2-(4-methylpyridin-2-yl)-1*H*-benzimidazole derivatives. Part II, ^{1}H nmr Characterization

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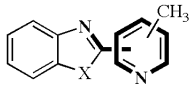
Received August 13, 2002
Received Revised April 29, 2003

A selected series of 2-(4-methylpyridin-2-yl)-1*H*-benzimidazole derivatives, bases and cyclic mono- and bis-salts, were synthesized. Complete ^{1}H nmr characterization is reported. Ambiguous assignments were solved using ^{1}H-^{1}H NOESY analysis. Significant ir and ^{1}H nmr data are presented concerning: i) tautomeric equilibrium of imidazole hydrogen; ii) hydrogen bonds; iii) conformational inversion of partially saturated rings.

J. Heterocyclic Chem., **40**, 649(2003).

Introduction.

Heterocyclic rings, assembled together by C-C bond (**I**), are used as intermediates [1], fine products for drugs [2-5] and color industries [6], complex-forming agents [7-9], redox systems for solar energy conversion [10], and organized molecular assemblies [11].



X = O, S, Se, NH, NR

I

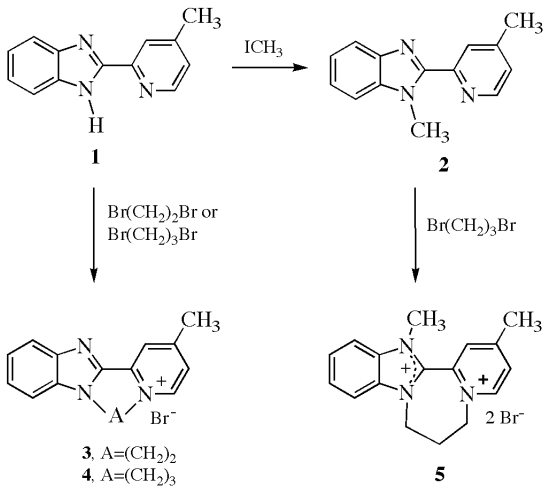
Extensive synthetic work has been performed and general qualitative structure-properties relationships obtained. In particular, their spectral behaviors were discussed extensively [12]. Some imidazole derivatives (bases and salts) showed particular spectroscopic properties, related to distortion effects of pyridylideneimino chromogen [13,14], shown in formula **I** by bold lines, as a function of electrostatic repulsion of positive charges and steric hindrance.

A selected series of 2-(4-methylpyridin-2-yl)-1*H*-benzimidazole derivatives (compounds **1**-**5**) were synthesized, as depicted in Scheme 1 of the present part, following literature procedures, except for compound **3**, whose original synthesis is reported here.

In part I of the work [15], X-ray diffraction technique was used to study the structure of compounds **2**-**5** in the solid state and to acquire the parametric data for a quantitative interpretation of spectroscopic properties, *e.g.* CNDO/S calculations.

In the present part II, the complete ^{1}H nmr characterization of compounds **1**-**5** by a high field instrument (Jeol EX 400 spectrometer) is reported (Table 1). The literature ^{1}H nmr data are partial; only picoline signals were assigned for compounds **1** [20], **4** and **5** [14] since resolution from the low field (60 MHz) nmr equipment was insufficient for precisely assigning benzimidazole and aliphatic bridge proton signals. ^{1}H-^{1}H NOESY analysis was used to solve ambiguous assignments successfully, by observing spatial relationships between nuclei in a molecule by allowing the observation of nuclear Overhauser effect (nOe) cross peaks between neighboring nuclei [16]. Significant ir spectroscopic data are reported and commented on here .

Scheme 1

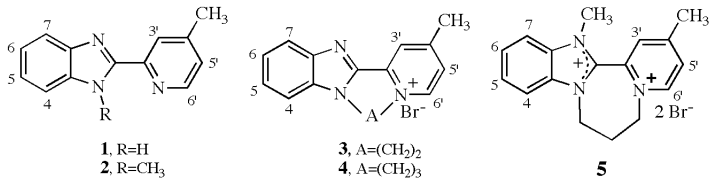


Results and Discussion.

