in DMSO-d_6) ppm: 3.95 (2H, singlet, -CH_2-), 6.02 (2H, singlet, CH_2=). MS *m/e*: 260 (M^+). *Anal.* Calcd. for $C_{14}H_{16}N_2OS \cdot C_2H_2O_4 \cdot 1/2H_2O$: C, 53.47; H, 5.33; N, 7.80; S, 8.92. Found: C, 53.52; H, 5.10; N, 7.88; S, 8.90.

3-Bromomethyl-1,2-benzisothiazole (5)——Compound **2** (0.5 g) was heated at 95 ° for 30 min and chromatographed on silicagel. The fraction eluted with benzene–hexane (1: 3) was evaporated and the residue was recrystallized from MeOH to give **5** (0.4 g, 95%), mp 44—46°. NMR (δ in $CDCl_3$) ppm: 4.85 (2H, singlet, CH_2Br). MS *m/e*: 227, 229 (M^+). *Anal.* Calcd. for C_8H_6BrNS: C, 42.12; H, 2.65; Br, 35.03; N, 6.14; S, 14.06. Found: C, 42.07; H, 2.87; Br, 34.72; N, 5.93; S, 14.06.

3-Iodomethyl-1,2-benzisothiazole (6)——The solution of **5** (0.20 g) and KI (0.35 g) in acetone (10 ml) was refluxed for 2 hr and filtrated. The filtrate was evaporated and the residue was chromatographed on silicagel. The fraction eluted with benzene–hexane (3: 7) was evaporated and the residue was recrystallized from MeOH to give **6** (0.23 g, 96%), mp 66—67°. *Anal.* Calcd. for C_8H_6INS: C, 34.92; H, 2.20; I, 46.13; N, 5.09; S, 11.66. Found: C, 35.01; H, 2.27; I, 45.71; N, 4.92; S, 11.76.

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Syntheses of N-Alkyl-N-(hydroxy- or oxo-alkyl)nitrosamines related to N-Butyl-N-(4-hydroxybutyl)nitroamine, a Potent Bladder Carcinogen

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Nineteen N-alkyl-N-(hydroxy- or oxo-alkyl)nitrosamines structurally related to N-butyl-N-(4-hydroxybutyl)nitrosamine, a potent bladder carcinogen, were synthesized for the purpose of investigating their carcinogenic effects in rats. They are N-alkyl-N-(4-hydroxybutyl)nitrosamines, N-alkyl-(3-hydroxypropyl)-nitrosamines, N-alkyl-N-(2-hydroxyalkyl)nitrosamines, and N-alkyl-N-(2- or 3-oxoalkyl)nitrosamines. They were mostly prepared by the nitrosation of the corresponding N-alkyl-N-(hydroxyalkyl)amines. The nitrosamines with an oxo group were prepared by chromium trioxide oxidation of the corresponding N-alkyl-N-(hydroxyalkyl)nitrosamines with a secondary hydroxyl group.

Keywords——N-nitrosamine; N-alkyl-N-(ω-hydroxyalkyl)nitrosamine; N-alkyl-N-(oxoalkyl)nitrosamine; nitrosation; bladder carcinogen; organotropic carcinogen; structure-carcinogenicity relationship

A great number of N-nitroso compounds are now known to be carcinogenic in experimental animals,[2-4)] largely because of the extensive studies of Druckrey and his colleagues.[3)] One of the most intriguing findings by these workers was that of 65 compounds examined in rats, only two, namely N,N-dibutylnitrosamine (DBN) and its ω-hydroxylated derivative, N-butyl-N-(4-hydroxybutyl)nitrosamine (butyl-butanol-(4) nitrosamine: BBN), induced

1) Location: *Takada 3-chome, Toshima-ku, Tokyo, 171, Japan.*
2) P.N. Magee and J.M. Barnes, *Adv. Cancer Res.*, **10**, 163 (1967).
3) H. Druckrey, R. Preussmann, S. Ivankovic, and D. Schmähl, *Z. Krebsforsch. Klin. Onkol.*, **69**, 103 (1967).
4) P.N. Magee, R. Montesano, and R. Preussmann, "Chemical Carcinogens," ed. by C.E. Searle, American Chemical Society, Washington, D.C., 1976, Chapter 11.

tumors of the urinary bladder (Chart 1). In particular, BBN, a presumed metabolite of DBN,[5] has a potent and specific action on the bladder when administered orally.

The principal target organ, on the other hand, of symmetric as well as asymmetric N,N-dialkylnitrosamines was found to be the liver or the esophagus.[3,4] It was assumed that the dibutyl structure is responsible for the induction of bladder tumors, because neither symmetric N,N-dialkylnitrosamines other than DBN nor asymmetric ones having a butyl chain, such as N-methyl-N-butylnitrosamine[6] and N-ethyl-N-butylnitrosamine,[3] induced bladder tumors.

