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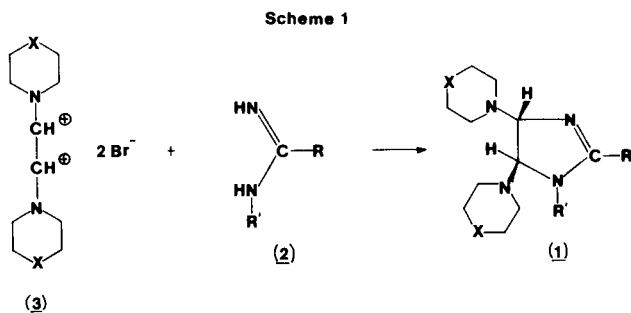
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During the preparation of 1-aryl- and 1-acyl-4,5-dipiperidino-4,5-dihydroimidazoles (**1**) from diimmonium salts (**3**), derivatives in which one of the piperidino groups was substituted by an hydroxy group were often isolated. The structure and the genesis of these compounds are discussed.

J. Heterocyclic Chem., **18**, 921 (1981).

Recently, we reported the preparation of 1-aryl- and 1-acyl-4,5-diamino-4,5-dihydroimidazoles (**1**) by reacting amidines (**2**) with the diimmonium dibromides (**3**) (1,2,3,4).

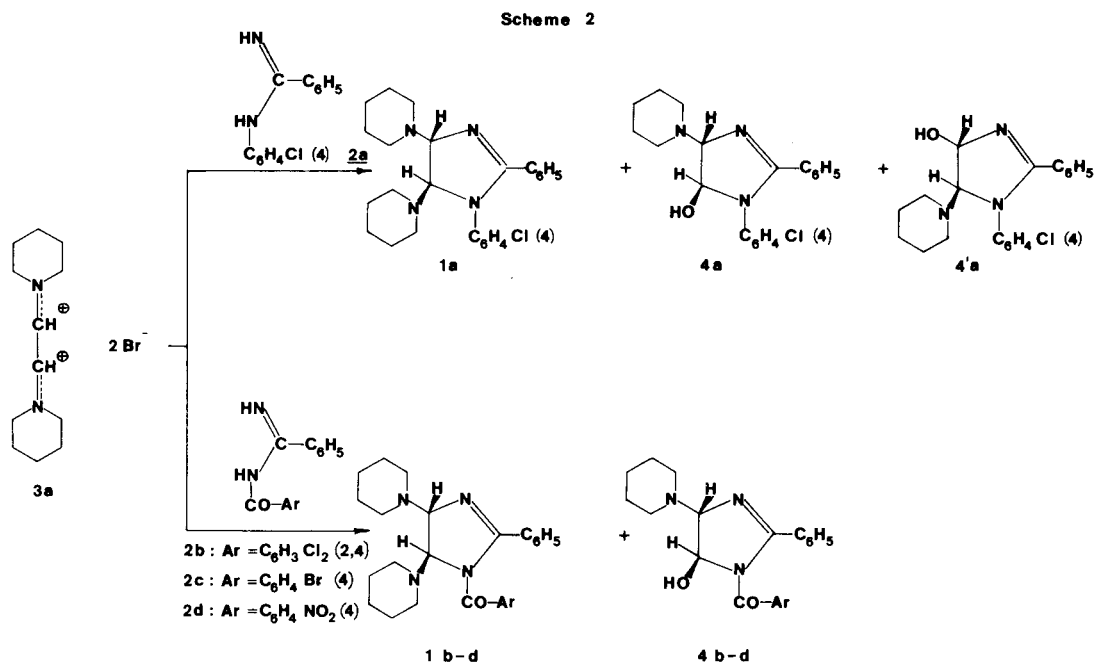


In this paper we wish to report some anomalous results which were obtained when the piperidino derivative (**3a**) (X = CH₂) were employed as the diimmonium salt. When

