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SYNTHESIS OF NEW HETEROCYCLIC PHENOLS : 8-HYDROXY-IMIDAZO [1,2-a] PYRIDINE

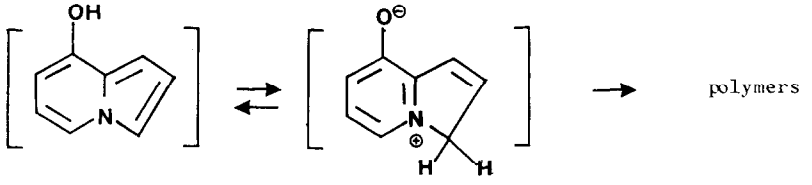
R. RYDZKOWSKI, D. BLONDEAU and H. SLIWA*

Laboratoire de Chimie Organique, Université des Sciences et Techniques de Lille
59655 Villeneuve d'Ascq Cédex, France.

Summary : Preparation of the unknown title compound has been achieved by condensation of 2-amino-3-hydroxy-pyridine with chloroacetaldehyde. Activation by the free phenolic hydroxyl allows preferential nitration of the pyridine ring, in marked contrast to the behavior of the related ethers which suffer electrophilic substitution on the imidazole moiety, as usual in the series.

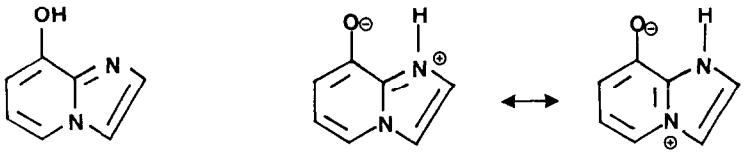
The electron-donating properties of an hydroxyl group endows aromatic structures bearing this substituent with an enhanced reactivity as a consequence of activation towards electrophilic substitution. Furthermore, synthesis of heterocyclic phenols presents interest not only for synthetic purposes but also for tautomerism studies since interaction of the OH group with the heteroatom(s) can lead to prototropism.

In the field of fused heterocycles derived from 3-hydroxy-pyridine, we have previously investigated the 8- and 6- indolizinols series[1], and shown that the corresponding free phenolic structures were stable if the indolizine nucleus was substituted at the 3-position by a withdrawing group. The unstability of the parent phenols was assumed to result from the high reactivity of their zwitterionic tautomers of the oxido-pyridinium type[2] (scheme 1).



Scheme 1

In the present paper we report the preparation of 8-hydroxy-imidazo(1,2-a)pyridine 1 and preliminary results in the study of its reactivity[3]. By comparaison with the above cases, the extra nitrogen atom was expected to stabilize the free phenolic structure by preserving aromaticity of the five membered ring in the zwitterionic tautomer 2 (scheme 2).



1 2

Scheme 2

Although several variously substituted imidazo(1,2-a)pyridine have been prepared, no synthetic route to 8-hydroxy-imidazo(1,2-a)pyridine itself have been reported[4,5] ; only a recent patent[6] claimed the synthesis of 8-hydroxy-2-methyl-imidazo(1,2-a)pyridine but with no mention of yield, spectral data and reactivity study. This publication prompts us to describe our results in this field especially for the unknown 8-hydroxy unsubstituted imidazo-(1,2-a)pyridine.

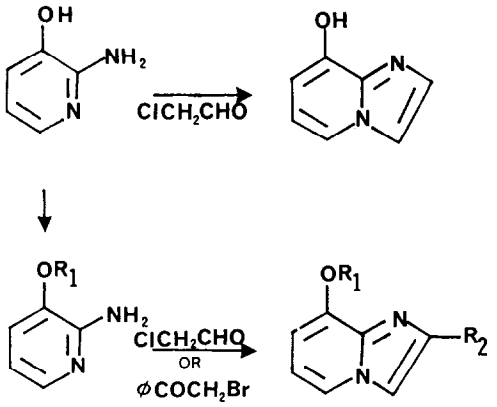
The preparation of this new "phenol" was carried out by reacting 2-amino-3-hydroxy--pyridine with chloroacetaldehyde (1.05 eq.) in absolute ethyl alcohol at reflux for 12 hours ; after work up the product was isolated in a quantitative yield as its hydrogen chloride salt. The free base was liberated by dissolution of the hydrochloride in distilled water and subsequent neutralization ; filtration of the water insoluble 8-hydroxy-imidazo-(1,2-a)pyridine followed by crystallization from water or absolute ethyl alcohol afforded in high yield (82%) the purified compound which presented the following data : mp 186°C (EtOH, H_2O) ; ^{1}H-NMR (D_2O, 1% DSS) δ : 7.8-7.6 (m, H-2, H-5, H-3), 7.0 (m, H-6), 6.7 (m, H-7) ppm ; ^{13}C-NMR (D_2O, 1% DSS) δ : 123,9 (C-2), 116.7 (C-3), 117.5 (C-5), 115.7 (C-6), 121.2 (C-7), 154.0 (C-8), 141.1 (C-8a) ppm ; UV (H_2O) λ_{max} (log ε) : 298 (4), 277 (3.88), 222 (4.23) nm ; IR (KBr) ν : 2800-2300 (bonded OH), 1630, 1550, 1480 (aromatic ring) cm^{-1}.

