Tetrahedron Vol 47, No 34, pp 7157-7170 1991
Printed in Great Britain

0040-4020/91 $3 00+ 00

Influence of the Heterocyclic Side Ring During the Boulton-Katritzky Rearrangement of 1,2-Alkylenedioxy-nitrobenzofuroxans

Ioannis M. Takakis*, Phaedon M. Hadjimihalakis and Georgia G. Tsantali

Laboratory of Organic Chemistry, University of Thessaloniki,
GR-540 06, Thessaloniki, Greece

(*Received in UK* 21 *May* 1991)

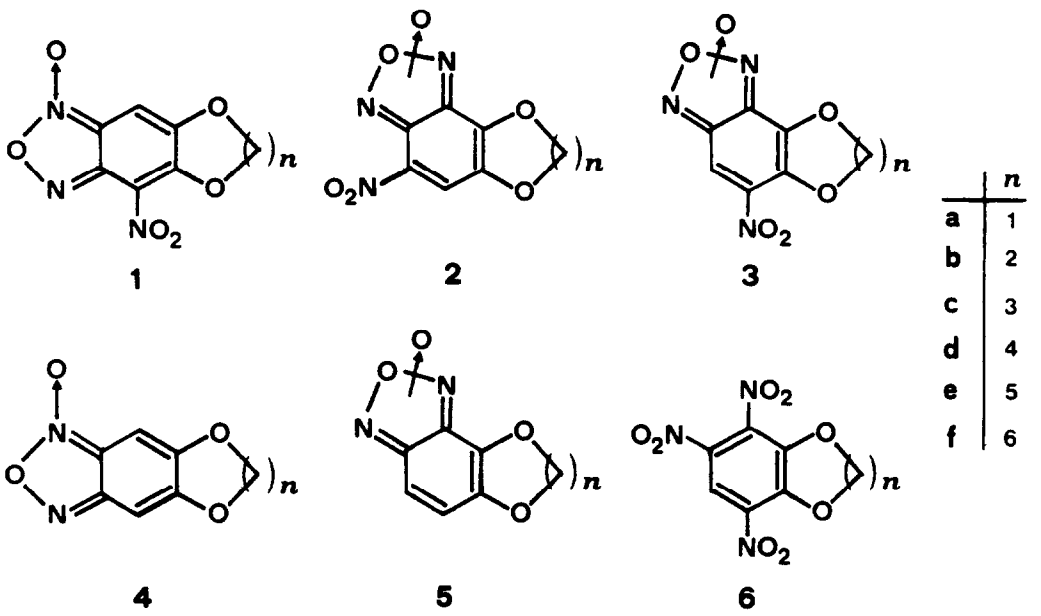
Key Words: 1,2-Alkylenedioxy-benzofuroxans and nitro-benzofuroxans; Boulton-Katritzky rearrangement.

Abstract: *Preparation of the 1,2-alkylenedioxy-benzofuroxans* ***4e,f, 5a-c,e,f,*** *and nitrobenzofuroxans* ***1a-c,e,f, 2a-c,e,f, 3b,c*** *is described. The nitrobenzofuroxans* ***1b-e*** *isomerize thermally to* ***2b-e,*** *whereas* ***2a*** *isomerizes to* ***1a.*** *A thermostationary state is obtained from* ***1f*** *or* ***2f*** *(****1f:2f*** *= 44:56). The role of the heterocyclic alkylenedioxy ring is discussed.*

The synthesis of furoxans (2,1,3-oxadiazole-1-oxides) is pursued with great interest, since these compounds show significant biological activity and have found many industrial applications.[1] Our interest in the synthesis and study of novel hetero-annelated benzofuroxans[2] has prompted us to prepare the six homologous nitrobenzofuroxans 1 with intent to ascertain the effect of the heterocyclic side ring during the Boulton-Katritzky rearrangement.[3] We note that nitrobenzofuroxans are reported to be potential antileukemic and immunosuppressive compounds.[4] Even though several examples of the Boulton-Katritzky rearrangement are known,[3,5] a systematic study aimed at determining the effects of subtle

changes taking place away from the reactive center, is hitherto unprecedented.

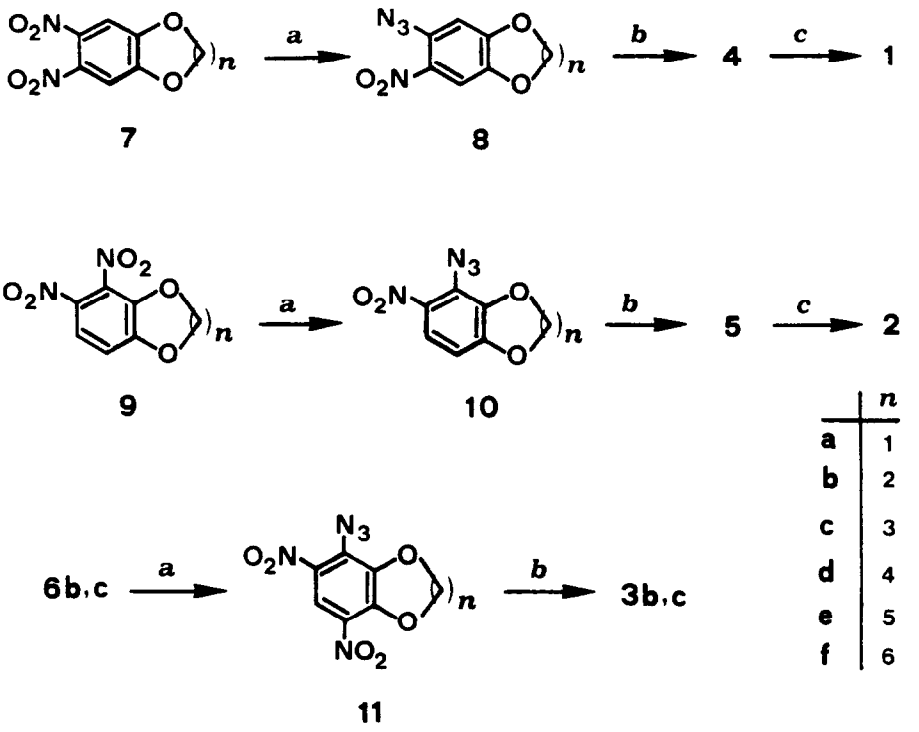
We have recently reported on the preparation of nitrobenzofuroxan **1d** and its thermal isomerization to **2d**.[2d] An authentic sample of the latter



