A Reinvestigation of the Cyclodesulfurization of Thiosemicarbazides

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A recent report describing the preparation of 2-(substituted-amino)-3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones (**3**), by the cyclodesulfurization of hydrazides prepared from *o*-aminobenzoylhydrazine (**1**) and isothiocyanates, is erroneus. The products resulting from this reaction sequence are, instead, 2-(substituted-amino)-5-(*o*-aminophenyl)-1,3,4-oxadiazoles (**4**). Alternate syntheses of the oxadiazoles led to the correct structural assignments.

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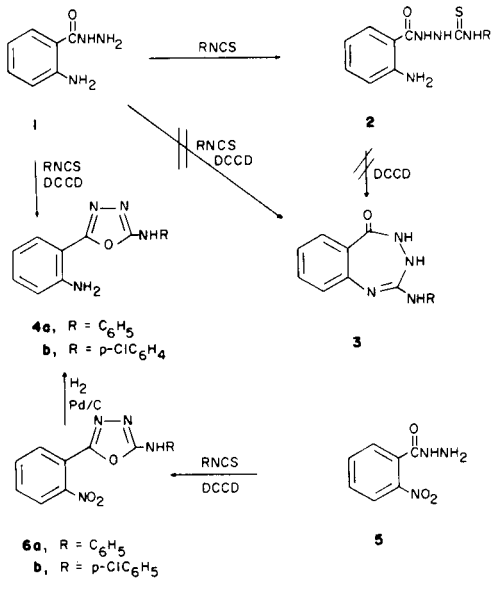
A recent article by Omar, Ashour and Bourdais (1) described the preparation of 2-(substituted-amino)-3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones (**3**) from *o*-aminobenzoylhydrazine (**1**) as shown in Scheme I. Treatment of **1** with isothiocyanates gave hydrazides **2**, which reportedly cyclized on treatment with dicyclohexylcarbodiimide (DCCD) to **3**. Alternatively, the same products resulted when **1** was treated with isothiocyanates and DCCD simultaneously.

Our reinvestigation of this work has shown it to be in error. The compounds assigned as 2-(subsituted-amino)-3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones (**3**) are, instead, 2-(substitued-amino)-5-(*o*-aminophenyl)-1,3,4-oxadiazoles (**4**). The correct structural assignments are based on the unequivocal synthesis of three of the oxadiazoles which were purported to be benzotriazepinones.

Treatment of *o*-nitrobenzoylhydrazine (**5**) with phenyl isothiocyanate and *p*-chlorophenyl isothiocyanate in the presence of *N,N'*-dicyclohexylcarbodiimide (DCCD) produced 2-phenylamino-5-(*o*-nitrophenyl)-1,3,4-oxadiazole (**6a**) and its chloro analog **6b**, respectively. Catalytic reduction of nitro compounds, **6a** and **6b**, gave the respective amino compounds, **4a** and **4b**. The oxadiazoles **4a** and **4b** prepared in this fashion were identical to the products obtained by treating *o*-aminobenzoylhydrazine (**1**) with DCCD and phenyl isothiocyanate and *p*-chlorophenyl isothiocyanate, respectively, using the procedure of Omar, *et al.*, (1), see Scheme I.

