SYNTHESES OF 3,8-DIHYDROXYIMIDAZO[1,2-a]PYRIDINES AND [1,2-a]PYRAZINES

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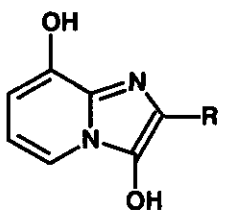
Abstract -3,8-Dihydroxyimidazo[1,2-a]pyridines and [1,2-a]-pyrazines were prepared by condensation of glyoxal derivatives with methyl or benzyl ethers of 2-amino-3-hydroxypyridine and pyrazine followed by cleavage of the ether group.

In our preceding studies, we have synthesized heterocyclic phenols derived from fused heterocycles with a bridgehead nitrogen atom.[1-6] As a development in this field, the present paper describes the synthesis of compounds bearing a second hydroxyl group located in the imidazol ring. The additional hydroxyl group was expected to provide a potentiel tautomerism and to modify the complexing properties of these new heterocyclic diphenols.

More particularly 3,8-dihydroxyimidazo[1,2-a]pyridines (**1**) and [1,2-a]pyrazines (**2**) have been prepared as their 2-substituted derivatives. In addition, extension of the studied synthesis to 3-hydroxy-8-nitroimidazo[1,2-a]pyridines (**3**) has been also realized.



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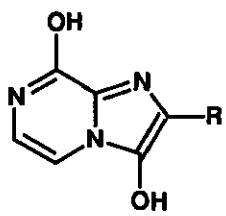

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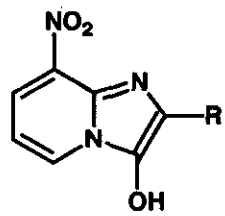

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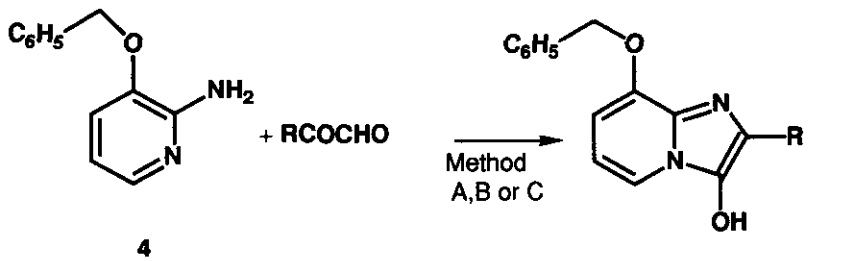
The reaction of some glyoxal derivatives with different 2-amino heterocycles in acidic medium or in organic solvent with or without $BF_3 \cdot Et_2O$ complex as a catalyst has been already described. Thus Goto,[7] Alcaide,[8] and Barlin[9] have reported the synthesis of 3-hydroxyimidazo[1,2-a]pyrimidines and pyrazines, 3-hydroxyimidazo-[1,2-a]pyrimidines and [1,2-b]pyridazines. Alcaide described also the synthesis of 3-hydroxy-8-methoxy-2-phenylimidazo[1,2-a]pyridine as the unique product of this class of compounds,[8] but no mention of dihydroxylic derivatives was reported in literature. Previous work in our laboratory has shown that methyl or benzyl ethers of 2-amino-3-hydroxyazines are judicious starting material for the synthesis of fused heterocyclic phenols bearing their hydroxyl group in the azine ring In order to introduce a second hydroxylic group in the imidazole moiety, the condensation of such compounds with glyoxal and its derivatives appeared to be a promising way. So the condensation of phenylglyoxal with 2-amino-3-benzyloxypyridine (4) was realized according to the procedure described by Alcaide for the preparation of 2-aryl-3-hydroxyimidazo[1,2-a]pyridines. The reaction was performed by mixing equimolecular amounts of the two compounds at ambient temperature in benzene solution for 48 hours. This procedure represented the first method (A).

