Preparation of Benzofuroxans and Benzofurazans of 2,3,4,5-Tetrahydrobenzo[*b*][1,4]dioxocin and Related Compounds

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The novel benzofuroxans **1d**, **2** and benzofurazans **3**, **4** have been prepared in good yields. Nitration of **5c** furnished the mononitro-derivatives **6a** and **6b** in the unusually high relative ratio **6a**:**6b** of 23:77. Direct nitration of **5c** or **6a** + **6b** afforded the unexpected dinitro-derivative **8b** as the major product along with the isomeric **8a**, **8c** and **8d**. Improvement in the yield of **5c** (to 86%) is reported.

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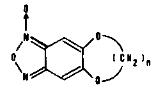
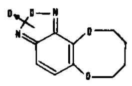
Benzofuroxans (2,1,3-benzoxadiazole-1-oxides) and benzofurazans (2,1,3-benzoxadiazoles) [1] have found a wide spectrum of pharmacological and industrial applications [1,2]. As a consequence, their synthesis is pursued with great interest. We have previously reported preparation of the dioxano annelated benzofuroxan **1b** [3] and have given a brief account on the dioxepino homolog **1c** [4]. Prompted by a recent report [5a] on the synthesis of the known homologous benzofuroxans **1a** [6] and **1b** [3], we describe herein convenient preparation of the novel benzofuroxans **1d**, **2** and benzofurazans **3**, **4** in good yields.

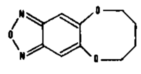


1



2

a, n = 1
b, n = 2
c, n = 3
d, n = 4



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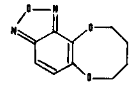
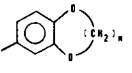


4

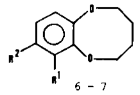
The starting benzodioxocin **5c** was furnished as described in the literature [7]. We note that with a few minor modifications in the initial procedure, we have reliably obtained 85-86% yields in one step as compared to 40% originally recorded [7b]. Conventional nitration with excess nitric acid afforded the isomeric mononitro derivatives **6a** and **6b** (86% isolated yield) in a relative ratio **6a**:**6b** of 23:77 as determined by analytical gc. This is the highest *ortho:para* (*i.e.*, Ar-α:Ar-β) ratio ever recorded in electrophylic aromatic substitution concerning homologous compounds of type **5** and is explicable in terms of deviations of the heterocyclic side ring and the benzene nucleus from coplanarity, in combination with the operation of the Mills-Nixon effect [8] which seems to decrease the reactivity at the *ortho*-position to a lesser extent than in **5a** or **5b**.

Enticed by the facile conversion of vicinal dinitroarenes to benzofuroxan rings [5] and also considering that nitration of **5a** [9a] or **5d** [9a] and **5b** [9b] or **5e** [9c] afford exclusively the 5,6- or 6,7-dinitro derivatives respectively, we carried out nitration of **5c** with fuming nitric acid expecting to obtain the analogous 8,9-dinitro compound **8d** as the major product. Our apparently reasonable expectations not materializing, the nitration of **5c** afforded **8d** in only 3% yield, along with **8a** (18%), **8b** (47%) and **8c** (4%). Similarly, nitration of the mononitro mixture **6** furnished **8a** (21%), **8b** (58%), **8c** (10%) and **8d** (5%). Differentiation between the positional isomers **8c** (δ 7.44, aromatic H) and **8d** (δ 7.51, aromatic H) was accomplished through conversion of each to the trinitro derivative **8e** (80% yield) or **8f** (77% yield) and comparison of the ^{1}H nmr spectra. The aromatic proton in **8e** is flanked between two nitro groups and is thus deshielded (δ 8.36) relative to that in **8f** (δ 7.71). We note that a previous attempt to prepare a product analogous to **8b** by direct nitration of the six-membered heterocycle **5b** was unfruitful [10]. A product of this type with the two nitro groups in a *meta*-arrangement was obtained from **5** for the first time; more important, it was furnished as the major reaction product.



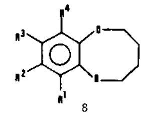
5

a, R=H, n=1
b, R=H, n=2
c, R=H, n=4
d, R=NO_2, n=1
e, R=NO_2, n=2



6 - 7

6a, R^1=NO_2, R^2=H
6b, R^1=H, R^2=NO_2
7a, R^1=NH_2, R^2=H
7b, R^1=H, R^2=NH_2

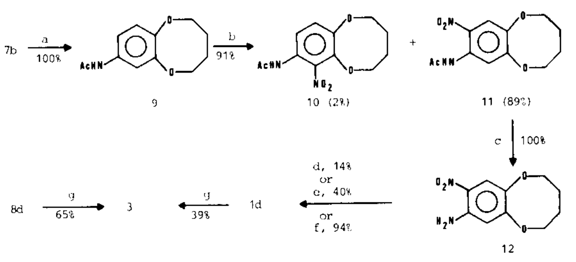


8

a, R^1=R^2=NO_2, R^3=R^4=H
b, R^1=R^3=NO_2, R^2=R^4=H
c, R^1=R^4=NO_2, R^2=R^3=H
d, R^1=R^4=H, R^2=R^3=NO_2
e, R^1=R^2=R^4=NO_2, R^3=H
f, R^1=R^2=R^3=NO_2, R^4=H

