Abstract — The behaviour of isoselenazoles towards electrophilic reagents including reversible protonation at the nitrogen atom, hydrogen-deuterium exchange, bromination and nitration is explored. Electrophilic substitutions take place only in the 4 position.

Some years ago some of us reported a general synthesis of 4-unsubstituted isoselenazoles that made this class of products, comprehensive of the parent compound as well as of variously mono or disubstituted derivatives in the position 3 and 5, readily available. Afterwards we prepared for the first time several isoselenazole carboxylic acids as a result of a study of the specific action of the selenium dioxide on alkylisoselenazoles.

The present paper explores the behaviour of isoselenazoles towards electrophilic reagents including reversible protonation at the nitrogen atom with determination of acidic constants, hydrogen-deuterium exchange, bromination, and nitration.

PROTONATION

Isoselenazole and its 3- and 5-substituted alkyl or aryl derivatives have shown good stability in presence of concentrated mineral acids. With hydrochloric acid in anhydrous ethereal solution they precipitate the corresponding white hydrochlorides that release the isoselenazole derivative by hydrolysis or alkaline displacement.

The acidic constants of the protonated form of 3-methyl- and 3,5-dimethylisoselenazole have been determined by a standard spectrophotometric method (see experimental). The obtained pKa values, uncorrected for zero ionic strength, are compared in Table 1 with those of the corresponding isoxazoles and isothiazoles.
Table 1. Basicity characteristics of 3-methyl and 3,5-dimethyl derivatives of isoselenazole, isothiazole and isoxazole at 25 °C.

<table>
<thead>
<tr>
<th>Compound</th>
<th>UV maxima</th>
<th>pKa</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Neutral form</td>
<td>Protonated form</td>
<td></td>
</tr>
<tr>
<td></td>
<td>nm</td>
<td>log ε</td>
<td>nm</td>
</tr>
<tr>
<td>3-Methylisoselenazole</td>
<td>269</td>
<td>3.83</td>
<td>277</td>
</tr>
<tr>
<td>3,5-Dimethylisoselenazole</td>
<td>268</td>
<td>3.81</td>
<td>276</td>
</tr>
<tr>
<td>3-Methylisothiazole</td>
<td>+0.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3,5-Dimethylisothiazole</td>
<td>+1.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-Methylisoxazole</td>
<td>-1.62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3,5-Dimethylisoxazole</td>
<td>-1.61</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Isoselenazoles are weak bases, but less weak than other compared heterocycles; the basicity increases in the order oxygen, sulfur, selenium, being enhanced by the presence of methyl groups, as expected and evidenced from the comparison between monomethyl and dimethyl derivatives of the same class.

HYDROGEN-DEUTERIUM EXCHANGE

Electrophilic hydrogen exchange experiments, performed on isoselenazole and 3,5-dimethylisoselenazole with 100% deuteriosulfuric acid, and checked by nmr spectra, revealed the high reluctance to hydrogen-deuterium exchange of the parent compound also under prolonged treatment (48 h) with the deuterating agent at 100 °C. On the contrary the dimethyl derivative, probably owing to the activating effect of the methyl groups, after 24 h at 100 °C showed a complete exchange with deuterium of the proton in position 4.

BROMINATION

The examined isoselenazoles, with the exception of the parent compound, have shown fairly good reactivity towards electrophilic substitution at a carbon atom under different bromination conditions, while other reactions like addition at the selenium atom have never been observed.

3 or 5 Mono and 3,5-disubstituted isoselenazoles treated for some hours with bromine at room temperature in the dark without solvent or catalyst afford bromination products exclusively in position 4.

Analogous brominations in 4 position only are obtained through ionic reaction with N-bromosuccinimide (NBS) in acetic acid at room temperature (Scheme 1).
It is worthy of note that the unsubstituted isoselenazole reveals a poor stability in both procedures, rapidly affording only decomposition products. Moreover 1d showed no traces of products brominated in the benzene ring.

Table 2 collects yields and characteristic data of the obtained bromoisoselenazoles.

Table 2. Yields and physical and spectral data of the bromoisoselenazoles 2a-d

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield [%]</th>
<th>bp [°C]/torr</th>
<th>IR* [cm⁻¹]</th>
<th>¹H-NMR</th>
<th>Mass*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Br₂</td>
<td>NBS or mp [°C]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2a</td>
<td>8</td>
<td>48</td>
<td>73-75/6</td>
<td>1515,1430,470</td>
<td>9.12(s,1H),2.54(s,3H)</td>
</tr>
<tr>
<td>2b</td>
<td>-</td>
<td>65</td>
<td>32-33</td>
<td>1530,1415,450</td>
<td>8.84(s,1H),2.57(s,3H)</td>
</tr>
<tr>
<td>2c</td>
<td>56</td>
<td>35</td>
<td>82-83/7</td>
<td>1544,1404,472</td>
<td>2.56(s,3H),2.48(s,3H)</td>
</tr>
<tr>
<td>2d</td>
<td>83</td>
<td>-</td>
<td>oil</td>
<td>1535,1400,455</td>
<td>7.68-7.38(m,5H),2.56</td>
</tr>
</tbody>
</table>

* see experimental

Yields obtained with NBS are good when those with bromine are poor and vice versa, so the choice of the proper bromination method allows the attaining of yields between 48 and 83%.