The highfield portion of ^{1}H nmr spectrum of compound **1** shows the singlet of methyl at 2.47 ppm, while the signals shifted downfield at 8.60 ppm, 8.21 ppm and 7.37 ppm are attributable to $H_{6'}$, $H_{3'}$ and $H_{5'}$ pyridine protons

Table 1

^{1}H NMR data of bases and salts.



1, R=H
2, R=CH_3

3, A=$(CH_2)_2$
4, A=$(CH_2)_3$

5

Compound number	Structure R	A	N-H	N-CH_3	C-CH_3	+N-CH_2	+N-CH_2	N-CH_2	CH_2	$H_{3'}$	$H_{5'}$	$H_{6'}$	H_4	H_5	H_6	H_7
						Chemical Shifts, δ (ppm)										
1	H		13.06		2.47					8.21	7.37	8.60	7.56 [a]	7.24 [a]	7.24 [a]	7.68 [a]
2	CH_3			4.23	2.45					8.18	7.34	8.61	7.65	7.34	7.29	7.73
3		$(CH_2)_2$			2.74	5.21		4.88		8.73	8.05	9.03	7.83	7.53	7.44	7.90
4		$(CH_2)_3$			2.74	4.78		4.55	2.75	8.61	8.13	9.12	7.87	7.52	7.44	7.87
5		$(CH_2)_3$		4.32	2.83	5.28 [b]	5.04 [b]		2.83	8.67	8.46	9.47	8.34	7.92	7.92	8.34
						4.29	4.80									

[a] Broad signal; [b] Two large splitted signals appeared for each proton.

respectively (Figure 1). At 25° the aromatic benzimidazole protons give broad signals in the 7.56-7.68 ppm range (H_4 and H_7) and at 7.24 ppm (H_5 and H_6), involved in exchanging phenomena owing to the tautomeric equilibrium of imidazole proton, that gives a singlet at 13.06 ppm. The assignments were obtained by analogy to the assignments of compound **2**, where tautomery is not present. Similar spectral pattern was observed in CD_3OD at –50°C with overlap of $H_{5'}$ and $H_{4'}$ signals.

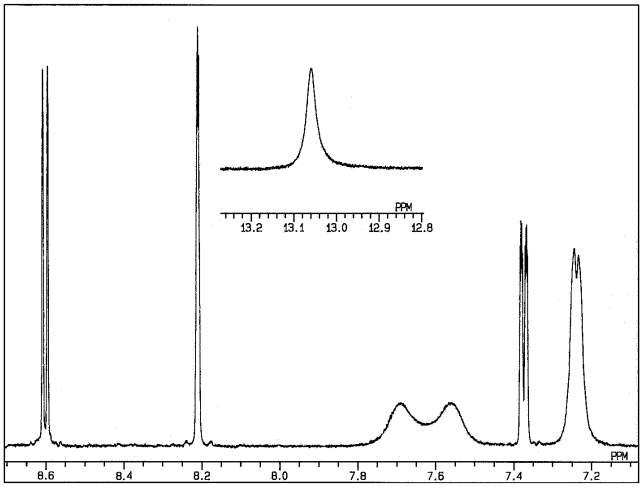


Figure 1. Downfield portion of ^{1}H nmr spectrum of base **1**.