Preparation of the benzofuroxan **1d** was carried out through a series of reactions analogous to those previously reported for the synthesis of **1b** [3, 11]. Reduction of the mixture **6a** + **6b** afforded the amino derivatives **7a** (19%) and **7b** (61%), separated by column chromatography. The transformation of **7b** to **1d** and **3** is shown in Chart I. Method f for the conversion of **12** to **1d** seems to be superior to the two oxidation methods d and e. The benzofurazan **3** was also prepared from derivative **8d** according to a method described in the literature [15]. Thermolysis of the dinitro derivative **8a** in the presence of excess sodium azide [15] furnished the angular benzofurazan **4** in 75% yield (complete conversion). When the reaction was repeated using one equivalent of sodium azide and the time course was followed, tlc analysis indicated formation of a product with a lower R_f value than that of **4**, identified as the benzofuroxan, **2**. As the reaction proceeded, **2** was slowly deoxygenated to **4** so that the final mixture consisted of unreacted **8a** (73% conversion), **2** (30% based on converted **8a**) and **4** (47% based on converted **8a**). Thus this one-pot method is advantageous for the preparation of furazans, but care must be taken if one wishes to stop at the furoxan stage. Finally the benzofuroxan **2** was prepared in 90% yield by the recently reported method [5a].

Chart I [a]



[a] (a) Ac_2O; (b) HNO_3 (d = 1.52), HOAc; (c) H_3O^+; (d) $PhI(OAc)_2$, C_6H_6, 5h (ref 12); (e) OCl^-, KOH, 0 °C (ref 13); (f) $NaNO_2$, HCl, THF, 0 °C, followed by NaN_3, 0 °C, followed by thermolysis at 110-120 °C in ethylene glycol (ref 14); (g) NaN_3, ethylene glycol, 140-150 °C (ref 15).

In conclusion, we have accomplished material improvement in the preparation of the diether **5c**, provided some unexpected results in the nitration of **5c** and **6a** + **6b** and prepared in good yields the pharmacologically interesting benzofuroxans **1d** and **2** and benzofurazans **3** and **4**.

EXPERIMENTAL

General

Melting points were determined on a Gallenkamp melting point 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 column was eluted with a solution of petroleum ether (bp 65-71°): ethyl acetate of 4:1 (v:v). Analytical gas chromatography (gc) was performed on a Perkin-Elmer Model 990 gas chromatograph equipped with a flame ionization detector. Preparative gc was carried out on an Aerograph Model A-90-P gas chromatograph equipped with a thermal conductivity detector. A 5.6 ft x 1/8 in stainless steel column packed with 1.7 g of 5% SE-30 on Chromosorb W-HMDS (100/120 mesh) was used for the analytical determinations, whereas a 5.6 ft x ¼ in aluminum column packed with 7.0 g of 5% SE-30 on Chromosorb W-HMDS (100/120 mesh) was employed for the preparative separations. Helium was the carrier gas in both cases. The uv spectra (absolute ethanol solution) were obtained on a Perkin-Elmer Hitachi Model 200 instrument. The ir spectra (neat for liquids, KBr for solids) were recorded on a Perkin-Elmer Model 1430 infrared spectrophotometer. The ^1H nmr spectra were obtained on a Bruker Model AW 80 (80 MHz) nmr spectrometer in deuteriochloroform solution containing 2% tetramethylsilane as internal standard. 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. Nitric acid refers to the concentrated solution (65%, d = 1.42). Fuming nitric acid refers to 100% (d = 1.52) nitric acid. Solutions were dried over anhydrous sodium sulfate for *ca.* 15 hours. Exceptions to the above are noted.

2,3,4,5-Tetrahydrobenzo[*b*][1,4]dioxocin (**5c**).