was furnished by direct nitration of the unsubstituted furoxan **5d** in glacial acetic acid, whereas the third isomer **3d** was obtained *via* nucleophilic displacement of the trinitro derivative **6d** with azide ion followed by thermolysis in refluxing toluene. The required nitrobenzofuroxans **1** and **2** for this work were prepared in an analogous fashion as shown in Scheme 1. In two cases (**3b,c**), the third isomer was also made available for spectral comparison. In addition to **1d**, **2d** and **3d**,[2d] the unsubstituted furoxans **4a** and **4b** have been previously reported.[2a,6] Differentiation among the series of isomers **1**, **2** and **3** was based mainly on the reaction paths, ^{1}H NMR (chemical shift of pseudoaromatic proton) and UV data. Thus for **1**: δ 6.77-7.12, λ_{max} (ε) 390-405 (5000-8500) nm; for **3b-d**: δ 7.36-7.55, λ_{max} (ε) 392-413 (3000-5000) nm; and for **2**: δ 8.11-8.46, λ_{max} (ε) 442-492 (7000-10000) nm.

Heating of the furoxans **1b,c,e** in toluene under reflux resulted in their complete and irreversible rearrangement to the isomeric derivatives

Scheme 1[a]

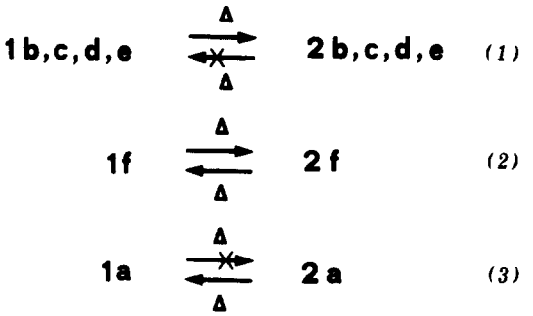


[a](a) NaN_3, DMSO; (b) Δ, C_6H_5Me; (c) HNO_3 (d=1.52), AcOH.

2b,c,e within 10, 1, and 2h, respectively. Attempts to determine the mp of 1b,c were unsuccessful as they both gave the mp of their corresponding isomers 2b,c apparently after Boulton-Katritzky rearrangement in the solid state. In contrast, no sign of reaction was detected after heating the furoxans 2b,c,e in refluxing toluene for at least 4h each. Similar results have been reported with the isomeric pair 1d, 2d.[2d]

Heating each of the isomeric furoxans 1f or 2f in toluene under reflux for 4 or 10h, gave a thermostationary equilibrium of 1f:2f = 44:56(±1) as determined by ^1H NMR spectroscopy. An identical result was obtained after dry heating of 1f at 150-160 °C for 1h, but some decomposition was also observed.

Surprisingly, attempts to convert 1a to 2a failed, as starting material was recovered unreacted after heating in toluene under reflux for 10h, or in DMSO at 140-150 °C for 1h. Decomposition was observed during dry heating at 210 °C for 10 min. The isomeric 2a however, rearranged smoothly to 1a after refluxing in chloroform for 1h. These results are summarized in equations (1)-(3). Authentic samples of all rearranged nitrobenzofuroxans were provided *via* independent reactions (see: Experimental Section).



Assuming coplanarity of the nitro group with the benzene ring, we have estimated roughly from models the distance (*d*) between the nitro group oxygen and the heterocyclic ring oxygen nearest to the nitro group in 1, considering the most stable conformations of the heterocyclic rings.[7] For the five-membered heterocycle 1a, $d \approx 2.80$-2.90 Å, while for the higher homologs 1b-f we found a nearly constant value of $d \approx 2.50$-2.60 Å. More important, as the heterocyclic ring is progressively increased, there is an analogous increase in steric interference between the nitro group oxygen and the methylene group adjacent to the heterocyclic ring oxygen (NO_2-OCH_2 repulsions). These factors are responsible for the steric inhibition to resonance of the nitro substituent with the benzene nucleus, first proposed by Boulton and Katritzky,[3] thus providing the driving force for the rearrangement of 1b-f to 2b-f. In contrast, coplanarity of the nitro group with the benzene ring is not inhibited in 1a. This, synergistically with the effective electron release from the diether oxygens of the rigid five-membered ring to the benzene ring (n-π conjugation)[8] stabilizes the system by favorable resonance structures thus preventing rearrangement to 2a.

Our experimental results suggest the following qualitative order of reactivity for the isomerization of 1b-e to 2b-e: 1c ≈ 1d >1e >> 1b. The greater stability (lower reactivity) of 1b is attributed to the more effective n-π interactions in combination with the less pronounced NO_2-OCH_2 steric interference. In the larger heterocycles 1c and 1d, n-π conjugation is reduced as a result of C_{aryl}-O-C_{alkyl} bond angle deformations and the NO_2-OCH_2 steric repulsions are increased. These systems are destabilized relative to 1b thus their rearrangement to 2c and 2d is enhanced. The intermediate reactivity of 1e is rationalized in terms of the tendency of the two oxygens to become more coplanar with the benzene ring, compared to 1c,d, as a result of the greater conformational flexibility[8] of the heterocyclic ring and perhaps as a result of a "built-in-solvation" effect.[9]

Turning to the isomeric nitrobenzofuroxans 2, the destabilizing NO_2-OCH_2 repulsion factors have now been nullified. Only in the ten-membered heterocycle 2f, models indicate some steric hindrance between the N-oxide oxygen of the furoxan ring and the methylene hydrogens nearest to the furoxan ring. In this case, the energy difference between 2f and 1f is small and the two systems equilibrate. Finally, the facile rearrangement of 2a to 1a is attributed to the relief of strain imposed by the double bond at the junction of the two rings in 2a, thus the endocyclic double bond of the five-membered ring in 2a becomes exocyclic in 1a. Apparently, the propensity for relief of strain preponderates over the presumably stabilizing effect that stems from the quasiaromatic nature (according to the literature[8]) of the five-membered ring.