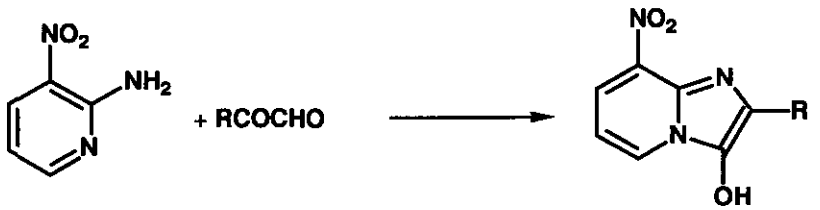
A lesser reactivity was observed for the phenylglyoxals that are para-substituted by electron withdrawing group such as chloro and nitro groups, no formation of condensation products were observed in these conditions. To realize the condensation, it was necessary to operate in the presence of a catalytic amount (one drop) of $BF_3 \cdot Et_2O$ complex in dichloromethane; this procedure represented the second method (B).



4

5 R=C_6H_5 ,Method A
6 R=p-Cl-C_6H_4 ,Method B
7 R=p-NO_2-C_6H_4 ,Method B
8 R=CH_3 , Method C

For methylglyoxal, the methods A and B were ineffective. In order to observe the condensation, it was necessary to realize it in a concentrated and warmed hydrochloric acid solution; this procedure constituted the method C. But applying these reaction conditions to phenylglyoxal and its derivatives afforded polymeric materials probably as a consequence of reaction of cationic species on phenyl groups. The influence of a substituent borne by the starting aminoazine in the course of the reaction was illustrated with the reaction of 2-amino-3-nitro-(9) and 5-nitropyridine (10) with different glyoxals. When 2-amino-3-nitropyridine was allowed to react with phenylglyoxal, the condensation occurred in dichloromethane in the presence of a



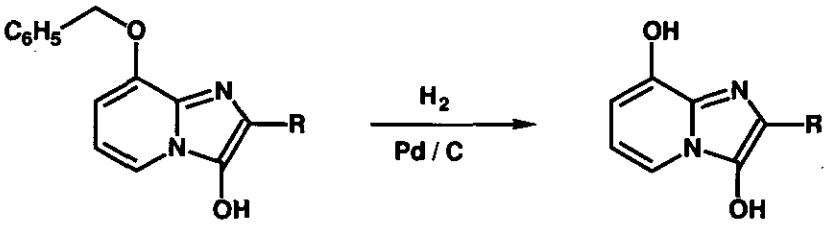
9

11 R=CH_3 ,Method C
12 R=C_6H_5,Method B

catalytic amount of $BF_3{\cdot}Et_2O$ complex. Methylglyoxal did not react under these conditions but reacted if the reaction was performed in acidic solution at 100°C. By contrast, 2-amino-5-nitropyridine was recovered whatever were the employed conditions and the glyoxal derivatives. All these results showed that the reaction is very sensitive to the influence of the group substituting either the pyridine ring or the

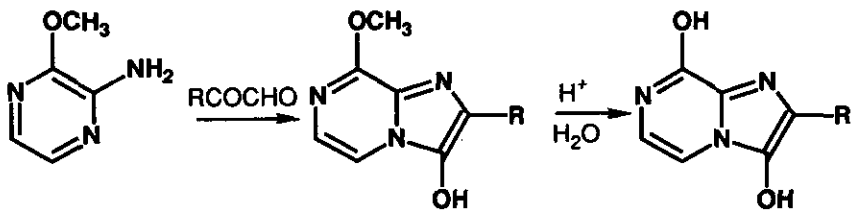
glyoxal. It is noticeable that no reaction was observed whatever were the conditions when 4-amino-5-benzyloxypyrimidine was allowed to react with methylglyoxal, phenylglyoxal, p-chloro-, and p-nitrophenylglyoxal by contrast with what was observed, on the other hand, when alkoxyaminoazines were condensed with β-dicarbonyl compounds. [4]

The preparation of free phenols corresponding to the previous 8-benzyloxyethers was realized by a classical method: the hydrogenolysis by hydrogen in the presence of palladium according to the method described by Augustine.[10] But in our case, a partial hydrogenation of the six membered ring occurred and furnished tetrahydro derivatives as minor by-products.