This was prepared by a slightly modified Ziegler [7] procedure as follows: To a vigorously stirred mixture of anhydrous potassium carbonate (15 g, 109 mmoles) and isoamyl alcohol (800 ml) heated under vigorous reflux, was added a solution (100 ml) of 2-(4-bromobutoxy)phenol (8.9 g, 36 mmoles) [7] and isoamyl alcohol within 20 hours. The mixture was refluxed for an additional 3 hours and the solvent was removed by careful distillation at atmospheric pressure over a 2 ft Vigreux column. To the pot residue water (200 ml) was added and the mixture was extracted several times with ether. The ether solution was dried and concentrated to give an oily residue. The above reaction was repeated two more times (a total of 8.9 x 3 = 26.7 g, 108 mmoles were used) and the three residues were combined and distilled over a short Vigreux column to furnish **5c** (15.2 g, 85%) as a colorless viscous liquid, bp 122-126° (16 torr) (lit [7b], bp 112° (12 torr)). A different preparation afforded 15.4 g (86%). Analytical gc indicated >99% purity; ir: ν max 1594 (w), 1573 (w), 1486 (s), 1296 (m), 1237 (m), 1176 (w), 1093 (m), 1072 (m), 968 (m), 748 (m) cm^{-1}; ^1H nmr: δ 1.87 (m, 4H), 4.30 (m, 4H), 6.93 (s, 4H); the mass spectrum is similar to that reported [16].

7-and 8-Nitro-2,3,4,5-tetrahydrobenzo[*b*][1,4]dioxocin (**6a** and **6b**).

To benzodioxocin **5c** (2.34 g, 14.3 mmoles) nitric acid (8.0 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 and decanted into water (200 ml). The aqueous oily mixture was extracted several times with ethyl ether and the ether solution was washed with 5% sodium carbonate, dried and concentrated *in vacuo* to afford 2.56 g (86%) of a yellow oil. Analytical gc indicated this to be a mixture of **6a**:**6b** = 23:77 with **6a** having a smaller retention time. Separation of the two isomers by column chromatography was unsuccessful.

Analytical samples were obtained however, by preparative gc.

Compound **6a** had ir: ν max 1597 (w), 1567 (w), 1524 (s), 1472 (m), 1359 (m), 1290 (m), 1252 (m), 1083 (m), 985 (m), 787 (m), 731 (m) cm^{-1}; ^1H nmr: δ 2.00 (m, 4H), 4.44 (m, 4H), 6.84-7.41 with maxima at 6.96, 7.05, 7.06, 7.09, 7.12, 7.29, 7.31, 7.38 (m, 3H); ms: m/z (% relative intensity) 209 ($M^{+\cdot}$, 32), 166 (4), 155 (16), 120 (5), 109 (9), 107 (31), 79 (9), 65 (11), 63 (8), 55 (100).

Anal. Calcd. for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.19; H, 5.38; N, 6.61.

Compound **6b** had ir: ν max 1601 (w), 1576 (m), 1514 (s), 1487 (s), 1340 (s), 1310 (s), 1275 (s), 1257 (s), 1076 (m), 975 (m), 797 (w), 744 (m) cm^{-1}; ^1H nmr: δ 1.94 (m, 4H), 4.27 (t, J = 5 Hz, 2H), 4.58 (t, J = 5 Hz, 2H), 6.98 (d, J = 10 Hz, 1H), 7.76-7.99 with maxima at 7.81, 7.86, 7.89 (m, 2H); ms: m/z (% relative intensity) 209 ($M^{+\cdot}$, 30), 166 (3), 155 (15), 120 (4), 109 (8), 107 (30), 79 (9), 65 (11), 63

(7), 55 (100).

Anal. Calcd. for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.21; H, 5.51; N, 6.58.

7,8-, 7,9-, 7,10- and 8,9-Dinitro-2,3,4,5-tetrahydrobenzo[b][1,4]dioxocin (**8a**, **8b**, **8c** and **8d**).

The benzodioxocin **5c** (0.82 g, 5.0 mmoles) was slowly treated with fuming nitric acid (2.5 ml) while keeping the temperature between 0-10° by means of an ice bath. The mixture was stirred for a total of 2 hours and it was worked up as described above to obtain a yellow semisolid. Column chromatography afforded three fractions. The fraction eluted first was identified as **8c** (56 mg, 4%), the second fraction was **8b** (591 mg, 47%) and the third fraction was a mixture of **8a** + **8d** which was incompletely separated by fractional crystallization (ethanol) to give **8a** (first crop) and **8d** (second crop). Further purification of each crop by column chromatography using benzene to elute the column furnished pure **8a** (227 mg, 18%) and **8d** (36 mg, 3%). A mixture of the mononitrobenzodioxocins **6a** + **6b** (4.61 g, 22 mmoles) was nitrated similarly with fuming nitric acid (7.0 ml) to furnish **8c** (547 mg, 10%), **8b** (3.230 g, 58%), **8a** (1.156 g, 21%) and **8d** (282 mg, 5%).