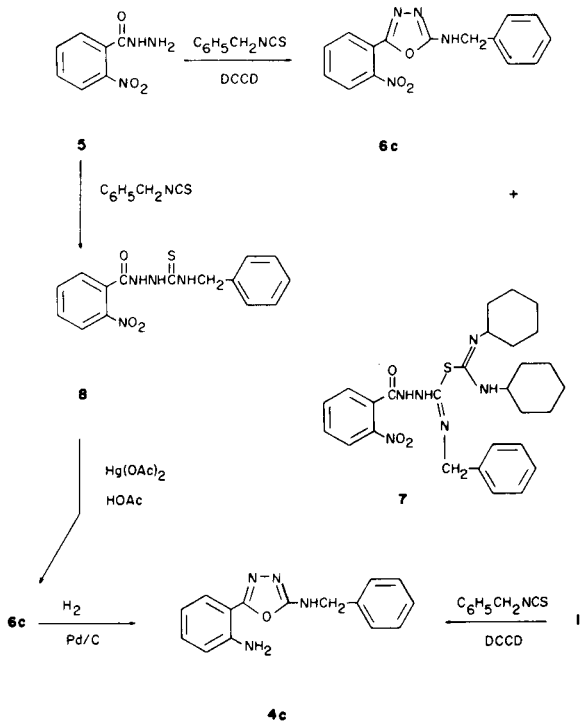
Scheme I



Synthesis of a third compound, 2-benzylamino-5-(*o*-nitrophenyl)-1,3,4-oxadiazole (**6c**), whose structure was also misassigned as a benzotriazepinone by Omar, *et al.*, (1), is shown in Scheme II. Although **6c** could be made using our procedure of Scheme I from *o*-nitrobenzoylhydrazine (**5**), benzyl isothiocyanate and DCCD, we were not satisfied with the preparation, since **6c** was produced in low yield and chromatography was necessary for its isolation. One of the coproducts (**7**) of this reaction was the DCCD adduct of acylthiosemicarbazide **8**, which we were able to characterize. We assiged the imino tautomer **7** to this compound, rather than the other possible imino tautomer, since the benzyl methylene group appeared as a singlet in the nmr spectrum. In compounds **4c**, **6c** and **8**, the benzyl methylene groups are coupled to the adjacent amino proton and appear as doublets.

Since it is known that 1-acylsemicarbazides upon treatment with phosphorous oxychloride cyclize to oxadiazoles (2), we considered preparing the appropriate 1-acylsemicarbazide (compound **8**, where S is replaced by O) as a precursor to oxadiazole **6c**. However, benzyl isocyanate is not commercially available, and we employed, instead, a documented procedure for the cyclization of 1-acylthiosemicarbazides which uses mercuric acetate (3,4). Treatment of acythiosemicarbazide **8**, which was prepared from **5** and benzyl isothiocyanate, with mercuric acetate in acetic acid cleanly produced oxadiazole **6c**. Catalytic reduction of **6c** then gave oxadiazole **4c**, which was identical to the product obtained by treating *o*-aminobenzoylhydrazine (**1**) with benzyl isothiocyanate and DCCD.

Scheme II



The mass spectral fragmentation scheme presented by Omar, *et al.*, (1) is incorrect, of course, since they had failed to prepare benzotriazepinones. The loss of two hydrogen radicals (not protons, as their scheme indicates) from the amino group of their ion C (m/e 120) to give their ion E (m/e 118) is implausible. The formation of fragments m/e 120 and m/e 118 from oxadiazoles **4a**, **4b** and **4c**, however, is very reasonable (Scheme III). The fragments which they observed are, indeed, in complete accord with anticipated fragmentation patterns for oxadiazoles. Fragmentation pathways a, b, and c are all well-documented for oxadiazoles, as is the rearrangement (aryl migration) depicted in Scheme III, with the subsequent loss of nitrogen and carbon monoxide (6).

An earlier report by Langis (7) also described the preparation of 2-(substituted-amino)-3,4-dihydro-5*H*-1,2,4-benzotriazepin-5-ones. Langis (7) treated isatoic anhydrides with hydrazides to produce diacylhydrazines, which he cyclized with polyphosphoric acid. The cyclization products, which Langis (7) assigned as benzotriazepinones, were reinvestigated by Takahashi, Onizawa and Satoh (8) and found to be isomeric 1,3,4-oxadiazoles, instead. We have also reinvestigated and corrected the inaccuracies in several other reported syntheses of benzotriazepine systems. These syntheses have, instead, resulted in the formation of smaller-sized heterocycles (9,10,11).