Insolubility in CCl_4 or CS_2 does not allow IR study at variable dilution of the nature of hydrogen bonding, but hypothesis of an intramolecular bond can be ruled out by the large concentration dependence of the hydroxyl PMR signal in $CDCl_3$ (from 9 to 4.4 ppm). ^{1}H-NMR of the hydrochloride in D_2O (see table) shows that protonation occurs at N-1, as usual in the series[7], and not at C-3 as for indolizines[8], since the whole spectrum is deshielded by comparison with that of the free base, attesting that aromaticity is still maintained in the cation. This conclusion is corroborated by the IR spectrum (KBr) which presents an additional band at 3320 cm^{-1} (νN-H) and a shift to higher frequency (c.a. 1660, 1580 and 1520 cm^{-1}) for the ring stretching vibrations in accordance with a pyridinium structure[9].

It should be noticed that the condensation was not performed in the presence of sodium hydrogenocarbonate which is generally used[10] during synthesis of imidazo(1,2-a)pyridines with α-haloketones (or aldehydes). This reagent is introduced in excess at the beginning of the reaction to prevent formation of protonated species that would lack nucleophilicity required as well for the displacement of halide ion, as for the condensation on the carbonyl group. However recent mechanism investigation of condensation of phenacyl bromide with

2-amino-pyridine had led Paudler[11] to the proposal that absence of sodium bicarbonate may be beneficial, since the reaction involves a dehydration step which is subject to acid catalysis.

In our case no definite product was isolated if $NaHCO_3$ was added to the reaction mixture, owing probably to formation of more reactive phenolate anion that can condense itself on chloroacetaldehyde, while synthesis of a wide range of akyl ethers related to this new "phenol" could be performed in presence of this base if the hydroxyl group was first alkylated (scheme 3). Among these derivatives special mention should be made of the benzyl and allyl ethers since they can be easily cleaved to the free phenol by known procedures ; for instance the compound 5 has been quantitatively debenzylated at reflux of cyclohexene in presence of $Pd(OH)_2$[12].



R_1	R_2 H	R_2 Ø
CH_3	3	4
$CH_2Ø$	5	6
CH_2-CH = CH_2	7	8
CH_2-C≡CH	9	10

Scheme 3

Table : ^{1}H-NMR data ($CDCl_3$, TMS, ppm)

	H_2	H_3	H_5	H_6	H_7	R_1	R_2*
3		7.55 m	7.72 dd	6.67 dd	6.4 dd	3.99 s	
4		7.83 s	7.75 dd	6.66 dd	6.42 dd	4.04 s	
5		7.61 m	7.80 dd	6.4 - 6.8 m		5.36 s ; 7.35-7.55 m	
6		7.9 s	7.80 dd	6.4 - 6.8 m		5,45 s ; 7.1 -7.7 m	
7		7.60 m	7.81 dd	6.4 - 6.8 m		4.78 dt; 6.2 5.5 5.3 m	
8		7.86 s	7.78 dd	6.5 - 6.8 m		4.87 dt; 6.3 5.5 5.3 m	
9		7.63 m	7.86 dd	6.6 - 6.9 m		5.02 d ; 2,54 t	
10		7.9 s	7.84 m	6.5 - 6.8 m		5.06 d ; 2.56 t	
1, HCl**	7.9 d	8.06 d	8.16 dd	7.05- 7.4 m			

* For the 2-substituted ethers, the phenyl group gives rise to two multiplets at 7.35-7.6 and 7.9-8.25ppm.

** In D_2O, 1% DSS.

Study of the reactivity of this new class of compounds is presently in progress[13] and shows that activation of the pyridine ring by the free phenolic OH is sufficient to render the 5- and 7-positions more reactive towards electrophiles (e.g. nitration) than the 3-position ; in contrast, the phenolic ethers show the normal reactivity of imidazo(1,2-a)pyridine for which substitution by electrophilic reagents occurs preferentially at the 3-position[10,14]. These results are in agreement with theoretical reactivity study by MNDO method developped by us for this class of compounds[15].

Further studies in this field are now underway ; all compounds reported in this text gave satisfactory accurate mass measurements, elemental analysis and consistent n.m.r. spectra as shown in the above table for some representatives synthetized in this work.

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