Derivatives of 3,4-Dihydro-2*H*-benzo[*b*][1,4]dioxepin. Preparation of 7,8-Dihydro-6*H*-[1,4]dioxepino[2,3-*f*]-2,1,3-benzoxadiazole 1-Oxide.

Phaedon M. Hadjimihalakis

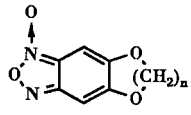
Laboratory of Organic Chemistry, University of Thessaloniki,
GR-540 06, Thessaloniki, Greece

Received January 4, 1991

A novel annelated benzofuroxan **4** and a benzofurazan **4a** have been prepared in good yields. Nitration of **5** afforded both trinitro derivatives **6** and **7**. Low temperature nmr spectroscopy was applied on compound **4** and the value ΔG^* is reported.

J. Heterocyclic Chem., **28**, 1111 (1991).

The synthesis of benzofuroxans annelated with a five-**A** [1], six-**B** [1,2], and eight-**C** [3] membered heterocyclic diether have already been reported.



	n
A	1
B	2
C	4

Benzofuroxans (2,1,3-benzoxadiazole 1-oxides) have found a wide spectrum of pharmacological and industrial applications [4,5].

We now wish to report the synthesis of the missing homologue, that with a seven-membered heterocyclic diether **4** for which a brief account has already been given [6]. This dioxepinofuroxan **4** was prepared by two methods; either by the oxidation of the *ortho*-aminonitro derivative **2** using alkaline hypochlorite according to the method of Green and Rowe [7a] in a moderate yield, or by thermolysis of the *ortho*-nitroazide **3** [1,8] in very good yield.

Both methods start from the 7,8-dinitro derivative **1** isolated during nitration of the 7-nitro derivative **5** [9].

Compound **5** [10] was directly nitrated with fuming nitric acid, at room temperature, to give both trinitro derivatives **6** and **7** which were separated by column chromatography.

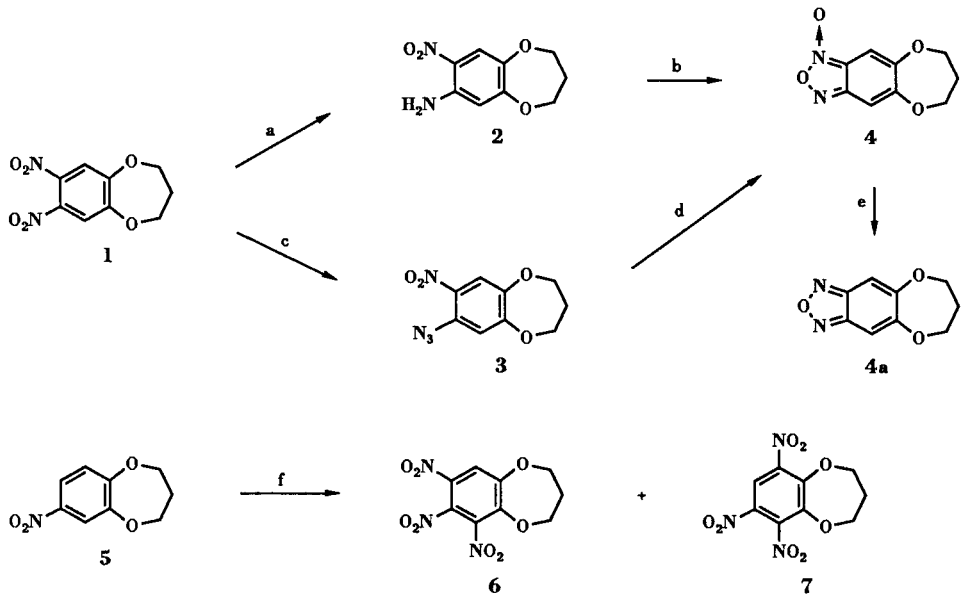
Conversion of **1** to 7-amino-8-nitro-3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin (**2**) was effected by heating **1** with concentrated aqueous ammonia and ethanol for 3 hours in a sealed tube, by analogy to the preparation of the lower homologue [11].

The furoxan **4** was deoxygenated to the corresponding furazan **4a** by treatment with triphenylphosphine.

Discussion of Spectra.

