ISOELECTRONIC ANALOGS OF INDOLIZINE

VII. Protonation of Pyrrolo[1, 2-a]benzimidazoles*

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Khimiya Geterotsiklicheskikh Soedinenii, Vol. 4, No. 5, pp. 905–908, 1968

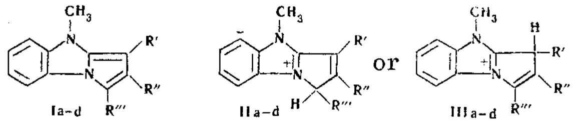
UDC 547.759'785.5:541.67

The structure of the perchlorates of 2, 3, 4-trimethyl-, 1, 2, 4-trimethyl-, 1, 2, 3, 4-tetramethyl-, and 1, 4-dimethyl-2-phenylpyrrolo[1, 2-a]benzimidazoles in trifluoroacetic acid has been studied by the PMR method. It has been established that in all cases on salt formation the proton adds to the carbon atom in position 1. The molecular diagram of pyrrolo[1, 2-a]benzimidazole has been calculated by the MO LCAO method.

In a preceding paper we proposed a method for synthesizing pyrrolo[1, 2-a]benzimidazoles—derivatives of a new heterocyclic system belonging to the isoelectronic analogs of indolizine—and studied some of their properties [1].

Since the molecules of the pyrrolo[1, 2-a]benzimidazoles (I) have two positions active with respect to electrophilic reagents (1 and 3), reactions with these agents may give compounds substituted in position 1 or 3 or mixtures of them. Electrophilic addition may take place analogously.

The present paper describes the simplest electrophilic addition reaction—protonation—of the pyrrolo[1, 2-a]benzimidazoles Ia–d. These compounds are bases forming stable crystalline salts with mineral acids:



Ia–d IIa–d IIIa–d

	R′	R″	R‴
a	CH_3	CH_3	—
b	—	CH_3	CH_3
c	CH_3	CH_3	CH_3
d	—	C_6H_5	CH_3

The choice between the possible structures II and III was made on the basis of proton magnetic resonance spectra by studying the influence on the signals of substitution in the pyrrolo[1, 2-a]benzimidazolium cation and by observing multiplicity in them produced by spin-spin coupling. Similar studies have recently been carried out in the indolizine [2–4] and pyrrolo[2, 1-b]thiazole [5] series.

As solvent we used trifluoroacetic acid, which readily dissolves the salts concerned and does not give signals in the region of the spectrum studied (2–9τ).**

The PMR spectra of pyrrolo[1, 2-a]benzimidazolium salts have no broad bands or a triplet, which enables the nitrogen atom to be excluded as the site of protonation. Protonation of the carbon atom of the pyrrole nucleus of base I leads to the appearance of a methylene or substituted methylene group (formulas II or III). There are only isolated signals in the spectrum of the salt from base Ia, apart from the signals in the region of the aromatic protons. This permits the deduction that the salt has structure IIa, i.e., that protonation takes place in position 1. The addition of a proton in position 3 should be shown in the form of the splitting of the signal of the 3-methyl group into a doublet. Assignment of individual signals can be carried out be comparison with the spectra of other salts. The peak at 5.3τ (2 H) corresponds in its position and intensity to a methylene group. The signal at 6.05τ (3 H) is repeated in the spectrum of all four salts over a narrow range of values (±0.1) and is indisputably due to the protons of the N—CH_3 group. The remaining two closely adjacent peaks (7.81 and 7.75τ) correspond to the two methyl groups in the pyrrole nucleus. The stronger-field signal (7.81τ) must apparently be ascribed to the methyl group in position 3, which is not conjugated with a quaternary nitrogen atom and, therefore, must be screened to a greater extent than the methyl group in position 2. The aromatic protons form an ABCD system and give a complex multiplet with a center at about 2.6τ.

The spectrum of the isomeric salt from the base Ib has a quadruplet with a center at 5.0τ (1 H) and a doublet with a center at 8.40τ (3 H) with the same spin-spin coupling constant (7.5 Hz). This pattern also corresponds to protonation in position 1, since only in this case does a A_3X spin system arise with the splitting of the signals corresponding to it. On protonation in position 3, the spectrum would consist of isolated signals (disregarding the region of the aromatic protons) as in the case of salt IIa. At 6.15τ there is a sharp isolated peak corresponding to the protons of the N—CH_3 group. The signal of the 2-methyl group (7.78τ) is weakly split ($J_{2\text{-}CH_3,H\text{-}3}$ = 1 Hz) because of spin-spin coupling with the ethylenic proton. The latter appears at 3.4τ in the form of a not absolutely well-defined quadruplet. In the region of the aromatic protons, there is a multiplet with a center at about 2.55τ.

The spectrum of the salt from the base Ic resembles that from the preceding compound, but instead of the signal of the ethylenic proton, of course, a peak appears corresponding to the third methyl group in the pyrrole nucleus and, in addition, the signal of the 2-methyl group is split. The aromatic protons form a complex multiplet with a center at about 2.5τ. A quadruplet (5.05τ) and a doublet (8.32τ), arising from a

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*For part VI, see [1].

**At high amplification, a weak triplet with a center at about 4.5τ and a spin-spin coupling constant of 53 Hz due to the presence of difluoroacetic acid as an impurity was observed.