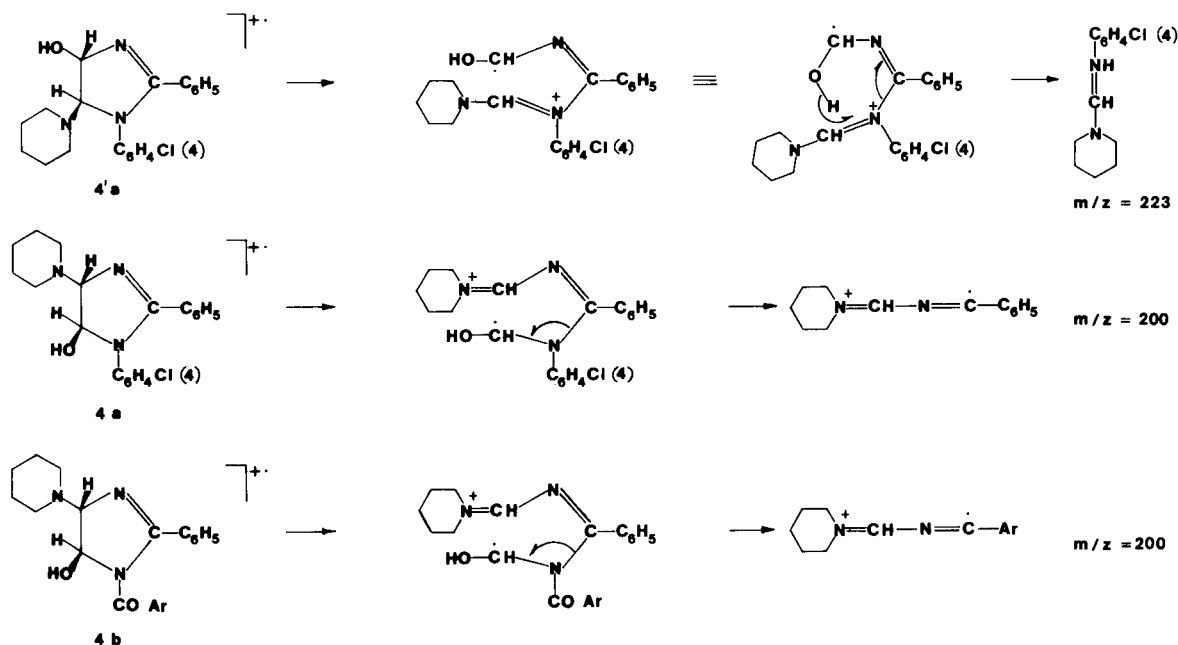
3a was reacted with 1-aryl- or 1-acylamidines, the hydroxy derivatives (**4**) were often isolated in addition to the expected 4,5-diaminoimidazolines (**1**). Yields of these by-products are variable and not reproducible.

In all cases, only the *trans* hydroxy derivatives were isolated, as confirmed by the values of the H₄-H₅ coupling constants ranging between 1.0 and 2.5 Hz. The correct position of the hydroxy group was suggested by H₄ and H₅ chemical shifts and confirmed by fragmentation patterns upon electron impact.

The mass spectra of hydroxy derivatives **4a**, **4'a** and **4b** were studied (5). With regard to **4'a**, the most diagnostic peak (m/z = 223) (6) arises from the cleavage of 1,2 and 4,5 bonds with rearrangement of the hydroxylic hydrogen atom (Scheme 3). In **4a** the cleavage of the same bonds accounts for the peak corresponding to m/z = 200. In the case of **4b**, the structure of the 5-hydroxy derivative was



Scheme 3



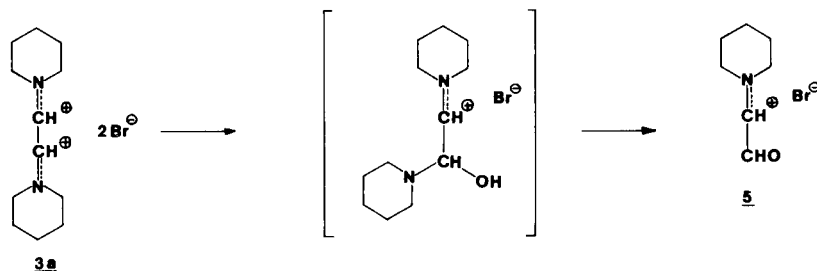
confirmed both by the presence of the peak at $m/z = 200$ and by the lack of a peak at $m/z = 285$, which would be associated with the 4-hydroxy isomer.

Another difference between the spectra of **4a** and **4'a** is noteworthy: **4a** shows a low peak (6%) associated with the $M-H_2O$ ion ($m/z = 337$), whereas in the spectrum of **4'a**, this peak is remarkably higher (49%). Moreover, **4a** shows an M -piperidine ion ($m/z = 270$) which is absent in the spectrum of **4'a**. These facts are perfectly in line with the chemical behaviour of the 4,5-diaminoimidazoles which preferably lose the group in the 4 position. In the spectrum of **4b** the above mentioned considerations are sup-

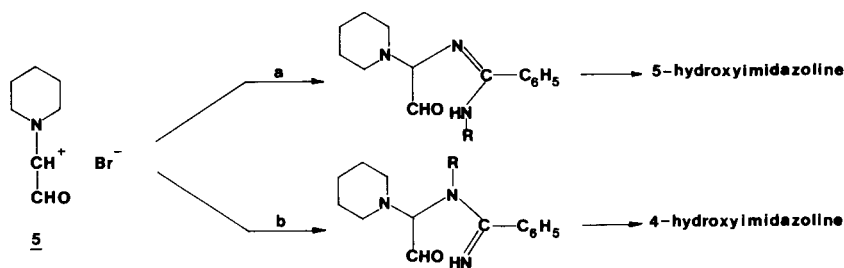
ported by the lack of the $M-H_2O$ ion and by the presence of an ion at $m/z = 297$ ($M-Cl$ -piperidine).

