

Paula Aulaskari,\* Markku Ahlgrén, Juha Rouvinen, and Pirjo Vainiotalo

Department of Chemistry, University of Joensuu, P.O. Box 111, FIN-80101 Joensuu, Finland

Esko Pohjala

Leiras Oy, P.O. Box 33, FIN-33721 Tampere, Finland

Jouko Vepsäläinen

Department of Chemistry, University of Kuopio, P.O. Box 1627, FIN-70211 Kuopio, Finland

Received February 21, 1996

1-*R*-5-[(2-Nitro-2-phenyl)ethenyl]imidazoles (R = Bn, Me, H) **6a,b,c** were synthesized by the Knoevenagel reaction of the corresponding aldehydes **4a,b,c** with phenylnitromethane **5**. The *E*-isomers **6a,b,c** were precipitated from the reaction mixture as crystalline compounds in 89, 81 and 60% yields, respectively. Traces of the *Z*-isomers **6a'b',c'** were found in the reaction mixtures but could be obtained in a ratio of 4:3 from the *E*-form with UV irradiation. The *E*-forms were more stable and the *Z*-isomers changed again to the *E*-isomers in several weeks.

*J. Heterocyclic Chem.*, **33**, 1345 (1996).

Several research groups have been interested in investigating imidazole derivatives because of their biologically active nature [1]. Histidine, the essential amino acid for growth, and its decarboxylation product histamine [2] are the most common imidazole structures in the tissues of a human being. Nitroalkenes are powerful dienophiles in the Diels-Alder reaction, as electrophiles they readily undergo addition reactions with many different nucleophiles [3,4]. Because of the easy transformation of the nitro group to other functionalities nitroalkenes are particularly versatile compounds in synthetic organic chemistry [5,6].

Nitroethenylimidazoles are useful intermediates [7] for a preparation of a series of new 4- or 5-[2-aryl-2-(functional group)ethyl]imidazoles as new lipophilic histidine analogues and H<sub>3</sub> receptor agonists [8], and on the other hand as homologues of some on α<sub>2</sub>-adrenoceptor active agents [9]. The structure determination serving a better knowledge of the structural requirements is an essential part for studying the properties of potential biological active agents. The nitro group of the title compounds provides a good comparable object as a basis for further structure elucidation in the series. It is relatively easy to determine with spectroscopic tools. Although the preparation of nitroethylenes by the Knoevenagel [10] reaction is already familiar there is no report regarding the nitroethenyl compounds **6a,b,c** synthesized in this work.

Our main goal has been to prepare nitroethenylimidazoles with different protective groups as a part of our elaboration towards synthetic routes to a series of new biologically active heterocyclic compounds. The structures have been verified using ir, <sup>1</sup>H nmr and <sup>13</sup>C nmr spectroscopy, mass spectrometry, X-ray crystallography, and elemental analysis. For more elucidation the compounds have been explored

using molecular modeling and uv irradiation and also in some cases <sup>1</sup>H-<sup>1</sup>H correlated COSY, NOESY and <sup>1</sup>H-<sup>13</sup>C spectra. For comparison the structures and properties of some intermediates were studied as well (nmr, X-ray, ms).

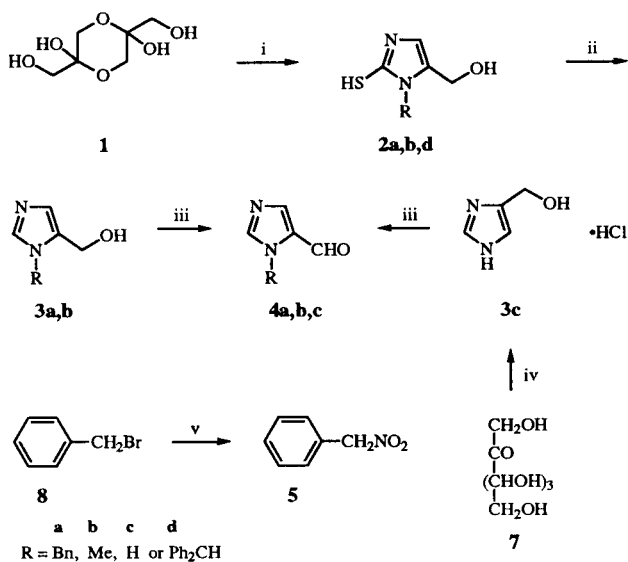
#### Results and Discussion.

The imidazolecarboxaldehydes **4a,b,c** for the Knoevenagel [10] reaction were prepared in moderate to good yields according to literature procedures after some modifications by a three step synthesis starting from dihydroxyacetone dimer **1** [11] using benzyl-, methyl- or (diphenylmethyl)amines depending on the desired protective group at nitrogen 1. The aldehyde **4c** (R = H) was made by three step synthesis starting from fructose **7** [12]. Phenylnitromethane **5** was prepared from benzylbromide **8** and sodium nitrite (Scheme 1) [13].

An ideal protective group on nitrogen 1 was the benzyl group, the isolation, the precipitation and recrystallization proceeded most easily in every step, while the compounds with the diphenylmethyl group were rejected after several attempts because of very low yields in the removal of the mercapto group (Scheme 1).

The title compounds **6a,b,c** were made *via* the Schiff base of the corresponding aldehydes using *n*-butylamine as a catalyst (Scheme 2). The amount of side products was adjusted to a minimum by removal of water as an azeotrope with benzene or toluene and by trapping basic amine with glacial acetic acid. According to the literature most methods for the preparation of nitroalkenes [14] produce generally *E*-nitroalkenes [15]. We want to report an easy and convenient way to convert the *E*-isomer to the *Z*-isomer **6a'b',c'** simply by uv irradiation. The nitroethenyl compounds were irradiated by uv using perdeuteriomethanol or deuterio-

Scheme 1

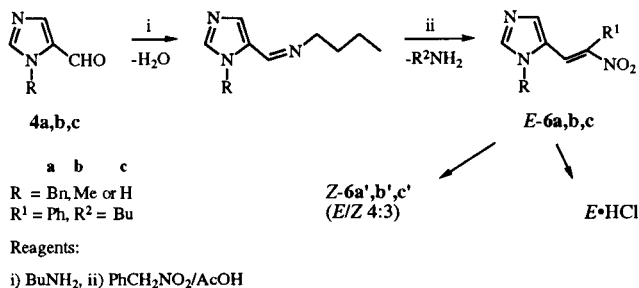


Reagents:

- i. (a) RNH<sub>2</sub>; (b) KCNS; (c) BuOH; ii, HNO<sub>3</sub>; iii, act. MnO<sub>2</sub>;  
 iv, (a) 37% CH<sub>2</sub>O; (b) 25% NH<sub>3</sub>; (c) CuCO<sub>3</sub>·Cu(OH)<sub>2</sub>;  
 (d) 37% HCl; v, (a) NaNO<sub>2</sub>; (b) urea.

chloroform as a solvent. The isomerization reactions were followed by nmr and first signs of the conversion of the *E*-isomer to the *Z*-isomer were seen after two hours irradiation in deuteriochloroform. After six hours the ratio of *E* and *Z* was 4:3, and the ratios did not change any more upon further irradiation. After standing for about three weeks the *Z*-isomers had totally converted back to the more stable *E*-isomers. In a methanolic solvent the conversion did not happen at all. The reason probably was that the conversion in deuteriochloroform was catalysed by an acid formed from chloroform during storing. The product mixture seemed to be stable enough for storing for several days and might be used in synthesis starting from the *Z*-isomer.

Scheme 2



The substitution pattern in the imidazole ring and *cis-trans* isomerism of the double bond between the rings were explored using nmr and X-ray techniques. The nitroethenylimidazole **6a** was the major compound studied. The mass spectrometry and molecular modeling supported these studies, and all these methods together, but especially

X-ray crystallography and nmr, completed with elemental analysis, finally proved structure of **6a** to be 5-substituted *trans* imidazolyl-nitro isomer.

### NMR Spectroscopy.

The relation between chemical shifts and protective group at nitrogen 1 both in products and intermediates was studied by nmr. The <sup>1</sup>H and <sup>13</sup>C nmr chemical shifts are listed in the experimental part. The relation was very much dependent on a substituent of the imidazole ring. Proton and carbon-13 shifts C(4)H in mercaptoimidazoles **2a,b,d** as well as in ethenylimidazoles **6a,b,c** were not dependent on the protective group. In a series of imidazolealcohols **3a,b,c** protons C(4)H and C(2)H of the unprotected imidazole **3c** were observed most downfield while the corresponding carbon-13 shifts were most upfield. In the case of imidazolecarboxaldehydes **4a,b,c** protons C(4)H and C(2)H of benzylimidazole had shifts most downfield, the unprotected imidazole most upfield. Similar behavior was noted with carbon-13 shifts. The ethenyl proton in **6** shifted downfield in order of R = Bn, Me, H.