Compound **8a** had mp (ethanol, cream leaflets) 123-124°; ir: ν max 1599 (m), 1574 (m), 1550 (s), 1530 (s), 1320 (s), 1280 (s), 1087 (w), 1054 (w), 1010 (w), 982 (m), 903 (w), 831 (w), 809 (w), 734 (w) cm^{-1}; ^{1}H nmr: δ 1.96 (m, 4H), 4.33 (t, J = 5 Hz, 2H), 4.66 (t, J = 5 Hz, 2H), 7.09 (d, J = 9 Hz, 1H), 7.90 (d, J = 9 Hz, 1H); ms: m/z (% relative intensity) 254 ($M^{+\cdot}$, 20), 211 (2), 200 (1), 165 (2), 120 (4), 119 (7), 106 (5), 80 (9), 78 (13), 77 (22), 64 (6), 63 (8), 62 (10), 57 (8), 55 (100).

Anal. Calcd. for $C_{10}H_{10}N_2O_6$: C, 47.25; H, 3.97; N, 11.02. Found: C, 47.18; H, 3.97; N, 11.02.

Compound **8b** had mp (ethanol, pale-yellow needles) 89-90°; ir: ν max 1593 (w), 1527 (s), 1372 (m), 1343 (m), 1310 (m), 1294 (m), 1231 (w), 1085 (w), 1016 (w), 950 (w), 922 (w), 745 (w) cm^{-1}; ^{1}H nmr: δ 2.02 (m, 4H), 4.35 (t, J = 5 Hz, 2H), 4.65 (t, J = 5 Hz, 2H), 7.98 (d, J = 3 Hz, 1H), 8.24 (d, J = 3 Hz, 1H); ms: m/z (% relative intensity) 254 ($M^{+\cdot}$, 25), 223 (2), 211 (2), 200 (1), 165 (3), 155 (2), 152 (3), 120 (2), 119 (3), 109 (3), 80 (3), 78 (5), 77 (4), 69 (7), 57 (8), 55 (100).

Anal. Calcd. for $C_{10}H_{10}N_2O_6$: C, 47.25; H, 3.97; N, 11.02. Found: C, 47.10; H, 4.19; N, 11.09.

Compound **8c** had mp (ethanol, yellow leaflets) 75-76°; ir: ν max 1607 (w), 1540 (s), 1360 (s), 1347 (s), 1279 (s), 1084 (w), 1014 (m), 925 (m), 849 (m), 807 (m), 730 (m) cm^{-1}; ^{1}H nmr: δ 2.04 (m, 4H), 4.51 (m, 4H), 7.44 (s, 2H); ms: m/z (% relative intensity) 254 ($M^{+\cdot}$, 21), 223 (1), 211 (2), 200 (4), 165 (2), 110 (3), 109 (2), 108 (3), 80 (6), 78 (5), 77 (5), 64 (6), 57 (4), 55 (100).

Anal. Calcd. for $C_{10}H_{10}N_2O_6$: C, 47.25; H, 3.97; N, 11.02. Found: C, 47.31; H, 4.12; N, 11.11.

Compound **8d** had mp (ethanol, off-white needles) 104-105°; ir: ν max 1600 (m), 1577 (m), 1550 (s), 1530 (s), 1495 (s), 1370 (m), 1323 (m), 1280 (m), 1261 (m), 1058 (w), 974 (m), 863 (w), 800 (w), 735 (w) cm^{-1}; ^{1}H nmr: δ 2.00 (m, 4H), 4.50 (m, 4H), 7.51 (s, 2H); ms: m/z (% relative intensity) 254 ($M^{+\cdot}$, 21), 223 (5), 211 (3), 167 (7), 165 (6), 155 (12), 119 (9), 111 (7), 109 (7), 97 (10), 95 (10) 85 (8), 83 (11), 81 (9), 71 (13), 69 (16), 57 (23), 55 (100).

Anal. Calcd. for $C_{10}H_{10}N_2O_6$: C, 47.25; H, 3.97; N, 11.02. Found: C, 47.01; H, 3.92; N, 10.99.

7,8,10-Trinitro-2,3,4,5-tetrahydrobenzo[*b*][1,4]dioxocin (**8e**).

Compound **8c** (30 mg, 0.12 mmole) was nitrated as above with fuming nitric acid (1 ml). After stirring for 30 minutes, the mixture was decanted into water (5 ml) and the solid was collected on a sintered glass funnel and washed with water to obtain 28 mg (80%), mp (ethanol, pale-yellow needles) 119-121°; ir: ν max 1595 (w), 1557 (s), 1534 (s), 1370 (m), 1342 (m), 1305 (m), 1281 (m), 1028 (w), 895 (w), 820 (w), 775 (w) cm^{-1}; ^{1}H nmr: δ 2.07 (m, 4H), 4.44 (t, J = 5 Hz, 2H), 4.77 (t, J = 5 Hz, 2H), 8.36 (s, 1H); ms: m/z (% relative intensity) 299 ($M^{+\cdot}$, 17), 254 (3), 119 (4), 109 (5), 107 (14, 97 (5), 95 (5), 91 (5), 83 (5), 81 (5), 77 (12), 69 (7), 67 (5), 57 (9), 55 (100).