13 R=CH_3
14 R=C_6H_5
15 R=p-Cl-C_6H_4

When the preceding reactions were performed starting from 2-amino-3-methoxypyrazine (**16**) and glyoxals, the condensation was observed with phenylglyoxal using the method B and with methylglyoxal only when the method C was employed. In the second case, hot acidic medium did not allow the isolation of 3-hydroxy-8-methoxy-2-methylimidazo[1,2-a]pyrazine (**17**) but furnished directly 3,8-dihydroxy-2-methylimidazo[1,2-a]pyrazine (**18**) as a result of the easy hydrolytic scission of the methoxy group as we have precedently observed for other series. In the first case, the method was milder so that 3-hydroxy-8-methoxy-2-phenylimidazo[1,2-a]pyrazine (**19**) could be obtained. Treatment with concentrated hydrochloric acid provided 3,8-dihydroxy-2-phenylimidazo[1,2-a]pyrazine (**20**) in a similar manner, accompanied with some decomposition products.



16

17 R=CH_3 ,Method C
19 R=C_6H_5,Method B

18 R=CH_3
20 R=C_6H_5

In accordance with the results obtained by Manson[11] in a uv study of β-hydroxyazines and with those observed by Alcaide for 3-hydroxy-2-phenylimidazo-[1,2-a]pyridine, the synthesized compounds exhibited a zwitterionic structure in solution in neutral medium as shown by the bathochromic shift observed in the uv spectra comparatively to the spectra recorded in acidic solution. We have not attempted to obtain any model compound to assign definite zwitterionic structure, since both acetylation and methylation, in different reaction media and reaction conditions, were fruitless for compounds that beared only one hydroxyl group, as described by Alcaide.[8]

Concerning ^1H nmr and ^{13}C nmr studies, all assignments were made either by comparison with published results of Alcaide[8] or by an incremental method using shifts and increments noted for benzene, pyridine, imidazo[1,2-a]pyridine and pyrazine[12] or also by use of a DEPT technique. The amide structure of the compound (18) was undoubtly established by the observation of a coupling between the proton of the NH group and H_6. In most all cases, for the imidazo[1,2-a]pyridine series bearing a benzyloxy group in 8-position, H_5 was the most deshielded proton, followed by H_7 and H_6 upfield. In ^{13}C nmr, DEPT, relative intensity of the observed signals and already described deshielding effects led to assignments which, in most all cases, respected the following sequence $C_8 > C_{8a} > C_3 > C_5 > C_7 > C_2 > C_6$. In the case of the products which were substituted at 2-position by a phenyl, p-chloro or p-nitrophenyl group, the signal of carbon C_2 appeared at a more deshielded value just after the signal of C_3 and before those of C_5 and C_7. The nitro group deshielded more extensively the signals of carbons C_8 and C_6. Attributions for the pyrazine series were accomplished in a

similar manner and did not appeal special comments. In a few cases, ^{1}H nmr and ^{13}C nmr could not be recorded in a reproducible manner owing to the insolubility of the compounds in various common nmr solvents and to the degradation which occurred when one tried to solubilize these products by heating as it was already described by Standborough[13] for similar compounds.

In conclusion, a number of new heterocyclic phenols and diphenols in the imidazo-[1,2-a]pyridine and pyrazine series have been synthesized. The influence of the substituents present on the starting aminoazine and the type of glyoxal derivative used in the condensation led to three types of reaction conditions depending on the facility of the reaction. If the reaction is not novel, the synthetized compounds may be judicious starting material for the syntheses of *N*-(2-pyridyl)-α-amino acids in which the heterocyclic moiety bears a functional group as described in a following report.

EXPERIMENTAL SECTION

Melting points were determined in capillary tubes on a Buchi SMP 20 apparatus and are uncorrected. ^{1}H and ^{13}C nmr spectra were recorded on Bruker WP60 (60 MHz), Bruker WP80 (80 MHz), and Bruker AM 400WB (400 MHz) spectrometers. The following abbreviations are used: br = broad, d = doublet, dd = double doublet, m = multiplet, q = quadruplet, s = singlet, t = triplet, i = ipso, m = meta, p = para, o = ortho. Chemical shifts were related to tetramethylsilane as an internal standard in DMSO-D_6 (hexadeuteriodimethyl sulfoxide) and $CDCl_3$ (deuteriochloroform). Uv spectra were determined on a Beckman 5270 or Perkin Elmer Lambda 15 spectrophotometer. Mass spectra were measured on a Riber 10-10 apparatus operating with an activation energy of 70 ev or on Kratos Concept II NH spectrometer in a FAB mode (1mA, 7kV, Xe). Combustion analysis for C, H, and N were performed by Service Central de Microanalyse du CNRS.