The <sup>1</sup>H and <sup>13</sup>C chemical shifts were verified using <sup>1</sup>H-<sup>1</sup>H and <sup>1</sup>H-<sup>13</sup>C correlated techniques and are listed in the experimental part. It is possible to determine the solution stereochemistry of **6a** by nmr spectroscopy using several methods, but normally chemical shifts,

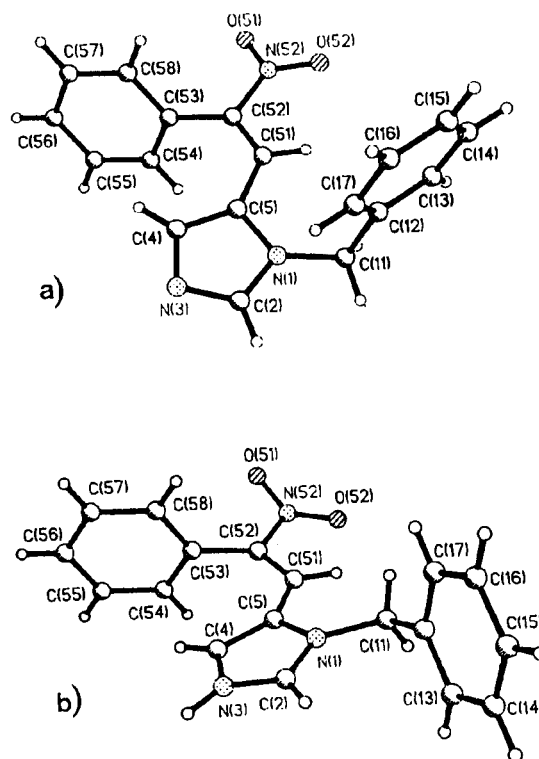


Figure 1a) The molecular structure of C<sub>18</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub> (**6a**); b) The structure of the cation in C<sub>18</sub>H<sub>16</sub>N<sub>3</sub>O<sub>2</sub><sup>+</sup> Cl<sup>-</sup> (**6a·HCl**).

coupling constants and NOE are the most informative. Unfortunately, the  $^4J_{CH}$  coupling from C58 to C(51)H (Figure 1), which is the best probe in this case for the double bond orientation, was useless since the signal of C53 was overlapped by other carbon signals in the coupled  $^{13}C$  spectrum. However, the cross peak in the NOESY spectrum is possible to explain only, if the nitro-group and the imidazole moiety are *trans* respect to each other. The best evidence for that configuration are strong dipolar couplings from C(4)H to phenyl ring protons attached to C54, C55 and C56. On the other hand, the missing cross peak between C(51)H and C(54)H proved that these groups are in the *trans* orientation.

The conformations of phenyl and imidazole group comparing to the double bond were possible to clarify using chemical shift information in both  $^1H$  and  $^{13}C$  spectra. In the  $^{13}C$  nmr spectra double bond and aromatic ring chemical shifts evidently depend on conjugation (upfield shift) in the system. In this molecule **6a** the imidazole ring and the double bond are obviously in-plane since a large upfield shift (20 ppm) of C(5) is observed due to conjugation effect. Phenyl ring is out-of-plane as X-ray studies showed because of missing conjugation effect. More over, the large upfield shift (0.9 ppm) of C(4)H is due to potent aromatic ring current effect indicating that C(4)H ought to be near the centre of the adjacent phenyl ring.

#### Molecular Modeling.

The conformational analysis of 1-benzyl-5-[(2-nitro-2-phenyl)ethenyl]imidazole (**6a**) was performed by using the modeling program Sybyl, version 6.03 (Tripos Associates). The molecule was built by using the Sybyl program and the structure was fully optimized by using molecular mechanics. The conformational analysis was carried out in two steps by using the force field method of the program without atomic charges: firstly by rotating the single bond C52-C53, and secondly by rotating both the bonds N1-C11 as well as C11-C12 simultaneously. The first calculation showed clearly two energy minimum for the bond C52-C53, where the torsion angle of C54-C53-C52-C51 had the values  $-100^\circ$  to  $-20^\circ$  and  $80^\circ$  to  $160^\circ$ . The similar results were obtained both by rotating the molecule as a rigid entity or by optimizing the structure after every rotation. The two equivalent conformational minimum are due to the symmetry of phenyl substituent.

The second calculation showed that the bond C11-C12 can rotate almost freely when the torsion angle of C5-N1-C11-C12 has the approximate values  $70^\circ$  to  $120^\circ$  or  $-90^\circ$  to  $-110^\circ$ . The rotation is more restricted in the latter case. The calculation showed that the molecule has the highest energy when the torsion angle of C5-N1-C11-C12 has the value  $-30^\circ$  to  $10^\circ$ .

#### X-ray Crystallography.

5-Hydroxymethylimidazole (**3c**) was crystallized from a methanol/hydrogen chloride solution as a hydrochloride. The structure of the cation is shown in Figure 2. The imidazolium ring is planar as expected and possesses nearly  $C_{2v}$  symmetry. The bond lengths and angles are presented in Table 1 and they agree well with those reported for imidazolium cation [16,17]. The C(5)-C(6) bond of 1.490(3) Å is a normal  $C(sp^2)$ - $C(sp^3)$  single bond and the hydroxymethyl group affects very little to the geometry of the imidazolium ring similarly to the substituents on the imidazolium ring in cyclo-(L-histidyl-L-aspartyl) trihydrate [18], L-histidinium dihydrogen monophosphate monohydrate [19], histaminium dinitrate [20] and diprotonated DL-histidinium dinitrate [21]. The oxygen atom of the hydroxymethyl group is twisted out of the plane of the imidazolium ring the N(1)-C(5)-C(6)-O torsion angle being  $55.4(2)^\circ$  and the N(1)...O distance of 2.996(2) Å.

1-Benzyl-5-[(2-nitro-2-phenyl)ethenyl]imidazole (**6a**) was crystallized from an ethanol solution in the orthorhombic crystal system (O) and from a methanol solution in the monoclinic crystal system (M). In both structures the molecule is equal and in the *E*-form. The 2-nitroethenylimidazole

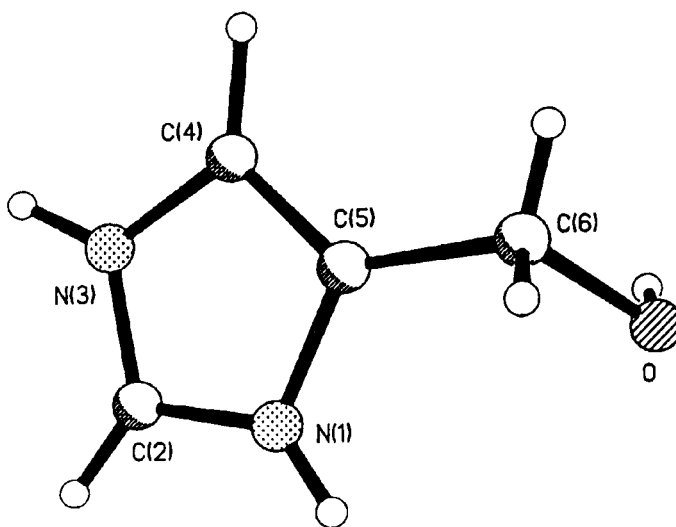


Figure 2. The structure of the cation in  $C_4H_7N_2O^+ Cl^-$  (**3c·HCl**).

Table 1  
Bond Lengths/Å and Angles/ $^\circ$  for  $C_4H_7N_2O^+ Cl^-$  (**3c·HCl**)

|           |          |                |          |
|-----------|----------|----------------|----------|
| N(1)-C(2) | 1.326(2) | N(1)-C(2)-N(3) | 107.8(2) |
| N(3)-C(2) | 1.327(2) | C(2)-N(1)-C(5) | 109.7(1) |
| N(1)-C(5) | 1.379(2) | C(2)-N(3)-C(4) | 109.4(1) |
| N(3)-C(4) | 1.374(2) | N(1)-C(5)-C(4) | 106.1(1) |
| C(4)-C(5) | 1.360(2) | N(3)-C(4)-C(5) | 107.0(1) |
| C(5)-C(6) | 1.490(3) | N(1)-C(5)-C(6) | 122.5(1) |
| C(6)-O    | 1.417(2) | C(4)-C(5)-C(6) | 131.4(2) |
|           |          | C(C)-C(6)-O    | 112.1(2) |

moiety is roughly planar forming a conjugated double bond system. The benzyl substituent is twisted out of the plane the C(5)-N(1)-C(11)-C(12) and N(1)-C(11)-C(12)-C(17) torsion angles being 74.3(3) and 41.6(4)° in the monoclinic phase **6aM** and 75.6(8) and 41.0(7)° in the orthorhombic phase **6aO**, respectively. The results are in agreement with those obtained by molecular modeling. Selected bond lengths and angles are presented in Tables 2 and 3, and the molecular structure in Figure 1a. The C(5)-C(51) bond possesses double bond character being 1.435(4) Å in **6aM** and 1.441(10) Å in **6aO**. On the other hand the C(52)-C(53) bond is a normal single bond being 1.489(3) Å in **6aM** and 1.494(9) Å in **6aO**. The torsion angle of C(51)-C(52)-C(53)-C(58) is 116.4(3)° in (**6aM**) and 113.5(7)° in (**6aO**). The results of nmr and molecular modeling studies are consistent. In both phases the imidazole ring is asymmetric. The N(1)-C(2) bond length is a little longer than the N(3)-C(2) bond, the C(2)-N(1)-C(5) angle slightly larger than the C(2)-

N(3)-C(4) angle and the N(3)-C(4)-C(5) angle remarkably larger than the N(1)-C(5)-C(4) angle as found in comparable structures [22-24].