The nmr spectrum of the furoxan **4** in deuteriochloroform gives one sharp singlet (Figure 1a) at δ 6.97 for the two aromatic protons. However, at lower temperatures the signal becomes broad (Figure 1b,c), and at -19° the coalescence temperature Tc is reached (Figure 1d). As the temperature becomes lower two distinct singlets of almost

Scheme 1 [a]



[a] Reagents: a) NH_4OH, EtOH, Δ. b) OCl^-. c) NaN_3, DMSO. d) $C_6H_5CH_3$, Δ. e) PPh_3, Δ. f) HNO_3 (d = 1.52).

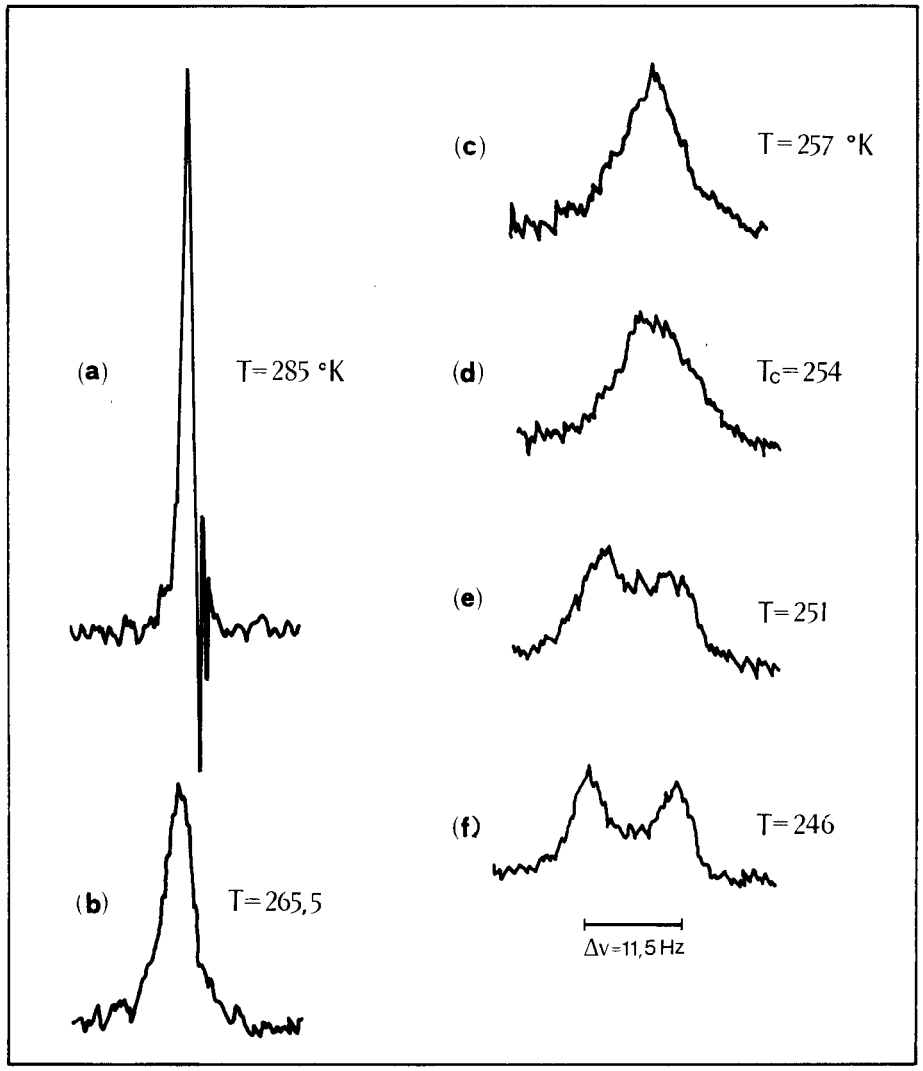


Figure 1. Influence of temperature on the nmr spectrum of furoxan **4**.

equal area are obtained corresponding to the two aromatic protons at δ 7.07 and δ 6.87 respectively (Figure 1f).

From the coalescence temperature for the fusion of these two signals, the free energy of activation ΔG^* (for the isomerization of the two furoxan forms) was determined to be 13.2 Kcal/mole. (The free energy of activation ΔG^* for the lower homologue **B** was found to be 13.1 Kcal/mole) [2].

EXPERIMENTAL

General.