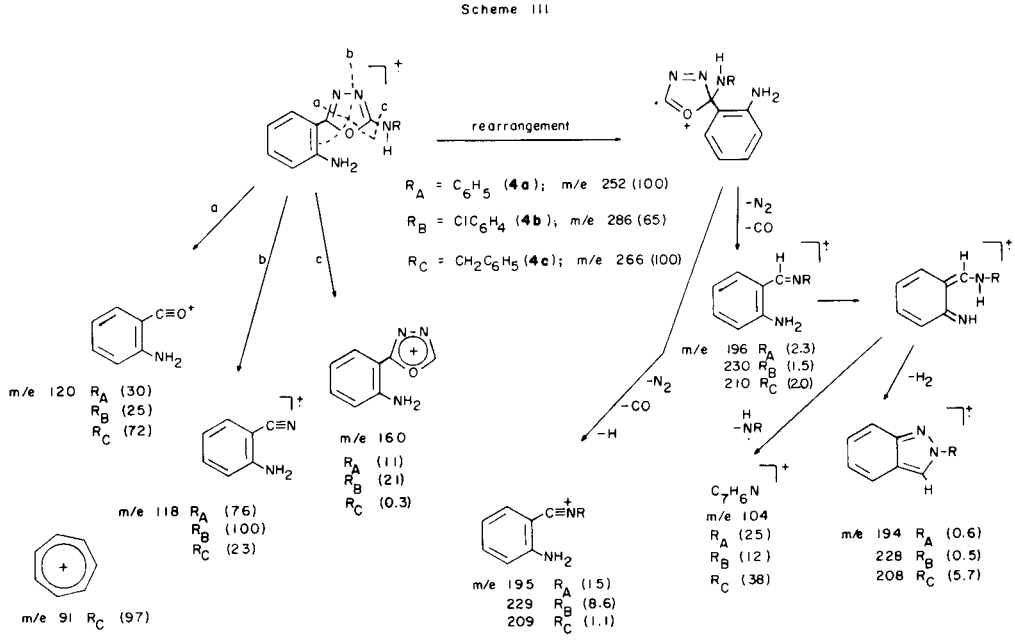
EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded with a Perkin-Elmer Model 727B spectrophotometer, nmr spectra with Varian EM-360A and Perkin-Elmer R-32 (90 MHz) spectrometers, and mass spectra with a Finnigan gc/ms Model 4023 (electron impact and chemical ionization) mass spectrometer. Combustion analysis for C, H and N were performed by Dow Analytical Laboratories, Midland MI.

o-Nitobenzoylhydrazine (**5**).

A mixture of 59.8 g (0.330 mole) of methyl *o*-nitrobenzoate (Aldrich), 35.0 g (0.699 mole) of hydrazine hydrate and 25 ml of water were heated at reflux for 3 hours. The resulting solution was cooled and diluted with water and the resulting solid was collected (in two crops) and air-dried to yield 35.2 g (59%) of **5**, mp 120-121° [lit (12) mp 123°, lit (13) mp 124°];ir

Scheme III



(Nujol): 3280 and 3160 (NH), 1635 (C=O), 1520, 1335 and 850 (NO_2) cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 10.67 (broad s, 1H, CONH), 8.10-7.92 (m, 1H, aromatic), 7.78-7.48 (m, 3H, aromatic), 4.30 (broad s, 2H, NH_2).

Anal. Calcd. for $C_7H_7N_3O_3$: C, 46.41; H, 3.90; N, 23.20. Found: C, 46.44; H, 4.04; N, 23.52.

2-(*o*-Nitrophenyl)-5-phenylamino-1,3,4-oxadiazole (**6a**).

A mixture of 18.1 g (0.100 mole) of **5**, 13.5 g (0.100 mole) of phenyl isothiocyanate (Aldrich) and 250 ml of toluene were heated at reflux for 30 minutes and 30.9 g (0.150 mole) of *N,N'*-dicyclohexylcarbodiimide (DCCD) was added. After 7 hours at reflux the mixture was cooled and the solid was collected to give 26.4 g. Recrystallization from ethanol-benzene (14) afforded 11.9 g (42%) of **6a**, mp 164-165°; ir (potassium bromide): 3250-2600 (NH), 1670 (C=N), 1530, 1345 and 855 (NO_2) cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 10.77 (s, 1H, NH), 8.25-6.95 (m, 9H, aromatic); ms: (70 eV, chemical ionization, methane) m/e 283 ($M^+ + 1$), 311 ($M^+ + 29$), 323 ($M^+ + 41$).

Anal. Calcd. for $C_{14}H_{10}N_4O_3$: C, 59.57; H, 3.57; N, 19.85. Found: C, 59.40; H, 3.75; N, 20.02.

From the filtrate were obtained yellow crystals which were collected and recrystallized to afford a sample of the coproduct *N,N'*-dicyclohexylthiourea, mp 179-180° [lit (15) mp 179-180°]; nmr (dimethylsulfoxide-d_6): δ 7.03 (d, J = 8 Hz, 2H, both NH groups), 4.20-3.75 (m, 2H, methine protons), 2.00-0.80 (m, 20H, methylene groups); ms: (70 eV, electron impact) m/e 240 (molecular ion).