The ir spectrum showed a complex absorption in the 2600-3350 cm^{-1} region, that may be ascribed to the imidazole NH group involved in strong hydrogen bonds, which justifies the high melting point: 228-229° [17]. The bands may be due to Fermi resonance of ν_{NH} with the in-plane, δ_{NH}, and out-of-plane, γ_{NH}, bending modes, *i.e.* $2\delta_{NH}$ and $2\gamma_{NH}$, while the minima may represent the overtone frequency [18]. In accordance with Bellocq *et al.* [17] and Emsley [18], the shift from the non-hydrogen-bonding signal (3518 cm^{-1}) is proposed as a parameter to estimate the intensity of a hydrogen bond. By adopting the center of absorption as the fundamental frequency of ν_{NH} [17], a value $\Delta\delta_{NH}$=543 cm^{-1} is obtained for compound 1. Consequently, the hydrogen bond is weaker than that in imidazole ($\Delta\delta_{NH}$=700 cm^{-1}) [17].

As a consequence of the alkylation of imidazole NH group (compound **2**) only the stretchings of aromatic and aliphatic CH groups are detectable in the 2900-3100 cm^{-1} range of the ir spectrum and a dramatic decrease of the melting point is observable; compound **2** melts at 80-82°. In the highfield

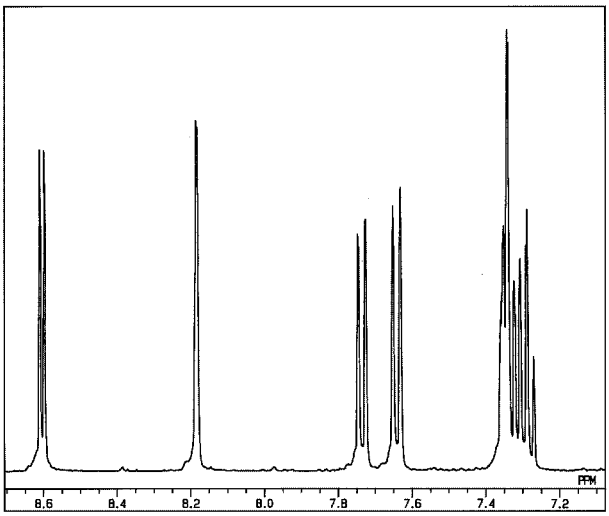


Figure 2. Downfield portion of ^{1}H nmr spectrum of base **2**.

portion of the ^{1}H nmr spectrum, besides the signal of picoline methyl at 2.45 ppm, the singlet of N-methyl is detectable at 4.23 ppm. The signals of pyridine protons appear unchanged (Figure 2) with the superimposition at 7.34 ppm of H_5, signal with one of the two triplets of the benzene protons.

with the group of signals at 7.34 ppm, so assigned to the picoline $H_{3'}$ proton also contains to the benzene H_5 signal. At last, two cross peaks connect the singlet of picoline methyl at 2.45 ppm with the signal of $H_{3'}$ (8.18 ppm) and $H_{5'}$ (7.35 ppm) protons, confirming their assignments.