1-Benzyl-5-[(2-nitro-2-phenyl)ethenyl]imidazole was crystallized also as a hydrochloride (**6a•HCl**) from a methanol/hydrogen chloride solution. Selected bond lengths and angles are presented in Tables 2 and 3, and the molecular structure of the cation in Figure 1b. The conformation of the 5-[(2-nitro-2-phenyl)ethenyl]imidazolium moiety is much the same as in **6aM** and **6aO** the C(51)-C(52)-C(53)-C(58) torsion angle of 81.8(8)° being about 35° more acute, however. The benzyl substituent is now approximately perpendicular to the imidazolium ring the torsion angles of C(5)-N(1)-C(11)-C(12) and N(1)-C(11)-C(12)-C(13) being 163.9(6)° and 83.8(6)°, respectively. The bond lengths of the imidazolium ring are quite comparable to those found in the unprotonated forms within experimental errors (Table 2) but the bond angles indicates an appreciable aromatic character for the imidazolium ring (Table 3) as in **3c** and in other N(1) and C(5) substituted structures [25-27].

Table 2

Selected Bond Lengths/Å for C<sub>18</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub> in the Monoclinic (**6aM**) and Orthorhombic (**6aO**) Phases, and for C<sub>18</sub>H<sub>16</sub>N<sub>3</sub>O<sub>2</sub>•Cl<sup>-</sup> (**6a•HCl**)

|             | <b>6aM</b> | <b>6aO</b> | <b>6a•HCl</b> |
|-------------|------------|------------|---------------|
| N(1)-C(2)   | 1.349(4)   | 1.333(10)  | 1.335(10)     |
| N(3)-C(2)   | 1.318(3)   | 1.323(11)  | 1.339(11)     |
| N(1)-C(5)   | 1.397(3)   | 1.405(9)   | 1.403(10)     |
| N(3)-C(4)   | 1.366(4)   | 1.375(12)  | 1.370(12)     |
| C(4)-C(5)   | 1.377(4)   | 1.385(10)  | 1.376(12)     |
| N(1)-C(11)  | 1.469(3)   | 1.460(9)   | 1.497(11)     |
| C(11)-C(12) | 1.511(4)   | 1.521(10)  | 1.494(12)     |
| C(5)-C(51)  | 1.435(4)   | 1.441(10)  | 1.439(11)     |
| C(51)-C(52) | 1.340(3)   | 1.343(11)  | 1.328(12)     |
| C(52)-C(53) | 1.489(3)   | 1.494(9)   | 1.464(12)     |
| C(52)-N(52) | 1.476(3)   | 1.466(9)   | 1.492(10)     |
| N(52)-O(51) | 1.215(3)   | 1.230(11)  | 1.247(10)     |
| N(52)-O(52) | 1.219(3)   | 1.227(9)   | 1.215(11)     |

Table 3

Selected Bond Angles/° for C<sub>18</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub> in the Monoclinic (**6aM**) and Orthorhombic (**6aO**) Phases, and for C<sub>18</sub>H<sub>16</sub>N<sub>3</sub>O<sub>2</sub>•Cl<sup>-</sup> (**6a•HCl**)

|                   | <b>6aM</b> | <b>6aO</b> | <b>6a•HCl</b> |
|-------------------|------------|------------|---------------|
| N(1)-C(2)-N(3)    | 112.3(2)   | 113.7(7)   | 108.0(7)      |
| C(2)-N(1)-C(5)    | 107.3(2)   | 106.8(6)   | 109.4(7)      |
| C(2)-N(3)-C(4)    | 104.9(2)   | 104.2(7)   | 109.6(7)      |
| N(1)-C(5)-C(4)    | 103.8(2)   | 104.1(6)   | 105.4(7)      |
| N(3)-C(4)-C(5)    | 111.6(2)   | 111.1(7)   | 107.6(8)      |
| C(2)-N(1)-C(11)   | 125.8(2)   | 125.3(6)   | 126.2(7)      |
| C(5)-N(1)-C(11)   | 126.9(2)   | 127.8(6)   | 124.1(6)      |
| N(1)-C(11)-C(12)  | 112.3(2)   | 111.7(5)   | 114.0(7)      |
| N(1)-C(5)-C(51)   | 120.6(2)   | 120.4(6)   | 120.7(7)      |
| C(4)-C(5)-C(51)   | 135.6(2)   | 135.5(7)   | 133.9(8)      |
| C(5)-C(51)-C(52)  | 127.7(2)   | 127.0(7)   | 124.6(8)      |
| C(51)-C(52)-C(53) | 129.1(2)   | 128.2(6)   | 129.2(7)      |
| C(51)-C(52)-N(52) | 115.3(2)   | 115.5(7)   | 115.2(8)      |
| C(53)-C(52)-N(52) | 115.6(2)   | 116.2(6)   | 115.5(7)      |
| C(52)-N(52)-O(51) | 117.6(2)   | 117.4(6)   | 116.0(7)      |
| C(52)-N(52)-O(52) | 120.1(2)   | 120.6(7)   | 120.5(7)      |
| O(51)-N(52)-O(52) | 122.4(2)   | 122.0(7)   | 123.5(7)      |

### Mass Spectrometry.

The structural information in the electron ionization (EI) mass spectra of 1-benzyl substituted imidazoles **2a**, **3a**, **4a**, **6a** was scarce because the spectra were extremely simple (Table 4). They all showed a molecular ion peak, the relative intensity of which varied from 10 to 28%. The benzyl group, however, dominated the fragmentations so that besides the m/z 91 ion, which always represented the base peak in the spectra, very few significant fragment ions were observed. Compounds **2a**, **3a**, and **4a** eliminated a small amount of water and compound **6a** lost its nitro group. It is noteworthy, that an interaction between the 1- and 5-substituents in the form previously observed

Table 4

70 eV Mass Spectra of the Compounds Synthesized. The Peaks with Relative Intensities Greater than 3% of the Intensity of the Base Peak are Included unless not Due to a Molecular Ion

| Compound  | m/z (relative intensity)   |
|-----------|--|
| <b>2a</b> | M <sup>+</sup> 220 (10), 190 (36), 91 (100), 65 (13), 30 (11), 29 (18), 15 (19)        |
| <b>2b</b> | M <sup>+</sup> 144 (100), 143 (29), 129 (14), 127 (16), 42 (21)                        |
| <b>3a</b> | M <sup>+</sup> 188 (16), 110 (18), 92 (10), 91 (100), 65 (15)                          |
| <b>3b</b> | M <sup>+</sup> 112 (98), 111 (33), 95 (100), 83 (33), 54 (30), 42 (66), 41 (19)        |
| <b>3c</b> | M <sup>+</sup> 98 (24), 97 (37), 81 (11), 69 (16), 42 (16), 38 (32), 36 (100), 35 (12) |
| <b>4a</b> | M <sup>+</sup> 186 (38), 92 (10), 91 (100), 65 (16)                                    |
| <b>4b</b> | M <sup>+</sup> 110 (100), 109 (38), 81 (26), 54 (32), 27 (97)                          |
| <b>4c</b> | 97 (19), M <sup>+</sup> 96 (100), 95 (44), 68 (20), 67 (30), 41 (14), 40 (39)          |
| <b>6a</b> | M <sup>+</sup> 305 (18), 186 (13), 92 (8), 91 (100), 65 (9)                            |
| <b>6b</b> | M <sup>+</sup> 229 (9), 178 (45), 110 (65), 105 (100), 91 (45), 77 (63)                |
| <b>6c</b> | M <sup>+</sup> 215 (30), 169 (34), 115 (100), 96 (21)                                  |

Table 5

Crystal Data and Details of the Crystallographic Analyses for  $C_4H_7N_2O^+ Cl^-$  (**3c**·HCl), for  $C_{18}H_{15}N_3O_2$  in the Monoclinic (**6aM**) and Orthorhombic (**6aO**) Phases, and for  $C_{18}H_{16}N_3O_2^+ Cl^- \cdot 1/2H_2O$  (**6a**·HCl·1/2H<sub>2</sub>O)