Anal. Calcd. for $C_{13}H_{24}N_2S$: C, 64.96; H, 10.06; N, 11.66. Found: C, 64.90; H, 10.04; N, 11.72.

2-(*p*-Chlorophenylamino)-5-(*o*-nitrophenyl)-1,3,4-oxadiazole (**6b**).

A mixture of 9.06 g (50.0 mmoles) of **5**, 8.48 g (50.0 mmoles) of *p*-chlorophenyl isothiocyanate (Trans World Chemicals) and 200 ml of benzene were heated at reflux for 30 minutes and 15.5 g (75.0 mmoles) of DCCD in 50 ml of benzene was added. After seven hours, the mixture was partially cooled and the solid was collected by filtration, washed with benzene and air-dried to yield 13.0 g (82%) of **6b**, mp 223-225°; mp 225° (dimethylformamide-water); ir (potassium bromide): 3200-2600 (NH), 1670 (C=N), 1540, 1360 and 855 (NO_2) cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 10.90 (s, 1H, NH), 8.25-7.83 (m, 4H, aromatic), 7.66 (d, J = 9 Hz, 2H, aromatic), 7.43 (d, J = 9 Hz, 2H, aromatic); ms: (70 eV, electron impact): m/e 316 (molecular ion).

Anal. Calcd. for $C_{14}H_9ClN_4O_3$: C, 53.09; H, 2.86; N, 17.69. Found: C, 53.30; H, 3.16; N, 17.76.

2-(*o*-Aminophenyl)-5-phenylamino-1,3,4-oxadiazole (**4a**).

A solution of 4.10 g (14.5 mmoles) of **6a** in 200 ml of ethanol was hydrogenated at 50 psi in a Parr apparatus in the presence of 5% Pd/C. After 1 hour, hydrogen uptake had stopped but tlc still indicated the presence of **6a**. The catalyst was removed by filtration and hydrogenation was continued for an additional 2 hours in the presence of fresh catalyst. A white solid was present which was dissolved by the addition of 300 ml of ethanol and heating. The catalyst was removed by filtration and the filtrate was concentrated and cooled to give light yellow crystals. Collection and air-drying gave 3.08 g (84%) of **4a**, mp 250°; ir (potassium bromide): 3450-2500, with spikes at 3400 and 3225 (NH), 1670 (C=N) cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 10.55 (s, 1H, NH, deuterium oxide-exchangeable), 7.75-6.50 [m, 11H, aromatic and NH_2, with NH_2 s (deuterium oxide-exchangeable) at 6.65]; ms: (70 eV, electron impact) m/e 252 (molecular ion).

Anal. Calcd. for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79; N, 22.21. Found: C, 66.80; H, 4.87; N, 22.47.

A mixture melting point of the sample of **4a** prepared above and a sample of **4a** generated from **1**, phenyl isothiocyanate and DCCD using the procedure (Route B) of Omar, *et al.*, (1), was undepressed. Spectral data (ir, nmr and ms) gathered for both of these samples pf **4a** showed them to be identical.

2-(*o*-Aminophenyl)-5-(*p*-chlorophenylamino)-1,3,4-oxadiazole (**4b**).

A solution of 1.60 g (5.05 mmoles) of **6b** in 150 ml of acetic acid was hydrogenated at 50 psi in a Parr apparatus in the presence of 5% Pd/C. After 1 hour the reduction was complete and a precipitate was present. The mixture was heated to dissolve the precipitate and the catalyst was removed by filtration. A white solid crystallized from the filtrate, which was collected and air-dried to yield 0.920 g. (64%) of **4b**, mp 265-266°, mp 271-273° (ethanol); ir (potassium bromide): 3450-2500, with spikes at 3390 and 3315 (NH), 1665 (C=N) cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 10.73 (broad s, 1H, NH. deuterium oxide-exchangeable), 7.80-6.50 [m, 10H, aromatic and NH_2, with NH_2 s (deuterium oxide-exchangeable) at 6.66]; ms: (70 eV, chemical ionization, methane) m/e 287 ($M^+ + 1$), 315 ($M^+ + 29$), 327 ($M^+ + 41$).