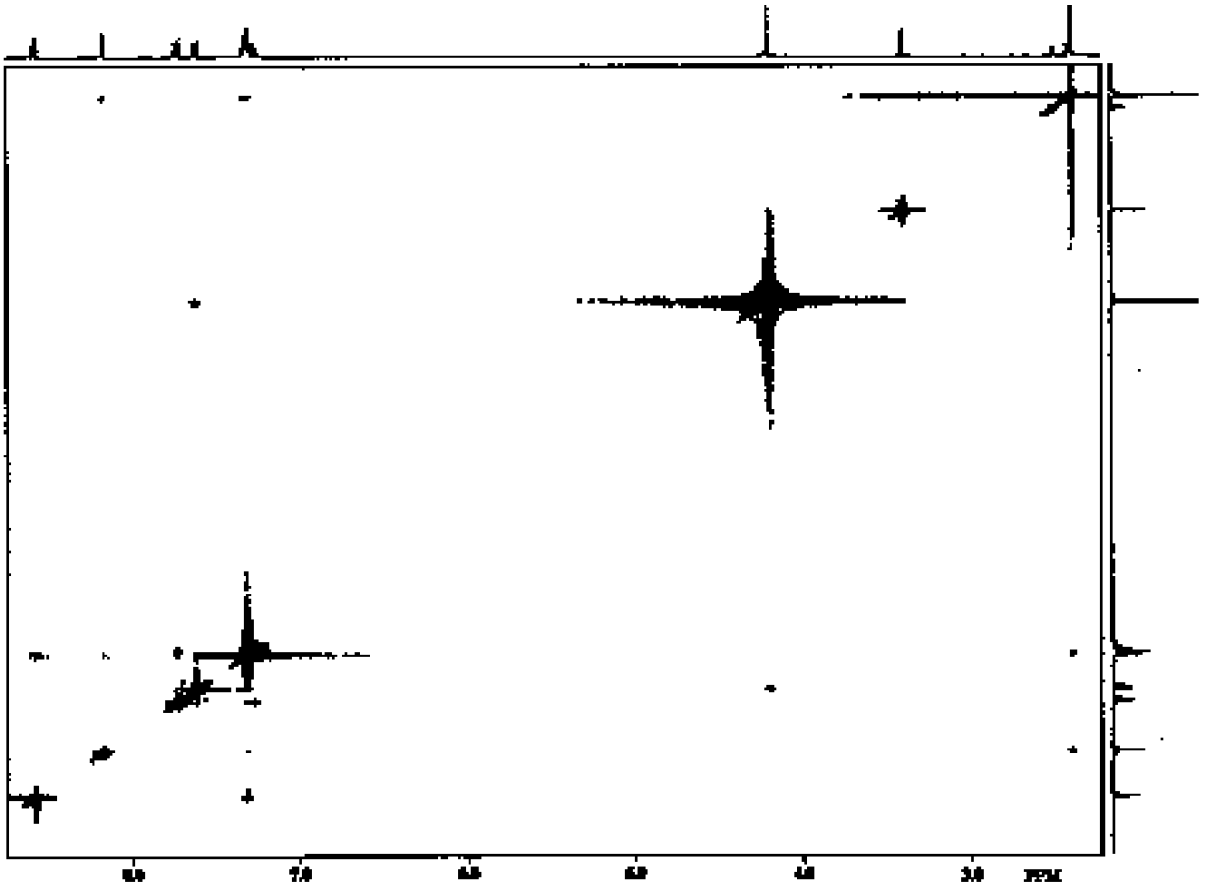


Figure 3. ^{1}H-^{1}H NOESY spectrum of base **2**.

Because there is no tautometry in compound **2**, the benzene signals appear well resolved and detectable. Nevertheless the interpretation of this part of the spectrum was not so immediate and required a ^{1}H-^{1}H NOESY experiment (Figures 3 and 4). The following spatial correlations allowed the corresponding assignments of the benzene protons: i) the cross peak, connecting the singlet of N-CH_3 group at 4.23 ppm and the doublet at 7.65 ppm, allows benzene H_4 proton to be assigned to this last signal; so, the remaining doublet at 7.73 ppm can be assigned to H_7 unambiguously; ii) the cross peak between the doublet of H_7 (7.73 ppm) and the triplet at 7.20 ppm, is assigned to H_6; (ii) the cross peak between the doublet of H_4 (7.65 ppm)

Reaction of base **1** with αω-dibromides gave salts **3** and **4**. The contemporary alkylation of imidazole and quaternization of picoline nitrogen are in agreement with: i) the disappearance of the characteristic spectroscopic pattern of imidazole NH group in the ir spectra; ii) a lower downfield shift of benzene protons ($\Delta\delta$=0.20÷0.29 ppm) and analogous but higher shift of picoline ones ($\Delta\delta$=0.40÷0.76 ppm) in ^{1}H nmr spectra; iii) the appearance in the upfield region of the ^{1}H nmr spectra of the bridges methylene signals: two triplets at 4.88 ppm and 5.21 ppm for salt **3**, two triplets at 4.78 ppm and 4.55 ppm, and a multiplet at 2.75 ppm, superimposed partially to the singlet of picoline methyl, for salt **4**. The fast ring inversion makes the hydro-

