Heterocyclic X-azolopyridine Intermediates

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A series of heterocyclic coupling agents having tuned hydrophobic chains, has been prepared by reaction of diamino or hydroxy-aminopyridines and *p*-aminosalicylic acid. The acetylation of amino group and hydroxyl in oxazole derivatives showed a selectivity depending on wheter acetic anhydride or acetyl chloride was used. Correlations between structure and spectroscopic data, including related compounds previously described, are reported.

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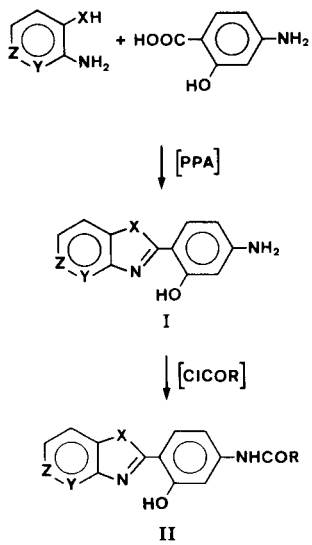
The use of polyphosphoric acid as a reagent for the synthesis of X-azolopyridine systems from *ortho*-disubstituted pyridines and carboxylic acids has been frequently studied and successfully applied to the synthesis of heterocyclic compounds interesting the pharmacological domain [1-4]. The same reaction pathway was applied for the synthesis of intermediates of colouristic interest [5-9].

This paper deals with the synthesis of a series of oxazole and imidazole derivatives **I**, which, by acylation, yielded a series of coupling components **II**, suitable for the synthesis of tuned hydrophobic monoazo dyes.

The pathway of the synthesis is outlined in Scheme 1. As already observed in the preparation of benzo-X-azoles [5] it was found convenient to run first the cyclization step thus avoiding decarboxylation or deacylation during the reaction with polyphosphoric acid.

Scheme 1



X=O, NH; Y=N, CH; Z=CH, N; R=CH_3, C_7H_{15}.

As above mentioned, we were interested in obtaining coupling components having a free hydroxyl (for allowing the formation of an 'azo' chromophore in the *para*-position) and an acylated amino group with short and long chains in order to check the effect of tuned hydrophobicity.

If the acylation step of imidazoles did not provide any surprise, *i.e.* only the amino group was (i) acetylated with acetic anhydride and (ii) acylated with octanoyl chloride, a peculiar behaviour was instead shown by oxazoles. Scheme 2 outlines the reactivity of the oxazole derivative **1** towards common acetylating agents. With acetic anhydride, at room temperature, the undesired acetyl ester **10** was obtained whereas the suitable coupling agent **4** was only obtained by resorting to acetyl chloride. The further treatment of both **4** and **10** with acetic anhydride or acetyl chloride gave the bis-acetyl derivative **11**. The amine **10** was tested as a diazo component for the formation of dye **16**, by coupling to *N*,*N*-diethylaniline (mp 137-138°, λ max 490 nm, log ϵ 4.67, R_f 0.87). Finally, as the reaction with octanoyl chloride was concerned, compound **1** gave only the expected octanamido derivative.

Analytical and spectroscopic data of compounds **1-11** are reported in Table 1. By way of comparison, in Table 2 literature [5,7] data of some related compounds are summarized.

As previously observed [5,6,9] the melting points of the imidazole derivatives are higher than those of their oxazole counterparts, probably because of intermolecular hydrogen bonding. Furthermore, the melting point decrease with the increasing of the alkyl chain length can be ascribed to the negative effect of weighted hydrophobic structures towards the accomodation into a crystalline lattice. Pyridine ring causes a general increase of melting points if compared to benzo-ring, and [4,5-*c*] isomers show lower melting points than [4,5-*b*] ones. Due to the polarity of the substrate, the Rf values of amines are lower than those of the corresponding amides, in agreement with their more polar character. The imidazole derivative systematically show lower Rf values than the corresponding oxazoles, with the lowest values for [4,5-*c*]imidazo isomers, as previously observed [9].

Figures 1 and 2 show the spectral patterns of compounds **I** and of selected acyl derivatives, respectively.

