2,4,4-Trisubstituted 5-Amino-4*H*-imidazoles. A New Synthetic Approach and Reactivity

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The scope and limitations of the reaction between imidates and α,α-disubstituted α-aminoacetonitriles to give 5-amino-4*H*-imidazoles are studied. The reactivity of compounds **1a-b** has been explored.

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Introduction.

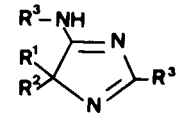
Almost all known examples of 4*H*-imidazoles contain at least one heterolinked substituent [1]. Despite 5-dimethylamino-4*H*-imidazoles are common products from reactions of 3-dimethylaminoazirines with cyclic amides [2-5], and 4-imino-5,5-dimethylimidazolidine-2-thiones have been transformed into 5-alkylamino-4*H*-imidazoles [6], only few examples of 5-amino-4*H*-imidazoles have been reported. Some of them, formed from benzamidine and some iminonitriles, are described as structures having exocyclic C=N bonds [7].

Previous results on the reactivity of ethyl carbethoxyformimidate [8] showed that it was able to react with α,α-disubstituted α-aminoacetonitriles to give 2,4,4-trisubstituted 5-amino-4*H*-imidazoles with moderate yields (up to 45%). This reaction involved a cyclization similar to that described by Hosmane *et al.* [9]. Considering that this type of reaction could be a very simple one step method to achieve 5-amino-4*H*-imidazoles, we tried to extend it to other imidates (Scheme 1).

Synthesis.

Heterocyclizations were carried out in ethereal solutions at room temperature. While some imidates such as methyl 2-pyridylformimidate gave **1a** (R^1,R^2 = pentamethylene, R^3 = 2-pyridyl) with yields up to 86%, other imidates, even those with electron withdrawing groups, gave traces or no yields of **1**. In some cases, derivatives **2** (Figure 1) were obtained with very low yields. Such structures can be generated by nucleophilic substitution of the non isolated intermediate **1** on the 2- or 4-positions of the imidate aromatic rings. Similar displacements have been reported for ethoxyformimidoyl and cyanopyridinium salts [10].

Figure 1



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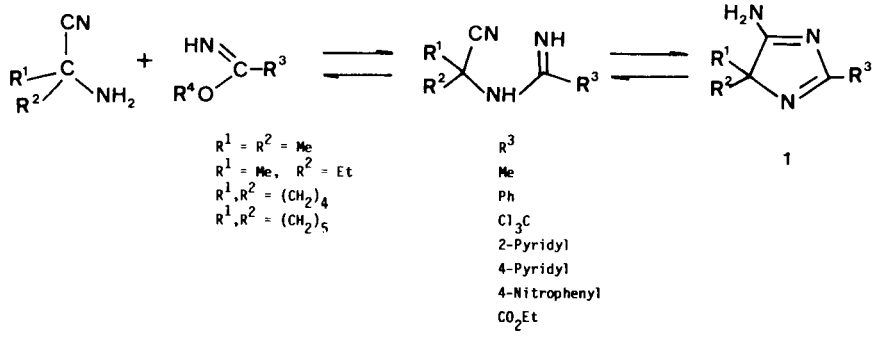
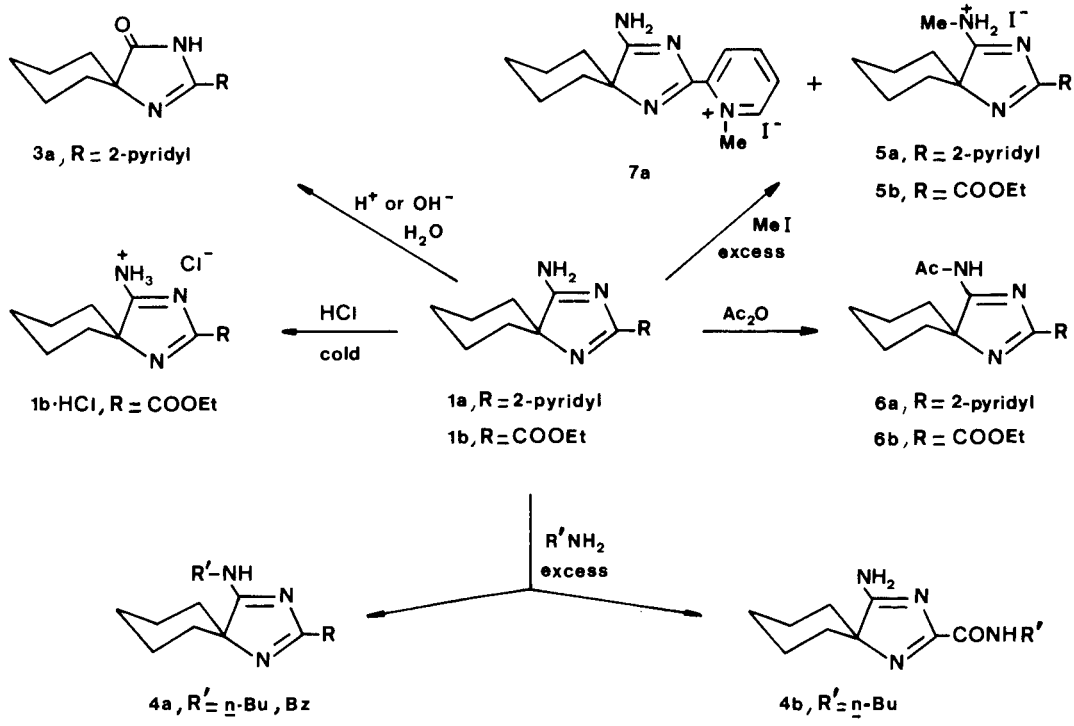
In refluxing ethanol, ammonolysis of the imidates to the corresponding amidines was the general reaction pattern together with the dimerization of α,α-pentamethylene α-aminoacetonitrile to bis (1-cyanocyclohexyl)amine [11] when that reagent was used. Ethyl 4-nitrobenzeneformimidate hydrochloride had to be used in ethanol to give the corresponding **2** derivatives in very low yield.