Melting points were determined on a Gallenkamp or a Kofler hot-stage apparatus and are uncorrected. Thin layer chromatography (tlc) was performed on Merck Kieselgel 60 F_{254} (Art. 5715) precoated silica gel plates. Column chromatography was carried out on Merck Kieselgel 60, 70-230 mesh (Art. 7734). The mixtures were dissolved in a minimum amount of chloroform before they were placed on the column. The uv spectra (absolute ethanol solution) were obtained on a Shimadzu UV-210 A instrument. The ir spectra were recorded on a Perkin-Elmer 297 or 1310 infrared spectrophotometer. The ^{1}H nmr spectra were obtained on a Bruker Model AW 80 (80 MHz) nmr spectrometer in deuteriochloroform solution containing 2% tetramethylsilane as internal standard. Low temperature nmr spectra were obtained with a Varian Associates A-60 A (60 MHz) instrument. The mass spectra (ms) were taken at 70 eV on a Hitachi Perkin-Elmer Model RMU-6L single focusing mass spectrometer equipped with a direct inlet system, or on a VG TRITECH VGTS-250 instrument at low resolution. Fuming nitric acid refers to 100% (d = 1.52). Solutions were dried over anhydrous sodium sulfate for *ca.* 15 hours.

7-Amino-8-nitro-3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin (**2**).

7,8-Dinitro derivative **1** (0.51 g, 2.42 mmoles) [9], ammonium hydroxide (0.55 ml, d = 0.90, 27-30% in ammonia) and ethanol (2 ml) were heated in a sealed tube between 123-134° for 3 hours. The reaction mixture was filtered on a sintered glass funnel and

recrystallized from ethanol. The nmr spectrum showed that it contained a considerable amount of starting material. The red solid thus obtained was purified by column chromatography using silica gel. Elution with chloroform gave first the starting material **1** and then compound **2** (210 mg, 48%).

Compound **2** had mp (ethanol, orange-red crystals) 116-117°; ir (nujol): ν max 3492 (w), 3470 (m), 3360 (m), 1640 (w), 1585 (w), 1550 (w), 1395 (w), 1295 (m), 1245 (s), 1230 (s), 1210 (s), 1045 (m), 980 (m), 870 (w) cm^{-1}; ^1H nmr: δ 2.24 (qn, J = 6 Hz, 2H), 4.20 (t, J = 6 Hz, 2H), 4.37 (t, J = 6 Hz, 2H), 5.94 (br s, 2H, exchangeable), 6.37 (s, 1H), 7.83 (s, 1H); ms: m/z (% relative intensity) 210 ($M^{+\cdot}$, 100), 182 (2), 181 (3), 180 (4), 169 (9), 164 (7), 155 (4), 152 (4), 136 (23), 124 (6), 123 (7), 106 (6), 95 (8), 94 (24), 83 (6), 80 (7), 71 (10), 70 (10), 57 (16), 54 (13), 52 (18), 44 (17), 41 (42).

Anal. Calcd. for $C_9H_{10}N_2O_4$: C, 51.42; H, 4.80; N, 13.33. Found: C, 51.21; H, 4.75; N, 13.42.

7,8-Dihydro-6*H*-[1,4]dioxepino[2,3-*f*]-2,1,3-benzoxadiazole 1-Oxide (**4**).

A. By Oxidation of **2** with Hypochlorite [7].

To a solution of potassium hydroxide (60 mg, 1.06 mmoles) in ethanol (5 ml) was added the aminonitro derivative **2** (87 mg, 0.41 mmole) and the red solution was cooled to 0°. A commercial hypochlorite solution (*ca.* 3.5%) was added until the mixture was decolorized. Work up [7b] afforded **4** as fine gold-yellow needles (42 mg, 48%), mp (ethanol 70%) 155-156°.

B. By Thermolysis of the *ortho*-Nitroazide **3**.

The dinitro derivative **1** (526 mg, 2.190 mmoles), excess sodium azide (588 mg, 9.045 mmoles) and dimethyl sulfoxide (7 ml) were thermostated at 60-70° for 1 hour [1]. Work up with water and filtration gave 508 mg (98%) of crude azide **3**, as white needles.

Compound **3** had ^1H nmr: δ 2.26 (qn, J = 6 Hz, 2H), 4.26 (t, J = 6 Hz, 2H), 4.36 (t, J = 6 Hz, 2H), 6.84 (s, 1H), 7.68 (s, 1H).