Scheme 2

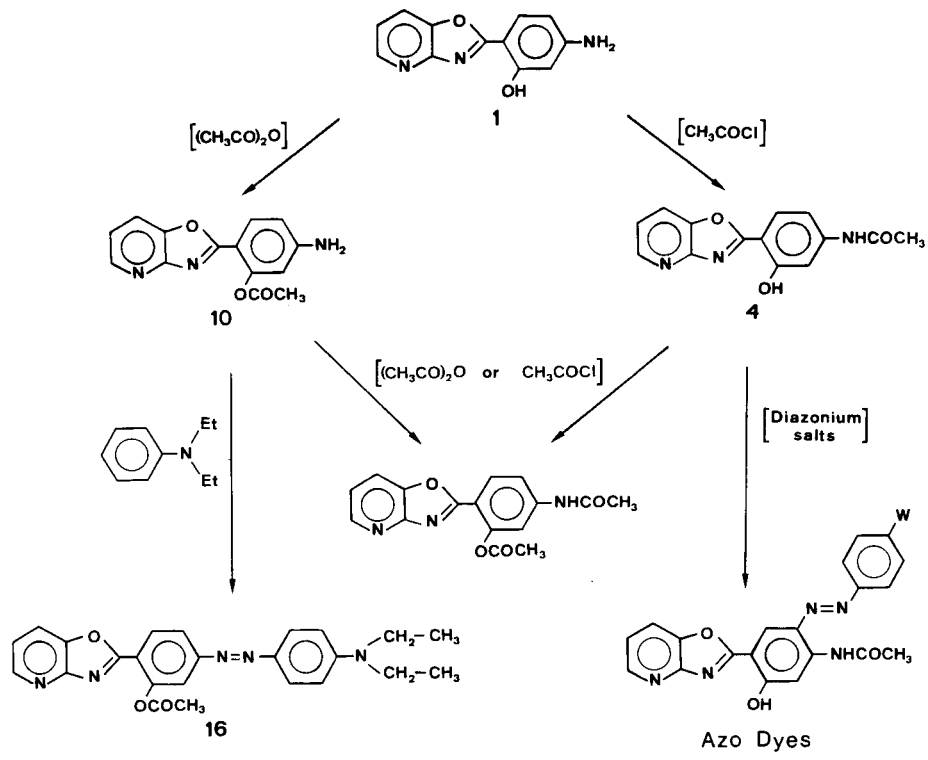
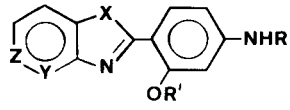


Table 1

Analytical and spectroscopic data of compounds 1-11



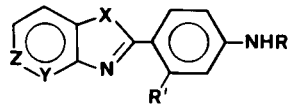
Compound number	Structure X	Y	Z	R	R'	Mp °C	Rf	Empirical Formula	Elemental Analyses Calcd/Found C	H	N	Electronic absorption spectra λmax (nm)[b] (logε)	Crystallization Solvent[a]
1	O	N	CH	H	H	283-5	0.81	$C_{12}H_9N_3O_2$	63.43 63.54	3.99 3.90	18.49 18.53	363 (4.62)	A
2	NH	N	CH	H	H	307-9	0.75	$C_{12}H_{10}N_4O$	63.71 63.58	4.45 4.51	24.76 24.84	353 (4.48)	A
3	NH	CH	N	H	H	296-8	0.48	$C_{12}H_{10}N_4O$	63.71 63.82	4.45 4.47	24.76 24.70	340 (4.38)	B
4	O	N	CH	$COCH_3$	H	304-6	0.81	$C_{14}H_{11}N_3O_3$	62.45 62.53	4.12 4.11	15.61 15.57	355 (4.59)	A
5	O	N	CH	COC_7H_{15}	H	181-3	0.94	$C_{20}H_{23}N_3O_3$	67.97 67.92	6.56 6.63	11.89 11.80	355 (4.58)	A
6	NH	N	CH	$COCH_3$	H	>330	0.75	$C_{14}H_{12}N_4O_2$	62.69 62.55	4.51 4.58	20.88 20.93	336 (4.56)	A
7	NH	N	CH	COC_7H_{15}	H	291-3	0.88	$C_{20}H_{24}N_4O_2$	68.16 68.23	6.86 6.85	15.90 15.84	336 (4.56)	B
8	NH	CH	N	$COCH_3$	H	>330	0.49	$C_{14}H_{12}N_4O_2$	62.68 62.51	4.51 4.57	20.88 20.86	326 (4.45)	A
9	NH	CH	N	COC_7H_{15}	H	240-2	0.67	$C_{20}H_{24}N_4O_2$	68.16 68.02	6.86 6.92	15.90 15.97	326 (4.47)	B
10	O	N	CH	H	$COCH_3$	198-200	0.86	$C_{14}H_{11}N_3O_3$	62.45 62.37	4.12 4.19	15.61 15.69	345 (4.54)	A
11	O	N	CH	$COCH_3$	$COCH_3$	291-3	0.81	$C_{16}H_{13}N_3O_4$	61.73 61.84	4.03 3.95	13.50 13.53	325 (4.59)	A

[a] A = 95% ethanol, B = ethanol/water.