|                                   | <b>3c</b> ·HCl                 | <b>6a m</b>              | <b>6aO</b>               | <b>6a</b> ·HCl·1/2H <sub>2</sub> O        |       |
|-----------------------------------|--------------------------------|--------------------------|--------------------------|---|-------|
| Formula                           | $C_4H_7N_2O^+ Cl^-$            | $C_{18}H_{15}N_3O_2$     | $C_{15}H_{15}N_3O_2$     | $C_{18}H_{16}N_3O_2^+ Cl^- \cdot 1/2H_2O$ |       |
| $M_r$                             | 134.6                          | 305.3                    | 305.3                    | 349.8                                     |       |
| Space group                       | $P2_1/c$                       | $P2_1/c$                 | $Pna2_1$                 | $P2_1/n$                                  |       |
| $a/\text{Å}$                      | 6.875(1)                       | 19.866(4)                | 12.953(4)                | 12.876(6)                                 |       |
| $b/\text{Å}$                      | 7.342(1)                       | 6.106(1)                 | 5.896(1)                 | 5.386(2)                                  |       |
| $c/\text{Å}$                      | 12.580(2)                      | 12.932(3)                | 20.914(6)                | 25.810(11)                                |       |
| $\beta/^\circ$                    | 104.08(2)                      | 98.03(2)                 |                          | 100.19(3)                                 |       |
| $V/\text{Å}^3$                    | 615.9(2)                       | 1553.3(6)                | 1597.2(8)                | 1762(1)                                   |       |
| Z                                 | 4                              | 4                        | 4                        | 4   |       |
| $D_c/g\text{ cm}^{-3}$            | 1.455                          | 1.305                    | 1.270                    | 1.323                                     |       |
| F (000)                           | 280                            | 640                      | 640                      | 732                                       |       |
| Radiation                         | Mo-K $\alpha$                  | Mo-K $\alpha$            | Mo-K $\alpha$            | Mo-K $\alpha$                             |       |
| $\mu\text{cm}^{-1}$               | 5.2                            | 0.8                      | 0.8                      | 2.3                                       |       |
| Scan type                         | $\omega$                       | $\omega$                 | $\omega$                 | $\omega$                                  |       |
| Scan range/ $^\circ$              | $4 \leq 2\theta \leq 6\theta$  | $5 \leq 2\theta \leq 55$ | $5 \leq 2\theta \leq 55$ | $4 \leq 2\theta \leq 5\theta$             |       |
| Scan width/ $^\circ$              | 1.5                            | 1.4                      | 1.6                      | 1.8                                       |       |
| Number of unique data             | 1801                           | 3577                     | 1896                     | 3126                                      |       |
| Number $F_{obs} \geq 4\sigma$ (F) | 1500                           | 1944                     | 901                      | 1097                                      |       |
| Number of variables               | 101                            | 268                      | 123                      | 206                                       |       |
| $(\Delta/\sigma)_{max}$           | 0.002                          | 0.002                    | 0.0005                   | 0.0005                                    |       |
| Residue density:                  |                                |                          |                          |   |       |
|                                   | Maximum ( $e\text{ cm}^{-3}$ ) | 0.26                     | 0.24                     | 0.28                                      | 0.27  |
|                                   | Minimum ( $e\text{ cm}^{-3}$ ) | -0.20                    | -0.19                    | -0.24                                     | -0.32 |
| R                                 | 0.031                          | 0.051                    | 0.061                    | 0.069                                     |       |
| wR                                | 0.051                          | 0.055                    | 0.070                    | 0.072                                     |       |
| g                                 | 0.0008                         | 0.0005                   | 0.001                    | 0.001                                     |       |
| Goodness of fit                   | 1.39                           | 1.46                     | 1.40                     | 1.37                                      |       |

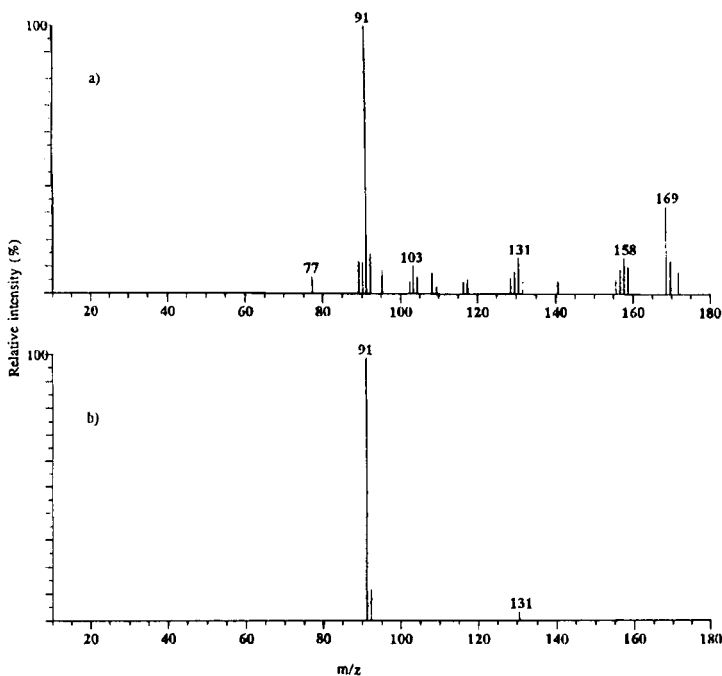


Figure 3. The CID mass spectra of the  $m/z$  186 ions generated from a) 1-benzyl imidazole-5-carboxyaldehyde (**4a**); b) 1-benzyl-5-[(2-nitro-2-phenyl)ethenyl]imidazole (**6a**).

with 1-benzyl-5-hydroxymethylimidazoles [28] was practically absent with compounds **2a**, **3a**, **4a** and **6a**. This interaction would lead to distonic ion with separate charge and radical sites through the loss of benzene molecule from the benzyl group. Instead, the hydrogen needed for the elimination of water must come from the benzyl group because this fragmentation was not observed when benzyl group was replaced with methyl group or hydrogen atom.

An interesting feature in the spectrum of compound **6a** was that there was quite intense  $m/z$  186 ion peak (13% rel. int.). The elemental composition of this ion,  $C_{11}H_{10}N_2O$  (Calcd. 186.0794, Obs. 186.0795), is the same as the molecular ion of 1-benzylimidazole-5-carboxyaldehyde (**4a**). The collision induced dissociation (CID) spectra of the  $m/z$  186 ions generated from compounds **4a** and **6a** (Figure 3), however, were not identical showing that at least partly some other than carboxaldehyde structure must be present in the case of compound **6a**.

In order to get more structural information the methane chemical ionization spectra of compounds **3a**, **4a** and **6a** were also recorded. Although the  $m/z$  91 ion peak were present the  $[M+H]^+$  ion always gave rise to the base peak in the spectrum. Compound **3a** lost water and formaldehyde from its  $[M+H]^+$  ions whereas compound **4a** eliminated only carbon monoxide. It should be noted that a tiny  $[M+H-C_6H_6]^+$  ion peak was present in the spectrum of

Table 6

Atomic Fractional Coordinates ( $\times 10^4$ ) for  $C_4H_7N_2O^{++} Cl^-$  (**3c**·HCl)

|       | x        | y        | z        |
|-------|----------|----------|----------|
| Cl    | 1930(1)  | -3574(1) | 4302(1)  |
| O     | -298(1)  | 65(2)    | 3572(1)  |
| N(1)  | 2409(2)  | 831(2)   | 2084(1)  |
| N(3)  | 5601(2)  | 728(2)   | 2707(1)  |
| C(2)  | 4131(2)  | 589(3)   | 1805(1)  |
| C(4)  | 4801(2)  | 1073(2)  | 3586(1)  |
| C(5)  | 2776(2)  | 1150(2)  | 3196(1)  |
| C(6)  | 1138(3)  | 1486(3)  | 3759(2)  |
| H     | 303(39)  | -929(39) | 3770(21) |
| H(1)  | 1230(40) | 844(40)  | 1726(22) |
| H(2)  | 4218(33) | 388(33)  | 1059(18) |
| H(3)  | 6987(37) | 681(38)  | 2744(19) |
| H(4)  | 5627(37) | 1216(34) | 4416(22) |
| H(61) | 405(36)  | 2560(40) | 3451(20) |
| H(62) | 1684(31) | 1553(31) | 4480(20) |

Table 7

Atomic Fractional Coordinates ( $\times 10^4$ ) for  $C_{18}H_{15}N_3O_2$  in the Monoclinic Phase (**6aM**)

|        | x        | y         | z        |
|--------|----------|-----------|----------|
| O(51)  | 1082(1)  | -6290(3)  | 4457(2)  |
| O(52)  | 1933(1)  | -5689(3)  | 5620(2)  |
| N(1)   | 2988(1)  | 1211(3)   | 4891(2)  |
| N(3)   | 2906(1)  | 2650(4)   | 3306(2)  |
| N(52)  | 1583(1)  | -5237(4)  | 4797(2)  |
| C(2)   | 3182(1)  | 2835(5)   | 4290(2)  |
| C(4)   | 2509(1)  | 817(5)    | 3276(2)  |
| C(5)   | 2540(1)  | -135(4)   | 4246(2)  |
| C(11)  | 3205(2)  | 944(5)    | 6017(2)  |
| C(12)  | 3707(1)  | -910(4)   | 6255(2)  |
| C(13)  | 3657(2)  | -2301(5)  | 7087(2)  |
| C(14)  | 4115(2)  | -3994(6)  | 7325(3)  |
| C(15)  | 4633(2)  | -4311(6)  | 6742(3)  |
| C(16)  | 4686(2)  | -2940(6)  | 5912(3)  |
| C(17)  | 4225(2)  | -1251(5)  | 5666(3)  |
| C(51)  | 2248(1)  | -2036(4)  | 4662(2)  |
| C(52)  | 1753(1)  | -3322(4)  | 4187(2)  |
| C(53)  | 1333(1)  | -3043(4)  | 3148(2)  |
| C(54)  | 904(1)   | -1235(5)  | 2975(2)  |
| C(55)  | 506(2)   | -957(5)   | 2011(2)  |
| C(56)  | 540(2)   | -2469(5)  | 1221(2)  |
| C(57)  | 964(2)   | -4249(5)  | 1389(2)  |
| C(58)  | 1362(1)  | -4538(5)  | 2347(2)  |
| H(2)   | 3485(14) | 4041(48)  | 4580(21) |
| H(4)   | 2244(13) | 254(44)   | 2627(21) |
| H(111) | 3413(14) | 2464(46)  | 6226(20) |
| H(112) | 2774(14) | 676(45)   | 6360(21) |
| H(13)  | 3272(14) | -1993(44) | 7542(21) |
| H(14)  | 4071(16) | -5028(55) | 7957(28) |
| H(15)  | 4969(17) | -5540(57) | 6912(25) |
| H(16)  | 5023(18) | -3125(57) | 5492(25) |
| H(17)  | 4264(14) | -313(47)  | 5087(23) |
| H(51)  | 2429(12) | -2451(40) | 5376(20) |
| H(54)  | 887(13)  | -237(45)  | 3575(21) |
| H(55)  | 176(15)  | 234(52)   | 1891(23) |
| H(56)  | 232(15)  | -2360(49) | 546(24)  |
| H(57)  | 897(13)  | -5324(47) | 847(22)  |
| H(58)  | 1679(15) | -5448(48) | 2494(21) |

both compounds. Compound **6a** behaved typically for nitro compounds under chemical ionization [29] especially the loss of nitrous acid was favourable. In analogy to electron ionization protonated 1-benzylimidazole-5-carboxaldehyde at  $m/z$  187 was also formed.