It seems that this type of rearrangements depend on a fine balance of steric, electronic, conformational, and strain effects appropriately imposed by the structural requirements of a particular system under investigation.

EXPERIMENTAL SECTION

The general experimental as well as general procedures for azidations, thermolyses of *ortho*-nitro azides and nitrations of furoxans have been described recently.[2b,d] All nitrations were carried out with fuming nitric acid (d=1.52) at room temperature. All solids were recrystallized from boiling ethanol. ^1H NMR spectra were obtained at 80 MHz in $CDCl_3$ containing 2% TMS. UV spectra were taken in absolute ethanol and IR

spectra were obtained in $CHCl_3$. Exceptions are noted.

[1,3]Dioxolo[2,3-f]-2,1,3-benzoxadiazole 1-Oxide (4a).[6] This was prepared according to a slightly modified procedure[2d] than that described in the literature.[6] A mixture of the dinitrobenzodioxole **7a** (1.01 g, 4.76 mmol) and sodium azide (1.55 g, 23.8 mmol) in DMSO (15 ml) furnished after 3h at room temperature, the *ortho*-nitroazide **8a** (903 mg) as a yellow solid: IR $\tilde{\nu}$ 2110(s), 1650(w), 1617(s), 1522(m), 1505(m), 1484 (s), 1474(s), 1393(m), 1336(s) 1285(m), 1241(m), 1160(m), 1037(w), 1007 (w), 961(w), 823(w) cm^{-1}; ^1H NMR δ 6.11(s, 2H), 6.72(s, 1H), 7.48(s, 1H). The crude azide **8a** in toluene (10 ml) was heated at reflux for 1h to afford 780 mg (91% overall) of the furoxan **4a**: mp (pale-yellow prisms) 181-182 °C (lit.[7] mp 171 °C dec.); the ^1H NMR spectrum was identical to that reported.[7]

4-Nitro[1,3]dioxolo[2,3-f]-2,1,3-benzoxadiazole 1-Oxide (1a). (a) From Nitration of Benzofuroxan 4a. Compound **4a** (204 mg, 1.13 mmol) in acetic acid (3 ml) was treated with nitric acid (1.0 ml), 1h, to furnish 168 mg (66%) of the nitrobenzofuroxan **1a**: mp (ethanol:acetone = 1:1 v:v at 50 °C, yellow granules) 207-209 °C closed tube; UV λ_{max} (ε) 395(7500), 344(7500), 327(8500), 313sh(7000), 299sh(5000), 265sh(5000), 223(20500) nm; IR (KBr) $\tilde{\nu}$ 1645(w), 1613(s), 1583(s), 1522(s), 1476(s), 1357(s), 1314(s), 1208(m), 1051(s), 959(m) cm^{-1}; ^1H NMR δ 6.38(s, 2H), 6.84(s, 1H); ^1H NMR (Me_2CO-d_6) δ 6.62(s, 2H), 7.06(s, 1H). Anal. Calcd for $C_7H_3N_3O_6$: C, 37.35; H, 1.34; N, 18.67. Found: C, 37.10; H, 1.41; N, 18.77.

Compound **1a** (65 mg, 0.26 mmol) was stable after refluxing in toluene (5 ml) for 10h, or after heating in DMSO (1 ml) at 140-150 °C for 1h. Decomposition was observed after heating in the solid state at 210 °C for 10 min.

(b) From Isomerization of Nitrobenzofuroxan 2a. Compound **2a** (18 mg, 0.08 mmol) in refluxing chloroform (5 ml), 1h, furnished, after purification by column chromatography (petroleum ether:EtOAc = 1:1 v:v), 18 mg (100%) of the isomer **1a**.

[1,3]Dioxolo[2,3-e]-2,1,3-benzoxadiazole 1-Oxide (5a). A mixture of dinitrobenzodioxole **9a** (366 mg, 1.73 mmol)[10] and sodium azide (132 mg, 2.03 mmol) in DMSO (5 ml) was thermostated at 50-52 °C for 1h to afford 359 mg of the *ortho*-nitroazide **10a** as a yellow solid: IR $\tilde{\nu}$ 2115(s),

1628(m), 1597(m), 1525(s), 1464(s), 1343(s), 1301(s), 1260(m), 1183(w), 1055(m), 1004(m), 922(m), 820(m) cm^{-1}; ^1H NMR δ 6.17(s, 2H), 6.65(d, J=9Hz, 1H), 7.66(d, J=9Hz, 1H). Crude **10a** was heated in refluxing toluene (5 ml) for 20 min. Column chromatography (benzene) gave 267 mg (86% overall) of benzofuroxan **5a**: mp (orange needles) 110-111 °C; UV λ_{max} (ε) 421(4000), 333(8500), 320(7500), 307sh(5000), 277(3500), 224(24500), 209(20500) nm; IR $\tilde{\nu}$ 1634(s), 1589(s), 1507(m), 1488(m), 1420(w), 1290(s), 1071(m), 1042(m), 1007(w), 994(w), 908(w) cm^{-1}; ^1H NMR δ 6.23(s, 2H), 7.02(s, 2H). Anal. Calcd for $C_7H_4N_2O_4$: C, 46.68; H, 2.24; N, 15.55. Found: C, 46.61; H, 2.26; N, 15.46.

