Synthesis of 1*H*-Imidazo[1,2-*a*]imidazole

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The synthesis and structure analysis of the unknown 1*H*-imidazo[1,2-*a*]imidazole (**1**) is described. The preparation involves alkylation of 2-aminoimidazole with bromoacetaldehyde diethyl acetal and subsequent hydrolysis and cyclization with hydrochloric acid. The structure was characterized by mass spectrometry and by ^{1}H-, ^{15}N- and ^{13}C-nmr of **1** and by ^{1}H-nmr of its 1-benzyl derivative **8**. An independent synthesis of **8** was accomplished *via* cyclization of 2-(*N*-dichloroethyl-*N*-benzyl)aminoimidazole (**11**).

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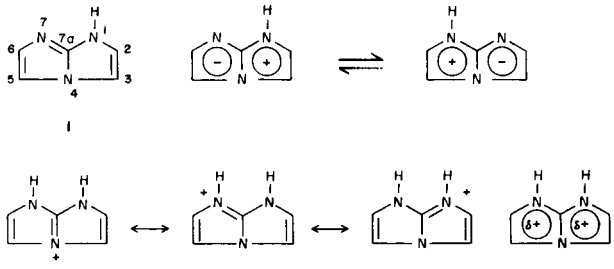
The present paper deals with the synthesis and structure analysis of the unknown 1*H*-imidazo[1,2-*a*]imidazole (**1**). This compound, which belongs to the general class of aromatic azapentalenes, is classified as a parent compound by *Chemical Abstracts* and has been the subject of a few theoretical studies [1,2]. The structure of the free base may be represented as an equilibrium of two identical tautomers having an excess of positive charge on the ring bearing the NH-group.

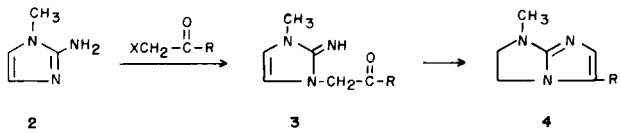


1

Three main resonance forms contribute to the structure of the imidazolium conjugate acid, showing that the positive charge is distributed evenly over the two rings.

Several alkyl- and aryl-substituted derivatives of **1** have been reported [3-13], first by Lawson [3] and extensively by Priimenko and Kochergin [4-7]. A convenient method [4-6,-10] for the preparation of 1-methyl-6-alkyl (or aryl) derivatives **4** involves ring *N*-alkylation of 1-methyl-2-aminoimidazole with an α-halo ketone and subsequent cyclization of **3** with mineral acid (Scheme 1).

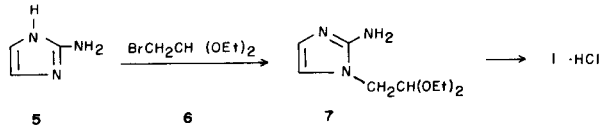
Scheme 1



2 **3** **4**

The synthesis of compound **1** presented in this work is based on analogous reactions (Scheme 2). 2-Aminoimidazole is alkylated with bromoacetaldehyde diethyl acetal and the resulting intermediate **7** is hydrolyzed with hydrochloric acid to give the hydrochloride salt of **1** in an overall yield of 16%.

Scheme 2



5 **6** **7**

Alkylation of 2-aminoimidazoles generally proceeds on the more basic ring nitrogen atom rather than on the amino group [10,14]. The reaction was performed by slow addition of an excess of sodium amide to a mixture of **5** sulfate and **6** in dimethylformamide. Mass spectral analysis of the reaction mixture revealed the presence of the desired alkylation product **7** [molecular ion ($M^{+\cdot}$) 199] besides starting materials **5** and **6**. A formyl derivative of **5** also was identified ($M^{+\cdot}$ 111). This side product presumably forms by reaction of the anion of **5** with dimethylformamide. Compound **7** was partially purified by solvent extraction.

Hydrolysis of **7** by reflux in 2*N* hydrochloric acid yielded the hydrochloride salt of **1** which was purified by cation exchange chromatography. The salt readily loses hydrogen chloride when heated in the ion source of the mass spectrometer. The mass spectrum displays a prominent molecular ion ($M^{+\cdot}$ 107), a doubly charged molecular ion (M^{++} 53.5) and further low-intensity peaks corresponding to loss of H, HCN, HCN + H, and 2 HCN.

