[Chem. Pharm. Bull. 28(6)1909—1912(1980)]

Synthesis of Bisfurazanobenzo-2,1,3-thiadiazole and Related Compounds

Toshio Uno, Kaname Takagi,[1a] and Munemitsu Tomoeda[1b]

Kampoh Research Laboratories, Kanebo Co., Ltd.[1a] *and Eisai Co., Ltd.*[1b]

(Received December 18, 1979)

Nitration of 4,7-dibromobenzo-2,1,3-thiadiazole (I) with fuming nitric acid afforded 4,7-dibromo-5,6-dinitrobenzo-2,1,3-thiadiazole (II) and, unexpectedly, the tribromo derivative: $C_6Br_3N_3O_2S$ (III). Compound II was readily converted by treatment with sodium azide into bisfuroxanobenzo-2,1,3-thiadiazole (IV), which was reduced with triethylphosphite to give bisfurazanobenzo-2,1,3-thiadiazole (VII). Compound VII was also synthesized starting from 4-bromo-6,7-(2′,1′,3′-oxadiazole)benzo-2,1,3-thiadiazole (VIII). Reduction of VII with sodium hydrosulfite gave 4,5-diamino-6,7-(2′,1′,3′-oxadiazole)-benzo-2,1,3-thiadiazole (XI), which was cyclized to 4,5-(2′,1′,3′-oxadiazole)benzo[1,2-*c*: 3,4-*c*′]bis[1,2,5]thiadiazole (XII) by treatment with N-sulfinylaniline. The transformation of XII to benzo[1,2-*c*: 3,4-*c*′: 5,6-*c*″]tris[1,2,5]thiadiazole (XIV), *via* 4,5-diaminobenzo-[1,2-*c*: 3,4-*c*′]bis[1,2,5]thiadiazole (XIII), is also described.

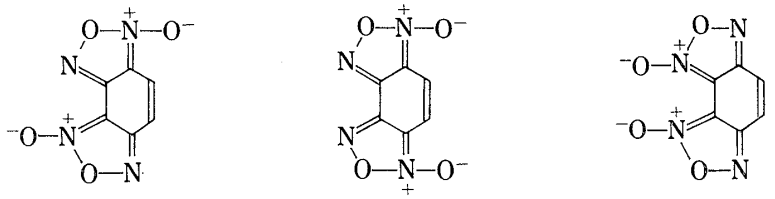
Keywords——bisfuroxanobenzo-2,1,3-thiadiazole; bisfurazanobenzo-2,1,3-thiadiazole; 4,5-(2′,1′,3′-oxadiazole)benzo[1,2-*c*: 3,4-*c*′]bis[1,2,5]thiadiazole; nitration of bromobenzo-2,1,3-thiadiazoles; benzo[1,2-*c*: 3,4-*c*′: 5,6-*c*″]tris[1,2,5]thiadiazole

In the previous paper,[2] we described a new method for synthesizing furazanobenzo-2,1,3-thiadiazole, which has vasodilatory and hypotensive activities, and some chemical reactions of this tricyclic ring system. In connection with this study, we now wish to report the synthesis of bisfurazanobenzo-2,1,3-thiadiazole and related tetracyclic compounds starting from 4,7-dibromobenzo-2,1,3-thiadiazole (I).

It has been reported that the nitration of I with nitric acid (*d* 1.42) in concentrated sulfuric acid at 5° gives exclusively 4,7-dibromo-5-nitrobenzo-2,1,3-thiadiazole.[2,3] However, when I was treated with a mixture of fuming nitric acid (*d* 1.52) and concentrated sulfuric acid at 0—5°, the following two products were isolated: 4,7-dibromo-5,6-dinitrobenzo-2,1,3-thiadiazole (II, 20% yield) and, unexpectedly, the tribromo derivative, $C_6Br_3N_3O_2S$ (III, 19% yield). The latter compound did not correspond to 5-nitro-4,6,7-tribromobenzo-2,1,3-thiadiazole, prepared by Pesin *et al.*[4] The formation of III might be due to the bromine cation, produced by the partial oxidative decomposition of I under the influence of fuming nitric acid. Analogous results in the nitration of I by heating in 70% nitric acid have been reported.[5]