4-Nitro[1,3]dioxolo[2,3-e]-2,1,3-benzoxadiazole 1-Oxide (2a). Benzofuroxan **5a** (70 mg, 0.39 mmol) in acetic acid (2 ml) was treated with nitric acid (0.1 ml), 10 min. Column chromatography (ethyl ether) followed by evaporation of ether *in vacuo* at 15 °C furnished 18 mg (21%) of **2a** as a dark-red solid. Several attempts to recrystallize a sample at 40-50 °C failed, as **2a** isomerized rapidly to **1a**: UV λ_{max} (ε) 492 nm; IR $\tilde{\nu}$ 1640(w), 1620(w), 1588(w), 1552(m), 1535(w), 1358(w), 1317(s) cm^{-1}; ^1H NMR δ 6.39(s, 2H), 8.22(s, 1H); ^1H NMR (Me_2CO-d_6) δ 6.62(s, 2H), 8.46(s, 1H); MS m/z 225($M^{+\cdot}$). A partially rearranged sample gave correct combustion analysis.

6,7-Dihydro-4-nitro[1,4]dioxino[2,3-f]-2,1,3-benzoxadiazole 1-Oxide (1b). Benzofuroxan **4b** (243 mg, 1.25 mmol)[2a,6] in acetic acid (2 ml) was treated with nitric acid (0.5 ml), 0.5h. Recrystallization of the crude product from acetone:ethanol = 2:1 v:v at 60 °C afforded 242 mg (81%) of **1b** as orange rhombohedral crystals or leaflets: mp rearranges to **2b**; UV λ_{max} (ε) 406(7000), 352(6000), 337(6500), 321sh(5000), 226(20000), 207sh(15000) nm; IR (KBr) $\tilde{\nu}$ 1627(m), 1592(m), 1515(s), 1484(s), 1450(m), 1408(m), 1343(s), 1300(s), 1234(s), 1210(s), 1160(m), 1078(s), 1019(m), 967(m), 927(m), 878(m), 846(m), 782(m), 717(m) cm^{-1}; ^1H NMR (Me_2CO-d_6) δ 4.49-4.85 with maxima at 4.65, 4.71(m, 4H), 7.11(s, 1H). Anal. Calcd for $C_8H_5N_3O_6$: C, 40.18; H, 2.11; N, 17.57. Found: C, 40.22; H, 2.11; N, 17.54.

7,8-Dihydro[1,4]dioxino[2,3-e]-2,1,3-benzoxadiazole 1-Oxide (5b). Dinitrobenzodioxin **9b** (302 mg, 1.34 mmol)[10,11] and sodium azide (347 mg, 5.34 mmol) in DMSO (5 ml) were heated at 57-63 °C for 0.5h to give 297 mg of nitroazide **10b** as a pale yellow solid: IR (CCl_4) $\tilde{\nu}$ 2120(s), 2110(s),

1619(w), 1591(m), 1526(s), 1476(s), 1345(m), 1323(m), 1281(m), 1259(w), 1241(w), 1168(w), 1076(m), 977(w), 909(w), 873(w) cm^{-1}; ^1H NMR δ 4.39(s, 4H), 6.70(d, J=9Hz, 1H), 7.50(d, J=9Hz, 1H). Crude **10b** in toluene (5 ml) was heated at reflux for 2h to furnish 259 mg (100% overall) of **5b**: mp (yellow needles or leaflets) 157-158 °C; UV λ_{max} (ε) 393(4000), 326(7500), 313(7500), 300sh(5000), 225(25500), 209sh(15500) nm; IR $\tilde{\nu}$ 1622(s), 1596(s), 1502(s), 1457(m), 1319(w), 1276(s), 1257(m), 1232(m), 1172(w), 1099(m), 1074(s), 1004(m), 983(m) cm^{-1}; ^1H NMR δ 4.42(s, 4H), 6.87(s, 2H). Anal. Calcd for $C_8H_6N_2O_4$: C, 49.49; H, 3.12; N, 14.43. Found: C, 49.18; H, 2.98; N, 14.21.

7,8-Dihydro-4-nitro[1,4]dioxino[2,3-e]-2,1,3- benzoxadiazole 1-Oxide (2b). (a) From Nitration of Benzofuroxan 5b. Compound **5b** (122 mg, 0.628 mmol) in acetic acid (2 ml) was treated with nitric acid (0.5 ml), 0.5h, to furnish, after recrystallization, 126 mg (84%) of nitrobenzofuroxan **2b**: mp (Me_2CO, red granules) 197-199 °C; UV λ_{max}(ε) 459(9000), 333sh(1500), 303(3000), 227(17500), 207(15000) nm; IR (KBr) $\tilde{\nu}$ 1631(m), 1588(m), 1536 (m), 1516(m), 1502(m), 1437(s), 1400(m), 1310(s), 1244(s), 1223(s), 1132 (s), 1111(s), 1093(m), 1033(s), 996(s), 951(m), 943(m), 904(m), 861(m) cm^{-1}; ^1H NMR (Me_2CO-d_6) δ 4.59(m, 4H), 8.21(s, 1H). Anal. Calcd for $C_8H_5N_3O_6$: C, 40.18; H, 2.11; N, 17.57. Found: C, 39.89; H, 2.20; N, 17.39.

(b) From Isomerization of Nitrobenzofuroxan 1b. Compound **1b** (46 mg, 0.19 mmol) in toluene (5 ml) was heated at reflux for 10h. Column chromatography ($CHCl_3$) furnished 38 mg (83%) of **2b**. Similarly, **1b** (30 mg, 0.13 mmol) rearranged to **2b** (30 mg, 100%) after dry heating at 170-180 °C for 75 min.

Nitrobenzofuroxan **2b** (25 mg, 0.10 mmol) was recovered unreacted after refluxing in toluene for 4h.

