On the Boulton-Katritzky Rearrangement of 5,6- and 6,7-Dimethoxy-4-nitrobenzofuroxans: A Reinvestigation

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5,6-Dimethoxy-4-nitrobenzofuroxan (**6**) or its 6,7-isomer **7** equilibrate on heating to a 66:34 = 6:7 thermostationary mixture, in contrast to a previous report. The systems **6:7** and **1f:2f** are compared.

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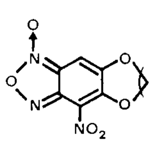
We have recently reported [1] on the thermal isomerization of nitrobenzofuroxans **1** and **2**. We have found that **1b,c,d,e** undergo the Boulton-Katritzky rearrangement [2] on heating to furnish the isomeric **2b,c,d,e** whereas **2a** isomerizes to **1a**. The ten-membered heterocycles **1f** or **2f** equilibrate to a 44:56 = **1f:2f** thermostationary state.



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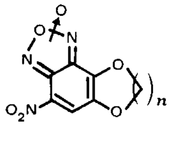
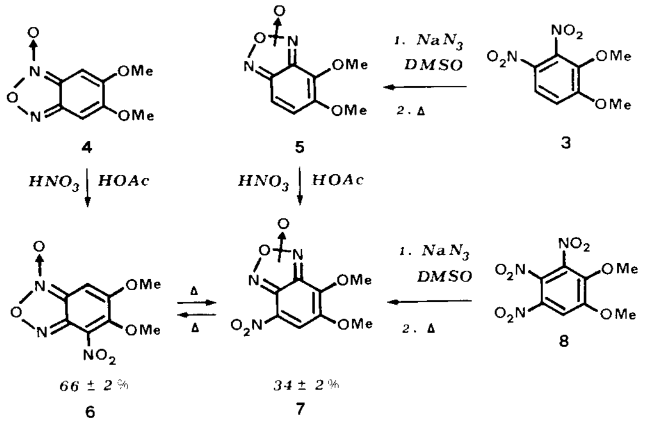


2

	n
a	1
b	2
c	3
d	4
e	5
f	6

In light of the above results we were rather surprised by a recent report claiming that the isomeric nitrobenzofuroxans **6** and **7** "do not rearrange into one another on heating" [3]. In this case as well, we expected at least one isomer, *i.e.*, **6** to rearrange into the other. To test this possibility, we prepared both **6** and **7** in ≥98% purity as previously described [1] for the preparation of **1**. Thus, nucleophilic displacement of one of nitro groups in dinitroveratrole **3** [4] by azide ion followed by thermolysis, afforded the benzofuroxan **5**. Authentic samples of the nitrobenzofuroxans **6** and **7** were provided by treatment of the respective benzofuroxans **4** [3] and **5** with fuming nitric acid (d = 1.52) at room temperature.



6

7

Heating of **6** or **7** or mixtures of both isomers resulted in an equilibrium of **6:7** = 66:34 (±2), as revealed by ^{1}H nmr spectroscopy, under the following conditions: (a) heating of **6** in toluene under reflux for 4, 19 and 40 hours; (b) heating of **6** in the solid state at 140-150° for 2 hours; (c) heating of **7** in refluxing toluene for 2 and 4 hours; (d) heating a mixture of **6** (90%) and **7** (10%) in toluene under reflux for 4 hours; (e) heating a mixture of **6** (48%) and **7** (52%) in refluxing toluene for 4 and 8 hours.

In an effort to repeat the original authors' results, we prepared a mixture of the three isomeric dinitro azides, as shown by tlc and ^{1}H nmr, starting from 1,2,3-trinitroveratrole (**8**) and following the method described in the literature [3].

Thermolysis of the azide mixture in toluene under reflux for 4 hours afforded both isomers **6** and **7** in the same ratio cited above. Here however, decomposition was observed to a large extent. Apparently, dry heating of isomer **7** at 130° for 10 minutes by the first authors [3] does not allow for equilibration to **6**, whereas thermolysis of the azide mixture, obtained from **8**, in refluxing chlorobenzene for 10 minutes only, furnishes **6** and **7** in the erroneous ratio of 54:43, respectively [3]. Moreover, we have observed partial decomposition of **6** (but not of **7**) on purification of their mixture by column chromatography on silica gel.