Thermolysis of the azide **3** in toluene (6 ml) at 115-125° for 2 hours, afforded furoxan **4** (407 mg, 89% overall), mp (ethanol, gold-yellow needles) 153-154°; uv: λ max (ε) 366 (7000), 345 (6500), 320 sh (6000), 233 (17500), 219 sh (16000) nm; ir (chloroform): ν max 1632 (m), 1588 (m), 1522 (w), 1490 (m), 1481 (s), 1327 (s), 1315 (m), 1170 (w), 1130 (w), 1015 (w), 980 (w) cm^{-1}; ^1H nmr: δ 2.28 (qn, J = 6 Hz, 2H), 3.55 (t, J = 6 Hz, 4H), 6.97 (s, 2H); (at -27°, the singlet of the two aromatic protons splits into two signals of equal intensity at δ 7.07 and δ 6.87). ms: m/z (% relative intensity) 208 ($M^{+\cdot}$, 100), 192 ($M^{+\cdot}$ -O, 14), 164 (4), 163 (2), 148 ($M^{+\cdot}$ -N_2O_2, 50), 138 (4), 120 (20), 119 (48), 108 (5), 78 (8), 77 (4), 69 (17), 68 (18), 64 (11), 62 (23), 55 (40), 53 (11), 50 (37), 41 (64), 39 (20), 30 (16).

Anal. Calcd. for $C_9H_8N_2O_4$: C, 51.92; H, 3.87; N, 13.46. Found: C, 52.08; H, 4.00; N, 13.61.

7,8-Dihydro-6*H*-[1,4]dioxepino[2,3-*f*]-2,1,3-benzoxadiazole (**4a**).

A mixture of furoxan **4** (113 mg, 0.543 mmole) and triphenyl phosphine (159 mg, 0.606 mmole) in toluene (5 ml) was heated at reflux for 1 hour. Evaporation of the solvent *in vacuo* followed by column chromatography (elution with benzene) furnished furazan **4a** (101 mg, 97%), mp (ethanol, white prismatic needles) 103.5-105°; uv: λ max (ε) 299 (12000), 213 (13000) nm; ir (carbon tetrachloride): ν max 1495 (s), 1468 (w), 1337 (s), 1329 (s), 1268 (w), 1208 (s), 1158 (w), 1105 (w), 1052 (m), 1038 (m), 1001 (m), 983 (m), 945 (w), 878 (w), 853 (m) cm^{-1}; ^1H nmr: δ 2.26 (qn, J = 6 Hz, 2H), 4.33 (t, J = 6 Hz, 4H), 7.22 (s, 2H); ms: m/z (% relative intensity) 192 ($M^{+\cdot}$, 83), 164 (23), 163 (19), 152 (2), 135 (5), 134 (21), 124 (6), 122 (5), 106 (6), 104 (8), 92 (14), 83 (8), 79 (10), 78 (14), 77 (8), 76 (25), 69 (11), 68 (20), 67 (21), 64 (29), 55 (15), 53 (31), 41 (100), 39 (49), 30 (20).

Anal. Calcd. for $C_9H_8N_2O_3$: C, 56.25; H, 4.20; N, 14.58. Found: C, 56.34; H, 4.11; N, 14.52.

6,7,8- and 6,7,9-Trinitro-3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepins **6** and **7**.

To 7-nitro derivative **5** (0.71 g, 3.64 mmoles) [10], fuming nitric acid (6 ml) was slowly added at 25° while controlling the exotherm by means of an ice-bath. The mixture was stirred for a total of 1 hour, while the reaction was followed by tlc. It was decanted into a mixture of ice-water (~150 ml) and stirred for another hour. The precipitate was filtered with suction, washed with water and dried in the air (0.956 g, 92%). The solid was easily dissolved in acetone and gave two kinds of crystals. Tlc showed two components. Washing the crystals with chloroform and filtering in a sintered glass funnel gave colorless rhombohedral crystals of a pure compound **6** (320 mg, tlc one spot). From the mother liquor another crop of the same crystals were obtained (110 mg).

The new mother liquor contained both isomers **6** and **7** in equal quantities, as shown by tlc, and was subjected to column chromatography. Elution by a mixture of petroleum ether:ethyl acetate 4:1 (v:v) gave 232 mg of **7**, and after that elution with methylene chloride gave another 227 mg of **6**.