According to these results, this method is only useful for R^3 = 2-pyridyl or ethoxycarbonyl and R^1,R^2 = tetra or pentamethylene. The good yields achieved in these cases (compounds **1a-c**) could be explained by the stabilization

Scheme 1



Scheme 2



provided by conjugation between the C-2 substituent and the imidazole ring. An x-ray diffraction analysis of compounds **1a** and **7a** [12] has shown that the 2-pyridyl ring is nearly coplanar with the imidazole ring. Other R^3 substituents such as 4-pyridyl or 4-nitrophenyl would have an extra *o*-hydrogen atom which could prevent such coplanarity.

The amino-imino tautomerism is studied elsewhere [12].

Reactivity.

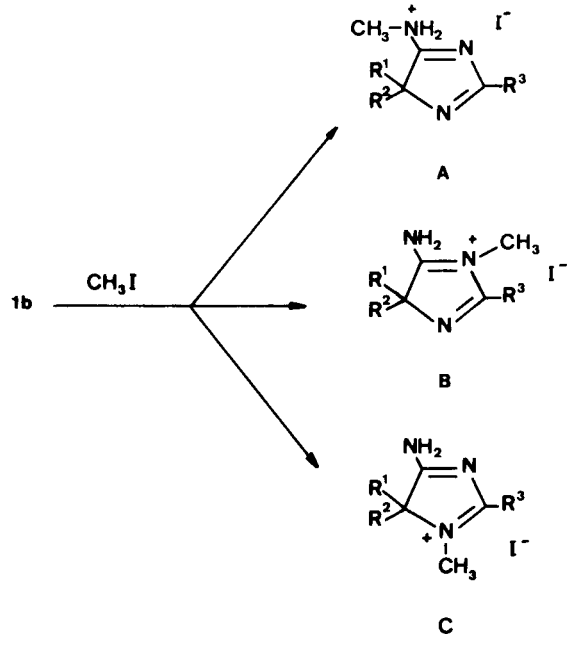
Compounds **1a** and **1b** showed in their reactions the behaviour of the amidine-like moiety formed by their H_2N-C^5=N^1 portion although the carbethoxy group of **1b** showed a higher reactivity against nucleophiles (Scheme 2).

The amino group of **1a** was very easily displaced with formation of a carbonyl group by treatment with dilute aqueous hydrogen chloride at room temperature. Similar treatment readily hydrolyzed dimethylamino groups of related compounds giving also imidazolone derivatives [2, 4]. The imidazolone **3a** was also produced by refluxing **1a** in alkali and was not further hydrolyzed. The steric effect of the spirocyclohexane ring at the 4(5)-position of **3a** must prevent a subsequent basic hydrolysis. Compound **1b** was more stable to acid hydrolysis at room temperature giving **1b** hydrochloride. By refluxing in aqueous hydrogen chloride the carbethoxy group was hydrolyzed giving several unidentified products.