7,8-Dihydro-5-nitro[1,4]dioxino[2,3-e]-2,1,3-benzoxadiazole 1-Oxide (3b). Trinitrobenzodioxin **6b** (181 mg, 0.668 mmol)[11] and sodium azide (173 mg, 2.66 mmol) in DMSO (3 ml) were heated at 51-54 °C for 0.5h to afford 139 mg of the dinitroazide **11b** as a yellow solid: IR $\tilde{\nu}$ 2120(s), 1588(m), 1526(s), 1465(w), 1445(w), 1339(s), 1313(m), 1267(w), 1251(w), 1147(w), 1079(m), 996(vw), 891(w), 870(w), 798(vw) cm^{-1}; ^1H NMR δ 4.55(s, 4H), 8.27(s, 1H). The crude azide **11b** was heated in refluxing toluene (3 ml) for 1h to give 124 mg (78% overall) of **3b**: mp (orange leaflets) 112-114 °C; UV λ_{max} (ε) 413(3000), 319(6000), 260sh(5500), 225(15500) nm;

IR $\tilde{\nu}$ 1618(s), 1600(m), 1543(s), 1500(m), 1457(m), 1367(m), 1343(m), 1319(m), 1280(m), 1121(m), 1093(s), 949(w) cm^{-1}; ^1H NMR δ 4.53(m, 4H), 7.55(s, 1H). Anal. Calcd for $C_8H_5N_3O_6$: C, 40.18; H, 2.11; N, 17.57. Found: C, 40.28; H, 2.11; N, 17.49.

7,8-Dihydro-4-nitro-6H-[1,4]dioxepino[2,3-f]-2,1,3-benzoxadiazole 1-Oxide (1c). Benzofuroxan **4c** (147 mg, 0.706 mmol)[2c] in acetic acid (2 ml) was treated with nitric acid (0.4 ml), 15 min. Evaporation of the solvent (ethyl ether) *in vacuo* at 15 °C afforded 128 mg (72%) of a yellow solid, identified as **1c**: mp rearranges to **2c**; UV λ_{max} (ε) 394(6500), 340 (5000), 221(20000) nm; IR $\tilde{\nu}$ 1631(s), 1598(s), 1542(s), 1535(s), 1488(m), 1365(m), 1350(m), 1320(s), 1254(m), 1057(m), 992(m) cm^{-1}; ^1H NMR δ 2.38 (qn, J=6Hz, 2H), 4.38(t, J=6Hz, 2H), 4.58(t, J=6Hz, 2H), 7.05(s, 1H). Anal. Calcd for $C_9H_7N_3O_6$: C, 42.70; H, 2.79; N, 16.60. Found: C, 42.61; H, 2.69; N, 16.69.

8,9-Dihydro-7H-[1,4]dioxepino[2,3-e]-2,1,3-benzoxadiazole 1-Oxide (5c). A mixture of dinitrobenzodioxepin **9c** (158 mg, 0.658 mmol)[10] and sodium azide (183 mg, 2.81 mmol) in DMSO (4 ml) was thermostated at 55-56 °C for 45 min to afford 155 mg of nitroazide **10c** as a pale-yellow solid: IR (CCl_4) $\tilde{\nu}$ 2125(s), 1590(m), 1528(s), 1478(s), 1461(m), 1437(m), 1347 (s), 1316(s), 1255(s), 1065(m), 1052(m), 1007(w), 992(w) cm^{-1}; ^1H NMR δ 2.29(qn, J=6Hz, 2H), 4.35(t, J=6Hz, 4H), 6.75(d, J=9Hz, 1H), 7.49(d, J=6Hz, 1H). Crude **10c** was heated in refluxing toluene (5 ml) for 1h to furnish 134 mg (98% overall) of **5c**: mp (yellow needles) 117-118 °C; UV λ_{max} (ε) 382(3000), 328(4000), 314(4000), 302sh(2500), 221(13500), 209sh (11000) nm; IR (CCl_4) $\tilde{\nu}$ 1618(s), 1592(m), 1544(w), 1500(s), 1387(w), 1231 (m), 1078(m), 1069(m), 1029(w), 994(w) cm^{-1}; ^1H NMR δ 2.31(qn, J=5.5Hz, 2H), 4.32(t, J=5.5Hz, 2H), 4.48(t, J=5.5Hz, 2H), 6.88(s, 2H). Anal. Calcd for $C_9H_8N_2O_4$: C, 51.93; H, 3.87; N, 13.46. Found: C, 51.90; H, 4.00; N, 13.36.

8,9-Dihydro-4-nitro-7H-[1,4]dioxepino[2,3-e]-2,1,3-benzoxadiazole 1-Oxide (2c). **(a) From Nitration of Benzofuroxan 5c.** Compound **5c** (116 mg, 0.557 mmol) in acetic acid (2 ml) was treated with nitric acid (0.3 ml), 15 min. Column chromatography (benzene) afforded 33 mg (23%) of **2c**: mp (ethanol:acetone 1:1 v:v, orange needles) 194-195 °C; UV λ_{max} (ε) 447(7000), 331sh(1000), 299(2500), 223(15500) nm; IR $\tilde{\nu}$ 1636(m), 1584(m), 1544(s), 1533(s), 1505(w), 1432(w), 1331(s), 1314(m), 1273(w), 1130(w),

1078(w), 992(w), 984(w) cm^{-1}; ^1H NMR δ 2.38(qn, J=6Hz, 2H), 4.43(t, J=6Hz, 2H), 4.62(t, J=6Hz, 2H), 8.11(s, 1H).

Anal. Calcd for $C_9H_7N_3O_6$: C, 42.70; H, 2.79; N, 16.60. Found: C, 42.77; H, 2.68; N, 16.46.

(b) From Isomerization of Nitrobenzofuroxan 1c. Compound 1c (26 mg, 0.10 mmol) was heated in refluxing toluene (2 ml) for 1h to afford 26 mg (100%) of 2c.

Nitrobenzofuroxan 2c (26 mg, 0.10 mmol) was recovered unreacted after refluxing in toluene (2 ml) for 4h.