Treatment of II with sodium azide in acetone–methanol gave 4,5-(2′,1′,3′-oxadiazole-1′-oxide)-6,7-(2′,1′,3′-oxadiazole-1′-oxide)benzo-2,1,3-thiadiazole (bisfuroxanobenzo-2,1,3-thiadiazole) (IV) in 79% yield, presumably *via* the azido compound (V), which was not isolated. Boulton *et al.*[6] showed that furoxanobenzofuroxane could exist in three isomeric forms, VIa, VIb and VIc, of which VIc was expected to be sterically highly unfavorable (Chart 1). Therefore, it is possible that bisfuroxanobenzo-2,1,3-thiadiazole IV also exists in two interconvertible forms, IVa and IVb. Reduction of IV using triethylphosphite in ethanol afforded 4,5-(2′,1′,3′-

1) Location: *a) 1-3-80, Tomobuchi-cho, Miyakojima-ku, Osaka, 534, Japan*; *b) 4, Koishikawa, Bunkyo-ku, Tokyo, 112, Japan.*
2) T. Uno, K. Takagi, and M. Tomoeda, *Chem. Pharm. Bull.*, **26**, 3896 (1978).
3) V.G. Pesin, A.M. Khaletskii, and V.A. Sergeev, *Zh. Obshch. Khim.*, 33, 1759 (1963) [*Chem. Abstr.*, **60**, 1734 (1964)].
4) V.G. Pesin and V.A. Sergeev, *Khim. Geterotsikl. Soedin*, **1967**, 839 [*Chem. Abstr.*, **68**, 105110 (1968)].
5) K. Pilgram and M. Zupan, *J. Org. Chem.*, **36**, 207 (1971).
6) A.J. Boulton, A.C. Gripper Gray, and A.R. Katritzky, *J. Chem. Soc.*, **1965**, 5958.



VIa VIb VIc

Chart 1

oxadiazole)-6,7-(2′,1′,3′-oxadiazole)benzo-2,1,3-thiadiazole (bisfurazanobenzo-2,1,3-thiadiazole) (VII) in 86% yield (Chart 2).

On the other hand, we also synthesized VII starting from 4-bromo-6,7-(2′,1′,3′-oxadiazole)benzo-2,1,3-thiadiazole (VIII), prepared in our previous work.[2] Nitration of VIII afforded 4-bromo-5-nitro-6,7-(2′,1′,3′-oxadiazole)-benzo-2,1,3-thiadiazole (IX), which was readily converted by treatment with sodium azide to 6,7-(2′,1′,3′-oxadiazole)-4,5-(2′,1′,3′-oxadiazole-1′-oxide)benzo-2,1,3-thiadiazole (X; this compound may also exist in two forms,