The appearance of the mass spectra changed drastically when benzyl group at position 1 was replaced with methyl group or hydrogen atom **2**, **3**, **4**, **6**, **b** and **c**. Now the molecular ion always represented the base peak in the spectrum (Table 4). A general feature almost completely absent with 1-benzyl derivatives was also the loss of hydrogen atom from the molecular ion. Compound **2b** gave very little fragmentation and especially the loss of thiol group was scarce. 1-Methyl-5-hydroxymethylimidazole **3b** behaved analogously to that of benzyl alcohol [30] eliminating  $H\cdot$ ,  $OH\cdot$  and  $HCO\cdot$  from its molecular ion and CO from the  $[M-H]^+$  ion. The spectra of compounds **4b** and **4c** have been presented in literature [31] and the spectra recorded from our compounds were identical with them proving that carboxaldehyde group in compound **4b** really was in the position 5.

### Conclusions.

A high-yield route for the synthesis of 5-substituted nitrothenylimidazoles **6a,b,c** was developed. The major product precipitated was *E* imidazolyl-nitro-isomer, which could be converted to *Z*-isomer **6a',b',c'** in a ratio of 4:3 with uv irradiation using deuteriochloroform as a solvent. The purification of the intermediates and the products

Table 8

Non-hydrogen Atomic Fractional Coordinates ( $\times 10^4$ ) for  $C_{18}H_{15}N_3O_2$  in Orthorhombic Form (**6aO**)

|       | x       | y         | z        |
|-------|---------|-----------|----------|
| O(51) | 4840(4) | 11283(9)  | -1397(4) |
| O(52) | 5780(4) | 10735(9)  | -564(4)  |
| N(1)  | 4692(4) | 3698(10)  | 468      |
| N(3)  | 3109(6) | 2282(13)  | 361(4)   |
| N(52) | 5044(5) | 10231(11) | -905(4)  |
| C(2)  | 4024(7) | 2083(14)  | 636(4)   |
| C(4)  | 3208(6) | 4151(13)  | -28(5)   |
| C(5)  | 4185(5) | 5089(12)  | 22(4)    |
| C(11) | 5747(5) | 3909(13)  | 706(4)   |
| C(12) | 5848(3) | 5832(9)   | 1187(3)  |
| C(13) | 6725    | 7205      | 1183     |
| C(14) | 6833    | 8923      | 1637     |
| C(15) | 6065    | 9267      | 2094     |
| C(16) | 5188    | 7894      | 2098     |
| C(17) | 5079    | 6177      | 1644     |
| C(51) | 4705(5) | 7021(12)  | -251(4)  |
| C(52) | 4382(5) | 8297(12)  | -744(4)  |
| C(53) | 3458(3) | 7946(7)   | -1160(3) |
| C(54) | 3428    | 6108      | -1580    |
| C(55) | 2581    | 5810      | -1983    |
| C(56) | 1764    | 7350      | -1967    |
| C(57) | 1794    | 9188      | -1547    |
| C(58) | 2641    | 9486      | -1144    |

Table 9

Non-hydrogen Atomic Fractional Coordinates ( $\times 10^4$ ) for  $C_{18}H_{16}N_3O_2^{+} \cdot Cl^{-} \cdot 1/2H_2O$  (**6a**•HCl)

|       | x        | y         | z       |
|-------|----------|-----------|---------|
| Cl    | 3534(2)  | 1011(5)   | 337(1)  |
| O(1)  | 1892(11) | 5680(35)  | 146(5)  |
| O(51) | 8695(5)  | -2247(12) | 2178(2) |
| O(52) | 7027(5)  | -2919(11) | 2155(2) |
| N(1)  | 5285(5)  | 4443(12)  | 1222(2) |
| N(3)  | 5867(5)  | 6005(16)  | 556(3)  |
| N(52) | 7745(7)  | -1840(13) | 2002(3) |
| C(2)  | 5109(6)  | 6184(17)  | 848(3)  |
| C(4)  | 6540(7)  | 4110(18)  | 742(3)  |
| C(5)  | 6195(6)  | 3099(16)  | 1171(3) |
| C(11) | 4583(6)  | 3828(18)  | 1609(3) |
| C(12) | 3851(6)  | 5878(14)  | 1694(3) |
| C(13) | 2892     | 6200      | 1352    |
| C(14) | 2204     | 8085      | 1444    |
| C(15) | 2475     | 9648      | 1878    |
| C(16) | 3433     | 9327      | 2220    |
| C(17) | 4121     | 7442      | 2128    |
| C(51) | 6560(7)  | 1097(16)  | 1526(3) |
| C(52) | 7520(7)  | 114(15)   | 1588(3) |
| C(53) | 8409(6)  | 791(12)   | 1333(3) |
| C(54) | 8583     | -455      | 882     |
| C(55) | 9397     | 302       | 626     |
| C(56) | 10036    | 2304      | 820     |
| C(57) | 9861     | 3550      | 1271    |
| C(58) | 9048     | 2793      | 1527    |

proved to be laborious, the most ideal compounds were with benzyl at nitrogen 1 protected imidazoles, which affected advantageously on the solubility and thus the title compound could be crystallized cleanly. The final proof for the position of the side chain in the imidazole ring was obtained with the X-ray crystallography. Because the nitroethylenes can be transformed to many interesting new biologically active compounds, the spatial arrangement of the double bond substituents was determined in detail.

## EXPERIMENTAL

Melting points were determined with a Büchi 510 melting point apparatus and are uncorrected. The IR spectra were measured with Nicolet 20 SXC FTIR spectrometer. Elemental analysis were made with Carlo Erba 1106 CHN + O Analyzer and UV irradiation with Mineralight<sup>R</sup> Lamp Model UVSL 58.

### NMR Spectroscopy.

The <sup>1</sup>H nmr and <sup>13</sup>C nmr spectra were recorded on a Bruker AM 400 WB or AM 250 spectrometer operating at 400.1 and 100.6 MHz or 250.1 and 62.9 MHz respectively. The sample solutions were prepared in 10 or 5 mm tubes using TMS as a reference. The spectra were acquired using 32 kW data points with resolution enhancement and zero filling to point resolution better than 0.1 Hz. <sup>1</sup>H-<sup>1</sup>H correlated COSY and NOESY spectra were 256\*512 with zerofilling, and <sup>1</sup>H-<sup>13</sup>C spectrum using 256\*4K matrix.

### Mass Spectrometry.

Mass spectra were measured with a Jeol JMS D300 15 mass spectrometer equipped with a combined EI/CI ion source and connected to a Jeol JMA 2000H data system. Samples were introduced through a direct inlet probe at temperatures 313-453 K. Typical source conditions were: temperature 443 K, electron energy 70 eV for EI and 200 eV for CI, accelerating voltage 3 kV and ionization current 300  $\mu$ A. Accurate mass measurements were made at resolution 5000 using the data system. Fragmentation pathways were verified with metastable ion analysis and/or CID spectra using linked scans at constant B/E. CID spectra were measured by leading helium into first field-free region so that transmission of the main beam was 33%. CID spectra for structural studies were recorded one after another, with conditions kept as constant as possible. In chemical ionization the reagent gas flow was adjusted by monitoring the source housing pressure ( $8 \times 10^{-6}$  Torr).

### Crystallography.

Details of crystal parameters, data collection parameters and refined data for compounds **3c** and **6a** are summarized in Table 5. Intensity measurements were made on a Nicolet R3m diffractometer using graphite-monochromatized Mo-K $\alpha$  radiation. ( $\lambda = 0.71073$  Å). Monitoring of two check reflections showed no crystal decay during data collections. The data sets were corrected for Lorentz and polarization factors but not for absorption since it was found to be insignificant for all compounds on the basis of empirical  $\Psi$ -scan data.