8,9-Dihydro-5-nitro-7H-[1,4]dioxepino[2,3-e]-2,1,3-benzoxadiazole 1-Oxide (3c). Trinitrobenzodioxepin 6c (272 mg, 0.954 mmol)[2c] and sodium azide (295 mg, 4.54 mmol) in DMSO (5 ml) furnished, after 1h at room temperature, 241 mg of a yellow solid identified as 11c: IR $\tilde{\nu}$ 2120(s), 1590(s), 1532(s), 1450(w), 1345(s), 1322(s), 1251(w), 1150(vw), 1070(m), 1018(vw) cm^{-1}; ^1H NMR δ 2.41(qn, J=5.5Hz, 2H), 4.47(t, J=5.5Hz, 2H), 4.51(t, J=5.5Hz, 2H), 8.11(s, 1H). Crude 11c in toluene (5 ml) was heated at reflux for 1h and recrystallized to obtain 215 mg (89% overall) of 3c: mp (yellow granular plates) 128-130 °C; UV λ_{max} (ε) 392(4000), 333sh(5000), 320(5000), 309sh(5000), 259sh(5000), 221(17500) nm; IR $\tilde{\nu}$ 1617(s), 1542(s), 1498(m), 1453(w), 1380(w), 1358(w), 1317(w), 1258(w), 1194(vw), 1138(vw), 1098(m) 1082(m), 1032(vw), 957(vw) cm^{-1}; ^1H NMR δ 2.40(qn, J=6Hz, 2H), 4.43(t, J=6Hz, 2H), 4.58(t, J=6Hz, 2H), 7.42(s, 1H). Anal. Calcd for $C_9H_7N_3O_6$: C, 42.70; H, 2.79; N, 16.60. Found: C, 42.49; H, 2.73; N, 16.48.

7,8,9,10-Tetrahydro-6H-[1,4]dioxonino[2,3-f]-2,1,3-benzoxadiazole 1-Oxide (4e). A mixture of dinitrobenzodioxonin 7e (606 mg, 2.26 mmol)[10] and sodium azide (613 mg, 9.43 mmol) in DMSO (10 ml) was heated at 57-63 °C for 1h to obtain 596 mg of the nitroazide 8e as a pale-yellow semisolid: IR (CCl_4) $\tilde{\nu}$ 2115(s), 1630(w), 1610(w), 1590(w), 1570(m), 1523(s), 1493(s), 1322(s), 1297(s), 1243(s), 1182(w), 1068(w), 1055(w), 1024(w), 987(w), 970(w) cm^{-1}; ^1H NMR δ 1.85(m, 6H), 4.19(m, 2H), 4.58(m, 2H), 6.83(s, 1H), 7.71(s, 1H). Crude 8e was heated in refluxing toluene (18 ml) for 2h. Column chromatography followed by recrystallization furnished 525 mg (98% overall) of 4e: mp (pale-yellow needles) 73-74 °C; UV λ_{max} (ε) 376sh(7000), 361(8500), 335(7500), 319sh(6000), 304sh(4000), 229(22500), 211sh(16000) nm; IR (CCl_4) $\tilde{\nu}$ 1633(s), 1591(s), 1527(m), 1484(s), 1379(w), 1319(s), 1237(m), 1175(m), 1135(m), 1016(m), 993(w),

968(w), 916(w), 857(w) cm^{-1}; ^1H NMR δ 1.85(m, 6H), 4.28(m, 4H), 6.93(s, 2H). Anal. Calcd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.86. Found: C, 55.83; H, 4.99; N, 12.03.

7,8,9,10-Tetrahydro-4-nitro-6H-[1,4]dioxonino[2,3-f]-2,1,3-benzoxadiazole 1-Oxide (1e). Benzofuroxan **4e** (194 mg, 0.821 mmol) in acetic acid (2 ml) was treated with nitric acid (0.4 ml), 15 min. After work-up, the solvent (ethyl ether) was evaporated *in vacuo* at 15 °C to obtain 182 mg (79%) of a yellow solid, identified as nitrobenzofuroxan **1e**: mp (crude) 68-74 °C rapid heating; UV λ_{max} (ε) 390(5000), 338(5000), 305sh(3500), 223(17000) nm; IR $\tilde{\nu}$ 1630(m), 1597(m), 1543(m), 1536(m), 1489(w), 1355(w), 1315(s), 1252(w), 982(m) cm^{-1}; ^1H NMR δ 1.92(m, 6H), 4.30(t, J=4Hz, 2H), 4.61(t, J=4Hz, 2H), 7.11(s, 1H). Anal. Calcd for $C_{11}H_{11}N_3O_6$: C, 46.98; H, 3.94; N, 14.94. Found: C, 46.78; H, 3.94; N, 14.91.

8,9,10,11-Tetrahydro-7H-[1,4]dioxonino[2,3-e]-2,1,3-benzoxadiazole 1-Oxide (5e). Dinitrobenzodioxonin **9e** (359 mg, 1.34 mmol)[10] and sodium azide (350 mg, 5.38 mmol) in DMSO (6 ml) were thermostated at 57-60 °C for 45 min to furnish 354 mg of nitroazide **10e** as an orange semisolid: IR (CCl_4) $\tilde{\nu}$ 2115(s), 1613(w), 1589(m), 1580(m), 1525(s), 1474(m), 1442(m), 1347(m), 1317(s), 1252(m), 1070(w), 1016(m), 987(m) cm^{-1}; ^1H NMR δ 1.89 (m, 6H), 4.32(m, 4H), 6.82(d, J=9Hz, 1H), 7.55(d, J=9Hz, 1H). Crude **10e** in toluene (10 ml) was heated at reflux for 2h to afford 304 mg (96% overall) of **5e**: mp (yellow needles) 112-113 °C; UV λ_{max} (ε) 380(1500), 327(2500), 314(2500), 302sh(2000), 220(7000), 207sh(6000) nm; IR (CCl_4) $\tilde{\nu}$ 1614(s), 1594(m), 1499(s), 1372(w), 1312(w), 1228(m), 1063(m), 1029(m), 984(m) cm^{-1}; ^1H NMR δ 1.85(m, 6H), 4.44(t, J=5.5Hz, 2H), 4.61(t, J=5.5Hz, 2H), 6.81(d, J=9.5Hz, 1H), 6.97(d, J=9.5Hz, 1H). Anal. Calcd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.86. Found: C, 55.97; H, 4.99; N, 11.89.