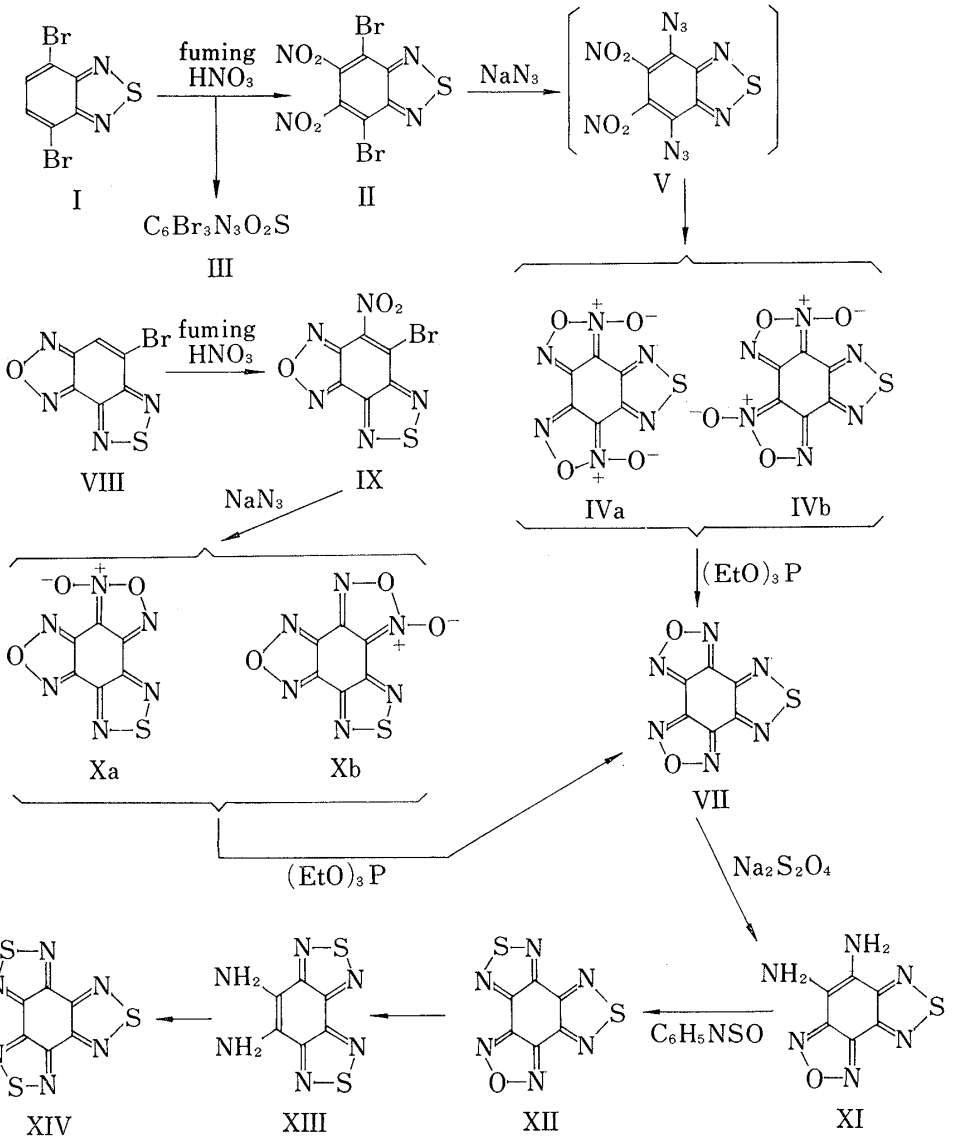


Chart 2

Xa and Xb). Subsequently, X was reduced to VII with triethylphosphite in ethanol (Chart 2).

It is known that the reduction of benzofurazans with sodium hydrosulfite or by catalytic hydrogenation induces a cleavage of the oxadiazole ring to give *o*-phenylenediamine derivatives.[2,7] Our attempt to reduce VII with sodium hydrosulfite in ethanol–water resulted in cleavage of the oxadiazole ring of VII, giving 4,5-diamino-6,7-(2′,1′,3′-oxadiazole)benzo-2,1,3-thiadiazole (XI) which was cyclized into 4,5-(2′,1′,3′-oxadiazole)benzo[1,2-*c*: 3,4-*c*′]-bis[1,2,5]thiadiazole (XII) with N-sulfinylaniline[8] in pyridine. Analogously, XII was reduced with sodium hydrosulfite to give 4,5-diaminobenzo[1,2-*c*: 3,4-*c*′]bis[1,2,5]thiadiazole (XIII) which had previously been prepared by Komin *et al.*[9] from 4-nitro-5-amino[1,2-*c*: 3,4-*c*′]-bis[1,2,5-]thiadiazole. On treatment with N-sulfinylaniline, the diamine XIII was converted to benzo[1,2-*c*: 3,4-*c*′: 5,6-*c*″]tris[1,2,5]thiadiazole (XIV). The infrared spectrum of our XIV is identical with that of benzotris[1,2,5]thiadiazole XIV synthesized from alkoxybenzenes and tetrasulfur tetranitride by Mataka *et al.*[10]

The mass spectra of VII and XII showed intense molecular ion peaks and several fragment peaks, among which M—30^{+} (loss of NO) is characteristic of the furazan ring.[11] The structures of all the new compounds described herein were deduced from their elemental analysis and spectral data.