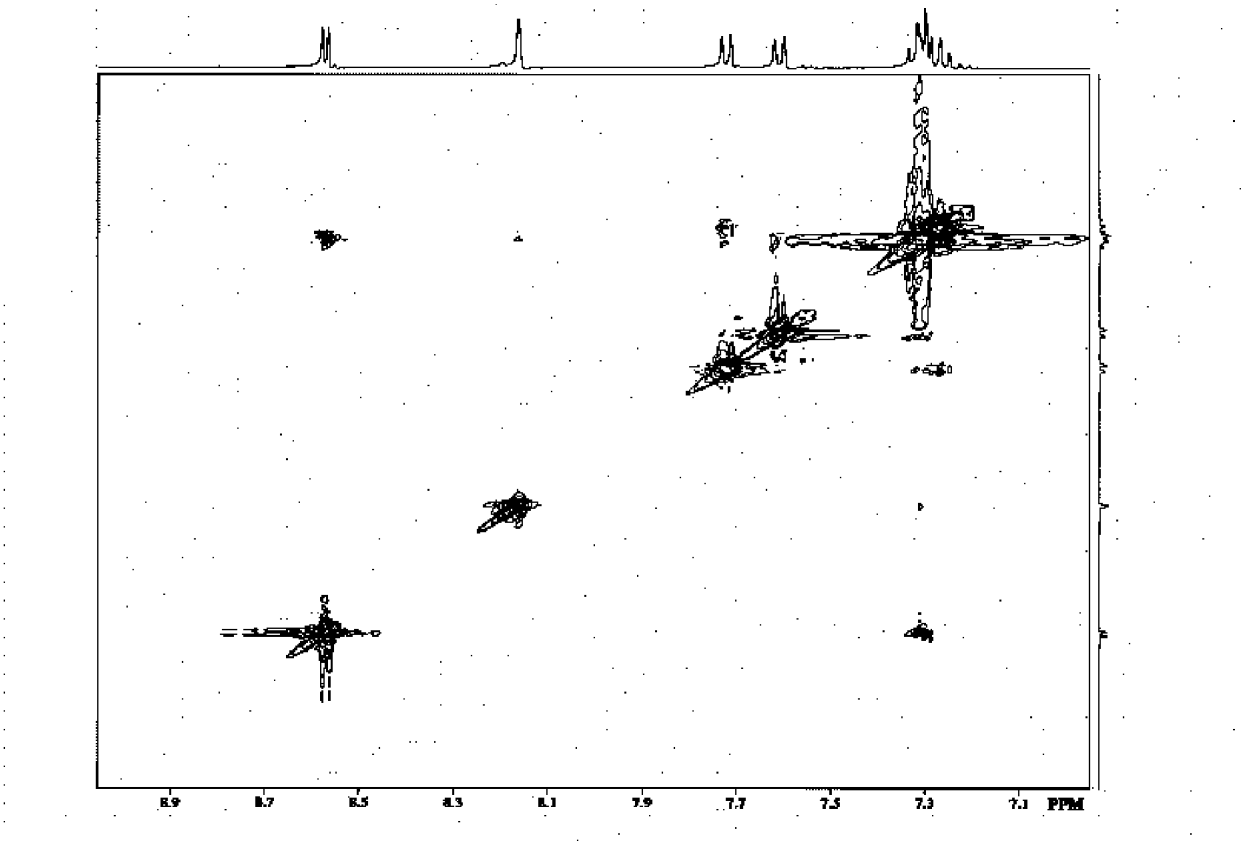


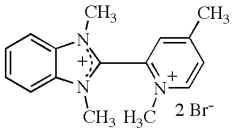
Figure 4. Downfield portion of ^{1}H-^{1}H NOESY spectrum of base **2**.