The ^{1}H- and ^{13}C-nmr spectra of hydrochloride **1** support a symmetric structure with equivalent positions 1 and 7, 2 and 6, and 3 and 5. Very similar spectra are observed for the free base which suggest the existence of a fast tautomeric equilibrium. The characteristic features of these spectra may also be compared to those of other azapentalenes [1,15,16].

The ^{1}H-nmr spectra of the salt in perdeuterated dimethylsulfoxide (Table 1) shows the expected doublets for

Table 1

^{1}H-NMR Spectra of **1**: A) 0.1 *M* Hydrochloride in Perdeuterated Dimethylsulfoxide, B) 0.1 *M* Hydrochloride in Trifluoroacetic Acic, and C) 0.1 *M* Free Base Obtained by Addition of an Excess of 1,4-Diazabicyclo[2,2,2]octane to Solution A.

Assignment	δ Values, Multiplicity and Coupling Constants		
	A	B	C
H-2, H-6	7.48 (d, ^{3}J = 2.0 Hz, 2H)	7.30 [b,c] (t, br, 2H)	6.96 (d, ^{3}J = 1.5 Hz, 2H)
H-3, H-5	7.64 [a] (d, ^{3}J = 2.0 Hz, 2H)	7.38 [b] (d, br, 2H)	7.15 (d, ^{3}J = 1.5 Hz, 2H)
H-1, H-7	13.7	10.6	not detected
(NH)	(br, 2H)	(br, 2H)	

[a] Signal disappears slowly upon addition of deuterium oxide. [b] Signal is converted to a sharp doublet ($^3J_{H\text{-}C\text{-}C\text{-}H}$ = 2.2 Hz) by decoupling of the NH protons. [c] Estimated value of $^3J_{H\text{-}N\text{-}C\text{-}H}$ = 1.8 Hz).

Table 2

^{13}C-NMR Spectra (^{1}H-Coupled and ^{1}H-Decoupled) of A) 0.5 *M* Hydrochloride **1** in Perdeuterated Dimethylsulfoxide and B) 0.1 *M* Free Base Obtained by Addition of an Excess of 1,4-Diazabicyclo[2,2,2]octane to a Solution of Hydrochloride **1** in Perdeuterated Dimethylsulfoxide

Assignment	A δ-Values ($^nJ_{C,H}$)	B δ-Values ($^nJ_{C,H}$) [c]
C-2, C-6	120.3 [a] (dd, ^{1}J = 199 Hz, ^{2}J = 12.4 Hz)	123.9 (dd, ^{1}J = 189 Hz, ^{2}J = 11.8 Hz)
C-3, C-5	108.7 [b] (dd, ^{1}J = 205.5 Hz, ^{2}J = 12.2 Hz)	105.0 (dd, ^{1}J = 196.5, ^{2}J = 14.5 Hz)
C-7a	138.9 (tt, ^{3}J = 8.5 Hz, ^{3}J = 6.5 Hz)	147.6 [c]

[a] Assignment confirmed by selective decoupling of H-2, H-6 protons. [b] Assignment confirmed by selective decoupling of H-3, H-5 protons. [c] The ^{1}H-coupled spectrum of this diluted solution was obtained with the DEPT pulse sequence (based on polarization transfer $^1H \rightarrow {}^{13}C$ through $^1J_{C\text{-}H}$ scalar coupling), yielding enhanced signals only for CH carbon atoms.

Table 3

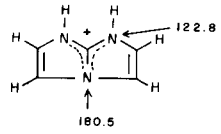
^{1}H-NMR Spectrum of 1-Benzyl-1*H*-imidazo[1,2-*a*]imidazole (**8**) in Deuteriochloroform

Assignment	δ-Values, Multiplicity and Coupling Constants
CH_2	5.17 (s, 2H)
H-2	6.64 (dd, ^{3}J = 2.5 Hz, ^{6}J = 0.95 Hz, 1H)
H-3	6.94 (d, ^{3}J = 2.5 Hz, 1H)
H-5	7.04 (d, ^{3}J = 1.4 Hz, 1H)
H-6	7.13 (dd, ^{3}J = 1.4 Hz, ^{6}J = 0.95 Hz, 1H)
PhH	7.25-7.40 (m, 5H)