Aminolysis with benzyl- or *n*-butylamine of **1a** also occurred at the 5-position to give **4a**. Treatment with aniline and diethylamine gave no appreciable reaction. Compound **1b** reacted in the same conditions exclusively at the carbethoxy group to give the carboxamide **4b**. Nucleophilic attack at the 5-position was not here detected.

Compounds **1a** and **1b** have several centers which can

Scheme 3



be attacked by electrophiles. Alkylation of some 4*H*-imidazoles at both exo- and endocyclic nitrogen atoms has been reported [1].

Iodomethylation of **1b** with 4:1 molar excess of methyl iodide in acetonitrile yielded compound **5b**. Three possible products (**A-C**, Scheme 3) could be proposed for this compound and each one could be in equilibrium with different tautomeric forms.

The ^{1}H nmr spectroscopic data showed that **5b** in deuteriodimethylsulfoxide solution had the methyl group attached to a cationic nitrogen atom (δ 3.6). The ir and Raman results agreed with the form **A**, mainly because neither amino nor imino bands were observed in the ν NH region [12]. The hydrochloride salt of **1b** was formulated as the protonation product at the amino group for similar spectroscopic reasons [12].

Alkylation of **1a** in the same conditions gave the iodomethylates **5a** and **7a**. Monocrystals were isolated and studied by x-ray diffraction and were identified as the methyl pyridinium salt **7a** [12]. However, the crystalline sample was a mixture 2:1 of **7a** and **5a** as it was revealed by ^{1}H nmr (See Experimental).

Acylation of **1a** had to be performed under anhydrous conditions since the acetyl derivative **6a** was even more sensitive to acid hydrolysis than **1a** to give **3a** and acetamide. Acetylation of **1b** gave **6b** following the same reactivity pattern.

Finally, attempts to diazotization of the 5-amino group failed as it was expected.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 457 spectrophotometer. Proton magnetic resonance spectra were taken on a Perkin-Elmer R24-B (60 MHz) and a Varian EM-390 (90 MHz) spectrometers at room temperature; data are given in ppm downfield from TMS.

5-Amino-4*H*-imidazoles **1**. General Procedure.

Equimolar amounts of the corresponding aminonitrile [13] and imidate, the latter obtained by addition of the alcohol to the nitrile under acid (for R^3 = methyl, phenyl, *p*-nitrophenyl) [14] or basic (for R^3 = trichloromethyl, 2-pyridyl, 4-pyridyl) [15] catalysis, in dry ether, were kept at room temperature for 1-15 days. The precipitated solid was collected by filtration. The solvent was then removed under vacuum and the resulting oil was treated with the adequate solvents to obtain further amounts of reaction products.

5-Amino-2-(2-pyridyl)-4,4-pentamethylene-4*H*-imidazole (**1a**).

This compound was recrystallized from benzene giving white needles (86%), mp 248-249°; nmr (deuteriotrifluoroacetic acid): δ 2 (m, 10H), 8.4 (m, 2H), 9.3 (m, 2H).

Anal. Calcd. for $C_{13}H_{16}N_4$: C, 68.39; H, 7.06; N, 24.54. Found: C, 68.39; H, 7.06; N, 24.54 [16].

5-Amino-2-ethoxycarbonyl-4,4-pentamethylene-4*H*-imidazole (**1b**).

This compound was recrystallized from benzene-petroleum ether, 44%, had mp 202-203°; nmr (deuteriochloroform): δ 4.45 (q, 2H), 2-1.5 (m, 10H), 1.45 (t, overlapped, 3H).

Anal. Calcd. for $C_{11}H_{17}N_3O_2$: C, 54.75; H, 7.93; N, 17.41. Found: C, 54.84; H, 8.09; N, 17.48.

5-Amino-2-(2-pyridyl)-4,4-tetramethylene-4*H*-imidazole (**1c**).

This compound was obtained with 63% yield, mp 220-221°, recrystallized from benzene;nmr (deuteriotrifluoroacetic acid): δ 2.35 (m, 8H), 8.3 (m, 2H), 9.3 (m, 2H).