All attempts to hydrolyze the pure 4,5-diaminoimidazoles **1a-d** to hydroxy derivatives **4** were unsuccessful. Under mild conditions the starting imidazoline was recovered unchanged, whereas in strong hydrolytic medium the amidines **2a-d** were isolated as the main reaction product. This behavior excludes the formation of the hydroxy derivatives during the usual working up of the reaction mixture and suggests that these compounds form concurrently or precede the formation of 4,5-diaminoimidazoles.

Scheme 4



Scheme 5



This formation mechanism could be explained by a partial hydrolysis of the diimmonium salt **3a** (7) to give a new reactive intermediate **5**, which is able to react with the nucleophilic nitrogen atoms of amidines (Scheme 4). Thus, two reaction paths can be foreseen (Scheme 5). Path a involves the attack of the electron-poor carbon of **5** on the more nucleophilic nitrogen of the amidine followed by cyclization to give the 5-hydroxy derivative. Path b shows the alternative and less favoured route of cyclization. In the case of acylamidines, only path a is followed, considering the low nucleophilic character of the nitrogen atom bonded to the acyl group.

The intervention of a hydrolytic process before reaction with amidines is also supported by the fact that in avoiding the isolation of the diimmonium salt and operating under strictly anhydrous conditions, no hydroxy derivatives were formed.

Further work is in progress to confirm the proposed mechanism and to exploit the potential of this reaction as an entry to this new class of imidazole derivatives.

EXPERIMENTAL

Melting points were determined using a Büchi capillary melting point apparatus and are uncorrected. Nmr spectra were recorded using a Varian 360-A spectrometer. The chemical shift values are expressed as δ values relative to a tetramethylsilane internal standard. Mass spectra were recorded with a Varian MAT 311-A mass spectrometer at an electron energy of 70 eV. The direct insertion technique was used with a probe temperature of 50-90° and an ion source temperature of 180-200°. Column chromatography was performed using Merck silica gel (60-120 mesh) and thin layer chromatography was run on silica gel GF 254 plates.

Isolation of 1-(4-Chlorophenyl)-2-phenyl-4-piperidino-5-hydroxy-4,5-dihydroimidazole (**4a**) and 1-(4-Chlorophenyl)-2-phenyl-4-hydroxy-5-piperidino-4,5-dihydroimidazole (**4'a**).

To a well stirred suspension of diimmonium salt **3a** (9.1 g, 25 mmoles) in dry dichloromethane (200 ml), cooled at -10°, a solution of *N*-(4-chlorophenyl)benzamidine (5.9 g, 25 mmoles) dissolved in 150 ml of dry dichloromethane containing 7.1 ml (51 mmoles) of triethylamine was added dropwise. The reaction mixture was stirred at room temperature until no more benzamidine was detectable by tlc (benzene:tetrahydrofuran 50:50). It was then washed twice with water.

The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The brown residue was crystallized from ethanol affording 4.5 g (41.5%) of pure 4,5-dipiperidinoimidazole **1a** melting at 192-194° [lit. (2) mp 192-195°]. The mother liquors from the crystallization were evaporated and the residue was chromatographed on a silica gel column [silica/crude mixture (40:1)] (eluent: ether) with increasing amounts of ethanol.

Under these conditions, the mixture components were eluted in the following order.

a) 4,5-Diaminoimidazole (**1a**).

Compound **1a** was obtained in the amount of 0.9 g.

b) 4-Hydroxy-5-piperidinoimidazole (**4'a**).

This compound was isolated as white crystals (from ethanol), (0.6 g), mp 186-188° dec; ¹H-nmr (deuteriochloroform): 1.50 (m, 6H, (CH₂)₃), 2.54 (m, 4H, CH₂-N-CH₂), 4.40 (d, J = 2.0 Hz, 1H, H₄), 5.02 (d, J = 2.0 Hz, 1H, H₅), 6.60-7.50 (m, 9H, aromatic); ms: 355 (19, M⁺), 337 (49, M-H₂O), 223

(60), 221 (28), 214 (21), 193 (31), 133 (14), 111 (42), 104 (56), 86 (38), 84 (100).

Anal. Calcd. for C₂₀H₂₂C1N₃O: C, 67.50; H, 6.23; N, 11.81. Found: C, 67.68; H, 6.35; N, 11.93.

c) 4-Piperidino-5-hydroxyimidazole (**4a**).