Chemical Shifts and Spin-Spin Coupling Constants of the Salts II

1-H	H-3	1-CH_3	2-CH_3	3-CH_3	4-CH_3
5.28	—	—	7.75	7.81	6.05
5.0	3.4	8.40 J (1-CH_3, 1-H) 7.5	7.8 J (2-CH_3, 3-H) 1.0	—	6.15
5.05	—	8.32 J (1-CH_3, 1-H) 7.5	7.69	7.81	5.95
*	3.0**	8.10 (**); 8.40 J (1-CH_3, 1-H) 7.5	—	—	6.17**

*Signal at the noise level

**Signal of the base I

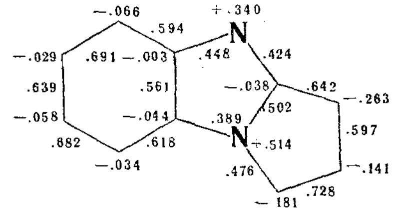
A_3X spin system (J = 7.5 Hz) remain in the same range of values as in the case of salt IIb. This fact, and also the absence of other signals, shows that in this case protonation takes place only in position 1, i.e., the 1-H form (IIc) is produced. The methyl signal of the 3-H form should appear in a stronger field, since the 3-H proton is further from the quaternary nitrogen atom than the 1-H proton and, therefore, must be more strongly screened. We assume that the signal in the stronger field (7.81τ) belongs to the 3-methyl group, as in the case of salt IIa, since the signal in the weaker field (7.69τ) must be ascribed to the 2-methyl group.

The quaternary salt IId exhibits a number of peculiarities. In the spectrum of its solution there are no signals in the region of methylene or methyl protons, and it can be shown that we are dealing with the spectrum of the base Id: in the field of the aromatic protons there are two separate multiplets corresponding (judging from their intensities) to the four protons of the benzene ring condensed with the heterocyclic system (2.3τ) and the five protons of the 2-phenyl group (2.6τ); at 2.98τ there is a narrow signal (1 H) of an ethylene proton, at 6.17τ the signal of an N—CH_3 group, and at 8.1τ an isolated peak corresponding to the 1-methyl group. However, at 8.4τ there is a weak but distinct doublet with a splitting constant of 7.5 Hz which can be formed only as a result of the fact that in equilibrium with the base Id in solution there is also a small amount (approximately 20%, judging from the ratio of the intensities of the signals at 8.1 and 8.4τ) of a salt having the IId structure. The formula of this salt also presupposes the presence in the spectrum of a quadruplet from the 1-H proton, but in view of its low intensity it exists at the level of the noise and is, therefore, not observed. Thus, the salt IId undergoes considerable solvolysis even in such a strong acid as trifluoroacetic. This agrees with the fact that the base Id is far weaker than the bases Ia-c (the salt IId, unlike the salts IIa-c, readily hydrolyzes and cannot be recrystallized from water).

The values of the chemical shifts and the spin-spin coupling constants of the salts II are given in the table.

Thus, the protonation of all four pyrrolo[1, 2-a]benzimidazoles that we have studied takes place in position 1. The predominant protonation of the pyrrolo[1, 2-a]benzimidazoles on carbon atom 1 is in agreement with the calculated values of the energies of electrophilic localization of this atom [6]. Calculation by the simple molecular orbital method with the following values of the parameters:

$$\alpha_N = \alpha_0 + \beta_0;\ \beta_{CN} = \beta_{CC} = \beta_0,$$



Molecular diagram of pyrrolo[1, 2-a]benzimidazole.

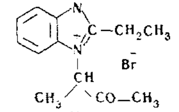
leads to an energy of the electrophilic localization of the C-1 atom of 1.7195 (β_0), for the C-3 atom one of 1.7663 (β_0), and for the C-2 atom one of 2.1658 (β_0). In addition to this, the calculation shows that the electron density in position 3 is higher than in position 1 (see figure). Consequently, we refrain from stating that position q must always be more reactive. Irreversible reactions with the participation of strong electrophiles [7, 8] may lead to addition or substitution in position 3, as well.

The calculations were carried out by the "ELA" program [9] on a M-20 electronic computer.

EXPERIMENTAL

The bases Ia, b, and d, and their perchlorates have been described previously [1].

1,2,3,4-Tetramethylpyrrolo[1,2-a]benzimidazole (Ic) was synthesized by heating the quaternary salt IV, obtained from 2-ethyl-1-methylbenzimidazole



IV

and 3-bromo-2-butanone [10], with sodium carbonate solution. Ten grams (62.5 mM) of 2-ethyl-1-methylbenzimidazole and 10.4 g (~68 mM) of 3-bromo-2-butanone were heated with 25 ml of propanol in the water bath for 3 hr. Ether (25 ml) was added to the mixture. The quaternary salt was carefully washed with ether and, without purification (it does not crystallize), was converted into 1,2,3,4-tetramethylpyrrolo[1,2-a]benzimidazole. For this purpose, a solution of the product in 30 ml of water was treated with 3.2 g of anhydrous sodium carbonate and 2.3 g of anhydrous sodium sulfite in 20 ml of water. Then the solution was extracted twice with 30 ml of ether and the clear aqueous solution was heated at 100° for 2.5 hr. The base formed (5 g) was filtered off and converted into the hydrochloride by the addition of 10 ml of hydrochloric acid. The unpurified base rapidly changes in the air, but the hydrochloride is stable. The colorless crystals of the base become red in the air, mp 165–166° (from ethanol). Found, %: N 12.99, 12.81. Calculated for $C_{14}H_{16}N_2$, %: N 13.20.

1,2,3,4-Tetramethylpyrrolo[1,2-a]benzimidazolium perchlorate (IIc) was obtained by treating the base with perchloric acid. The product was crystallized from glacial acetic acid and then from ethanol to give colorless crystals, mp 194–195°. Found, %: N 8.62; 8.93. Calculated for $C_{14}H_{17}ClN_2O_4$, %: N 8.95.

The PMR spectra were taken on an N-100 spectrometer (100 MHz) by Moscow University Instructor Yu. A. Ustynyuk, to whom the authors express their gratitude.

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29 August 1966

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