The molecular structures of all the brominated isoselenazoles have been clearly individuated on the basis of elemental analysis, nmr, ir and Mass spectra; moreover for the product 2d the eventual presence of bromine in the benzene ring has been further excluded by permanganate oxidation, which only affords benzoic acid.

NITRATION

The isoselenazole ring has shown a generally good inclination towards nitration undergoing substitution exclusively in the position 4. As an example the isoselenazoles 1a-c smoothly react at room temperature with a mixture of nitric acid and sulfuric acid according to the Scheme 2.
As for the bromination reaction the unsubstituted isoselenazole reveals a poor stability, rapidly affording only decomposition products.

It is relevant that, when the 3-methyl-5-phenylisoselenazole (1d) is submitted to nitration in the same conditions as for compounds la-c, the phenyl group reveals itself more reactive than the heterocyclic ring (Scheme 3). In this case in fact the reaction affords a mixture of products containing mononitro derivatives in the positions ortho and para, and dinitro derivatives in the position ortho or para and 4, but not the mononitro derivative in the position 4.

The product 7, obtained in traces, has been characterized only through the Mass spectrum. The reported molecular structures for all the other nitrated compounds have been unambiguously assigned on the basis of elemental analysis, nmr, ir, and Mass spectra.

Table 3 collects yields and characteristic data of the obtained nitrated compounds.
Table 3. Yields, physical data and spectral properties of the products isolated from the nitration reaction of the isoselenazoles 1a-d

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield [%]</th>
<th>mp [°C]</th>
<th>(\text{Irr} \ \nu [\text{cm}^{-1}])</th>
<th>(\text{\textsuperscript{1}H-Nmr} \ \delta [\text{ppm}])</th>
<th>Mass m/z, M⁺ (rel.int.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>36</td>
<td>51-52</td>
<td>1530, 1325(NO₂), 1515, 1425, 425</td>
<td>10.31 (s, 1H), 2.76 (s, 3H)</td>
<td>192 (39)</td>
</tr>
<tr>
<td>3b</td>
<td>89</td>
<td>85-86</td>
<td>1535, 1345(NO₂), 1500, 1440, 460</td>
<td>9.64 (s, 1H), 2.98 (s, 3H)</td>
<td>192 (50)</td>
</tr>
<tr>
<td>3c</td>
<td>64</td>
<td>62-64</td>
<td>1545, 1320(NO₂), 1490, 1425, 465</td>
<td>2.87 (s, 3H), 2.64 (s, 3H)</td>
<td>206 (53)</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>160-161</td>
<td>1510, 1340(NO₂), 1550, 1395</td>
<td>8.35 (m, 2H), 7.62 (m, 2H), 2.62 (s, 3H)</td>
<td>313 (100)</td>
</tr>
<tr>
<td>5</td>
<td>17</td>
<td>145-147</td>
<td>1525, 1330(NO₂), 1555, 1400</td>
<td>8.31 (m, 1H), 7.73 (m, 2H), 7.43 (m, 1H), 2.74 (s, 3H)</td>
<td>313 (5)</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>149-150</td>
<td>1510, 1335(NO₂), 1545, 1390, 420</td>
<td>8.30 (d, 2H), 7.70 (d, 2H), 7.51 (s, 1H), 2.56 (s, 3H)</td>
<td>268 (100)</td>
</tr>
<tr>
<td>7</td>
<td>traces</td>
<td></td>
<td></td>
<td></td>
<td>268 (100)</td>
</tr>
</tbody>
</table>

For a preliminary comparison of reactivity, a sample of 5-methylisothiazole purposely prepared has been submitted to nitration under the same conditions of the analogous compound 1b. While 1b undergoes 89% nitration, the isothiazole compound is fully recovered unreacted, except feeble traces of the nitration product detected by GLC.

CONCLUSIONS

Hydrogen-deuterium exchange, bromination, and nitration have shown that an electrophilic substitution in the isoselenazole ring is possible only at the position 4. Moreover the parent compound eludes each one of such reactions on different grounds: it is not reactive enough towards deuteriumsulfuric acid, while it is fully destroyed under bromination or nitration conditions. It has not been explored if
the decomposition precedes or follows the electrophilic substitution and if it is the consequence of an initial attack at the 4 position or at a different one. Some remarkable facts are: the electrophilic substitution only in the 4 position of isoselenazoles fully parallels the behaviour of isoxazoles and isothiazoles. Difficulties in involving the parent compound in electrophilic substitution are not peculiar of the isoselenazole, but concern to a different degree also isoxazole\(^7\) and isothiazole.\(^8\) Isoselenazoles are stronger bases than isothiazoles, which in turn are stronger than isoxazoles (Table 1), and easily afford crystalline hydrochlorides. At least for what concerns nitration, the collected preliminary results on the comparison of reactivity between 5-methylisothiazole and 5-methylisoselenazole indicate that the isoselenazole ring is more reactive than the isothiazole one. This observation must be cautiously considered because the experimental data are not such as to distinguish the operating mechanism, between reactions on the free base or on the conjugated acid.\(^9\)

