5–2.2 (m, 4 H, H6, H7), 2.6–3.1 (m, 2 H, H8), 3.7–4.1 (m, 2 H, H5), 6.8–7.8 (m, 5 H, Ar); ^{13}C NMR (DMSO-d_6) 139.6 (C9), 138.3 (C3), 128.9, 127.7, 127.2, 124.6 (Ar), 111.1 (C2), 41.7 (C5), 21.2 (C8), 20.6 (C7), 17.8 (C6); UV (MeOH) λ (log ϵ) 264 (4.24), 206 (4.08); mass spectrum (ei), m/z 214 (M). Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.90; H, 6.54; N, 13.08. Found: C, 72.88; H, 6.40; N, 13.18.

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Lewis Acid Promoted Condensation of Allylalkoxysilanes with Carbonyl Compounds. Synthesis of Tetrahydropyrans[1]

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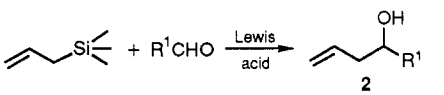
Allylalkoxysilanes **1** condense with aldehydes under Lewis acid conditions to give cis-2,4,6-trisubstituted tetrahydropyrans **3** or the homoallylic alcohols **2**. Factors affecting the reaction have been examined. The enantioselective synthesis of **2** using optically active **1** has also been studied. The reaction is applied to the enantioselective synthesis of (6′-methyl-2′-tetrahydropyranyl)acetic acid (**11**), a natural compound that has been isolated from the glandular secretion of the civet cat.

Introduction

The condensation of allylsilanes with carbonyl compounds (eq 1) under Lewis acid conditions to give homoallylic alcohols **2**, first reported by Sakurai and Hosomi,[2] has been found to be quite useful in organic synthesis. The silyl moiety usually bears three methyl groups. As



(1)

part of our program to examine the effect of substituents on reactions remote from silicon,[3-6] we studied the Lewis

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(2) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, 1295.

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