8,9,10,11-Tetrahydro-4-nitro-7H-[1,4]dioxonino[2,3-e]-2,1,3-benzoxadiazole 1-Oxide (2e). (a) From Nitration of Benzofuroxan 5e. Compound **5e** (54 mg, 0.23 mmol) in acetic acid (1 ml) was treated with nitric acid (0.1 ml), 10 min to furnish 36 mg (56%) of **2e** which was purified further by column chromatography: mp (ethanol at 60 °C, orange needles) 122-123 °C; UV λ_{max} (ε) 446(10000), 337sh(1500), 300(3500), 223(22500) nm; IR $\tilde{\nu}$ 1632(m), 1585(s), 1531(s), 1504(m), 1430(m), 1331(s), 1309(s), 1138(w),

1076(w), 998(m) cm^{-1}; ^1H NMR δ 1.89(m, 6H), 4.33(t, J=4.5Hz, 2H), 4.83(t, J=4.5Hz, 2H), 8.16(s, 1H). Anal. Calcd for $C_{11}H_{11}N_3O_6$: C, 46.98; H, 3.94; N, 14.94. Found: C, 46.81; H, 3.81; N, 14.81.

(b) From Isomerization of Nitrobenzofuroxan 1e. Compound **1e** (57 mg, 0.20 mmol) in toluene (3 ml) was heated at reflux for 2h to obtain 57 mg (100%) of **2e**.

Nitrobenzofuroxan **2e** (57 mg, 0.20 mmol) was stable after refluxing in toluene (3 ml) for 4h.

6,7,8,9,10,11-Hexahydro[1,4]dioxecino[2,3-f]-2,1,3-benzoxadiazole 1-Oxide (4f). Dinitrobenzodioxecin **7f** (1217 mg, 4.31 mmol)[10] and sodium azide (1129 mg, 17.4 mmol) in DMSO (20 ml) were thermostated at 57-60 °C for 90 min to afford 1.20 g of nitroazide **8f** as a pale-yellow solid: IR (CCl_4) $\tilde{\nu}$ 2115(s), 1628(m), 1593(m), 1572(m), 1524(s), 1498(s), 1322(s), 1288(m), 1250(s), 1015(m), 922(w) cm^{-1}; ^1H NMR δ 1.32-2.01 with maxima at 1.61, 1.71(m, 8H), 4.02-4.43 with maxima at 4.11, 4.17, 4.20, 4.29(m, 4H), 6.86(s, 1H), 7.78(s, 1H). Crude **8f** in toluene (20 ml) was heated at reflux for 2h followed by recrystallization to furnish 1075 mg (100% overall) of **4f**: mp (light-brown needles) 109-110 °C; UV λ_{max} (ε) 375sh(4000), 361(5000), 332(5000), 318(5000), 304sh(3500), 224(16500), 208sh(12500) nm; IR (CCl_4) $\tilde{\nu}$ 1629(s), 1593(s), 1499(s), 1484(s), 1466(m), 1320(s), 1230(m), 1013(m), 1005(m), 921(w), 854(w) cm^{-1}; ^1H NMR δ 1.75(m, 8H), 4.18(m, 4H), 6.82(s, 2H). Anal. Calcd for $C_{12}H_{14}N_2O_4$; C, 57.59; H, 5.64; N, 11.19. Found: C, 57.59; H, 5.76; N, 11.14.

6,7,8,9,10,11-Hexahydro-4-nitro[1,4]dioxecino[2,3-f]-2,1,3-benzoxadiazole 1-Oxide (1f). Benzofuroxan **4f** (323 mg, 1.29 mmol) in acetic acid (3 ml) was treated with nitric acid (0.7 ml), 0.5h. After work-up, ethyl ether was evaporated *in vacuo* at 15 °C to furnish 285 mg (75%) of nitrobenzofuroxan **1f**: mp (ethanol:acetone = 3:1 v:v at 60 °C, orange granular plates) 141-142 °C (rearranged partly?); UV λ_{max} (ε) 391(6000), 331(5500), 224(20000) nm; IR $\tilde{\nu}$ 1632(m), 1595(s), 1545(s), 1524(m), 1486(m), 1353(m), 1313(s), 1269(w), 1008(w), 971(w) cm^{-1}; ^1H NMR δ 1.82(m, 8H), 4.29(m, 4H), 6.77(s, 1H). Anal. Calcd for $C_{12}H_{13}N_3O_6$: C, 48.82; H, 4.44; N, 14.23. Found: C, 48.95; H, 4.22; N, 14.22.

7,8,9,10,11,12-Hexahydro[1,4]dioxecino[2,3-e]-2,1,3-benzoxadiazole 1-Oxide (5f). Dinitrobenzodioxecin **9f** (707 mg, 2.50 mmol)[10] and sodium azide (664 mg, 10.2 mmol) in DMSO (12 ml) were thermostated at 55-58 °C

for 1h to give 697 mg of nitroazide **10f** as a pale-yellow solid: IR (CCl_4) $\tilde{\nu}$ 2115(s), 1612(w), 1590(m), 1577(m), 1525(s), 1467(m), 1348(m), 1320(m), 1312(m), 1262(m), 1227(w), 1025(m), 1007(w), 928(w) cm^{-1}; ^1H NMR δ 1.75(m, 8H), 4.10(t, J=5Hz, 2H), 4.24(t, J=5Hz, 2H), 6.78(d, J=9Hz, 1H), 7.66(d, J=9Hz, 1H). Crude **10f** was heated in refluxing toluene (15 ml) for 2.5h followed by recrystallization to afford 625 mg (100% overall) of **5f**: mp (yellow needles) 93-94 °C; UV λ_{max} (ε) 380(6500), 330(8500), 316(8000), 304sh(6000), 220(26500) nm; IR (CCl_4) $\tilde{\nu}$ 1614(s), 1589(m), 1494(s), 1321(w), 1218(m), 1168(w), 1084(w), 1041(m), 967(w) cm^{-1}; ^1H NMR δ 1.75(m, 8H), 4.25(t, J=4Hz, 2H), 4.50(t, J=4Hz, 2H), 7.04(s, 2H). Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.77; H, 5.79; N, 11.27.