**EXPERIMENTAL**

Melting points were determined on a Reichert-Thermovar apparatus and are uncorrected. Ir spectra were recorded on a Perkin Elmer model 1330 spectrophotometer as KBr pellets or films; the reported bands, unless otherwise stated, are tentatively assigned to the isoselenazole ring on empirical basis. \(^\text{1H-Nmr}\) spectra in CDCl\(_3\) (TMS as int. ref.) were obtained on a W.M.300 Bruker spectrometer. Mass spectra were recorded on a Varian MAT CH5-DF apparatus at 70 eV; the expected isotopic pattern was always observed; the values are referred to the selenium isotope 80 and to the bromine isotope 79 when occurring. \(\text{pK}_a\) Measurements were performed with a Cary 118C UV/VIS spectrophotometer and an ORION Research model 701A digital pH-meter. Microanalyses of all the new products prepared were in satisfactory agreement with the calculated values (C±0.30, H±0.21, N±0.23).

**Materials**

Isoselenazole, 3-methylisoselenazole, 5-methylisoselenazole, 3,5-dimethylisoselenazole, and 3-methyl-5-phenylisoselenazole were prepared from proper \(\alpha\)-acetylenic aldehydes or ketones as previously described.\(^1\)

\(\text{pK}_a\) Measurements

For the low water solubility of the substrates \(\text{pK}_a\) measurements were performed by a standard spectrophotometric method\(^10\) in water containing 1.6\% methanol and sufficient hydrochloric acid and potassium chloride to keep the ionic strength at the value of 0.1. \(\text{UV}\) maxima of the measurements are reported in Table 1.

**Hydrogen-deuterium exchanges**

A mixture of the isoselenazole compound and 100\% deuteriosulfuric acid (molar ratio 1:30) in sealed vial was heated in a thermostatic bath at 100 °C for the desired time, then it was diluted under cooling with an equal volume of water, carefully neutralized with 25\% aqueous ammonia and extracted with ether. After drying over

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anhydrous sodium sulfate and removal of the solvent the extracts afforded the deuterated product whose deuterium content was determined by comparing the nmr signals of the proton in 4 position (δ = 7.38 and 6.89 ppm for unsubstituted iso-selenazole and 3,5-dimethylisoselenazole respectively) and of the other protons of the molecule.

**Bromination of isoselenazoles 1a-d**

a) with bromine

The isoselenazole derivative (0.10-0.30 g) was treated with an excess of bromine (molar ratio 1:4) and left at room temperature in the dark for 5 h. After removal of the excess bromine at reduced pressure, the residue was treated with a few milliliters of water, neutralized with sodium hydrogen carbonate and extracted with 60 ml of methylene chloride in 3 portions. The extracts after drying over anhydrous sodium sulfate and removal of the solvent afforded the crude products. Compounds 2a-c were purified through a bulb to bulb distillation on water bath at reduced pressure. The distilled compounds 2a, c remained in oily form. the compound 2b spontaneously solidified yielding white crystals. The pure oily compound 2d was obtained through preparative layer chromatography on Merck PF254+366 silica gel using a mixture of benzene/methanol 100/1 as eluent.

b) with N-bromosuccinimide (NBS) in acetic acid

The isoselenazole derivative (4 mmol) was dissolved in 8 ml of acetic acid and treated with 8 mmol of solid NBS in one portion. After 4 h stirring at room temperature, the mixture was neutralized with a saturated sodium hydrogen carbonate solution and extracted with 50 ml of ether in four portions. The extracts after drying over anhydrous sodium sulfate and removal of the solvent afforded crude products which were purified as above.

**Oxidation of the brominated product 2d with potassium permanganate**

The product 2d (0.061 g, 0.20 mmol) was treated with a solution of potassium permanganate (0.096 g, 0.60 mmol) in 1 ml of water and refluxed for 3 h. The mixture was diluted with water (10 ml), and filtered. The colourless filtrate was brought to pH=1 with sulfuric acid and extracted with 20 ml of diethyl ether in five portions. The extracts after drying over anhydrous sodium sulfate and removal of the solvent left 0.015 g (yield 60%) of pure benzoic acid.

**Nitration of isoselenazoles 1a-d**

A sample of the isoselenazole compound not exceeding 100 mg to avoid the danger of eventual explosions was dissolved in concentrated sulfuric acid (98%; 1 ml) and treated with 100% nitric acid (0.3 ml). The homogeneous solution after 3 h stirring at room temperature was poured into iced water (50 ml), neutralized with sodium hydrogen carbonate and extracted with 60 ml of diethyl ether in three
portions. The extracts after drying over anhydrous sodium sulfate and removal of the solvent afforded the crude products. Nitrated compounds 3a-c were obtained in a pure form by crystallization from n-pentane. Compounds 4-7 from the nitration of 1d were separated by preparative thin layer chromatography on Merck PF254-366 silica gel eluting the plates three times with benzene/acetone 97/3 and one time with benzene/acetone 96/4.

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REFERENCES

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