Anal. Calcd. for $C_{14}H_{11}ClN_4O$: C, 58.64; H, 3.86; N, 19.54. Found: C, 58.90; H, 4.10; N, 19.74.

A mixture melting point of the sample **4b** prepared above and a sample of **4b** generated from **1**, *p*-chlorophenyl isothiocyanate and DCCD using the procedure (Route B) of Omar, *et al.*, (1) was undepressed. Spectral data (ir, nmr and ms) gathered for both of these samples of **4b** showed them to be identical.

Treatment of *o*-Nitrobenzoylhydrazine (**5**) with Benzyl Isothiocyanate and DCCD.

A mixture of 9.06 g (50.0 mmoles) of **5**, 7.46 g (50.0 mmoles) of benzyl isothiocyanate and 200 ml of benzene was heated at reflux for 30 minutes and 15.5 g (75.0 mmoles) of DCCD was added. After 1 hour at reflux a clear solution resulted, which was heated at reflux for an additional 6 hours. After standing at room temperature for 15 hours, a small amount of white solid (1.71 g) was deposited. Collection and recrystallization from ethanol afforded 500 mg of *N,N'*-dicyclohexylurea, mp 225-227° [lit (16) mp 229-230°]; ms: (70 eV, electron impact) m/e 224 (molecular ion).

The clear filtrate was concentrated to a viscous, red oil. Trituration with ether gave a yellow solid which was collected and air-dried to yield 3.60 g of 2-nitrobenzoic acid 2-[((cyclohexylamino)cyclohexylimino)-methyl)thio)((phenylmethyl)imino)methyl]hydrazide (**7**), mp 192°; ir (potassium bromide): 3305 and 3130 (NH), 1640 (C=O), 1520, 1345 and 850 (NO_2) cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 9.56 (s, 1H, NH, deuterium oxide-exchangeable), 8.10-7.93 (m, 1H, aromatic), 7.80-7.10 (m, 8H, remaining aromatic), 6.57 (broad s, 2H, two NH groups, deuterium oxide-exchangeable), 5.19 (s, 2H, NCH_2), 3.50-3.00 (m, 2H, both NCH groups), 1.9-0.8 (m, 20H, cyclohexyl CH_2 groups); ms: [50 eV, direct chemical ioniation (17), methane] m/e 537 ($M^+ + 1$).

Anal. Calcd. for $C_{28}H_{36}N_6SO_3$: C, 62.66; H, 6.76; N, 15.66. Found: C, 62.90; H, 6.88; N, 15.78.

A 5.00-g. portion of the concentrated filtrate from above was dissolved in a minimum volume of chloroform and applied to a column of 300 g of silica gel 60 (70-230 mesh, EM Reagents) and eluted with 1ℓ of chloroform containing 1% methanol. Twenty-four fractions (100 ml) were collected and monitored by tlc (silica gel; 9:1::chloroform:methanol). Fractions 12,13 and 14 were combined and concentrated to leave 1.28 g of oil, which was triturated with ether. The decanted ether supernatant deposited a yellow solid, which was recrystallized form toluene (18) (10 ml) to give 170 mg of 2-benzylamino-5-(*o*-nitrophenyl)-1,3,4-oxadiazole (**6c**), mp 124-125°; ir (potassium bromide): 3400-2600 (NH), 1645 (C=N), 1525, 1340 and 855 (NO_2) cm^{-1}; nmr (deuteriochloroform): δ 8.00-7.56 [m, 5H, 4 aromatic protons and NH (deuterium oxide-exchangeable)], 7.56-7.20 (m, 5H, aromatic), 4.50 (d, J = 6 Hz, 2H, CH_2, collapses to a s at 4.50 after addition of deuterium oxide); ms: (70 eV, chemical ionization, methane) m/e 297 ($M^+ + 1$), 325 ($M^+ + 29$), 337 ($M^+ + 41$).

Anal. Calcd. for $C_{15}H_{12}N_4O_3$: C, 60.80; H, 4.08; N, 18.91. Found: C, 60.60; H, 4.18; N, 18.99.

4-Benzylamino-1-(*o*-nitrobenzoyl)-3-thiosemicarbazide (**8**).