7,8,9,10,11,12-Hexahydro-4-nitro[1,4]dioxecino[2,3-e]-2,1,3-benzoxadiazole 1-Oxide (2f). Benzofuroxan **5f** (92 mg, 0.37 mmol) in acetic acid (2 ml) was treated with nitric acid (0.1 ml), 20 min. Column chromatography (benzene) furnished 43 mg (40%) of nitrobenzofuroxan **2f**: mp (ethanol:acetone 2:1 v:v at 55 °C, orange needles) 121-123 °C (rearranged partly?); UV λ_{max} (ε) 442(9500), 298(3000), 221(22500) nm; IR $\tilde{\nu}$ 1631(m), 1583(m), 1532(s), 1502(w), 1427(w), 1332(s), 1128(w), 1083(w), 1003(w) cm^{-1}; ^1H NMR δ 1.78(m, 8H), 4.32(t, J=4Hz, 2H), 4.50(t, J=4Hz, 2H), 8.27(s, 1H). Anal. Calcd for $C_{12}H_{13}N_3O_6$: C, 48.82; H, 4.44; N, 14.23. Found: C, 48.61; H, 4.28; N, 14.31.

Interconversion of 1f and 2f. (a) **1f.** Nitrobenzofuroxan **1f** (93 mg, 0.31 mmol) in toluene (5 ml) was heated at reflux for 4 and 10h to obtain quantitatively mixtures of **1f:2f** = 45:55 and 43:57, respectively, as determined by ^1H NMR integration of the pseudoaromatic protons. Dry heating of **1f** at 150-160 °C for 1h furnished a mixture of **1f:2f** = 44:56.

(b) **2f.** Similarly, **2f** (39 mg, 0.13 mmol) in toluene (3 ml) was heated at reflux for 4h to afford quantitatively a mixture of **1f:2f** = 45:55.

ACKNOWLEDGEMENTS

We thank Mr. G.Barbaratsas for carrying out the combustion analyses and the referee for some assistance in nomenclature.

REFERENCES AND NOTES

1. Gasco, A.; Boulton, A.J. *Adv. Heterocyclic Chem.* **1981**, 29, 251. Paton, R.M. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A.R., Ed.; Pergamon Press: New York, 1984, Vol.6, p. 393. 'Sliwa, W.; Thomas, A. *Heterocycles* **1985**, 23, 399. Ghosh, P.B.; Ternai, B.; Whitehouse, M.W. *Med. Res. Rev.* **1981**, 1, 159.
2. (a) Hadjimihalakis, P.M. *J. Heterocycl. Chem.* **1976**, 13, 1327.
(b) Takakis, I.M.; Hadjimihalakis, P.M. *ibid.* **1990**, 27, 177.
(c) Hadjimihalakis, P.M. *ibid.* accepted.
(d) Takakis, I.M.; Hadjimihalakis, P.M. *ibid*, submitted.
3. Boulton, A.J.; Katritzky, A.R. *Proc. Chem. Soc.* **1962**, 257. Boulton, A.J.; Katritzky, A.R. *Rev. Chim. Acad. R.P. Roumanie* **1962**, 7, 691. Boulton, A.J.; Ghosh, P.B.; Katritzky, A.R. *Angew. Chem. Int. Ed. Engl.* **1964**, 3, 693.
4. Ghosh, P.B.; Whitehouse, M.W. *J. Med. Chem.* **1968**, 11, 305. Whitehouse, M.W.; Ghosh, P.B. *Biochem. Pharmacol.* **1968**, 17, 158. Ghosh, P.B.; Ternai, B.; Whitehouse, M.W. *J. Med. Chem.* **1972**, 15, 255.
5. Boulton, A.J.; Ghosh, P.B.; Katritzky, A.R. *J. Chem. Soc. B* **1966**, 1011. Ghosh, P.B. *ibid.* **1968**, 334. Hobin, T.P. *Tetrahedron* **1968**, 24, 6145. Boulton, A.J.; Brown, R.C. *J. Org. Chem.* **1970**, 35, 1662. Balasubrahmanyam, S.N.; Radhakrishna, A.S.; Boulton, A.J.; Thoe, K.-W. *ibid.* **1977**, 42, 897. Buncel, E.; Chuaqui-Offermans, N.; Norris, A.R. *Can. J. Chem.* **1979**, 57, 2512. Boulton, A.J.; Thoe, K.-W.; Balasubrahmanyam, S.N.; Mallick, I.M.; Radhakrishna, A.S. *J. Org. Chem.* **1980**, 45, 1653. Norris, W.P.; Chafin, A. *Heterocycles* **1984**, 22, 271.
6. Eswaran, S.V.; Sajadian,S.K. *J. Heterocycl. Chem.* **1988**, 25, 803.
7. Archer, A.W.; Claret, P.A.; Hayman, D.F. *J. Chem. Soc. B* **1971**, 1231. Menard, D.; St.-Jacques, M. *Can. J. Chem.* **1981**, 59, 1160.
8. Daukšas, V.K.; Purvaneckas, G.V.; Udrėnaitė, E.B.; Gineitytė, V.L.; Barauskaitė, A.V. *Heterocycles* **1981**, 15, 1395 and references therein.
9. Baddeley, G.; Smith, N.H.P. *J. Chem. Soc.* **1961**, 2516.
10. Takakis, I.M.; Hadjimihalakis, P.M. *J. Heterocycl. Chem.* accepted.
11. Heertjes, P.M.; Nijman-Knape, A.A.; Talsma, H,; Faasen, N.J. *J.Chem. Soc.* **1955**, 1313.