gens of each methylene chemically equivalent, simplifying the signals that appear as two triplets for salt **3** and two slightly large 4.78 ppm triplets and a slightly 2.75 ppm large quintuplet for salt **4** respectively. The multiplicity of the signal at 2.75 ppm allows its unambiguous assignment to the central methylene of salt **4** aliphatic bridge. By contrast, other signals were assigned by the spatial correlations in ^{1}H-^{1}H NOESY experiment between the triplets of bridge methylenes and the signals of picoline and benzene protons, easily assigned by their chemical shifts and multiplicity. The cross peak correlating the doublet at 9.03 ppm of picoline $H_{6'}$ proton with the triplet at 5.21 ppm suggests that this last signal has to be assigned to the bridge methylene linked to picoline nitrogen. Again, the spatial correlation between the doublet at 7.83 ppm, assigned to the H_4 benzene proton, and the triplet at 4.88 ppm allowed the last signal to be assigned to methylene linked to imidazole nitrogen.

In part I of the present work, X-ray study [15] showed that, in the crystalline state, the picoline and benzimidazole rings of compounds **3** and **4** are not coplanar. There is an angle between the planes of the two heterocycles (dihedral angle) of 10° and 19° respectively, as a consequence of the weight differences of the transannular and Pitzer strains in the partially saturated ring. It is reasonable to think that this configuration difference exists in solution too and that, on average, a higher conjugation acts in the pyridylideneimino chromogen **I** for compound **3**. In fact, UV-visible studies in ethanol solution showed more intense and red-shifted absorption for salt **3** than the counterpart **4**. A previous ^{1}H nmr study showed that the presence of a benzazolyl substituent determines a general downfield shift of picoline protons [19]. If this shift is a consequence of electronic effects and if, on average, the different dihedral angle remains in dimethylsulfoxide-d_6 too, as it is reasonable to think, we observe a more deshielded absorption for picoline protons in salt **3** than in salt **4**, owing to increased conjugation. The data show the opposite behavior for $H_{3'}$ and $H_{5'}$ protons, suggesting an important role of anisotropic effects of the benzimidazole ring. Obviously, the protons of benzene and picoline methyls were unaffected by the difference of the bridge length.

Reaction of base **2** with 1,3-dibromopropane gave salt **5**. The quaternization of imine nitrogen of both heterocyclic rings is in agreement with: i) a general downfield shift of

benzene and pyridine protons: $\Delta\delta$=0.49÷1.12 ppm; ii) a less marked but systematic downfield shift of picoline and imidazole methyls: $\Delta\delta$=0.38÷0.09 ppm; iii) the appearance of five large signals at 5.28 ppm (1H), 5.04 ppm (1H), 4.80 ppm (1H), 4.29 ppm (1H, partially superimposed to the singlet of benzimidazole *N*-methyl) and 2.83 ppm (2H, partially superimposed to the singlet of picoline methyl) in the upfield region at room temperature. The methylenes signals appear large and, in particular two distinct absorptions are detectable for each methylene linked to nitrogens, owing to the low rate of ring inversion. Because uv-visible spectra [15] suggest a less efficient conjugation in salt **5** than in salt **4** (salt **5** absorbs hypo-hypsochromically compared to salt **4**), it is reasonable to think that the dihedral angle is larger in salt **5** than in salt **4** both in solution and in solid state, for which X-ray analysis showed 45° and 19° angles respectively. The low rate of ring inversion and large dihedral angle appear correlated. When temperature is increased to 100° the signals at 5.28 ppm and 4.29 ppm disappear, and the signals at 5.04 ppm and 4.80 ppm coalesce in a large signal at 4.94 ppm, suggesting the kinetic origin of the splitting of methylene signals. ^{1}H-^{1}H NOESY analysis was unsuitable for assigning methylenes linked to nitrogens signals. Using salt **6** as a reference, the relative signal of methyl linked to pyridine nitrogen appeared downfield shifted (4.25 ppm) compared to the counterparts linked to imidazole nitrogen (4.09 ppm) [19]. Analogously, the two signals that coalesce at 100° in a signal at 4.94 were assigned to methylene linked to pyridine nitrogen while the two signals that disappear, whose medium value is 4.78 ppm, were assigned to methylene linked to imidazole nitrogen. The remaining large signal at 2.83 ppm was assigned to bridge central methylene. In accordance with the introduction of a second positive charge (salt **5** versus salt **4**) a general downfield shift of benzene and pyridine protons: $\Delta\delta$=0.33÷0.48 ppm is observable. $H_{3'}$ proton is an exception; it appears shifted only 0.06 ppm downfield, suggesting again the important role of anisotropic effects on the benzimidazole moiety.