H-2, H-6 and H-3, H-5. Addition of deuterium oxide gives rise to exchange at the more nucleophilic 3,5-positions [2,16], probably *via* deuteronation of the free base present in an acid-base equilibrium. The assignment of protons is confirmed by the coupling observed between H-2, H-6 and the NH protons in trifluoroacetic acid (Table 1) and the broadening of the signals for H-2, H-6 in perdeutereated acetone at low temperatures (−30 to −50°). The ^{1}H-nmr spectrum of the free base displays sharp doublets for two pairs of equivalent protons, *i.e.* H-2, H-6 and H-3, H-5 (Table 1), in agreement with the symmetry created by a fast proton exchange between the two tautomers.

The ^{1}H-decoupled ^{13}C-nmr spectra of hydrochloride **1** and the free base exhibit only three signals corresponding to the atom pairs C-2, C-6 and C-3, C-5 and to the angular carbon atom C-7a (Table 2). In the spectrum of the deuterated compound (partial exchange of H-3, H-5) the isotope effect gives rise to an upfield shift of the signals corresponding to C-2, C-6 and C-3, C-5. The latter signal appears as a triplet ($^1J_{C\text{-}D}$ = 31.5 Hz). The coupling constants observed for the ^{1}H-coupled spectrum of the hydrochloride are also given in Table 2. The characteristic pattern observed for C-7a indicates that this atom is coupled with both the H-2, H-6 and H-3, H-5 hydrogen pairs. Two similar coupling constants are observed (^{3}J = 8.5 and 6.5 Hz or *vice versa*). In each case the coupling may occur in a similar fashion over a three-bond system C-N-C-H involving either a bridge or a non-bridge nitrogen atom.

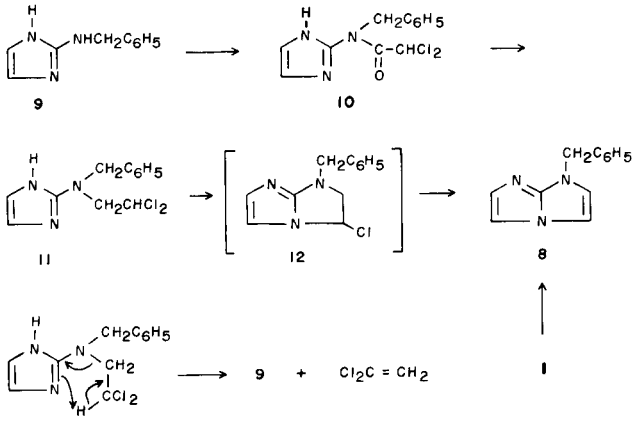
The ^{15}N-nmr spectrum of hydrochloride **1** was recorded by using several pulse sequences. On the liquid ammonia scale the two equivalent NH nitrogen absorb at δ 122.8 and the tertiary nitrogen at δ 180.5. Only the NH nitrogen



atoms were detected by the broad band decoupling technique with NOE enhancement. Both kinds of nitrogen atoms were detected with INEPT and DEPT pulse sequences, based on polarisation transfer through long range coupling (^2J and ^3J are approximately 3-4 Hz). Polarisation transfer *via* $^1J_{NH}$ for NH nitrogen atoms is prevented by the fast exchange of NH protons in the concentrated perdeuterated dimethylsulfoxide solution. Finally, a coupled spectrum was obtained with the DEPT pulse sequence, which revealed the NH signal as a triplet (sum of $^2J_{NH}$ and $^3J_{NH}$ = 6 Hz) and the signal for the tertiary nitrogen atom as a multiplet (sum of coupling constants ≅ 10 Hz).

The proposed structure was confirmed by benzylation of **1** to 1-benzyl-1*H*-imidazo[1,2-*a*]imidazole (**8**) which was identical to the product formed by independent synthesis (Scheme 3). Acylation of 2-benzylaminoimidazole **9** [14]

Scheme 3



with dichloroacetyl chloride gives amide **10**, which is reduced with borane in tetrahydrofuran to yield amine **11**. Pyrolysis of **11** finally affords cyclisation product **8** and amine **9**. The cyclisation probably involves nucleophilic substitution producing a labile monochloro intermediate **12**. Amine **9** may be formed by elimination of 1,1-dichloroethene *via* a six-membered transition state.