In connection with our studies[7] on a possible relationship between chemical structure, the metabolism *in vivo*, and organotropic specificity of BBN and DBN, a number of N,N-dialkylnitrosamines structurally related to these compounds were prepared, and their metabolic fate and carcinogenicity in rats were investigated. This paper deals with the syntheses of N-alkyl-N-(hydroxy- or oxo-alkyl)nitrosamines.

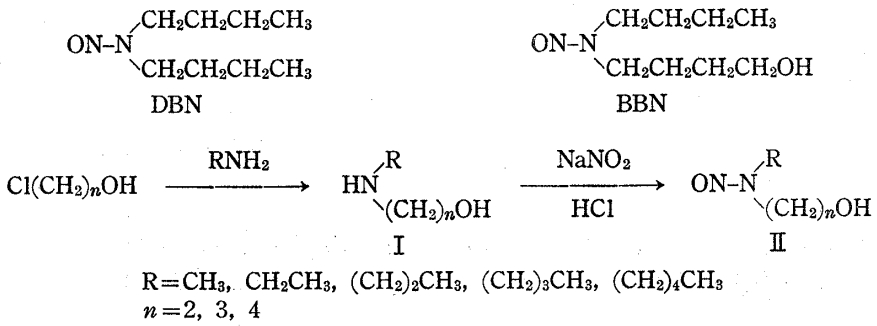

Chart 1

Generally, the homologs and analogs of BBN having an ω-hydroxyl group were prepared according to the scheme indicated in Chart 1. Chloroalkanols were treated with alkylamines at room temperature for a few days to afford N-alkyl-N-(ω-hydroxyalkyl)amines (I) in fairly good yields, which are listed in Table I. N-*tert*-Butyl-N-(4-hydroxybutyl)amine was prepared according to the method reported previously,[8] because it could not be obtained from 4-chloro-1-butanol and *tert*-butylamine.

N-Butyl-N-(3-hydroxybutyl)amine, N-butyl-N-(2-hydroxypropyl)amine, and N-pentyl-(=amyl)-N-(2-hydroxypropyl)amine were prepared in the same way using corresponding chloroalkanols and alkylamines, while N-butyl-N-(2-hydroxybutyl)amine was obtained by condensing 1,2-epoxybutane with butylamine. These amines with a secondary hydroxyl group are also included in Table I.

Nitrosation of the N-alkyl-N-(ω-hydroxyalkyl)amines (I) with sodium nitrite and hydrochloric acid at pH 4—5 gave corresponding N-alkyl-N-(ω-hydroxyalkyl)nitrosamines (II) in good yields, without concomitant formation of the nitrite ester. They are listed in Table II together with the N-alkyl-N-(hydroxyalkyl)nitrosamines having a secondary hydroxyl group, which were prepared also from the corresponding N-alkyl-N-(hydroxyalkyl)amines by nitro-

5) H. Druckrey, R. Preussmann, S. Ivankovic, C.H. Schmidt, H.D. Mennel, and K.W. Stahl, *Z. Krebsforsch. Klin. Onkol.*, **66**, 280 (1964).
6) H. Druckrey, C. Landschütz, and R. Preussmann, *Z. Krebsforsch. Klin. Onkol.*, **71**, 135 (1968); H. Druckrey and C. Landschütz, *ibid.* **75**, 221 (1971).
7) M. Okada, E. Suzuki, J. Aoki, M. Iiyoshi, and Y. Hashimoto, *GANN Monograph on Cancer Research*, **17**, 161 (1975); M. Okada, "Fundamentals in Cancer Prevention," ed. by P.N. Magee, S. Takayama, T. Sugimura, and T. Matsushima, University of Tokyo Press, Tokyo, 1976, pp. 251—266; M. Okada and M. Ishidate, *Xenobiotica*, **7**, 11 (1977).
8) K.C. Schreiber and V.T. Fernandez, *J. Org. Chem.*, **26**, 1744 (1961).

Table I. N-Alkyl-N-(hydroxyalkyl)amines

$HN<^{R_1}_{R_2}$		Yield (%)	bp (mmHg)
R_1	R_2		
CH_3	$CH_2CH_2CH_2CH_2OH$	33	75—77 (4)
C_2H_5	$CH_2CH_2CH_2CH_2OH$	50	85—87 (4)
C_3H_7	$CH_2CH_2CH_2CH_2OH$	59	110—112 (12)
C_5H_{11}	$CH_2CH_2CH_2CH_2OH$	49	115—118 (5)
C_3H_7	$CH_2CH_2CH_2OH$	60	73—76 (7)
C_4H_9	$CH_2CH_2CH_2OH$	74	96—97 (7)
C_5H_{11}	$CH_2CH_2CH_2OH$	52	116—119 (7)
C_4H_9	CH_2CH_2OH	56	95—97 (13)
C_5H_{11}	CH_2CH_2OH	29	104—107 (11)
C_4H_9	$CH_2CH_2CH(OH)CH_3$	77	118—123 (30)
C_4H_9	$CH_2CH(OH)CH_2CH_3$	73	85—87 (5)
C_4H_9	$CH_2CH(OH)CH_3$	54	80—82 (7)
C_5H_{11}	$CH_2CH(OH)CH_3$	60	86—88 (5)

sation in the similar way. Four N-alkyl-N-(hydroxyalkyl)nitrosamines with a secondary hydroxyl group were oxidized by chromium trioxide to give the corresponding oxo compounds which are also listed in the same table.[9]