### Structure Analysis and Refinement.

The crystal structures were determined by direct methods and subsequent Fourier synthesis using the SHELXTL program package [32]. Non-hydrogen atoms were refined anisotropically except the phenyl carbon atoms in **6aO**, which were refined isotropically and as a rigid group. The phenyl rings in **6a**•HCl were refined as a rigid group, too. In **3c**•HCl and **6aM** the hydrogen atoms were located from difference Fourier maps and refined isotropically. In **6a**•HCl only the H atom attached to N(3) was located from a difference Fourier map and refined. All the other H atoms except those of the water molecule were placed at calculated positions with fixed isotropic thermal parameters (C-H 0.96 Å and U 0.08 Å<sup>2</sup>) as in **6aO**, too. The weighting scheme  $w = 1/[\sigma^2(F) + g.F^2]$  was used in the refinements based on F. The final atomic coordinates are presented in Tables 6-9.

### The Preparation of the Compounds.

#### 1-*R*-5-Hydroxymethyl-2-mercaptoimidazoles **2a**, **2b**, **2d**.

The mixture of 50 ml of *n*-butanol, 24 ml of acetic acid, 120 mmoles of dihydroxyacetone dimer **1**, 360 mmoles of potassium thiocyanate and 260 mmoles of benzyl- (**2a**) methyl- (**2b**) or (diphenylmethyl)amine (**2d**) was stirred at room temperature for 50 hours. The precipitate was filtrated and washed with water. Benzyl- and diphenylmethyl compounds were dried first in air then in oven in about 100°, methylimidazole compound *in vacuo* (RT/10-12 mm Hg); yields 97% **2a**, 93% **2b** and 70% **2d**, mp 195-200°, 206-208°, and 195-199°; **2a** v (potassium bromide): cm<sup>-1</sup> 3206 (br, OH), 3030 (CH), 2925, 2850 (CH<sub>2</sub>), 2600, 2540 (SH), 1652, 1616, 1575, 1569, 1565, 1545, 1496, 1456 (benzene ring), 1554, 1506, 1487, 1378, 1257, 1003 (imidazole ring), 712, 694 (monosubst. benzene), 640 (C-S);  $\delta_H$  (250 MHz, DMSO-*d*<sub>6</sub>): 4.23 (2 H, s, CH<sub>2</sub>OH), 5.42 (2 H, s, CH<sub>2</sub>Ph), 5.80 (1 H, br, OH), 6.99 (1 H, s, C(4)H), 7.31-7.41 (5 H, m, Ph);  $\delta_C$  46.4 (CH<sub>2</sub>, t, CH<sub>2</sub>Ph),

53.3 (CH<sub>2</sub>, t, CH<sub>2</sub>OH), 113.1 (CH, d, C-4), 125.7-130.4 (CH, m, Ph), 137.3 (C, s, C-5), 162.4 (C, s, C-2).

*Anal.* Calcd. for C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>O<sub>5</sub>: C, 59.98; H, 5.45; N, 12.72; M<sup>+</sup> 220.0670. Found: C, 61.38; H, 5.45; N, 11.82; M<sup>+</sup> 220.0662.

Compound **2b** had  $\nu$  (potassium bromide): cm<sup>-1</sup> 3206 (br, OH), 3030 (CH), 2960, 2870 (CH<sub>3</sub>), 2925, 2850 (CH<sub>2</sub>), 2600, 2550 (SH), 1470 (CH<sub>2</sub>), 1485, 1446, 1295, 1013 (imidazole ring CH), 807, 660 (C-S);  $\delta_{\text{H}}$  (DMSO-d<sub>6</sub>): 3.54 (3 H, s, Me), 3.94 (1 H, br, OH), 4.42 (2 H, s, CH<sub>2</sub>OH), 6.89 (1 H, s, C(4)H);  $\delta_{\text{C}}$  30.7 (CH<sub>3</sub>, q), 53.1 (CH<sub>2</sub>, t), 112.4 (CH, d, C-4), 130.7 (C, s, C-5), 161.6 (C, s, C-2).

*Anal.* Calcd. for C<sub>5</sub>H<sub>8</sub>N<sub>2</sub>O<sub>5</sub>: C, 41.65; H, 5.59; N, 19.43; M<sup>+</sup> 144.0357. Found: C, 41.85; H, 5.74; N, 19.40; M<sup>+</sup> 144.0354.

Compound **2d** had  $\nu$  (potassium bromide): cm<sup>-1</sup> 3200 (br, OH), 3030, 3060 (arom CH), 2925, 2850 (CH<sub>2</sub>), 2890 (CH), 2550 (SH), 1660, 1600, 1550, 1450, 1250, 1150, 1050 (benzene ring), 1480, 1440, 1378, 1272, 1010 (imidazole ring CH), 1330 (CH), 750, 700 (monosubst benzene), 640 (C-S);  $\delta_{\text{H}}$  (DMSO-d<sub>6</sub>): 3.45 (2 H, s, CH<sub>2</sub>OH), 3.66 (1 H, s, CH), 5.18 (1 H, br, OH), 6.87 (1 H, s, C(4)H), 7.21-7.70 (10 H, m, Ph);  $\delta_{\text{C}}$  53.2 (CH<sub>2</sub>, t, CH<sub>2</sub>OH), 62.4 (CH, d, >CH-), 113.6 (CH, d, C-4), 125.1-132.8 (CH, m, Ph), 137.4 (C, s, C-5), 139.1 (C, s, Ph), 162.4 (C, s, C-2).

#### 1-R-5-hydroxymethylimidazoles **3a**, **3b**, **3c**.

##### 1-Benzyl-5-hydroxymethylimidazole **3a**.

The mixture of 27 ml of 65% nitric acid and 50 ml of water was heated to 35° and 95.45 mmoles of **2a** was added in small portions stirring and keeping the temperature between 35-37°. The reaction mixture was stirred at that temperature for an additional 5 hours, pH was adjusted to 10 with 30% of aqueous sodium hydroxide and the precipitate was filtered and the product was recrystallized from acetone. The yield was 53%, mp 131-138°; **3a**  $\nu$  (potassium bromide): cm<sup>-1</sup> 3206 (br, OH), 3030 (CH), 2925, 2850 (CH<sub>2</sub>), 1504, 1456, 1439 (benzene ring), 1495, 1103, 1017, 925 (imidazole ring CH), 1021 (OH), 743, 715 (monosubst benzene);  $\delta_{\text{H}}$  (250 MHz, DMSO-d<sub>6</sub>): 3.80 (1 H, br, OH), 4.42 (2H, s, CH<sub>2</sub>OH), 5.34 (2H, s, CH<sub>2</sub>Ph), 6.95 (1 H, s, C(4)H), 7.25-7.47 (5 H, m, Ph), 7.64 (1 H, s, C(2)H);  $\delta_{\text{C}}$  47.6 (CH<sub>2</sub>, t, CH<sub>2</sub>Ph), 52.8 (CH<sub>2</sub>, t, CH<sub>2</sub>OH), 125.8-130.0 (CH, m, Ph), 131.8 (C, s, C-5), 136.8 (C, s, Ph), 137.6 (C, s, C(5)), 138.9 (CH, d, C-2/C-4).

*Anal.* Calcd. for C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>O: C, 70.19; H, 6.38; N, 14.88; M<sup>+</sup> 188.0949. Found: C, 69.92; H, 6.62; N, 15.01; M<sup>+</sup> 188.0949.

##### 1-Methyl-5-hydroxymethylimidazole **3b**.

To a solution of 15 ml 65% nitric acid and 43 ml of water was added 2.9 mmoles of sodium nitrite and 70.8 mmoles of **2c** in small portions stirring and keeping the temperature lower than 35°. The mixture was stirred for an additional 1 hour and diluted with 300 ml of water, pH was adjusted with solid sodium carbonate to 8 and saturated with solid sodium chloride. The extraction with chloroform/2-propanol (3:1) gave after evaporation 85% yield, mp 102-106°;  $\nu$  (potassium bromide): cm<sup>-1</sup> 3206 (br, OH), 2960, 2870 (CH<sub>3</sub>), 2925, 2850 (CH<sub>2</sub>), 1472 (CH<sub>2</sub>), 1456 (CH<sub>3</sub>), 1514, 1483, 1245, 968, 927 (imidazole ring), 1019 (C-O);  $\delta_{\text{H}}$  (250 MHz, DMSO-d<sub>6</sub>): 3.71 (3 H, s, CH<sub>3</sub>), 4.52 (2 H, s, CH<sub>2</sub>OH), 4.82 (1 H, br, OH), 6.88 (1 H, s, C(4)H), 7.66 (1H, s, C(2)H);  $\delta_{\text{C}}$  (DMSO-d<sub>6</sub>): 31.0 (CH<sub>3</sub>, q), 52.5 (CH<sub>2</sub>, t, CH<sub>2</sub>OH), 127.0 (CH, d, C-4), 132.1 (C, s, C-5), 138.6 (CH, d, C-2).

*Anal.* Calcd. for C<sub>5</sub>H<sub>8</sub>N<sub>2</sub>O: C, 53.56; H, 7.19; N, 24.98; M<sup>+</sup> 112.0637. Found: C, 51.46; H, 6.92; N, 24.52; M<sup>+</sup> 112.0635.

1*H*-4(5)-Hydroxymethylimidazole hydrochloride **3c** was prepared as in ref [12].

#### A. Hydroxymethylimidazole Picrate.

This compound was obtained in 57% yield, mp 202-203°.