The ^{1}H-nmr spectrum of **8** (Table 3) displays four separate signals for the imidazole C-H protons, in accord with the loss of symmetry induced by the 1-benzyl group. This is reflected also by the observation of different coupling constants for H-2, H-3 and H-5, H-6 (^3J = 2.5 and 1.4 Hz). The lower value is characteristic for condensed imidazole ring systems [17] and may therefore be assigned to H-5, H-6. The assignment of protons is completed by the long-range coupling which interrelates the protons H-2 and H-6 located in a zig-zag pattern (^6J = 0.95 Hz).

EXPERIMENTAL

All reactions were carried out under an argon atmosphere. Solvents for reactions were dried and distilled prior to use. ^{1}H- and ^{13}C-nmr spectra were recorded on a Brucker Cryospec WM-250 instrument (250 MHz for ^{1}H, 62.9 MHz for ^{13}C). Chemical shifts are reported in parts per million relative to tetramethylsilane as an internal standard; s = singlet, d = doublet, dd = doublet of doublets, t = triplet, tt = triplet of triplets, m = multiplet, br = broad. Natural abundance ^{15}N-nmr spectra of 0.7 *M* hydrochloride **1** in perdeuterated dimethylsulfoxide were obtained at 25.35 MHz on a Bruker WM 250 with a selective 10 mm probe. The chemical shifts are given in parts per million relative to liquid ammonia (δ = 0). Neat nitromethane (δ = 380 ppm) was used as an external measuring reference and perdeuterated dimethylsulfoxide to obtain a deuterium lock signal. Melting points were determined on a Leitz Wetzlar 1100 melting point microscope and are uncorrected. Chemical ionization mass spectra (cims) were obtained on a Kratos AEI MS-12 instrument modified for chemical ionization. Electron ionization mass spectra (eims) were obtained on a Kratos AEI MS-902 S instrument: ionizing energy 70 eV, accelerating voltage 8 Kv and direct insertion into the ion source operated at 150-200° as required. Accurate mass measurements were performed at a dynamic resolution of 7,500 using a VG Analytical 2010 data system.

1*H*-Imidazo[1,2-*a*]imidazole (**1**).

To a magnetically stirred mixture of 2-aminoimidazole sulfate (1 g, 3.8 mmoles, 7.6 meq. of 2-aminoimidazole) and bromoacetaldehyde diethyl acetal (3.75 g, 19 mmoles) in anhydrous dimethylformamide (20 ml) is added sodium amide (1.18 g, 30 mmoles) in several portions over 1 hour. The reaction mixture is stirred for 2.5 hours, then another portion of sodium amide (0.30 g, 7.7 mmoles) is added and the reaction is allowed to proceed overnight at room temperature. Ice (50 ml) and 1*M* sodium carbonate (50 ml) are added and the mixture is extracted with dichloromethane (5 × 30 ml). The organic layer is washed with water (2 × 10 ml) and evaporated to dryness *in vacuo* to yield crude 1-(2,2-diethoxyethyl)-2-aminoimidazole (**7**); eims: 199 (M^+); cims: 200 (MH^+). Further extraction of the aqueous layers with ethyl acetate yields a formylation product of 2-aminoimidazole; eims: 111 (M^+); cims: 112 (MH^+).

Crude compound **7** is dissolved in 2*N* hydrochloric acid (10 ml) and the solution is extracted with dichloromethane (20 ml). The organic layer is discarded and the aqueous layer is refluxed under argon for 30 minutes. The solution is evaporated to dryness *in vacuo* and the residue is dissolved in water and applied onto a cation exchange column (Dowex 40, acid form, prepared by washing with 2*N* hydrochloric acid and then with water). The column is eluted first with water, then with 0.6*N* hydrochloric acid and finally with 1*N* hydrochloric acid. The fractions containing compound **1** are identified by evaporation of samples to dryness *in vacuo*, followed by tlc with chloroform:methanol (17:3) as the solvent. Compound **1** is visualized by heating the plates in an oven at 120°.