Anal. Calcd. for $C_{10}H_9N_3O_8$: C, 40.14; H, 3.03; N, 14.04. Found: C, 40.06; H, 2.99; N, 14.00.

7,8,9-Trinitro-2,3,4,5-tetrahydrobenzo[*b*][1,4]dioxocin (**8f**).

Nitration of **8d** was identical in every respect to that described above for **8c** to obtain **8f** (27 mg, 77%), mp (ethanol, pale yellow needles) 101-103° C; ir: ν max 1600 (m), 1553 (s), 1534 (s), 1353 (s), 1349 (s), 1315 (s), 1296 (s), 1090 (m), 1007 (m), 934 (m), 881 (m), 817 (m), 705 (m) cm^{-1}; ^{1}H nmr: δ 2.03 (m, 4H), 4.55 (m, 4H), 7.71 (s, 1H); ms: m/z (% relative intensity) 299 ($M^{+\cdot}$, 10), 119 (2), 109 (2), 107 (2), 105 (2), 97 (3), 95 (3), 91 (2), 85 (2), 83 (4), 81 (3), 79 (4), 77 (13), 69 (5), 67 (4), 57 (7), 55 (100).

Anal. Calcd. for $C_{10}H_9N_3O_8$: C, 40.14; H, 3.03; N, 14.04. Found: C, 39.99; H, 3.04; N, 14.16.

7- and 8-Amino-2,3,4,5-tetrahydrobenzo[*b*][1,4]dioxocin (**7a** and **7b**).

A mixture of the nitro derivatives **6a** + **6b** (1.52 g, 7.27 mmoles), zinc dust (12.0 g, 184 mmoles), concentrated hydrochloric acid (2 ml) and water (50 ml) was thermostated at 80-90° for 0.5 hour. The mixture was filtered through a Büchner funnel and the solid was washed thoroughly with water. The acidic aqueous solution was neutralized by the slow addition of solid sodium carbonate, extracted with ethyl ether, and the ether solution was dried and concentrated *in vacuo*. Column chromatography of the residue furnished **7a** (first fraction, 242 mg, 19%) and **7b** (second fraction, 793 mg, 61%) as yellow viscous liquids. Repetition of the reaction using smaller quantities of zinc dust gave much lower yields.

Compound **7a** had ir: ν max 3455 (m), 3355 (m), 3180 (w), 1603 (s), 1478 (s), 1322 (s), 1248 (s), 1196 (s), 1081 (s), 1003 (s), 947 (s), 773 (s), 728 (m), cm^{-1}; ^{1}H nmr: δ 1.88 (m, 4H), 4.31 (m, 4H), 4.63 (br s, 2H, exchangeable), 6.29-6.94 with maxima at 6.52, 6.60, 6.69, 6.77 (m, 3H); ms: m/z (% relative intensity) 179 ($M^{+\cdot}$, 100), 162 (3), 150(6), 137 (47), 136 (29), 125 (82), 124 (51), 123 (10), 122 (12), 109 (10), 108 (11), 107 (12), 96 (45), 95 (28), 80 (16), 79 (46), 67 (37), 55 (54), 52 (28), 41 (44).

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.03; H, 7.38; N, 7.68.

Compound **7b** had ir: ν max 3430 (m), 3350 (m), 3220 (w), 1615 (m), 1497 (s), 1430 (m), 1310 (s), 1190 (s), 1160 (m), 1078 (m), 989 (s), 940 (m), 843 (m), 805 (m) cm^{-1}; ^{1}H nmr: δ 1.82 (m, 4H), 3.80 (s, 2H, exchangeable), 4.11 (t, J = 5 Hz, 2H), 4.35 (t, J = 5 Hz, 2H), 6.15-6.40 with a maximum at 6.33 (m, 2H), 6.77 (d, J = 9 Hz, 1H); ms: m/z (% relative intensity) 179 ($M^{+\cdot}$, 100), 150 (11), 137 (17), 136 (17), 125 (49), 124 (44), 123 (15), 122 (35), 109 (7), 108 (14), 107 (6), 96 (38), 95 (33), 80 (14), 79 (23), 67 (30), 55 (25), 52 (17), 41 (30).

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.12; H, 7.41; N, 7.81.