Experimental[12]

4,7-Dibromo-5,6-dinitrobenzo-2,1,3-thiadiazole (II)——Compound I (20 g, 0.068 mol) was added in small portions to a mixture of conc. sulfuric acid and fuming nitric acid (*d* 1.52) (1:1, 200 ml) with stirring at 0—5° over 30 min. After stirring for 2 hr at room temperature, the mixture was poured into ice-water, and the precipitate was collected by filtration, washed with water, dried *in vacuo* and chromatographed on a silica gel column (Merck Kieselgel 60, 240 g) with benzene–cyclohexane (1:1, 970 ml). The eluate was concentrated and the residue was recrystallized from acetone–water to yield 2.1 g (19%) of the tribromo compound III. Further elution with benzene–cyclohexane (1:1, 790 ml) gave, after concentration, a yellow residue which was recrystallized from 95% ethanol with Norit to give 2.0 g (20%) of II.

Compound III, colorless plates, mp 170—171°. *Anal.* Calcd for $C_6Br_3N_3O_2S$: C, 17.25; N, 10.06. Found: C, 17.55; N, 9.94. IR ν_{max}^{KBr} cm^{-1}: 1629 (C=N), 1529 (C=C), 1442, 1373, 1359 (NO_2). MS *m/e*: 421, 419, 417, 415 (M^+).

Compound II, pale yellow plates, mp 202—203.5°. *Anal.* Calcd for $C_6Br_2N_4O_4S$: C, 18.77; N, 14.59. Found: C, 19.00; N, 14.40. IR ν_{max}^{KBr} cm^{-1}: 1632 (C=N), 1560 (C=C), 1458, 1378 (NO_2). MS *m/e*: 386, 384, 382 (M^+).

Bisfuroxanobenzo-2,1,3-thiadiazole (IV)——A solution of 143 mg (2.2 mmol) of sodium azide in acetone–methanol–water (1:2:1, 8 ml) was added dropwise to a solution of 384 mg (1 mmol) of II in acetone–methanol (1:1, 20 ml) with stirring at room temperature for 10 min (the light yellow azido compound V separated as a crystalline solid; IR ν_{max}^{KBr} cm^{-1}: 2130 (N_3)). The mixture was then heated at 60—65° for 30 min. The deep orange solution was concentrated *in vacuo* and poured into water (20 ml). The precipitate was collected by filtration, washed with water, dried *in vacuo* and recrystallized from benzene–cyclohexane (1:1) to yield 199 mg (79%) of IV, mp 154—155°. *Anal.* Calcd for $C_6N_6O_4S$: C, 28.58; N, 33.33. Found: C, 28.69; N, 33.42. IR ν_{max}^{KBr} cm^{-1}: 1626 (C=N), 1547 (C=C), 1499, 1476. MS *m/e*: 252 (M^+).

Bisfurazanobenzo-2,1,3-thiadiazole (VII)——A solution of 330 mg (1.3 mmol) of IV and 1 ml of triethylphosphite in ethanol (30 ml) was heated at 130—140° in a sealed tube for 16 hr. The reaction mixture was then concentrated *in vacuo* and the residue was chromatographed on a silica gel column (45 g) with benzene

7) V. Ceré, D. Dal Monte, and E. Sandri, *Tetrahedron*, **28**, 3271 (1972); W. Borsch and R. Weber, *Ann.*, **489**, 270 (1931).
8) K. Pilgram, *J. Heterocycl. Chem.*, **11**, 835 (1974); K. Pilgram and R.D. Skiles, *J. Heterocycl. Chem.*, **11**, 777 (1974).
9) A.P. Komin and M. Carmack, *J. Heterocycl. Chem.*, **12**, 829 (1975).
10) S. Mataka, K. Takahashi, and M. Tashiro, *J. Heterocycl. Chem.*, **14**, 963 (1977).
11) H.E. Ungnade and E.D. Loughran, *J. Heterocycl. Chem.*, **1**, 61 (1964); R.A. Olofson and J.S. Michelman, *J. Org. Chem.*, **30**, 1854 (1965).
12) Melting points were measured with Yanagimoto micro melting point apparatus, and are uncorrected. Infrared (IR) spectra were measured with a JASCO IRG spectrometer and mass spectra (MS) with a JEOL JMS-01SG machine.