8-Benzyloxy-3-hydroxy-2-phenylimidazo[1,2-a]pyridine (5):

To a solution of 1.32 g (6.59 mmol) of 2-amino-3-benzyloxypyridine (**4**) in 15 ml of benzene was added in one portion 1 g (6.59 mmol) of phenylglyoxal monohydrate. After 48 h at 20°C under stirring, the resulting mixture was filtered and the residue was recrystallized from methanol to give **5** (2 g, 98 %) as a crystalline solid: mp 220°C; ir ν max (KBr) cm^{-1}: 3050-2550 (OH); uv λ max (CH_3OH) nm: 350 (log ε 3.07), 288 (3.9), 225 (4.29); uv λ max (CH_3OH, HCl) nm: 315 (log ε 4.01), 245 (4.13); ^1H nmr (DMSO-D_6) δ ppm: 5.37 (s, $OCH_2C_6H_5$), 7.37-7.26 (m, $OCH_2C_6H_5$, C_6H_5), 7.57-7.20 (m, H_6, H_7, embedded by protons of phenyl groups), 8.15 (dd, J = 7.7 Hz, J = 1.0 Hz, H_5), 10.30 (s, OH); ^{13}C nmr (DMSO-D_6) δ ppm: 129.10 (C_2), 131.63 (C_3), 115.80 (C_5), 112.59 (C_6), 115.85 (C_7), 149.28 (C_8), 139.45 (C_{8a}), 69.50 ($OCH_2C_6H_5$), 130.06-121.60 (C_6H_5, $CH_2C_6H_5$); ms m/z (rel. int.): 316 ($M^{+\cdot}$, 15), 315 (2.96), 198 (100), 197 (25), 91 (100). *Anal.* Calcd for $C_{20}H_{16}N_2O_2 \cdot 2H_2O$: C, 68.16; H, 7.95; N, 5.72. Found: C, 68.45; H, 8.19; N, 5.50.

8-Benzyloxy-2-p-chlorophenyl-3-hydroxyimidazo[1,2-a]pyridine (6):

To a solution of 2-amino-3-benzyloxypyridine (**4**, 0.64 g, 3.2 mmol) in 10 ml of methylene dichloride, was added in one portion 0.537 g (3.2 mmol) of p-chlorophenyl glyoxal.[15] After 5 min, one drop of freshly distilled $BF_3 \cdot Et_2O$ was added. The first resulting precipitate slowly dissolved and then a new compound deposited. After 25 h, the resulting mixture was filtered and the residue was recrystallized from methanol to give **6** (0.77 g, 69 %) as crystalline compound: mp 146-148°C; ir ν max (KBr) cm^{-1}: 3200-3300 (phenolic OH); ^1H nmr (DMSO-D_6) δ ppm: 5.36 (s, $OCH_2C_6H_5$), 7.50-7.30 (m, H_6, H_7, masked by the signals of the protons of the phenyl groups), 7.31 (m, C_6H_4Cl), 7.43 (m, C_6H_5), 8.17 (dd, J=8.6 Hz, J=1.0 Hz, H_5), 11.50 (s, OH); ^{13}C nmr (DMSO-D_6) δ ppm: 128.50 (C_2), 126.12 (C3), 115.90 (C_5), 112.67 (C_6), 115.00 (C_7), 143.41 (C_8), 135.80 (C_{8a}), 70.35 ($OCH_2C_6H_5$), 131.28, 128.46, 128.17, 128.04 (i, m, p, o, CH_2-C_6H_5), 129.66, 127.94, 128.46, 123.80 (C_6H_4Cl); ms m/z (rel. int.): 352 ($M^{+\cdot}$, 1.01), 350 (2.67), 351 (1.96), 349 (4.17), 261 (6.93), 259 (20.07), 233 (8.34), 231 (23.98), 91 (100). *Anal.* Calcd for $C_{20}H_{15}N_2O_2Cl \cdot 2.5\ H_2O$: C, 60.68; H, 5.09; N,