Evaporation to dryness *in vacuo* yields the hydrochloride of **1**, mp 141-146° (177 mg, 1.26 mmoles, 16% calculated on 2-aminoimidazole). The salt is crystallized by dissolution in boiling acetone, filtration and partial evaporation, mp 145-148°.

The free base is obtained as a viscous oil by treatment of an aqueous solution of the salt with sodium acetate, evaporation to dryness *in vacuo*, and thorough extraction of the residue with boiling ethyl acetate; eims: 107 (M^+).

A picrate is prepared by treatment of the hydrochloride of **1** with an excess of picric acid in methanol, dec 206°.

Anal. Calcd. for $C_{11}H_8N_6O_7$: C, 39.30: H, 2.40; N, 25.00. Found: C, 39.20; H, 2.45; N, 24.95.

2-(*N*-Dichloroacetyl-*N*-benzyl)aminoimidazole (**10**).

2-Benzylaminoimidazole hydrogen chloride (200 mg, 0.95 mmole) is heated with 1.5 ml of dichloroacetyl chloride at 80° for 16 hours. The

crystalline product is collected by dilution with anhydrous ether, filtration and washing with dichloromethane to yield 200 mg (0.62 mmole, 65%) of the hydrochloride salt of **10**, mp 207-208° dec; nmr (perdeuterated dimethylsulfoxide): δ 5.12 (s, 2H, PhCH_2), 7.07 (s, 1H, CHCl$_2$), 7.43 (s, 2H, H-4 and H-5); cims: 284, 286 and 288 (MH^+); eims: 283, 285 and 287 ($M^{+\cdot}$).

The free base **10** is prepared by suspending the salt (100 mg) in dichloromethane and addition of triethylamine (0.2 ml). The dichloromethane solution is washed with cold 1*N* potassium carbonate and water, dried (magnesium sulfate), and evaporated to dryness to yield **10**, which is crystallized from ethyl acetate, mp 157-159°. The nmr spectrum (deuteriochloroform) reveals the presence of two amide forms [14] in a 2:1 ratio: δ 4.94 and 5.56 (s, 2H, PhCH_2), 6.26 and 6.43 (s, 1H, CHCl$_2$), 6.92 (s, 2H, H-4 and H-5), 7.25 (m, 5H, PhH); cims and eims: identical to those of the hydrochloride salt.

Anal. Calcd. for $C_{12}H_{11}Cl_2N_3O$: C, 50.72; H, 3.90; N, 14.79; Cl, 24.95. Found: C, 50.54; H, 3.60; N, 14.64; Cl, 24.60.

2-(*N*-2,2-Dichloroethyl-*N*-benzyl)aminoimidazole (**11**).

Compound **10** hydrogen chloride (230 mg, 0.70 mmole) is allowed to react with boron hydride in tetrahydrofuran (3 ml of a 1*M* solution, 3 mmoles) for 16 hours at room temperature. Ice (20 ml), 0.1*N* hydrochloric acid (20 ml) and methanol (30 ml) are added and the resulting solution is evaporated to dryness *in vacuo*. The residue is dissolved in methanol (20 ml) and the solvent is removed *in vacuo*. This treatment is repeated five times, and the residue is partitioned between 1*N* potassium carbonate and dichloromethane. The dichloromethane solution is washed with water, dried (magnesium sulfate) and evaporated to dryness to give **11** (0.18 g, 0.67 mmole, 95%, mp 154-155°). Crystallization from acetone-hexane yields the analytical sample, mp 154-155°; nmr (deuteriochloroform): δ 4.13 (d, J = 6 Hz, 2H, CH_2CHCl$_2$), 5.92 (t, J = 6 Hz, 1H, CHCl$_2$), 6.64 (s, 2H, H-4 and H-5), 7.18-7.33 (m, 5H, PhH); cims: 270, 272 and 274 (MH^+); eims: 269 , 271 and 273 ($M^{+\cdot}$).

Anal. Calcd. for $C_{12}H_{13}Cl_2N_3$: C, 53.25; H, 4.85; N, 15.55; Cl, 26.25. Found: C, 52.60; H, 4.79; N, 15.15; Cl, 26.68.