(360 ml). The eluate was concentrated and the residue was recrystallized from cyclohexane with Norit to give 244 mg (86%) of VII, mp 149—150°. *Anal.* Calcd for $C_6N_6O_2S$: C, 32.73; N, 38.17. Found: C, 32.96; N, 38.24. IR ν_{max}^{KBr} cm^{-1}: 1605 (C=N), 1530 (C=C), 1442, 1434. High resolution MS *m/e* (rel. intensity %): 219.977 (100), 189.983 (10), 159.985 (5), 137.972 (12). Calcd for $C_6N_6O_2S$: 219.980 (M^+), 189.982 (M−NO), 159.984 ($M-N_2O_2$), 137.976 ($M-C_2N_3O$).

4-Bromo-5-nitro-6,7-(2′,1′,3′-oxadiazole)benzo-2,1,3-thiadiazole (IX)——Compound VIII (1 g, 3.9 mmol) was added with stirring to a mixture of conc. sulfuric acid and fuming nitric acid (*d* 1.52) (1: 1, 40 ml) under ice cooling. After stirring for 2 hr at room temperature, the mixture was poured onto crushed ice, and the precipitate was collected by filtration, washed with water, dried *in vacuo* and recrystallized from cyclohexane to give 97 mg (8.2%) of IX as pale yellow plates, mp 137—140°. *Anal.* Calcd for $C_6BrN_5O_3S$: C, 23.86; N, 23.18. Found: C, 23.83; N, 23.01. IR ν_{max}^{KBr} cm^{-1}: 1621 (C=N), 1544 (C=C), 1397, 1352 (NO_2). MS *m/e*: 303, 301 (M^+).

6,7-(2′,1′,3′-Oxadiazole)-4,5-(2′,1′,3′-oxadiazole-1′-oxide)benzo-2,1,3-thiadiazole (X)——A solution of 37 mg (0.57 mmol) of sodium azide in acetone–methanol–water (1: 2: 1, 4 ml) was added to a solution of 120 mg (0.4 mmol) of IX in acetone–methanol (1: 1, 4 ml) at room temperature. The mixture was heated at 60—65° for 1 hr and poured into water (5 ml). The precipitate was collected by filtration, washed with water, dried *in vacuo* and recrystallized from cyclohexane to give 70 mg (75%) of X as colorless needles, mp 127—128°. *Anal.* Calcd for $C_6N_6O_3S$: C, 30.52; N, 35.58. Found: C, 30.35; N, 35.41. IR ν_{max}^{KBr} cm^{-1}: 1647 C=N), 1615, 1567. MS *m/e*: 236 (M^+).

Reduction of X into VII——A solution of 94 mg (0.4 mmol) of X and 0.5 ml of triethylphosphite in ethanol (10 ml) was heated at 130—140° in a sealed tube for 13 hr. The reaction mixture was evaporated to dryness *in vacuo* and the residue was chromatographed on a silica gel column (20 g) with benzene (150 ml). The eluate was concentrated and the residue was recrystallized from cyclohexane to yield 62 mg (70%) of VII, mp 149—150°, which was identical with VII obtained by the reduction of IV.

4,5-Diamino-6,7-(2′,1′,3′-oxadiazole)benzo-2,1,3-thiadiazole (XI)——A solution of 110 mg (0.5 mmol) of VII in ethanol (10 ml) was added to 10 ml of 2% aqueous solution of sodium hydrosulfite, which had been adjusted to pH 13 with 30% potassium hydroxide solution. The mixture was heated at 100° for 3 min. After the reaction mixture had been cooled, the precipitated red needles were collected by filtration, washed with a small amount of water, dried *in vacuo* and recrystallized from ethanol–water to yield 65 mg (62.5%) of XI as red needles, mp 253—254°. *Anal.* Calcd for $C_6H_4N_6OS$: C, 34.61; H, 1.94; N, 40.37. Found: C, 34.50; H, 2.11; N, 40.15. IR ν_{max}^{KBr} cm^{-1}: 3291 (NH), 1647, 1610 (C=N), 1577, 1532, 1462. MS *m/e*: 208 (M^+).