7.07. Found: C, 60.83; H, 4.86; N, 7.12.

8-Benzyloxy-3-hydroxy-2-p-nitrophenylimidazo[1,2-a]pyridine (7):

According to the preceding procedure, the compound (**7**) was obtained starting from p-nitrophenylglyoxal[15] and **4** in a 78 % yield after recrystallization from methanol: mp 225°C; ir ν_{max} (KBr) cm^{-1}: 3250-3000 (phenolic OH); ^1H nmr and ^{13}C nmr: due to its insolubility in most of the nmr solvents, nmr spectra gave no reproducible or interpretable analysis. In fact, nmr spectra showed that the product was accompanied by degradation products induced by the heating in DMSO-D_6; ms m/z (rel. int.): 360 ($M^{+\cdot}$-H$^{\cdot}$, 20), 269 (25), 241 (4.08), 91 (100). *Anal.* Calcd for $C_{20}H_{15}N_3O_4 \cdot 2.5\ H_2O$: C, 59.11; H, 4.96; N, 10.33. Found: C, 59.28; H, 4.58; N, 9.85.

8-Benzyloxy-3-hydroxy-2-methylimidazo[1,2-a]pyridine (8):

To a mixture of 2 g (10 mmol) of 2-amino-3-benzyloxypyridine (**4**) and pyruvic aldehyde aqueous solution (40 %, 1.7 ml, 10 mmol) was added dropwise 2 ml of concentrated hydrochloric acid. After heating at 90-100°C for 40 min, the mixture was cooled. The resulting precipitate was filtered and recrystallized from methanol to give **8** (1.82 g, 72 %) as a crystalline solid, mp 120-123°C, ir ν_{max} (KBr) cm^{-1}: 3500-2900 (OH); uv λ_{max} (MeOH) nm: 343 (log ε 3.40), 301 (3.79), 239 (4.14); uv λ_{max} (MeOH, HCl) nm: 307 (log ε 3.86), 250 (3.98); ^1H nmr (DMSO-D_6) δ ppm: 2.38 (s, CH_3), 5.40 (s, $OCH_2C_6H_5$), 7.28 (dd, J=6.4 Hz, J=7.2 Hz, H_6), 7.35 (dd, J=7.2 Hz, J=1.0 Hz, H_7), 7.39 (m, $OCH_2C_6H_5$), 8.11 (dd, J=6.4 Hz, J=1.0 Hz, H_5), 11.40 (s, OH); ^{13}C nmr (DMSO-D_6) δ ppm: 111.74 (C_2), 126.52 (C_3), 115.94 (C_5), 108.94 (C_6), 115.86 (C_7), 143.05 (C_8), 135.30 (C_{8a}), 70.86 ($OCH_2C_6H_5$), 135.25, 128.51, 128.06, 128.37 (i, m, o, p, C_6H_5), 8.50 (CH_3); ms m/z (rel. int): 254 ($M^{+\cdot}$, 10), 253 ($M^{+\cdot}$-H$^{\cdot}$, 1.29), 198 (100), 197 (25), 91 (100). *Anal.* Calcd for $C_{15}H_{14}N_2O_2 \cdot HCl \cdot 0.5\ H_2O$: C, 60.10; H, 5.30; N, 9.34. Found: C, 60.46; H, 5.64; N, 9.05.

3-Hydroxy-2-methyl-8-nitroimidazo[1,2-a]pyridine (11):