[b] The absorption maxima correspond to the most intense peak of the longwave band.

Table 2

Melting points and spectroscopic data of related compounds 12-18



Compound number	Structure X	Y	Z	R	R'	Mp °C	Electronic absorption spectra λmax (nm)	loge	References
12	O	CH	CH	H	OH	227-8	337	4.58	5
13	NH	CH	CH	H	OH	241-2	338	4.53	5
14	O	CH	CH	$COCH_3$	OH	232-3	330	4.56	5
15	NH	CH	CH	$COCH_3$	OH	>330	327	4.57	5
16	O	N	CH	H	H	262-3	347	4.51	6
17	NH	N	CH	H	H	>330	337	4.38	7
18	NH	CH	N	H	H	329-31	312	4.30	9

The main effects in the long wavelength band of the benzylideneimino chromogen (evidenced in structure **III**) are the following: (i) the pyridine ring in the [4,5-*b*] isomers affects bathochromically the maxima if compared with carbocyclic analogs (9-26 nm; pair: **1-12** 26 nm, **2-13** 15 nm, **4-14** 25 nm, **6-15** 9 nm) whereas [4,5-*c*] isomers show a negligible shift (pair: **3-13** 2 nm, **8-15** -1 nm). This indicates that only in the former isomers the pyridine nitrogen atom participates to the conjugation of the main

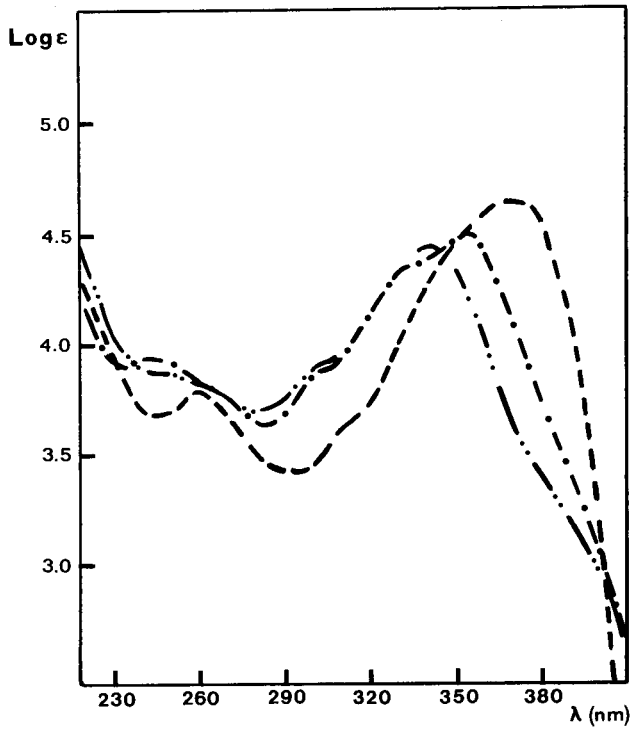


Figure 1. Electronic Absorption spectra of compounds: n. **1** — —, n. **2** —·—, n. **3** —··—.

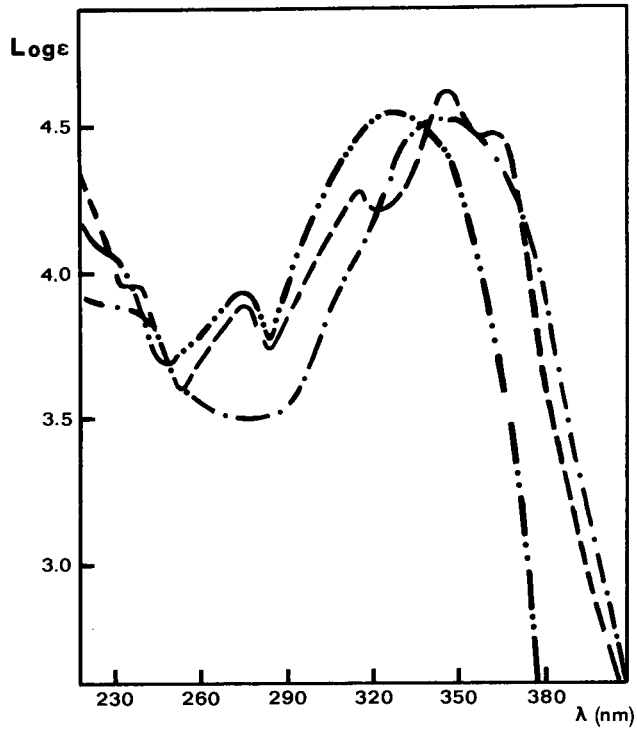
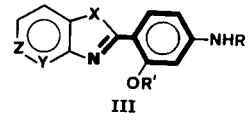