Anal. Calcd. for $C_{12}H_{14}N_4 \cdot 1/6C_6H_6 \cdot 1/2H_2O$: C, 66.07; H, 6.47; N, 23.94. Found: C, 66.12; H, 6.47; N, 23.94.

5-(2-Pyridyl)amino-2-(2-pyridyl)-4,4-dimethyl-4*H*-imidazole (**2a**).

This solid was recrystallized from ethanol (10%), mp 164-165°; nmr (deuteriochloroform-deuteriotrifluoroacetic acid): δ 1.8 (s, 3H), 1.9 (s, 3H), 8.2 (m, 4H), 8.6 (m, 4H).

Anal. Calcd. for $C_{15}H_{15}N_5$: C, 67.90; H, 5.69; N, 26.39. Found: C, 67.58; H, 5.69; N, 25.97.

5-(2-Pyridyl)amino-2-(2-pyridyl)-4-methyl-4-ethyl-4*H*-imidazole (**2b**).

This compound was recrystallized from ethanol, mp 147-148°; 12% yield; nmr (deuteriochloroform-deuteriotrifluoroacetic acid): δ 1.05 (t, 3H), 1.95 (s, 3H), 2.1 (q, 2H), 7.9 (m, 4H), 8.7 (m, 4H).

Anal. Calcd. for $C_{16}H_{17}N_5$: C, 68.79; H, 6.13; N, 25.07. Found: C, 68.48; H, 5.94; N, 24.72.

5-(4-Pyridyl)amino-2-(4-pyridyl)-4,4-pentamethylene-4*H*-imidazole (**2c**).

This compound had mp 253-254°, recrystallized from ethanol (4%); nmr (deuteriotrifluoroacetic acid): δ 1.7-2.6 (m, 10H), 9 (m, 4H), 9.25 (m, 4H).

Anal. Calcd. for $C_{18}H_{19}N_5$: C, 70.79; H, 6.27; N, 22.93. Found: C, 70.82; H, 6.32; N, 23.25.

5-(4-Nitrophenyl)amino-2-(4-nitrophenyl)-4,4-pentamethylene-4*H*-imidazole (**2d**).

An equimolar solution of ethyl 4-nitrobenzenecarboximidate hydrochloride and 1-aminocyclohexanecarbonitrile in ethanol, was kept at room temperature for 15 days. By removing the solvent, **2d** was obtained as a yellow crystalline solid with mp 261-263°, 11% yield, recrystallized from acetone; nmr (deuteriochloroform-deuteriotrifluoroacetic acid): δ 1.3 (m, 10H), 8.4 (m, 4H), 9.1 (m, 4H).

Anal. Calcd. for $C_{20}H_{19}N_5O_4 \cdot 1/2H_2O$: C, 59.65; H, 5.01; N, 17.46. Found: C, 59.62; H, 4.94; N, 17.02.

4,4-Pentamethylene-2-(2-pyridyl)-2-imidazolin-5-one (**3a**). a) Alkaline Hydrolysis.

By refluxing 1.5 g (6 mmoles) of **1a** with 40 ml of 2*M* sodium hydroxide for three hours, and subsequent neutralization, **3a** was obtained by concentrating the ethereal extract.

b) Acid Hydrolysis.

To 1.5 g (6 mmoles) of **1a** in 25 ml of water, 2 ml of concentrated hydrochloric acid was added to effect solution. After removal of the solvent under reduced pressure below 60°, a very hygroscopic solid was obtained as leaflets. Several crystallizations in ethanol-ether gave **3a** hydrochloride in 81% yield, mp 199-201°. This solid, after neutralization with potassium carbonate solution and extraction with ether, afforded **3a**, mp 86-87°, 32% yield; nmr (deuteriochloroform): δ 1.7 (m, 10H), 7.15-8.5 (m, 4H).

Anal. Calcd. for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.33. Found: C, 68.01; H, 6.73; N, 18.41.

4,4-Pentamethylene-2-ethoxycarbonyl-5-amino-4*H*-imidazole Hydrochloride (**1b**·HCl).