It is interesting to compare the equilibrium between **6** and **7** with that of **1f** and **2f**. Obviously, in both systems the energy difference between the isomeric pairs is small. However, in the latter equilibrium isomer **2f** predominates slightly by a factor of *ca.* 1.3, while in the former case, the nitrobenzofuroxan **6** outweighs **7** by a factor of nearly 2. The results in the case of **1f:2f** have been rationalized [1b] previously in terms of the slightly greater instability of **1f** (relative to **2f**) owed to steric inhibition to resonance of the nitro substituent with the benzene ring [2]. In dimethoxynitrobenzofuroxan **6**, steric interference between the nitro group and the methoxy hydrogens at C-5 is expected to be less pronounced than in **1f**, as a result of the greater conformational mobility of the methoxy groups. An additional stabilization factor for **6** relative to **1f** is the more effective electron release by the methoxy oxygens [5]. Granted these reasons, however, it it not quite clear yet why the equilibrium between **6** and **7** should be on the side of **6**, since **7** is not anticipated to be less stable than **6**. Clearly, there must be additional critical parameters, that determine the outcome of these rearrangements, not considered here or in the previous literature [1,2].

EXPERIMENTAL

The general experimental has been previously described [1].

5,6-Dimethoxy-4-nitro-2,1,3-benzoxadiazole 1-Oxide (**6**).

Benzofuroxan **4** (500 mg, 2.55 mmoles) [3] in glacial acetic acid (2 ml) was treated with fuming nitric acid (d = 1.52, 0.7 ml), 1 hour, room temperature. Recrystallization from ethanol at 60° afforded 266 mg (43%) of **6** as yellow needles, mp 117-118° (partially rearranged?); uv (absolute ethanol): λ max (ϵ) 392 (6000), 325 (5500), 223 (22000), 209 sh (18500) nm; ir (potassium bromide): ν 1631 (m), 1590 (s), 1543 (s), 1535 (s), 1487 (s), 1359 (s), 1326 (s), 1270 (m), 1235 (m), 1197 (m), 1021 (s), 982 (m), 938 (m), 828 (m), 767 (m) cm^{-1}; ^{1}H nmr (80 MHz, deuteriochloroform): δ 4.01 (s, 3H), 4.12 (s, 3H), 6.68 (s, 1H).

Anal. Calcd. for $C_8H_7N_3O_6$: C, 39.84; H, 2.93; N, 17.42. Found: C, 40.11; H, 2.69; N, 17.22.

4,5-Dimethoxy-2,1,3-benzoxadiazole 1-Oxide (**5**).

Following a standard procedure [1], a mixture of dinitroveratrole **3** (264 mg, 1.16 mmoles) [4] and sodium azide (305 mg, 4.69 mmoles) in dimethyl sulfoxide (5 ml), 57-63°, 0.5 hour, furnished 259 mg of a pale-yellow solid, tentatively identified as 3-azido-4-nitroveratrole by analogy to similar derivatives [1]; ^{1}H nmr (80 MHz, deuteriochloroform): δ 3.95 (s, 6H), 6.71 (d, J = 9.5 Hz, 1H), 7.74 (d, J = 9.5 Hz, 1H). Thermolysis of this in toluene (5 ml) under reflux for 2 hours followed by column chromatography (benzene) afforded 225 mg (99% overall) of furoxan **5**, mp (ethanol at 60°, orange needles) 64-65°; uv (absolute ethanol): λ max (ϵ) 387 (3500), 330 (6000), 317 (5500), 305 sh (3500), 221 (19000) nm; ir (carbon tetrachloride): ν 1610 (s), 1588 (s), 1543 (m), 1500 (s), 1460 (m), 1327 (s), 1242 (s), 1102 (m), 1076 (m), 1042 (s), 1015 (m), 969 (w), 848 (w) cm^{-1}; ^{1}H nmr (80 MHz, deuteriochloroform): δ 3.99 (s, 3H), 4.20 (s, 3H), 7.05 (s, 2H).