8-Acetamido-2,3,4,5-tetrahydrobenzo[*b*][1,4]dioxocin (**9**).

The aminodioxocin **7b** (2.34 g, 13 mmoles) was acetylated directly (not through its hydrochloride salt) [11] with acetic anhydride (7 ml) in the presence of sodium acetate trihydrate (3.51 g) to afford 2.90 g (100%) of crude **9**, mp (water at 50°, white leaflets) 73-74°; ir: ν max 3280 (w), 3245 (w), 3190 (w), 1656 (s), 1605 (s), 1553 (s), 1500 (s), 1412 (s), 1373 (m), 1284 (s), 1260 (s), 1197 (m), 1084 (m), 988 (m), 977 (m), 814 (w), 772 (w), 735 (w) cm^{-1}; ^{1}H nmr: δ 1.88 (m, 4H), 2.15 (s, 3H), 4.26 (m, 4H), 6.77-7.38 with major absorptions at 6.90, 6.97, 6.99, 7.16, 7.18, 7.34 (m, 3H), 7.85 (br s, 1H, exchangeable); ms: m/z (% relative intensity) 221 ($M^{+\cdot}$, 100), 179 (33), 178 (22), 150 (11), 137 (27), 136 (12), 125 (44), 124 (42), 123 (14), 122 (24), 109 (13), 96 (15), 95 (25), 80 (9), 79 (15), 77 (23), 67 (15), 57 (25), 55 (66), 52 (12), 43 (61), 41 (45).

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.01; H, 6.67; N, 6.11.

8-Acetamido-7-nitro- and 8-Acetamido-9-nitro-2,3,4,5-tetrahydrobenzo[*b*][1,4]dioxocin (**10** and **11**).

The acetamidodioxin **9** (1.26 g, 5.7 mmoles) in glacial acetic acid (10 ml) was treated with fuming nitric acid (0.40 ml) in glacial acetic acid (3 ml) according to a standard procedure [11]. After 60 minutes of stirring at room temperature, the mixture was poured into water (50 ml) and the yellow solid was collected on a Büchner funnel. This was identified as **11** (1.35 g, 89%). The mother liquor was neutralized by the careful addition of solid sodium carbonate and subjected to continuous extraction with ethyl ether for 10 hours. The ether solution was dried and concentrated *in vacuo* to give isomer **10** (30 mg, 2%).

Compound **10** had mp (ether, cream leaflets) 170-171°; ir: ν max 3210 (w), 1664 (s), 1538 (s), 1497 (s), 1373 (s), 1291 (s), 1266 (m), 1084 (w), 1041 (w), 995 (m), 985 (m), 821 (w) cm^{-1}; ^{1}H nmr: δ 1.94 (m, 4H), 2.11 (s, 3H), 4.38 (m, 4H), 7.07 (d, J = 9 Hz, 1H), 7.64 (d, J = 9 Hz, 1H), 7.79 (br s, 1H, exchangeable); ms: m/z (% relative intensity) 266 ($M^{+\cdot}$, 56), 224 (100), 220 (14), 178 (11), 170 (9), 169 (13), 152 (16), 125 (8), 124 (12), 123 (10), 122 (35), 121 (8), 109 (5), 108 (9), 107 (9), 95 (10), 80 (30), 59 (11), 55 (89), 52 (11), 43 (86), 41 (28).

Anal. Calcd. for $C_{12}H_{14}N_2O_5$: C, 54.13; H, 5.30; N, 10.52. Found: C, 54.05; H, 5.28; N, 10.43.

Compound **11** had mp (ethanol, yellow needles) 79-80°; ir: ν max 3355 (m), 1702 (s), 1618 (m), 1572 (s), 1503 (s), 1437 (s), 1301 (s), 1283 (s), 1264 (s), 1235 (s), 1086 (s), 983 (s), 902 (m), 871 (w), 690 (m) cm^{-1}; ^{1}H nmr: δ 1.88 (m, 4H), 2.29 (s, 3H), 4.17 (t, J = 5 Hz, 2H), 4.62 (t, J = 5 Hz, 2H), 7.87 (s, 1H), 8.28 (s, 1H), 10.37 (br s, 1H, exchangeable); ms: m/z (% relative intensity) 266 ($M^{+\cdot}$, 82), 224 (87), 220 (56), 178 (6), 170 (43), 169 (21), 152 (9), 150 (17), 137 (10), 136 (13), 125 (11), 124 (14), 123 (11), 122 (6), 121 (6), 109 (10), 105 (11), 95 (16), 94 (18), 69 (18), 67 (12), 57 (24), 55 (100), 52 (13), 43 (71), 41 (41).