1-Benzyl-1*H*-imidazo[1,2-*a*]imidazole (**8**).

(A) Cyclization of 2-(*N*-2,2-Dichloroethyl-*N*-benzyl)aminoimidazole (**11**).

Compound **11** (30 mg, 0.11 mmole) is heated under argon with dimethylamine hydrogen chloride (200 mg) at 180° for 5 minutes. The mixture is cooled, 1*M* sodium carbonate is added and the solution is extracted with dichloromethane. Cims reveals the presence of compound **8** (MH^+ 198) and 2-benzylaminoimidazole (MH^+ 174). Column chromatography on silica gel using the solvent system ethyl acetate:methanol (19:1) yields compound **8** as a colourless liquid (10 mg, 0.05 mmole, 45%); cims: 198 (MH^+); eims: 197 ($M^{+\cdot}$). Accurate mass calculated for $C_{12}H_{11}N_3$: 197.0953. Found: 197.0956.

(B) Benzylation of **1**.

Compound **1** hydrogen chloride (28 mg, 0.2 mmole) is dissolved in anhydrous acetone (5 ml). Anhydrous potassium carbonate (0.5 g) and benzyl bromide (68 mg, 0.4 mmole) are added and the resulting mixture is stirred at room temperature for 20 hours. The solution is filtered and evaporated *in vacuo*. The residue is purified by column chromatography as described under (A) to yield **8** (6 mg, 0.03 mmole, 15%); tlc, cims and eims analyses identical to those obtained for the cyclization product.

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REFERENCES AND NOTES

[1] J. Elguero, R. M. Claramunt and A. J. H. Summers in "Advances in Heterocyclic Chemistry", Vol 22, A. R. Katritzky and A. J. Boulton, eds, Academic Press, New York, 1978, p 183-320.

[2] V. A. Anisimova, N. I. Avdyunina, A. F. Pozharskii, A. M. Simonov and L. N. Talanova, *Khim. Geterotsikl. Soedin.*, 528 (1980).

[3] A. Lawson, *J. Chem. Soc.*, 307 (1956).

[4] P. M. Kochergin and B. A. Priimenko, *Khim. Geterotsikl. Soedin.*, 176 (1969).

[5] B. A. Priimenko and P. M. Kochergin, *Khim. Geterotsikl. Soedin.*, 1692 (1971).

[6] B. A. Priimenko and P. M. Kochergin, *Khim. Issled Farm. USSR*, 53 (1970); *Chem. Abstr.*, **76**, 34170 (1972).

[7] B. A. Priimenko and P. M. Kochergin, *Khim. Geterotsikl. Soedin.*, 1243 (1971).

[8] A. Hetzheim and H. Pusch, *Z. Chem.*, **10**, 385 (1970).

[9] H. Beyer, *Z. Chem.*, **10**, 289 (1970).

[10] L. F. Miller and R. E. Bambury, *J. Med. Chem.*, **15**, 415 (1972).

[11] L. F. Miller and R. E. Bambury, *J. Org. Chem.*, **38**, 1955 (1973).

[12] T. Muro, T. Nakao and K. Ogawa, Japanese Patent 76 11,784 (1976); *Chem. Abstr.*, **84**, 180225 (1976).

[13] N. S. Patalakha, P. B. Kurapov, I. I. Grundberg and B. A. Priimenko, *Izv. Timiryazevsk Skh. Acad.*, 145 (1983); *Chem. Abstr.*, **100**, 5670 (1984).

[14] F. Compernolle and N. Castagnoli, Jr., *J. Heterocyclic Chem.*, **19**, 1403 (1982).

[15] R. Faure, E. J. Vincent, R. M. Claramunt, J. M. Fabrega and J. Elguero, *Tetrahedron*, **32**, 341 (1976).

[16] R. Faure, E. J. Vincent, R. M. Claramunt and J. Elguero, *Org. Magn. Reson.*, **9**, 508 (1977).

[17] T. J. Battersham in "NMR Spectra of Simple Heterocycles", E. C. Taylor and A. Weissberger, eds, John Wiley and Sons, Inc., New York, N.Y. 1973, p 285.