Anal. Calcd. for $C_8H_8N_2O_4$: C, 48.98; H, 4.11; N, 14.28. Found: C, 48.88; H, 4.20; N, 14.38.

6,7-Dimethoxy-4-nitro-2,1,3-benzoxadiazole 1-Oxide (**7**) [3].

Benzofuroxan **5** (47 mg, 0.24 mmole) in glacial acetic acid (3 ml) was treated with fuming nitric acid (d = 1.52, 0.05 ml), room temperature, 0.5 hour. Column chromatography (chloroform) afforded 5 mg (9%) of **7** as a red solid, identical in all respects with that described in the literature [3].

Azidation of **8** and Subsequent Thermolysis [3].

Trinitroveratrole **8** (500 mg, 1.83 mmoles) [3] and sodium azide (363 mg, 5.58 mmoles) in dimethyl sulfoxide (10 ml) were stirred at room temperature for 3 hours to give a yellow solid. Column chromatography (petroleum ether:ethyl acetate = 4:1 v:v) furnished 47 mg (10%) of pure 3-azido-4,5-dinitroveratrole (**9**), 29 mg of pure 4-azido-5,6-dinitroveratrole (**10**) and 341 mg of a mixture consisting of **10** and 4-azido-3,5-dinitroveratrole (**11**). From the ^{1}H nmr integration of the aromatic protons of the mixture: **10** (244 + 29 = 273 mg, 55% total) and **11** (99 mg, 20%). The structural assignment was based on the chemical shift of the aromatic protons, by analogy to similar compounds [1] and is considered tentative.

Compound **9** had ^{1}H nmr (80 MHz, deuteriochloroform): δ 3.89 (s, 3H), 3.99 (s, 3H), 7.24 (s, 1H); ^{1}H nmr (80 MHz, carbon tetrachloride): δ 3.91 (s, 3H), 3.98 (s, 3H), 7.14 (s, 1H).

Compound **10** had ^{1}H nmr (80 MHz, deuteriochloroform): δ 3.89 (s, 3H), 3.93 (s, 3H), 6.45 (s, 1H).

Compound **11** had ^{1}H nmr (80 MHz, deuteriochloroform): δ 3.99 (s, 3H), 4.04 (s, 3H), 7.76 (s, 1H).

Thermolysis of the azide mixture **10** + **11** (341 mg, 1.27 mmoles) in refluxing toluene (10 ml) for 4 hours followed by column chromatography (benzene:ethyl acetate = 3:1 v:v) afforded 56 mg (18%) of a nitrobenzofuroxan mixture of **6**:**7** = 67:33 as revealed by ^{1}H nmr.

Attempted thermolysis of pure **9** or **10** in refluxing toluene resulted in decomposition of the material.

Interconversion of Nitrobenzofuroxans **6** and **7**.

(A) Compound **6**.

Nitrobenzofuroxan **6** (32 mg, 0.13 mmole) was heated in refluxing toluene (3 ml) for 4, 19 and 40 hours to furnish 31 mg (97%) of mixtures of **6**:**7** in the ratios 64:36, 68:32, 65:35, respectively, as determined by ^{1}H nmr integration of the pseudoaromatic protons.

Similarly, dry heating of **6** (24 mg, 0.10 mmole) at 140-150° for 2 hours afforded 22 mg (92%) of a mixture of **6**:**7** in the ratio of 68:32 as shown by ^{1}H nmr.

(B) Compound **7**.

Isomer **7** (5 mg, 0.02 mmole) was heated in refluxing toluene (2 ml) to obtain 5 mg (100%) of a mixture of **6**:**7** = 68:32 as revealed by ^{1}H nmr.

(C) Mixtures of **6** + **7**.

A mixture of **6** (90%) and **7** (10%) (5 mg, 0.02 mmole) in toluene (3 ml) was heated at reflux for 4 hours to give 5 mg (100%) of **6**:**7** = 68:32 as shown by ^{1}H nmr.

Likewise, a mixture of **6** (48%) and **7** (52%) (51 mg, 0.21 mmole) in toluene (5 ml) was heated at reflux for 4 and 8 hours to furnish 50 mg (98%) of **6**:**7** = 64:36 as determined by ^{1}H nmr.

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