#### B. 4(5)-Hydroxymethylimidazole Hydrochloride.

This compound was obtained in 45% yield from fructose, and in 88% yield from the picrate, mp 105-106°;  $\nu$  (potassium bromide): cm<sup>-1</sup> 3206 (br, OH), 3121 (br, NH), 2922, 2850 (CH<sub>2</sub>), 1616 (C=N), 1460, 1449, 1140, 1070, 1034, 975, 830, 746 (imidazole ring);  $\delta_{\text{H}}$  (250 MHz, deuterium oxide, dioxane): 4.61 (2 H, s, CH<sub>2</sub>OH), 7.40 (1 H, s, C(5/4)H), 8.62 (1 H, s, C(2)H);  $\delta_{\text{C}}$  54.2 (CH<sub>2</sub>, t, CH<sub>2</sub>OH), 118.4 (CH, d, C-4/5), 134.0 (C, s, C-4/5), 135.6 (CH, d, C-2).

*Anal.* Calcd. for C<sub>4</sub>H<sub>6</sub>N<sub>2</sub>O: C, 35.82; H, 5.22; N, 20.90; M<sup>+</sup> 98.0480. Found: C, 35.49; H, 5.17; N, 20.65; M<sup>+</sup> 98.0480.

#### 1-R-5-Imidazolecarboxaldehydes **4a**, **4b**, **4c**.

The mixture of 74.5 mmoles of hydroxymethylimidazole **3a**, **3b** or **3c** and 316.3 mmoles of activated manganese dioxide in 80 ml of dioxane was refluxed for 6 hours, when R = Bn and 24 hours, when R = Me or H. In the case of R = H the solvent was water and the imidazole alcohol was liberated from its hydrochloride with solid sodium carbonate. The mixture was filtered hot and manganese dioxide was washed with hot solvent, and the filtrate was evaporated *in vacuo*. 1-Benzyl-5-imidazolecarboxaldehyde **4a** was recrystallized from acetone, 1-methyl and 1*H*-carboxaldehydes **4b** and **4c** were sublimed *in vacuo*, 65-70°/10-12 mm Hg and 150-160°/10-12 mm Hg respectively; mp 50-52° (**4a**), 48-50° (**4b**) and 171-172° (**4c**), yields 80%, 80%, and 56%, respectively.

Compound **4a** had  $\nu$  (potassium bromide): cm<sup>-1</sup> 3030 (CH), 2925, 2850 (CH<sub>2</sub>), 2720, 1679 (CHO), 1347, 1257, 1125 (imidazole ring);  $\delta_{\text{H}}$  (250 MHz, DMSO-d<sub>6</sub>): 5.69 (2 H, s, CH<sub>2</sub>Ph), 7.14-7.50 (5 H, m, Ph), 8.04 (1 H, s, C(2)H), 8.21 (1 H, s, C(4)H), 9.81 (1 H, s, CHO);  $\delta_{\text{C}}$  48.9 (CH<sub>2</sub>, t, CH<sub>2</sub>Ph), 125.8-129.9 (CH, m, Ph), 137.2 (C, s, C-5), 143.7 (CH, d, C-2), 144.8 (CH, d, C-4), 180.1 (CH, d, CHO).

*Anal.* Calcd. for C<sub>11</sub>H<sub>10</sub>N<sub>2</sub>O: C, 70.95; H, 5.37; N, 15.04; M<sup>+</sup> 186.0793. Found: C, 71.20; H, 5.57; N, 15.36; M<sup>+</sup> 186.0795.

Compound **4b** had  $\nu$  (potassium bromide): cm<sup>-1</sup> 2960, 2870, 1460, 1378 (CH<sub>3</sub>), 2720, 1677 (CHO), 1533, 1499, 1493, 1269 (imidazole ring);  $\delta_{\text{H}}$  (DMSO-d<sub>6</sub>): 3.95 (3 H, s, CH<sub>3</sub>), 8.04 (1 H, s, C(2)H), 8.09 (1 H, s, C(4)H), 9.83 (1 H, s, CHO);  $\delta_{\text{C}}$  33.4 (CH<sub>3</sub>, q), 131.8 (C, s, C-5), 142.8 (CH, d, C-2), 144.8 (CH, d, C-4), 180.2 (CH, d, CHO).

*Anal.* Calcd. for C<sub>5</sub>H<sub>6</sub>N<sub>2</sub>O: C, 54.54; H, 5.45; N, 25.44; M<sup>+</sup> 110.0481. Found: C, 54.29; H, 5.41; N, 25.61; M<sup>+</sup> 110.0492.

Compound **4c** had  $\nu$  (potassium bromide): cm<sup>-1</sup> 2957 (br, NH), 2787, 1666 (CHO), 1449, 1336, 1309, 985, 867, 766 (imidazole ring);  $\delta_{\text{H}}$  (DMSO-d<sub>6</sub>): 7.74 (1 H, s, C-(2)H), 8.02 (1 H, s, C(4)H), 9.79 (1 H, s, CHO);  $\delta_{\text{C}}$  129.9 (CH, d, C-2), 140.8 (C, s, C-4/5), 139.3 (CH, d, C-4/5), 183.9 (CH, d, CHO).

*Anal.* Calcd. for C<sub>4</sub>H<sub>4</sub>N<sub>2</sub>O: C, 50.00; H, 4.20; N, 29.15; M<sup>+</sup> 96.0324. Found: C, 47.60; H, 4.11; N, 29.20; M<sup>+</sup> 96.0329.

#### Phenylnitromethane **5**.

This compound was prepared according to ref [13] in 84% yield;  $\delta_{\text{H}}$  (250 MHz, deuteriochloroform, TMS): 5.35 (2 H, s, CH<sub>2</sub>NO<sub>2</sub>), 7.30-7.41 (5 H, m, Ph);  $\delta_{\text{C}}$  80.3 (CH<sub>2</sub>, t, CH<sub>2</sub>NO<sub>2</sub>), 127.3-133.1 (CH, m, Ph).



1-*R*-5-[(2-Nitro-2-phenyl)ethenyl]imidazole **6a**, **6b**, **6c**.

General Procedure. R = Bn, CH<sub>3</sub>, H.

The mixture of 1-*R*-imidazolecarboxaldehyde **4a**, **4b**, **4c** (7 mmoles), *n*-butylamine (7 mmoles) and benzene (5 ml) was refluxed in a reaction vessel attached to a water separator until the theoretical amount of water had been collected. The solvent was then evaporated in vacuum. The crude product (Schiff's base) was used directly in the next step. The solution of phenyl-nitromethane (7 mmoles) in 1.8 ml of glacial acetic acid was added to Schiff's base (7 mmoles). The clear homogeneous mixture was allowed to stand at the room temperature until the orange product was crystallized. The solid was filtered and washed with water and recrystallized from ethanol, yield was 89%, mp 171-172° for **6a**, 81%, mp 103-105° for **6b**, and 60%, mp 109-111° for **6c**.

Compound **6a** had  $\nu$  (potassium bromide): cm<sup>-1</sup> 3030 (CH), 2925, 2850 (CH<sub>2</sub>), 1940, 1860, 1790, 1660 (benzene ring), 1630, 815 (-HC=C<), 1530, 1306 (C-NO<sub>2</sub>), 1533, 1485, 1460, 1380, 1270, 970, 908 (imidazole ring), 1340 (CH), 715, 693 (monosubst benzene);  $\delta_{\text{H}}$  (400 MHz, deuteriochloroform, TMS): 5.25 (2 H, s, CH<sub>2</sub>Ph), 6.35 (1 H, s, C(4)H), 7.15 (2 H, m, C(13)H), 7.27 (2 H, m, C(55)H), 7.37 (1 H, m, C(15)H), 7.40 (2 H, m, C(14)H), 7.50 (2 H, m, C(54)H), 7.52 (1 H, m, C(56)H), 7.64 (1 H, s, C(2)H), 8.09 (1 H, s, -HC(51)=C<);  $\delta_{\text{C}}$  49.2 (CH<sub>2</sub>, t, CH<sub>2</sub>Ph), 120.9 (CH, d, -CH=C<), 124.7 (C, s, C-5), 126.9 (CH, d, C-13), 128.8 (CH, d, C-15), 129.4 (CH, d, C-14), 129.6 (CH, d, C-54), 129.9 (CH, d, C-55), 130.4 (CH, d, C-56), 130.5 (C, s, C-53), 134.9 (C, s, C-12), 136.2 (CH, d, C-4), 141.4 (CH, d, C-2), 147.1 (C, s, C-52).

*Anal.* Calcd. for C<sub>18</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>: C, 70.81; H, 4.95; N, 13.76; M<sup>+</sup> 305.1165. Found: C, 70.84; H, 4.97; N, 13.67; M<sup>+</sup> 305.1168.

Compound **6b** had  $\nu$  (chloroform): cm<sup>-1</sup> 3030 (CH), 2960, 2870, 1460, 1380 (CH<sub>3</sub>), 2890, 1340 (CH), 1940, 1820, 1790, 1699, 1662 (arom CH), 1652, 815 (-HC=C<), 1533, 1310 (C-NO<sub>2</sub>), 1513, 1495, 1466, 1280, 970 (imidazole ring), 680, 640 (monosubst benzene);  $\delta_{\text{H}}$  (250 MHz, deuteriochloroform, TMS): 3.78 (3 H, s, CH<sub>3</sub>), 6.29 (1 H, s, C(4)H), 7.33-7.59 (5 H, m, Ph), 7.44 (1 H, s, C(2)H), 8.15 (1 H, s, -HC=C<);  $\delta_{\text{C}}$  32.0 (CH<sub>3</sub>, q), 120.5 (CH, d, -CH=C<), 125.1 (C, s, C-5), 128.3-130.8 (CH, m, Ph), 134.9 (CH, d, C-4), 141.5 (CH, d, C-2).