Anal. Calcd. for $C_{12}H_{14}N_2O_5$: C, 54.13; H, 5.30; N, 10.52. Found: C, 54.05; H, 5.29; N, 10.46.

8-Amino-9-nitro-2,3,4,5-tetrahydrobenzo[*b*][1,4]dioxocin (**12**).

Acidic hydrolysis of the acetamido nitro compound **11** (1.95 g, 7.3 mmoles) with 36% hydrochloric acid (5.0 ml) in ethanol (10 ml) [11] furnished 1.64 g (~100%) of **12**, mp (50% aqueous ethanol, yellow needles) 104-105°; ir: ν max 3475 (m), 3350 (m), 1632 (m), 1585 (w), 1551 (m), 1495 (m), 1272 (m), 1246 (s), 1220 (s), 1215 (s), 1085 (m), 974 (m), 898 (w), 848 (w), 773 (w), 692 (w), cm^{-1}; ^{1}H nmr: δ 1.86 (m, 4H), 4.10 (t, J = 5 Hz, 2H), 4.64 (t, J = 5 Hz, 2H), 5.85 (br s, 2H, exchangeable), 6.28 (s, 1H), 7.81 (s, 1H); ms: m/z (% relative intensity) 224 ($M^{+\cdot}$, 100), 182 (5), 181 (5), 178 (3), 170 (37), 169 (21), 153 (8), 152 (6), 150 (13), 136 (21), 124 (17), 123 (12), 119 (9), 95 (11), 94 (26), 91 (14), 80 (6), 66 (4), 57 (9), 55 (75), 52 (14), 43 (12), 41 (20).

Anal. Calcd. for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.49. Found: C, 53.78; H, 5.39; N, 12.46.

[1,4]Dioxocino[2,3-*f*]-6,7,8,9-tetrahydro-2,1,3-benzoxadiazole 1-oxide (**1d**).

A. By Oxidation of **12** with Iodosobenzenediacetate [12].

A mixture of **12** (84 mg, 0.37 mmole) and iodosobenzenediacetate (208 mg, 0.65 mmole) in benzene (30 ml) was stirred at room temperature for 5 hours to furnish, after column chromatography, the benzofuroxan **1d** (12 mg, 14%).

B. By Oxidation of **12** with Hypochlorite [13].

To a solution of potassium hydroxide (53 mg, 0.95 mmole) in ethanol (2 ml) was added the aminonitro derivative **12** (200 mg, 0.89 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 [13] afforded **1d** as a yellow solid (80 mg, 40%).

C. By Thermolysis of the *ortho*-Nitroazide of **12** [14].

The *ortho*-aminonitro compound **12** (966 mg, 4.30 mmoles) in THF (5 ml) was diazotized and the diazonium salt was treated *in situ* with sodium azide as described in the literature [14] to obtain 1.09 g of a red-brown oil which solidified on standing at room temperature; ir: ν max 2108 cm^{-1}. Thermolysis of this in ethylene glycol (5 ml) at 110-120° for 1 hour afforded furoxan **1d** (897 mg, 94% overall), mp (ethanol, pale-yellow needles) 112-113°. uv: λ max (ϵ) 371 (5500), 361 sh (5000), 340 (5000), 325 sh (4500), 229 (26000), 211 sh (19000) nm; ir: ν 1629 (s), 1588 (s), 1524 (s), 1485 (s), 1326 (s), 1257 (w), 1219 (m), 1166 (m), 1015 (m), 969 (s), 926 (w), 870 (w), 742 (w) cm^{-1}; ^{1}H nmr: δ 1.93 (m, 4H), 4.36 (m, 4H), 6.93 (s, 2H); ms: m/z (% relative intensity) 222 ($M^{+\cdot}$, 33), 206 (2), 180 (3), 168 (5), 162 (5), 119 (14), 109 (4), 108 (5), 105 (7), 97 (5), 95 (5), 69 (9), 57 (9), 55 (100), 50 (12), 43 (11), 41 (16).

Anal. Calcd. for $C_{10}H_{10}N_2O_4$: C, 54.06; H, 4.54; N, 12.61. Found: C, 54.10; H, 4.65; N, 12.71.

[1,4]Dioxocino[2,3-*f*]-6,7,8,9-tetrahydro-2,1,3-benzoxadiazole (**3**).

A. From **1d**.

The furoxan **1d** (100 mg, 0.45 mmole), sodium azide (40 mg, 0.62 mmole) and ethylene glycol (3 ml) were thermostated at 140-150° for 0.5 hour to obtain, after column chromatography 36 mg (39%) of the furazan **3**.