This compound was isolated as white crystals (from ethanol/isopropyl ether), (0.8 g). mp 165-166° dec; ¹H-nmr (deuteriochloroform): 1.53 (m, 6H, (CH₂)₃), 2.60 (m, 4H, CH₂-N-CH₂), 4.50 (d, J = 2.0 Hz, 1H, H₄), 5.60 (d, J = 2.0 Hz, 1H, H₅), 7-7.80 (m, 9H, aromatic); ms: 355 (10, M⁺), 337 (6, M-H₂O), 270 (16), 214 (72), 201 (22), 200 (25), 117 (92), 111 (51), 97 (70), 84 (100), 77 (68), 68 (69).

Anal. Calcd. for C₂₀H₂₂C1N₃O: C, 67.50; H, 6.23; N, 11.81. Found: C, 67.43; H, 6.33; N, 11.63.

Isolation of 1-(2,4-Dichlorobenzoyl)-2-phenyl-4-piperidino-5-hydroxy-4,5-dihydroimidazole (**4b**).

Compound **1a** (7.8 g, 22 mmoles) was reacted with 6.5 g (22 mmoles) of *N*-(2,4-dichlorobenzoyl)benzamidine and 6.08 ml (44.4 mmoles) of triethylamine in the same manner as described above. After the usual work up, the crude residue (12 g) was chromatographed on a silica gel column (300 g, eluent: benzene with increasing amounts of ethyl acetate). The mixture components were eluted in the following order.

a) *N*-(2,4-Dichlorobenzoyl)benzamidine (**2b**).

Compound **2b** was obtained in the amount of 0.8 g.

b) 1-(2',4'-Dichlorobenzoyl)-2-phenyl-4,5-dipiperidino-2-imidazole (**1b**).

This compound was obtained in 43% yield (4.6 g), mp 162° (lit. (2) mp 162).

c) 1-(2,4-dichlorobenzoyl)-2-phenyl-4-piperidino-5-hydroxy-2-imidazole (**4b**).

This compound was obtained in 23% (2.5 g), white crystals (from ethanol), mp 133° dec; ¹H-nmr (deuteriochloroform): 1.60 (m, 6H, (CH₂)₃), 2.80 (m, 4H, CH₂-N-CH₂), 4.64 (d, J = 2.5, 1H, H₄), 5.90 (d, J = 2.5, 1H, H₅), 7.0-7.6 (m, 8H, aromatic); ms: 417 (1, M⁺), 382 (18), 297 (7), 244 (31), 216 (40), 173 (80), 141 (42), 113 (88), 104 (100), 84 (57), 77 (42).

Anal. Calcd. for C₂₁H₂₁C1N₃O₂: C, 60.28; H, 5.02; N, 10.04. Found: C, 60.07; H, 5.15; N, 9.81.

The following compounds were isolated in similar manner.

1-(4-Bromobenzoyl)-2-phenyl-4-piperidino-5-hydroxy-4,5-dihydroimidazole (**4c**).

This compound was obtained as pink crystals (from DMSO/chloroform), mp 149-150° dec from acetone; ¹H-nmr (DMSO/deuteriochloroform): 2.60 (m, 6H, (CH₂)₃), 3.60 (m, 4H, CH₂-N-CH₂), 4.60 (d, J = 1.0 Hz, 1H, H₄), 5.35 (d, J = 1.0 Hz, 1H, H₅), 7.0-8.0 (m, 9H, aromatic).

Anal. Calcd. for C₂₁H₂₂BrN₃O₂: C, 58.88; H, 5.18; N, 9.81. Found: C, 58.67; H, 5.19; N, 9.64.

1-(4-Nitrobenzoyl)-2-phenyl-4-piperidino-4,5-dihydroimidazole (**4d**).

This compound was obtained as yellow crystals (from DMSO/chloroform): mp 140-142° dec; ¹H-nmr (DMSO/deuteriochloroform): 2.60 (m, 6H, (CH₂)₃), 3.55 (m, 4H, CH₂-N-CH₂), 4.60 (d, J = 1.8 Hz, 1H, H₄), 5.40 (d, J = 1.8 Hz, 1H, H₅), 7.0-8.5 (m, 9H, aromatic).

Anal. Calcd. for C₂₁H₂₂N₄O₄: C, 63.96; H, 5.58; N, 4.21. Found: C, 63.81; H, 5.68; N, 14.33.

Acknowledgement.

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helpful discussion on the analysis of mass spectra.

(6) B. Gioia, L. Citerio and R. Stradi, *Org. Mass Spectrum.*, 13, 319 (1978).

(7) Actually, the diimmonium salt **3a** was shown to be the more hydrolyzable between the salts which have been employed in our studies.