4,5-(2′,1′,3′-Oxadiazole)benzo[1,2-*c*: 3,4-*c*′]bis[1,2,5]thiadiazole (XII)——A solution of 100 mg (0.48 mmol) of XI and 1 ml of N-sulfinylaniline in anhyd. pyridine (20 ml) was heated at 130—135° for 2 hr. The solution was poured into ice-water (50 ml) and the mixture was extracted with benzene. The organic layer was washed successively with 2N hydrochloric acid, saturated sodium bicarbonate solution and water, and dried over anhyd. sodium sulfate. Removal of the solvent *in vacuo* gave a pale yellow residue which was chromatographed on a silica gel column (60 g) with benzene (440 ml). The eluate was concentrated and the residue was recrystallized from cyclohexane to yield 46 mg (40%) of XII as colorless needles, mp 180—181°. *Anal.* Calcd for $C_6N_6OS_2$: C, 30.51; N, 35.57. Found: C, 30.80; N, 35.79. IR ν_{max}^{KBr} cm^{-1}: 1632 (C=N), 1555, 1409, 1349. High resolution MS *m/e* (rel. intensity %): 235.955 (100), 205.957 (10), 167.957 (10). Calcd for $C_6N_6OS_2$: 235.957 (M^+), 205.959 (M−NO), 167.956 ($M-C_2N_2O$).

4,5-Diaminobenzo[1,2-*c*: 3,4-*c*′]bis[1,2,5]thiadiazole (XIII)——A solution of 50 mg (0.21 mmol) of XII in ethanol (6 ml) was added to 6 ml of 4% aqueous solution of sodium hydrosulfite which had been adjusted to pH 13 with 30% potassium hydroxide solution. The mixture was then treated by the method employed for the preparation of XI. Recrystallization from toluene gave 28 mg (59%) of XIII as red needles, mp> 300° (lit.[9] mp>360°). IR ν_{max}^{KBr} cm^{-1}: 3330, 3200 (NH), 1645, 1605 (C=N), 1505, 1440, 1275, 835, 820, 785, 765, 745 and 720 (identical with the data of Komin *et al.*[9]). MS *m/e*: 224 (M^+).

Benzo[1,2-*c*: 3,4-*c*′: 5,6-*c*″]tris[1,2,5]thiadiazole (XIV)——A solution of 20 mg (0.09 mmol) of XIII and 0.3 ml of N-sulfinylaniline in anhyd. pyridine (20 ml) was heated at 130—135° for 8 hr. The solution was evaporated to dryness and the residue was treated with water. The mixture was then extracted with benzene. The organic layer was washed with 2N hydrochloric acid and water, and dried over anhyd. sodium sulfate. Removal of the solvent *in vacuo* gave a residue, which was recrystallized from benzene to yield 9.6 mg (42%) of XIV as pale yellow needles, mp>300° (lit.[9,10] mp 344—346° and >300°). *Anal.* Calcd for $C_6N_6S_3$: C, 28.56; N, 33.31. Found: C, 28.87; N, 33.24. IR ν_{max}^{KBr} cm^{-1}: 1620, 1530, 1335, 1295, 1110, 840 and 710 (identical with the spectrum of the authentic sample of Mataka *et al.*[10]). High resolution MS *m/e* (rel. intensity %): 251.933 (100), 167.955 (15), 115.949 (49). Calcd for $C_6N_6S_3$: 251.934 (M^+), 167.956 ($M-C_2N_2S$), 115.950 ($M-C_4N_4S$).

Acknowledgement The authors are grateful to Professor S. Mataka of Kyushu University for the gift of an authentic sample of XIV. The authors also wish to express their gratitude to Professor T. Koga of Dai-ichi College of Pharmacy for his advice and to Mr. T. Itatani, Misses S. Ogasawara, T. Nakamichi and H. Hyuga of Kanazawa University for elemental analyses and mass spectral measurements.