B. From **8d**.

The dinitro compound **8d** (212 mg, 0.83 mmole), sodium azide (125 mg, 2.34 mmoles) and ethylene glycol (5 ml) were thermostated at 140-150° for 1 hour [15] to give 111 mg (65%) of **3** mp (ethanol, off-white rhombohedral crystals) 109-110°; uv: λ max (ϵ) 324 sh (4000), 295 (7500), 214 (19000) nm; ir: ν max 1534 (w), 1499 (s), 1335 (s), 1241 (m), 1198 (s), 1072 (m), 1000 (m), 970 (m), 927 (m), 862 (m), 845 (m), 748 (w) cm^{-1}; ^{1}H nmr: δ 1.95 (m, 4H), 4.39

(m, 4H), 7.25 (s, 2H); ms: m/z (% relative intensity) 206 ($M^{+\cdot}$, 27), 164 (7), 163 (6), 152 (5), 134 (7), 76 (7), 69 (6), 68 (5), 67 (6), 57 (6), 55 (100), 53 (11), 43 (7), 41 (16).

Anal. Calcd. for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.01; H, 4.91; N, 13.39.

[1,4]Dioxocino[2,3-*e*]-5,6,7,8-tetrahydro-2,1,3-benzoxadiazole (**4**) and its 1-Oxide (**2**).

A. Mixture of **4** and **2**.

The dinitro derivative **8a** (1.01 g, 3.96 mmoles), sodium azide (261 mg, 4.02 mmoles) and ethylene glycol (10 ml) were thermostated at 140-150° for 1 hour [15]. Work-up with water followed by column chromatography gave three fractions identified as furazan **4** (first fraction, 279 mg, 47% based on converted **8a**), furoxan **2** (second fraction, 192 mg, 30% based on converted **8a**) and starting material **8a** (third fraction, 273 mg, 73% conversion).

B. Pure **4**.

The dinitro derivative **8a** (240 mg, 0.94 mmole), excess sodium azide (200 mg, 3.08 mmoles) and ethylene glycol (5 ml) were thermostated at 140-150° for 2 hours [15] to give furazan **4** (147 mg, 75%), mp (ethanol, off-white large rhombohedral crystals) 71-72°; uv: λ max (ϵ) 346 (3000), 292 sh (2000), 280 (3000), 272 sh (3000), 218 (18000) nm; ir: ν max 1620 (s), 1548 (s), 1450 (s), 1363 (m), 1282 (s), 1255 (s), 1114 (s), 990 (s), 929 (m), 845 (m), 820 (m), 770 (m), 682 (m), 648 (m) cm^{-1}; ^1H nmr: δ 1.98 (m, 4H), 4.52 (m, 4H), 7.06 (d, J = 10 Hz, 1H), 7.38 (d, J = 10 Hz, 1H); ms: m/z (% relative intensity) 206 ($M^{+\cdot}$, 37), 164 (3), 163 (3), 152 (20), 134 (3), 122 (2), 104 (11), 80 (8), 76 (7), 64 (7), 55 (100), 53 (7), 41 (20).

Anal. Calcd. for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.11; H, 4.74; N, 13.31.

C. Pure **2**.

The dinitro derivative **8a** (241 mg, 0.95 mmole), excess sodium azide (428 mg, 6.59 mmoles) and dimethyl sulfoxide (4.3 ml) were thermostated at 60-70° for 40 minutes [5a]. Work-up with water and extraction with ether gave 267 mg of the azide as a yellow semisolid. Ethylene glycol (5 ml) was added to this and the mixture was thermostated at 120-130° for 1 hour. Work-up with water gave 189 mg (90% overall) of furoxan **2**, mp (ethanol, yellow needles) 114-115°; uv: ν max (ϵ) 379 (4000), 327 (6500), 314 (6500), 304 sh (4000), 221 (18000) nm; ir: ν max 1615 (s), 1500 (s), 1316 (m), 1295 (m), 1285 (m), 1250 (m), 1232 (m), 1178 (m), 1089 (m), 1040 (m), 1003 (m), 984 (m), 922 (m), 810 (m), 710 (w), 670 (w), 637 (w) cm^{-1}; ^1H nmr: δ 1.94 (m, 4H), 4.49 (m, 4H), 6.34-7.54 with maximum at 6.93 (m, 2H); ms: m/z (% relative intensity) 222 ($M^{+\cdot}$, 61), 206 (1), 180 (2), 168 (5), 162 (12), 123 (5), 120 (15), 119 (11), 108 (8), 94 (5), 91 (6), 80 (9), 79 (5), 78 (11), 77 (7), 64 (8), 62 (7), 55 (100), 53 (7), 41 (18).

Anal. Calcd. for $C_{10}H_{10}N_2O_4$: C, 54.06; H, 4.54; N, 12.61. Found: C, 54.09; H, 4.73; N, 12.89.

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