To a mixture of 1.39 g (10 mmol) of 2-amino-3-nitropyridine and aqueous pyruvic

aldehyde (40 %, 1.7 ml, 10 mmol), was added dropwise 2 ml of concentrated hydrochloric acid. The resulting mixture was warmed at 50-100°C for 1 h. After cooling, an orange solid precipitated. After filtration, the recrystallization from methanol give **11** (1.54 g, 80 %); mp 225-227°C; ir ν_{max} (KBr) cm^{-1}: 3010 -2500 (OH); uv λ_{max} (CH_3OH) nm: 505 (log ε 3.17), 340 (3.66), 295 (3.85), 259 (3.87); uv λ_{max} (CH_3OH, HCl) nm: 388 (log ε 3.61), 292 (3.60), 268 (4.07); ^1H nmr (DMSO-D6) δ ppm: 2.50 (s, CH_3), 7.58 (dd, J=6.5 Hz, J= 7.3 Hz, H_6), 8.75 (dd, J=1.0 Hz, J=7.3 Hz, H7), 8.96 (dd, J=6.5 Hz, J=1.0 Hz, H_5), 10.50 (s, OH); ^{13}C nmr (DMSO-D_6) δ ppm: 113.72 (C_2), 126.03 (C_3), 130.14 (C_5), 128.77 (C_6), 114.76 (C_7), 136.01 (C_8), 133.08 (C_{8a}), 8.93 (CH_3); ms m/z (rel. int.): 193 ($M^{+\cdot}$, 8.32), 139 (14.91), 93 (47.01), 66 (100). *Anal.* Calcd for $C_8H_7N_3O_3 \cdot HCl$: C, 41.84; H, 3.70; N, 18.29. Found: C, 41.90; H, 3.70; N, 18.11.

2-Phenyl-8-hydroxy-3-nitroimidazo[1,2-a]pyridine (12):

To a stirred a solution of 0.44 g (3.2 mmol) of 2-amino-3-nitropyridine in 10 ml of dichloromethane, was added in one portion 0.5 g (3.2 mmol) of phenylglyoxal monohydrate. After 5 min, a drop of freshly distillated $BF_3 \cdot Et_2O$ was added to the resulting mixture. After 168 h, the resulting mixture was filtered and the residue recrystallized from methanol to give **12** (0.57 g,70 %): mp 192-195°C; ir ν_{max} (KBr) cm^{-1}: 3300-2800 (phenolic OH); uv λ_{max} (CH_3OH) nm: 358 (log ε 3.91), 284 (4.20); uv λ_{max} (CH_3OH, HCl) nm: 325 (log ε 3.91), 277 (3.96); ^1H nmr and ^{13}C nmr: due to its relative insolubility in DMSO-D_6, the compound on heating afforded degradation products and so gave no reproducible and interpretable nmr spectra; ms m/z (rel. int.): 254 ($M^{+\cdot}$, 15.20), 226 (100), 150 (60.11). *Anal.* Calcd for $C_{13}H_9N_3O_3 \cdot 2.5\ H_2O$: C, 52.00; H, 4.69; N, 13.99. Found: C, 52.19; H, 4.47; N, 14.22.

3,8-Dihydroxy 2-methylimidazo[1,2-a]pyridine (13):

To a solution of 1g (3.9 mmol) of the compound (**8**) in 70 ml of ethanol 0.3 g of 10 % palladium on carbon was added in a 250 ml autoclave. The hydrogenation was performed under a pressure of 3 bars of hydrogen at 45°C during 8 h with continuous shaking. After cooling, the resulting mixture was filtered on 1 g of celite and the

filtrate was evaporated under reduced pressure to give, after recrystallization from methanol, **13** (0.27 g, 43 %) as a colourless product: mp 163-165°C; ir ν_{max} (KBr) cm^{-1}: 3200-2850 (OH phenolic); uv λ_{max} (H_2O) nm: 398 (log ε 2.98), 317 (3.63), 250 (3.60); uv λ_{max} (H_2O, HCl) nm: 315 (log ε 3.94), 240 (3.75); ^1H nmr (DMSO-D_6) δ ppm: 2.36 (s, CH_3), 7.12 (dd, J=0.9 Hz, J=7.3 Hz, H_7), 7.17 (dd, J=6.6 Hz, J=7.3 Hz, H_6), 7.96 (dd, J= 6.6 Hz, J=0.9 Hz, H_5), 12.10 (s, OH); ^{13}C nmr (DMSO-D_6) δ ppm: 111.36 (C_2), 127.16 (C_3), 116.48 (C_5), 110.50 (C_6), 114.16 (C_7), 142.51 (C_8), 134.94 (C_{8a}), 8.49 (CH_3); ms m/z (rel. int.): 164 ($M^{+\cdot}$, 34), 135 (100), 94 (58), 66 (58), 67 (100). *Anal.* Calcd for $C_8H_8N_2O_2 \cdot HCl \cdot 0.5\ H_2O$: C, 45.83; H, 4.80; N, 13.36. Found: C, 45.75; H, 4.86; N, 12.93.