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EXPERIMENTAL

Melting points were determined by a Stuart Scientific SMP3 melting point apparatus and are uncorrected. Infrared spectra were recorded with a Perkin Elmer 1600 FTIR on KBr plate (1%). Elemental analyses of C, H, and N were performed with Fison EA-1108. ^{1}H nmr spectra were recorded in dimethylsulfoxide-d_6 on a Jeol EX400 NMR spectrometer operating at 9.4T (corresponding to ^{1}H Larmor frequency of 400 MHz), relative to dimethylsulfoxide as internal reference. 2D NOESY experiments were performed in phase sensitive acquisition mode with a spectral width of 3600 Hz over 1024 data points, using a mixing time of 1 s for compound **2** and 500 ms for compound **3**. The spectra (24 scans) were obtained after multiplying the data with a sine square bell function in both dimensions. R_f values were determined on silica gel 60 F_{254} TLC plates (Merck) using B.A.W. (butanol: acetic acid: water; 4:1:5 by volume, organic solution) as eluant.

The following compounds were synthesized by literature procedures: 2-(4-methylpyridin-2-yl)-1*H*-benzimidazole (**1**) [20], 1 methyl-2-(4-methylpyridin-2-yl)-1*H*-benzimidazole (**2**) [21], 11-methyl-6,7-dihydro-5*H*-benzimidazo[2,1-*c*]pyrido[1,2-*a*]-[1,4]diazepin-8-ium (**4**) [14], 1,11-dimethyl-6,7-dihydro-5*H*-benzimidazo[2,1-*c*]pyrido[1,2-*a*][1,4]diazepin-1,8-diium (**5**) [14]; their physical, spectral and analytical data agree with previously published data.

10-Methyl-5,6-dihydrobenzimidazo[1,2-*a*]pyrido[2,1-*c*]pyrazin-7-ium (**3**).

An equimolar quantity of intermediate **1** (10 g, 48 mmoles) and 1,2-dibromoethane (4.1 ml, 48 mmoles) in dimethylformamide (30 ml) was stirred at reflux for four hours. After cooling, the reaction mixture was amply diluted with ether. The crude precipitate was collected, washed with ether, and crystallized from acetonitrile-ethanol mixture; 7.11 g (45%) of pure compound **3** was obtained, mp: >330°; Rf=0.19; uv: λmax 362 nm (ε=19,500); ir: ν 3040, 3020, 3000, 2970, 1640, 1590, 1570, 1530, 1510, 1490, 1460, 1450, 1440, 1380, 1340, 1305, 1280, 1250, 1170. 1150, 1080, 930, 880, 850, 780, 760 cm^1.

Anal. Calcd. for $C_{15}H_{14}BrN_3$ (316.20): C, 56.98; H, 4.46; N, 13.29. Found: C, 56.80; H, 4.49; N, 13.25.

Acknowledgement.

This work was supported by a contribution from the Ministero della Ricerca Scientifica e Tecnologica (MURST) and Centro Nazionale delle Ricerche (CNR). The authors thank the Compagnia di San Paolo and the Fondazione Cassa di Risparmio di Torino for supplying laboratory equipment.

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