Upon adding 2 ml of concentrated hydrochloric acid, 1.5 g (6 mmoles) of **1b** was dissolved in 25 ml of water. After removal of the solvent under reduced pressure to dryness and treatment of the resulting solid with acetone, 250 mg (29%) of **1b**·HCl was obtained by filtration, mp 190-191°; nmr (deuteriodimethylsulfoxide): δ 1.3 (t, 3H), 1.7 (m, 10H), 4.4

(q, 2H), 6.6 (s, 1H), 7.5 (s, 1H), 8.3 (s, 1H).

Anal. Calcd. for $C_{11}H_{18}ClN_3O_2$: C, 50.86; H, 6.98; N, 16.18. Found: C, 50.54; H, 7.22; N, 16.24.

5-Alkylamino-4,4-pentamethylene-2-(2-pyridyl)-4*H*-imidazoles **4a**. General Procedure.

An excess of the primary amine (0.03 mole) and 1 g (4 mmoles) of **1a** were refluxed in 25 ml of xylene for 5 hours. The excess of amine was extracted with water and the organic layer was evaporated under reduced pressure to give **4a** by treatment of the residue with petroleum ether.

5-Benzylamino-4,4-pentamethylene-2-(2-pyridyl)-4*H*-imidazole (**4a**), (R = Benzyl).

This compound was obtained in 97% yield and was recrystallized from acetone, mp 183-185°; nmr (deuteriochloroform): δ 1.6 (m, 10H), 4.8 (s, 2H), 7.3 (s, 5H), 7.6-8.9 (m, 4H).

Anal. Calcd. for $C_{20}H_{22}N_4$: C, 75.44; H, 6.96; N, 17.59. Found: C, 75.56; H, 6.72; N, 17.69.

5-*n*-Butylamino-4,4-pentamethylene-2-2(2-pyridyl)-4*H*-imidazole (**4b**), (R = *n*-Butyl).

This solid was obtained in 48% yield and recrystallized from acetone-petroleum ether, mp 148-150°; nmr (deuteriodimethylsulfoxide): δ 1.0 (t, 3H), 1.0-1.6 (m, 4H), 1.8 (m, 10H), 3.5 (t, 2H), 3.5 (s, 1H), 7.4-8.8 (m, 4H).

Anal. Calcd. for $C_{17}H_{24}N_4$: C, 71.79; H, 8.51; N, 19.70. Found: C, 71.47; H, 8.53; N, 20.01.

4,4-Pentamethylene-5-amino-4*H*-imidazole-*N*-*n*-butylcarboxamide (**4b**).

By applying a similar procedure to that described above, **1b** gave **4b**, mp 215-216°, recrystallized from acetone (61%); nmr (deuteriodimethylsulfoxide): δ 0.9-1.7 (m, 17H), 3.2 (t, 2H), 8.05 (t, 1H).

Anal. Calcd. for $C_{13}H_{22}N_4O$: C, 62.41; H, 8.80; N, 22.39. Found: C, 62.03; H, 8.91; N, 22.53.

Ethyl 5-Amino-4,4-pentamethylene-4*H*-imidazole-2-carboxylate Iodomethylate Salt (**5b**).

A stirred solution of 0.7 g (3 mmoles) of **1b** with 0.77 ml (12 mmoles) of methyl iodide in 8 ml of dry acetonitrile was kept at room temperature for three days. Afterwards, **5b** was filtered from the reaction and recrystallized from acetone (31% yield), mp 187-189°; nmr (deuteriodimethylsulfoxide): δ 1.35 (t, 3H), 1.75 (m, 10H), 3.55 (s, 3H), 4.4 (q, 2H).

Anal. Calcd. for $C_{12}H_{20}IN_3O_2$: C, 39.46; H, 5.52; N, 11.51. Found: C, 39.01; H, 5.48; N, 11.23.

5-Amino-4,4-pentamethylene-2-(2-pyridyl)-4*H*-imidazole Iodomethylates (**5a** and **7a**).

Methyl iodide (1.9 ml, 30 mmoles) and **1a** (1.72 g, 7 mmoles) in 15 ml of dry acetonitrile were stirred at room temperature for 3 days. After filtration, the solid was crystallized in acetone-ethanol-ether to give **5a** and **7a** in a 1:2 ratio as yellow crystals of mp 193-203°; nmr (deuteriodimethylsulfoxide): δ 2 (m, 10H), 3.6 (s, 1H), 4.8 (s, 2H), 8-9.3 (m, 4H).

Thin-layer chromatography of the crude product revealed the presence of a third product in the reaction mixture identified as the hydroidoide of **1a**.