3,8-Dihydroxy-2-phenylimidazo[1,2-a]pyridine (14):

According to the preceding procedure, the compound (**14**) was obtained starting from 8-benzyloxy-2-phenyl-3-hydroxyimidazo[1,2-a]pyridine (**5**) in 53 % yield after recrystallization from methanol: mp 170-171°C; ir ν_{max} (KBr) cm^{-1}: 3200-2900 (phenolic OH); uv λ_{max} (H_2O) nm: 394 (log ε 2.58), 297 (3.46), 249 (3.82); uv λ_{max} (H_2O, HCl) nm: 312 (log ε 3.69), 241 (3.78); ^1H nmr (DMSO-D_6) δ ppm: 6.71 (dd, J=7.9 Hz, J=1.0 Hz, H_7), 6.84 (dd, J=7.9 Hz, J=7.6 Hz, H_6), 7.42 (m, C_6H_5), 8.14 (dd, J=7.6 Hz, J=1.0 Hz, H_5), 10.30 (s, OH); ^{13}C nmr (DMSO-D_6) δ ppm: 128.00 (C_2), 132.36 (C_3), 113.2 (C_5), 112.30 (C_6), 114.45 (C_7), 142.25 (C_8), 138.60 (C_{8a}), 128.20, 122.10, 128.10, 123.30 (i, m, p, o, C_6H_5); ms m/z (rel. int.): 226 ($M^{+\cdot}$, 5), 197 (13.5), 94 (25), 66 (8.5), 67 (17). *Anal.* Calcd for $C_{13}H_{10}N_2O_2 \cdot H_2O$: C, 63.92; H, 11.47; N, 4.95. Found: C, 64.01; H, 11.71; N, 4.95.

2-p-Chlorophenyl-3,8-dihydroxyimidazo[1,2-a]pyridine (15):

According to the preceding procedure, the compound (**15**) was obtained starting from **6** (1.52 g, 3.85 mmol) in a 40 % yield after recrystallization from methanol: mp 215°C; ir ν_{max} (KBr) cm^{-1}: 3300-3000 (phenolic OH); ^1H nmr (DMSO-D_6) δ ppm: 6.91 (dd, J=7.5 Hz, J=1.0 Hz, H_7), 6.98 (dd, J=8.6 Hz, J=7.5 Hz, H_6), 7.37 (m, C_6H_4Cl), 8.05 (dd, J=8.6 Hz, J=1.0 Hz, H_5), 11.60 (s, OH); ^{13}C nmr (DMSO-D_6) δ ppm: 129.20 (C_2), 126.40

(C_3), 114.70 (C_5), 110.00 (C_6), 114.60 (C_7), 142.50, 142.34 (C_8 and C_{8a}), 124.50, 128.30, 124.90, 128.60 (i, m, p, o, C_6H_4Cl); ms m/z (rel. int.): 262 ($M^{+\cdot}$, 4.81), 260 (30.81), 234 (7.45), 232 (40.36), 197 (79.72), 95 (71.66), 67 (66.04). *Anal.* Calcd for $C_{13}H_9N_2O_2Cl \cdot 2.5\ H_2O$: C, 57.70; H, 5.22; N, 10.36. Found: C, 57.48; H, 5.01; N, 9.97.