Figure 2. Electronic Absorption spectra of compounds: n. **4** — —, n. **10** —·—, n. **11** —··—.

chromogen; (ii) an '*ortho*' hydroxyl causes a bathocromic shift, higher for [4,5-*c*] isomer (pair: **3-13** 28 nm) than for [4,5-*b*] isomers (pair: **1-16** 18 nm; **2-17** 15 nm); (iii) as previously observed [7,9], the oxazoles absorb at higher wavelengths than imidazoles (10-29 nm, pair: **1-2** 10 nm; **1-3** 23 nm; **4-6** 19 nm; **4-8** 29 nm) and the differences are more marked for the amides, as already noted in the carbocyclic series [5,7]; (iv) acylation of the amino group, decreasing the conjugative ability of the amine nitrogen, gives rise to a general hypsochromic shift, higher for imidazoles (pair: **2-6** 17 nm; **3-8** 14 nm) than for oxazoles (pair: **1-4** 8 nm).



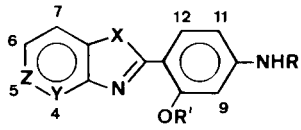
III

In the oxazole series the acetylation of the *ortho* hydroxyl, by lowering the conjugative ability of the hydroxyl and the aptitude to form hydrogen bonds, causes a stronger hypsochromic effect (pair: **1-10** 18 nm) than the acylation of the *para* amino group (pair: **1-4** 8 nm). In this context, acetylation of both the amino and hydroxy substituents is obviously accompanied by the maximum hypsochromic effect (pair: **1-11** 38 nm).

In Table 3 ^1H nmr chemical shifts are reported. All the

Table 3

^{1}H NMR data.



Compound	Structure					Chemical shifts (ppm)									
number	X	Y	Z	R	R'	4	5	6	7	9	11	12	$-COCH_n$[a]	$>CH_2$	$-CH_3$
1	O	N	CH	H	H	----	8.45	7.36	8.13	6.22	6.33	7.71	----	----	----
2	NH	N	CH	H	H	----	7.92	6.76	7.82	6.04	6.07	7.55	----	----	----
3	NH	CH	N	H	H	9.00	----	8.36	7.72	6.19	6.24	7.82	----	----	----
4	O	N	CH	$COCH_3$	H	----	8.55	7.48	8.26	7.57	7.26	8.00	2.12		
5	O	N	CH	COC_7H_{15}	H	----	8.54	7.47	8.25	7.58	7.27	7.99	2.37	1.45	0.88
6	NH	N	CH	$COCH_3$	H	----	8.37	7.29	8.04	7.44	7.19	8.04	2.11	----	----
7	NH	N	CH	COC_7H_{15}	H	----	8.37	7.29	8.08	7.45	7.22	8.01	2.35	1.45	0.86
8	NH	CH	N	$COCH_3$	H	8.96	----	8.33	7.66	7.47	7.19	8.06	2.10	----	----
9	NH	CH	N	COC_7H_{15}	H	8.95	----	8.33	7.65	7.48	7.22	8.05	2.35	1.45	0.88
10	O	N	CH	H	$COCH_3$	----	8.46	7.36	8.13	6.43	6.66	7.96	2.42	----	----
11	O	N	CH	$COCH_3$	$COCH_3$	----	8.56	7.49	8.26	7.78	7.63	8.26	2.46[b] 2.14[c]	----	----
12	O	CH	CH	H	H	7.68	7.36	7.36	7.68	6.22	6.31	7.68	----	----	----
13	NH	CH	CH	H	H	7.54	7.19	7.19	7.54	6.16	6.23	7.68	----	----	----
14	O	CH	CH	$COCH_3$	H	7.81	7.44	7.44	7.81	7.53	7.25	7.94	2.11	----	----
15	NH	CH	CH	$COCH_3$	H	7.64	7.25	7.25	7.64	7.42	7.23	7.96	2.11	----	----

[a] n = 2 for compounds 5, 7, 9.
n = 3 for compounds 4, 6, 8, 10, 11.