5-Acetylamino-4,4-pentamethylene-2-(2-pyridyl)-4*H*-imidazole (**6a**).

Compound **1a** (1.1 g, 4.8 mmoles) was refluxed for 45 minutes in 3 ml (32 mmoles) of acetic anhydride. After removal of the excess anhydride under reduced pressure, the residue was kept in dessicator over phosphorus pentoxide and sodium hydroxide pellets. Recrystallized from benzene, it gave a solid (65% yield), mp 122-123°; nmr (deuteriochloroform): δ 1.8 (m, 10H), 2.3 (s, 3H), 7.2 (s, 1H), 7.4-8.6 (m, 4H).

Ethyl 5-Acetylamino-4,4-pentamethylene-4*H*-imidazole-2-carboxylate (**6b**).

Compound **1b** (2.5 g, 0.01 mole) was refluxed for one hour in acetic anhydride (7 ml, 75 mmoles). After cooling by filtration and washing with ether, 2.05 g (71%) of **6b** was obtained and recrystallized from chloroform-benzene; mp 201-203°; nmr (deuteriochloroform): δ 1.4 (t, 3H), 1.8 (m, 10H), 2.3 (s, 3H, $CO\text{-}CH_3$), 4.45 (q, 2H).

Anal. Calcd. for $C_{13}H_{17}N_3O_3 \cdot 1/2H_2O$: C, 57.34; H, 6.66; N, 15.96. Found: C, 57.43; H, 7.02; N, 15.65.

REFERENCES AND NOTES

[1] M. P. Sammes and A. R. Katritzky, *Adv. Heterocyclic Chem.*, **35**, 409 (1983).

[2] S. Chaloupka, P. Vittorelli, H. Heimgartner, H. Schmid, H. Link, K. Bernauer and W. E. Oberhansli, *Helv. Chim. Acta*, **60**, 2476 (1977).

[3] B. Scholl, J. H. Bieri and H. Heimgartner, *Helv. Chim. Acta*, **61**, 3050 (1978).

[4] G. Mukherjee-Muller, S. Chaloupka, H. Heimgartner, H. Schmid, H. Link, K. Bernauer, P. Schonholzer and J. J. Daly, *Helv. Chim. Acta*, **62**, 768 (1979).

[5] H. Link, K. Bernauer, J. J. Daly, S. Chaloupka and H. Heimgartner, *Helv. Chim. Acta*, **64**, 49 (1981).

[6] A. F. McKay, C. Podesva and M. E. Kreling, *J. Org. Chem.*, **27**, 2884 (1962).

[7] T. K. Vinogradova, G. N. Mis'kevich and B. S. Drach, *Zh. Org. Khim.*, **16**, 1869 (1980); *Chem. Abstr.*, **94**, 84010 (1981).

[8] A. McKillop, A. Henderson, P. S. Ray, C. Avendaño and E. Gómez, *Tetrahedron Letters*, **23**, 3357 (1982).

[9] R. S. Hosmane, V. Bakthavachalam and N. J. Leonard, *J. Am. Chem. Soc.*, **104**, 235 (1982).

[10] E. J. Poziomek, *J. Org. Chem.*, **28**, 590 (1963).

[11] N. E. Noland, J. Sundberg and M. L. Michaelson, *J. Org. Chem.*, **28**, 3576 (1963).

[12a] J. Bellanato, C. Avendaño, M. T. Ramos, P. Smith-Verdier, F. Florencio and S. Garcia-Blanco, *Spectrochim. Acta* (in press). [b] C. Avendaño, M. T. Ramos and J. Bellanato, *Spectrochim. Acta* (in press).

[13] A. Strecker, *Ann. Chem.*, **75**, 27 (1850).

[14] A. Pinner, "Die Imidoaether und ihre Derivatives", Oppenheim, Berlin, 1892; R. H. de Wolfe and F. B. Augustine, *J. Org. Chem.*, **30**, 699 (1965).

[15] F. C. Schaefer and G. A. Peters, *J. Org. Chem.*, **26**, 412 (1961).

[16] The crystallized product had analytical data for $C_{13}H_{16}N_3{}^1\!/_4C_6H_6 \cdot {}^1\!/_2H_2O$. In order to remove water of crystallization, it was necessary to heat the sample at high vacuum for several hours.