To a mixture of 7.60 g (42 mmoles) of **5** and 100 ml of benzene was added 7.45 g (50.0 mmoles) of benzyl isothiocyanate. After heating at reflux for 1 hour, the mixture was cooled and the solid was collected, washed with ether and air-dried to yield 12.6 g (91%) of **8**, mp 185-187° mp 186-187° (ethanol); ir (Nujol): 3375, 3320 and 3160 (NH), 1675 (C=O),

1530, 1345 and 855 (NO_2) cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 10.63 (s, 1H, NH, deuterium oxide-exchangeable), 9.68 (s, 1H, NH, deuterium oxide-exchangeable), 8.40-7.57 (m, 5H, 4 aromatic protons plus N*H*CH_2 t, J = 7 Hz, at 8.26, deuterium oxide-exchangeable), 7.45-7.15 (m, 5H, aromatic), 4.80 (d, J = 7 Hz, 2H, CH_2, collapses to a s at 4.80 after addition of deuterium oxide).

Anal. Calcd. for $C_{15}H_{14}N_4O_3S$: C, 54.53; H, 4.27; N, 16.96. Found: C, 54.50; H, 4.39; N, 17.12.

Treatment of **8** with Mercuric Acetate.

To a solution of 3.19 g (10.0 mmoles) of mercuric acetate in 50 ml of acetic acid was added 3.30 g (10.0 mmoles) of **8** with stirring. A black precipitate soon developed. The mixture was heated at reflux for 1 hour, cooled, and the black precipitate (mercuric sulfide) was removed by filtration. The yellow filtrate was concentrated and treated with water. The resulting solid was collected, washed with water and air-dried to yield 2.30 g (78%) of **6c**, mp 122-123° (toluene) (18). A mixture melting point of this sample and the sample generated from **5**, benzyl isothiocyanate and DCCD was undepressed, and the infrared spectra of the two samples were identical.

2-(*o*-Aminophenyl)-5-benzylamino-1,3,4-oxadiazole (**4c**).

A solution of 4.00 g (13.5 mmoles) of **6c** in 180 ml. of warm ethanol was hydrogenated at 50 psi in a Parr apparatus in the presence of 5% Pd/C for 30 minutes. The catalyst was removed by filtration and the filtrate was concentrated to leave 3.20 g (89%) of **4c**, mp 160-161° (ethanol); ir (potassium bromide): 3400-2800, with spike at 3370 (NH), 1640 and 1625 (C=N) cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 8.27 (t, J = 6.5 Hz, 1H, NH, deuterium oxide-exchangeable), 7.55-6.40 [m, 11H, aromatic and NH_2, with NH_2 s (deuterium oxide-exchangeable) at 6.54], 4.47 (d, J = 6.5 Hz, 2H, CH_2, collapses to a s at 4.47 after addition of deuterium oxide); ms: (70 e V, electron impact) m/e 266 (molecular ion).

Anal. Calcd. for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.90; H, 5.42; N, 21.26.

A mixture melting point of the sample of **4c** prepared above and a sample of **4c** generated from **1**, benzyl isothiocyanate and DCCD using the procedure (Route B) of Omar, *et al.*,(1), was undepressed. Spectral data (ir, nmr and ms) gathered for both of these samples of **4c** showed them to be identical.

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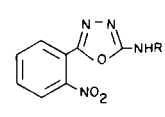
(14) When **6a** was recrystallized from ethanol, another crystalline form (same melting point) resulted, which we think is a tautomer. The solid state infrared spectrum (KBr) of the tautomer from ethanol was quite different, and displayed C=N stretching at 1610 cm^{-1}. The solution infrared spectra (chloroform) of the two tautomers were identical. Possible tautomeric forms of the 2-(substituted-amino)-5-(*o*-nitrophenyl)-1,3,4-oxadiazole are generalized structures **i** and **ii**.



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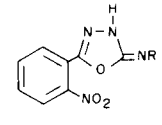

II

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(17) This mass spectrum was obtained by volatilization in the ion plasma from a gold wire. The source temperature was 150°.

(18) Upon recrystallization from toluene, **6c** was a mixture of white crystals and yellow crystals. When heated in a melting point apparatus (or oven-drying) the white crystalline form converted to the yellow crystalline form.