3,8-Dihydroxy-2-methylimidazo[1,2-a]pyrazine (18):

According to the procedure described for compound (**8**) and starting from 2-amino-3-methoxypyrazine[16] and pyruvic aldehyde, compound (**18**) was obtained after recrystallization from methanol in a 70 % yield: mp 230°C; ir ν_{max} (KBr) cm^{-1}: 3500-3400 (amide NH); uv λ_{max} (H_2O) nm: 348 (log ε 3.13), 338 (3.34), 222 (3.53); uv λ_{max} (H_2O, HCl) nm: 348 (log ε 3.13), 295 (3.64), 220 (3.85); uv λ max (H_2O, KOH) nm: 348 (log ε 3.13), 331 (3.52), 228 (3.58); ^1H nmr (DMSO-D_6) δ ppm: 2.40 (s, CH3), 4.20 (s, OH), 7.25 (dd, J=8.8 Hz, J=4.2 Hz, H_6), 7.50 (d, J=8.9 Hz, H_5), 12.20 (d, J=4.2 Hz, NH); ^{13}C nmr (DMSO-D_6) δ ppm: 114.30 (C_2), 137.70 (C_3), 119.70 (C_5), 102.60 (C_6), 149.90 (C_8), 124.40 (C_{8a}), 8.90 (CH_3); ms m/z (rel. int.): 165 ($M^{+\cdot}$, 47.42), 137 (41.63), 111 (17.12), 96 (100). *Anal.* Calcd for $C_7H_7N_3O_2 \cdot 2HCl$: C, 35.41; H, 3.81; N, 17.64. Found: C, 35.48; H, 3.66; N,17.27.

3-Hydroxy-8-methoxy-2-phenylimidazo[1,2-a]pyrazine (19):

According to the procedure described for compound (**6**) and starting from 2-amino-3-methoxypyrazine and phenylglyoxal monohydrate, the compound (**19**) was obtained after recrystallization from methanol in a 72 % yield: mp 171-173°C; ir ν_{max} (KBr) cm^{-1}: 3100-2600 (phenolic OH); uv λ_{max} (CH_3OH) nm: 388 (log ε 3.64), 270 (3.84), 227 (3.93); uv λ_{max} (CH_3OH, HCl) nm: 311 (log ε 3.87), 235 (4.12); uv λ_{max} (CH_3OH, NaOH) nm: 388 (log ε 3.64), 270 (3.84), 232 (4.09); ^1H nmr (DMSO-D_6) δ ppm: 3.35 (s, OH), 5.37 (s, CH_3), 7.37 (d, J=8.6 Hz, H_6), 7.00-7.80 (m, C_6H_5), 8.18 (d, J=8.6 Hz, H_5); ^{13}C nmr (DMSO-D_6) δ ppm: 123.75 (C_2), 131.28 (C_3), 112.66 (C_5), 115.91 (C_6), 142.50 (C_8), 135.82 (C_{8a}), 128.47-127.85 (C_6H_5), 70.84 (CH_3); ms m/z (rel. int.): 241 ($M^{+\cdot}$, 20.32), 240 (2.72), 212 (30.63), 109 (12.74), 79 (100). *Anal.* Calcd for $C_{13}H_{11}N_3O_2$: C, 60.22; H, 5.05; N, 16.20. Found: C, 59.87; H, 4.74; N, 16.00.

3,8-Dihydroxy-2-phenylimidazo[1,2-a]pyrazine (20):

The solution of **19** (1 g, 4.1 mmol) in concentrated hydrochloric acid (5 ml) was warmed at reflux for 2 h. After cooling, the mixture was filtered to give **20**, which was obtained in an almost quantitative yield (0.92 g) after recrystallization from methanol: mp 230°C; ir ν_{max} (KBr) cm^{-1}: 3450-2900 (phenolic OH, NH); uv λ_{max} (H_2O) nm: 359 (log ε 3.18), 272 (3.09), 196 (3.18), 236 (3.39); uv λ_{max} (H_2O, HCl) nm: 320 (log ε 3.39), 255 (3.52), 236 (5.60), 190 (4.35); uv λ_{max} (H_2O, KOH) nm: 361 (log ε 3.78), 257 (4.06), 233 (4.16), 209 (4.56); ^1H nmr and ^{13}C nmr: for the same reasons invoked for compound (**12**), ^1H nmr and ^{13}C nmr gave no reproducible and interpretable spectra; ms m/z (rel. int.): 227 ($M^{+\cdot}$, 25.20), 199 (13.43), 96 (100), 68 (38.02). *Anal.* Calcd for $C_{12}H_9N_3O_2 \cdot 0.5$ HCl: C, 58.72; H, 3.90; N, 17.11. Found: C, 58.35; H, 3.86; N, 17.38.

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