*Anal.* Calcd. for C<sub>12</sub>H<sub>11</sub>N<sub>3</sub>O<sub>2</sub>: C, 62.87; H, 4.80; N, 18.33; M<sup>+</sup> 229.0852. Found: C, 62.58; H, 4.99; N, 17.22; M<sup>+</sup> 229.0853.

Compound **6c** had  $\nu$  (chloroform): cm<sup>-1</sup> 3030 (CH), 2957 (br, NH), 2890, 1340 (CH), 1940, 1820, 1790 (arom CH), 1650, 815 (-HC=C<), 1530, 1310 (C-NO<sub>2</sub>), 1508, 1284 (imidazole ring), 712, 620 (monosubst benzene);  $\delta_{\text{H}}$  (deuteriochloroform, TMS): 6.32 (1 H, s, C(4/5)H), 7.16-7.75 (5 H, m, Ph), 7.72 (1 H, s, C(2)H), 8.28 (1H, s, -HC=C<);  $\delta_{\text{C}}$  124.2 (CH, d, -CH=C<), 124.5 (C, s, C-5), 125.9-132.7 (CH, m, Ph), 137.8 (CH, d, C-4), 143.0 (CH, d, C-2), 147.0 (C, s, HC=C<).

*Anal.* Calcd. for C<sub>11</sub>H<sub>9</sub>N<sub>3</sub>O<sub>2</sub>: C, 61.40; H, 4.19; N, 19.53; M<sup>+</sup> 215.0695. Found: C, 59.61; H, 4.62; N, 19.19; M<sup>+</sup> 215.0692.

## UV Irradiation.

The nitroethenyl compound *E*-**6a** (200 mg) was weighed into a 10 mm nmr tube and 4 ml of deuteriochloroform or perdeuterioethanol was added. The sample was irradiated with uv lamp at 254 nm for 80 hours at the room temperature. The reaction was followed with <sup>1</sup>H nmr and <sup>13</sup>C nmr. After two hours in

deuteriochloroform first signs of rising C-4 proton of *Z*-**6a'** were observed at 6.45 ppm and benzylic proton at 5.20 ppm (*E*-**6a**: 6.35 and 5.25 respectively), a new vinylic carbon appeared at 108.6 ppm (*E*-**6a**: 120.9 ppm, no change in benzylic carbon), in a ratio of *Z*:*E* 1:9. After four hours the ratio was 2:9 and after six hours 4:3. That ratio did not change after more irradiation. In perdeuterioethanol no changes were observed. The sample in the nmr tube was stored at the room temperature. The *Z*-isomer started slowly to transform back to *E*-isomer and in about three weeks it had totally been changed to a more stable isomer.

## REFERENCES AND NOTES

- \* Author to whom correspondence should be addressed.
- [1] D. W. Young, *Heterocyclic Chemistry*, Longman, London, 1975; p 110; A. A. Cordi, M. P. Snyers, D. Giraud-Mangin, C. Van der Maesen, J. P. Van Hoeck, S. Beuze, E. Ellens, F. Napora, G. L. Gillet, H. Gorissen, P. Calderon, M. D. Remacle, P. Janssens de Varebeke, W. Van Dorsser, and J. Roba, *Eur. J. Med. Chem.*, **25**, 557 (1990).
  - [2] K. T. Bunce, D. A. A. Owen, I. R. Smith, and M. R. Vickers, *Int. Rev. of Biochem. Physiol. and Pharmacol. Biochem.*, **26**, 207 (1979); D. L. Marquardt, *Clin. Rev. Allergy*, **1**, 343 (1983); L. A. Mejia, *Arch. Latinoamer. Nutrition*, **28**, 143 (1978).
  - [3] A. G. M. Barrett and G. G. Graboski, *Chem. Rev.*, **86**, 751 (1986).
  - [4] V. V. Perekalin, E. S. Lipina, V. M. Berestovitskaya, and D. A. Efremov, *Nitroalkenes, Conjugated Nitro Compounds*, Wiley, Chichester, 1994.
  - [5] G. Rosini, R. Ballini, *Synthesis*, 833 (1988); D. Seebach, E. W. Colvin, F. Lehr, and T. Weller, *Chimia*, **33**, 1 (1979).
  - [6] H. Chikashita, Y. Morita, and K. Itoh, *Synth. Commun.*, **17**, 677 (1987).
  - [7] P. Aulaskari, E. Pohjala, and P. Mätkönen, XIIIth European Colloquium on Heterocyclic Chemistry, Fribourg, Switzerland, Helvetiorum Universitas Friburgensis, 1988, p 20.
  - [8] C. B. Archer and M. W. Greaves, *Skin. Pharmacol.*, **6**, 81 (1993); Schlicker, M. Kathmann, S. Reidemeister, H. Stark, and W. Schunack; *Br. J. Pharmacol.*, **112**, 1043 (1994).
  - [9] J. C. McGrath, C. M. Brown, and V. G. Wilson, *Med. Res. Rev.* **9**, 40 (1989); M. Berlan, J.-L. Montastruc, and M. Lafontan, *TIPS Rev.*, **13**, 277 (1992); G. Scholtysik, *Prog. Hypertension*, **2**, 257 (1991); R. R. Ruffolo Jr, A. J. Nichols, J. M. Stadel, and J. P. Hieble, *Ann. Rev. Pharmacol. Toxicol.*, **32**, 243 (1993).
  - [10] D. N. Robertson, *J. Org. Chem.*, **25**, 47 (1960).
  - [11] S. S. Parhi, European Patent 146,228 (1984); *Chem. Abstr.*, **103**, P 141962x (1985).
  - [12] J. R. Totter and W. J. Darby, *Org. Synth., Coll. Vol. III*, E. C. Horning, ed, New York, John Wiley & Sons, 1955, p 460.
  - [13] N. Kornblum, H. O. Larson, R. K. Blackwood, D. D. Mooberry, E. P. Oliveto, and G. E. Graham, *J. Am. Chem. Soc.*, **78**, 1497 (1956).
  - [14] G. W. Kabalka, R. S. Varma, *Org. Prep. Proced. Int.*, **19**, 283 (1987).
  - [15] N. Ono, A. Kamimura, T. Kawai, and A. Kaji, *J. Chem. Soc., Chem. Commun.*, 1550 (1987).
  - [16] R. H. Blessing and E. L. McGandy, *J. Am. Chem. Soc.*, **94**, 4034 (1972).
  - [17] G. Levasseur and L. Beauchamp, *Acta Crystallogr., Sect. C*, **47**, 547 (1991).
  - [18] R. Ramani, K. Venkatesan and R. E. Marsh, *J. Am. Chem. Soc.*, **100**, 949 (1978).
  - [19] M. T. Averbuch-Pouchot, A. Durif and J. C. Guitel, *Acta Crystallogr., Sect. C*, **44**, 890 (1988).

- [20] A. Wojtczak, M. Jaskolski and Z. Kosturkiewics, *Acta Crystallogr., Sect. C*, **44**, 1779 (1988).
- [21] S. A. Bahadur, R. K. Rajaram and M. Nethaji, *Acta Crystallogr., Sect. C*, **47**, 1420 (1991).
- [22] P. Van Roey, K. A. Bullion, Y. Osawa, R. Bowman and D. G. Braun, *Acta Crystallogr., Sect. C*, **47**, 1015 (1991).
- [23] I. Ségalas, J. Poitras and A. L. Beauchamp, *Acta Crystallogr., Sect. C*, **48**, 295 (1992).
- [24] C. P. Huber, *Acta Crystallogr., Sect. C*, **41**, 1076 (1985).
- [25] P. W. Coddling and M. N. G. James, *Acta Crystallogr., Sect. B*, **40**, 429 (1984).
- [26] M. L. Glowka, Z. Galdecki and I. Iwanicka, *Acta Crystallogr., Sect. C*, **46**, 1025 (1990).
- [27] H. L. De Bondt, N. M. Blaton, O. M. Peeters and C. J. De Ranter, *Acta Crystallogr. Sect. C*, **47**, 2430 (1991).
- [28] A. Karjalainen, E. Pohjala and P. Vainiotalo, *Finn. Chem. Letters*, **25** (1983).
- [29] A. G. Harrison, *Chemical Ionization Mass Spectrometry*, CRC Press, Boca Raton, 1983, p. 109.
- [30] H. Budzikiewicz, C. Djerassi and D. H. Williams, *Mass Spectrometry of Organic Compounds*, Holden-Day, San Francisco, 1967.
- [31] A. Cert, P. Delgado-Cobos and M. Trujillo Pères-Lanzac, *Org. Mass. Spectrom.*, **21**, 499 (1986).
- [32] G. M. Sheldrick, *SHELXTL PLUS Release 4.11/V* Siemens Analytical X-ray Instruments, Inc., Madison, Wisconsin, USA, 1990.