[b] $-OCOCH_3$

[c] $-NHCOCH_3$

Table 4

Acylation Effects in the Oxazole Series

Compound number / 1	$\Delta\delta$, ppm [a]					
	5	6	7	9	11	12
4	0.11	0.12	0.13	1.35	0.92	0.29
10	0.01	0.00	-0.01	0.21	0.32	0.26
11	0.12	0.12	0.13	1.56	1.30	0.55

[a] $\Delta\delta$ = δ acylated compound - δ compound 1

spectra were of the first order, except for the benzo ring signals in compounds **11** and **13**. The data are consistent with the assigned structures. In particular, so far as compound **10** is concerned, the chemical shift values of protons 9, 11, 12 agree with the presence of an esther group. The pyridine protons, in the oxazole derivatives, are shifted downfield with respect to the imidazole analogs. Also the protons of the benzo ring show similar but less marked effects. The same trend can be observed in the benzo series, compounds **12-15**. Acylation of the amino group exerts a general deshielding effect on *pyrido* and *benzo* protons. Only in the [4,5-*c*]imidazoles weak shielding effects on the pyrido protons are observed. Table 4 summarizes the effects of acylation in the oxazole series. The acylation of the amino group produces a stronger deshielding effect, compound **4** than the acylation of the hydroxyl group, compound **10**. It is interesting to note that in compound **11**, in which both ester and amido groups are present, the shielding effects are almost additive.

The present paper is confined to describing the heterocyclic intermediates for the synthesis of heterocyclic azo dyes depicted in Scheme 1. The dyes will be described elsewhere including their technical properties. As a preview on this topic, the dyes show a very marked tendency to aggregation and interesting considerations will be made possible by investigating the spectra at different concentrations and in presence of surfactants.

EXPERIMENTAL

Commercial *p*-aminosalicylic acid (PAS), 2,3-diaminopyridine, 3,4-diaminopyridine, 2-amino-3-hydroxypyridine and acylchlorides were employed.

Compounds **1-3** were synthesized condensing *p*-aminosalicylic acid with the equimolar amount of the corresponding diamino or amino-hydroxypyridine, in polyphosphoric acid (85% phosphorus pentoxide) for three hours at 200°. The reaction mixture was poured into distilled water and the precipitate, after neutralization, was collected and slurried in dilute sodium carbonate. The base was finally collected by filtration, dried and crystallized. The ^{1}H nmr spectra of compounds **2** and **3** are also cited in [10-12].

Compound **4** was prepared by dropwise addition of acetyl chloride (1.2 moles) to a pyridine solution of compound **1** (1 mole) at room temperature for 7 hours under stirring. The reaction mixture, kept overnight, was concentrated to a small volume by vacuum distillation and poured into a large volume of distilled water. The solid was collected by filtration, dried and purified by crystallization.

Compounds **5-9** were prepared following the same procedure of compound **4**, reacting 1.2 moles of acyl chloride with one mole of compound **2** or **3**. Using acetic anhydride (2.5 moles) the same products have been recovered.

Compound **10** was similarly obtained, by reaction of compound **1** (1 mole) with acetic anhydride (2.5 moles) at 25°.

Compound **11** was synthesized reacting compound **4** or **11** (1 mole) with acetic anhydride or acetyl chloride (2.5 moles) at 50° and following the previously reported method.

Compound **16** was prepared by diazotization of compound **11** with hydrochloric acid and sodium nitrite, following the usual procedure and coupling with *N,N*-diethylaniline in acetic acid. The dye was precipitated at *p*H 4.5 by adding sodium acetate in aqueous solution and purified on a Kiesel-gel 60 column using ethyl acetate as eluent.

Electronic spectra were recorded in ethanolic solution on a Pye Unicam SP 8-100 spectrophotometer.

The ^{1}H nmr spectra were obtained on a Jeol GX/270 spectrometer in DMSO-d_6 solution (6% W/v), using the solvent signal (2.52 ppm) as internal standard. The measurement conditions were as follows: number of data points 32 K, spectral width 4 KHz, cycle times 5 sec, number of transients 25, flip angles 60°, line broadening factor 0.1, sample speed rotation 15 Hz, temperature 25°.

The Rf data were obtained on silica gel 60 F-254 tlc plates (Merck), using BAW 4:1:5 as eluent.

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