Compound **6** (657 mg, 63%) had mp (ethanol, off-white granules) 132.5-133.5°; ir (chloroform): ν max 1566 (s), 1552 (s), 1486 (w), 1461 (w), 1348 (m), 1335 (m), 1322 (m), 1297 (w), 1273 (w), 1060 (w), 991 (w), 856 (w), 822 (w) cm^{-1}; ^1H nmr: δ 2.40 (qn, J = 6 Hz, 2H), 4.49 (t, J = 6 Hz, 2H), 4.53 (t, J = 6 Hz, 2H), 7.75 (s, 1H); ms: m/z (% relative intensity) 285 ($M^{+\cdot}$, 100), 269 (1), 256 (2), 240 (1), 237 (5), 193 (4), 164 (2), 155 (5), 147 (6), 135 (3), 122 (5), 107 (9), 105 (7), 95 (7), 93 (15), 83 (10), 79 (11), 77 (46), 69 (8), 67 (11), 63 (8), 61 (14), 55 (21), 53 (16), 51 (10), 46 (11), 42 (16), 41 (55).

Anal. Calcd. for $C_9H_7N_3O_8$: C, 37.91; H, 2.47; N, 14.74. Found: C, 37.76; H, 2.47; N, 14.72.

Compound **7** (232 mg, 22%) had mp (ethanol, white needles) 119-120°; ir (chloroform): ν max 1606 (m), 1594 (m), 1567 (s), 1548 (s), 1483 (m), 1369 (m), 1338 (s), 1305 (m), 1268 (m), 1066 (m), 1056 (m), 1006 (w), 948 (w) cm^{-1}; ^1H nmr: δ 2.45 (qn, J = 6 Hz, 2H), 4.49 (t, J = 6 Hz, 2H), 4.62 (t, J = 6 Hz, 2H), 8.33 (s, 1H); ms: m/z (% relative intensity) 285 ($M^{+\cdot}$, 100), 269 (1), 256 (2), 240 (1), 193 (3), 165 (2), 164 (3), 135 (2), 122 (1), 107 (7), 105 (9), 97 (2), 95 (4), 93 (3), 77 (25), 63 (8), 62 (23), 53 (11), 46 (2), 42 (13), 41 (16).

Anal. Calcd. for $C_9H_7N_3O_8$: C, 37.91; H, 2.47; N, 14.74. Found: C, 38.12; H, 2.53; N, 14.91.

Acknowledgements.

The author wishes to thank G. Barbaratsas for carrying out the elemental microanalyses, D. Rigas for obtaining the mass spectra and G. G. Tsantali for technical assistance.

REFERENCES AND NOTES

[1] S. V. Eswaran and S. K. Sajadian, *J. Heterocyclic Chem.*, **25**, 803 (1988).

[2] P. M. Hadjimihalakis, *J. Heterocyclic Chem.*, **13**, 1327 (1976).

[3] I. M. Takakis and P. M. Hadjimihalakis, *J. Heterocyclic Chem.*,

27, 177 (1990).

[4] For comprehensive reviews see: [a] A. Gasco and A. J. Boulton, *Adv. Heterocyclic Chem.*, **29**, 251-340 (1981); [b] R. M. Paton, In Comprehensive Heterocyclic Chemistry, Vol **6**, A. R. Katritzky, ed, Pergamon Press, New York, 1984, pp 393-426.

[5] P. B. Ghosh, B. Ternai and M. W. Whitehouse, *Med. Res. Rev.*, **1**, 159 (1981).

[6] P. M. Hadjimihalakis, Proceedings, 9th Meeting of the Association of Greek Chemists, Athens, Greece, 1984, Vol **A**, p 102.

[7a] A. G. Green and F. M. Rowe, *J. Chem. Soc.*, **101**, 2452 (1912); [b] F. B. Mallory, *Org. Synth.*, **37**, 1 (1957).

[8] A. S. Bailey and J. R. Case, *Tetrahedron*, **3**, 113, (1958).

[9] I. M. Takakis and P. M. Hadjimihalakis, *J. Heterocyclic Chem.*, accepted.

[10] R. B. Thompson and T. Symon, *J. Am. Oil Chem. Soc.*, **33**, 414 (1956).

[11] P. M. Heertjes, A. A. Nijman-Knape, H. Talsma and N. J. Faasen, *J. Chem. Soc.*, 1313 (1955).