All the N-nitroso compounds synthesized gave a positive reaction for N-nitroso group with diphenylamine[10] and sulfanilic acid–N-[α-naphthyl]ethylenediamine[11] reagents. The structural confirmation[4] of these nitrosamines was made on the basis of ultraviolet (UV), infrared (IR), and nuclear magnetic resonance (NMR)[12] spectral measurements, and elemental analysis. The NMR data are not indicated in the table, but all the compounds except BOBN-2, BOPN and AOPN which have the oxo group at β-position showed signals at 3.4—4.3 ppm ascribable to 4 protons attached to α-carbon atom of the N-nitroso group. Moreover, a bathochromic shift of about 5 nm of the first maximum of the two UV absorption bands, which is more distinct than the second, was observed with these 2-oxo compounds (Table III).

Of 19 nitrosamines synthesized, 13 compounds were studied on their carcinogenicity in rats.[14,15] Selective induction of bladder cancer was demonstrated not only by BBN but also

9) The following abbreviations are used in the tables: MHBN, N-methyl-N-(4-hydroxybutyl)nitrosamine; EHBN, N-ethyl-N-(4-hydroxybutyl)nitrosamine; PHBN, N-propyl-N-(4-hydroxybutyl)nitrosamine; AHBN, N-amyl(=pentyl)-N-(4-hydroxybutyl)nitrosamine; *t*-BBN, N-*tert*-butyl-N-(4-hydroxybutyl)-nitrosamine; EHPN, N-ethyl-N-(3-hydroxypropyl)nitrosamine; PHPN, N-propyl-N-(3-hydroxypropyl)-nitrosamine; BHPN, N-butyl-N-(3-hydroxypropyl)nitrosamine; AHPN, N-amyl-N-(3-hydroxypropyl)-nitrosamine; BHEN, N-butyl-N-(2-hydroxyethyl)nitrosamine; AHEN, N-amyl-N-(2-hydroxyethyl)-nitrosamine; BHBN-3, N-butyl-N-(3-hydroxybutyl)nitrosamine; BHBN-2, N-butyl-N-(2-hydroxybutyl)nitrosamine; BHPN-2, N-butyl-N-(2-hydroxypropyl)nitrosamine; BOBN-3, N-butyl-N-(3-oxobutyl)nitrosamine; BOBN-2, N-butyl-N-(2-oxobutyl)nitrosamine; BOPN, N-butyl-N-(2-oxopropyl)-nitrosamine; AOPN, N-amyl-N-(2-oxopropyl)nitrosamine.

10) R. Preussmann, D. Daiber, and H. Hengy, *Nature* (London), **201**, 502 (1964).

11) G. Eisenbrand and R. Preussmann, *Arzneim. -Forsch.*, **20**, 1513 (1970).

12) NMR spectra were measured at 34° in deuteriochloroform at 60 MHz, using a Hitachi Model R-20A spectrometer. Chemical shifts are expressed in δ (parts per million) with tetramethylsilane as internal standard. Because of a partial double bond character of the N-N bond, *syn* and *anti* conformers occur in nitrosamines, which are in dynamic equilibrium.[13] The conformer ratios of the nitrosamines synthesized in the present work were determined by NMR and high-pressure liquid chromatography. The results will be reported elsewhere.

13) G. J. Karabatos and R. T. Taller, *J. Am. Chem. Soc.*, **86**, 4373 (1964); W. Lijinsky, L. Keefer, and J. Loo, *Tetrahedron*, **26**, 5137 (1970).

14) M. Okada and Y. Hashimoto, *Gann*, **65**, 13 (1974).

15) M. Okada, E. Suzuki, and Y. Hashimoto, *Gann*, **67**, 825 (1976).

Table II. N-Alkyl-N-(hydroxy- or oxo-alkyl)nitrosamines

Compound[9]	$ON-N<^{R_1}_{R_2}$ R_1	R_2	Yield (%)	bp (mmHg)	Formula	Analysis (%) Calcd. (Found) C	H	N
MHBN	CH_3	$(CH_2)_4OH$	60[a]	143—144 (4)	$C_5H_{12}N_2O_2$	45.44 (45.60	9.15 9.41	21.20 21.32)
EHBN	C_2H_5	$(CH_2)_4OH$	59[a]	139—140 (4)	$C_6H_{14}N_2O_2$	49.30 (49.33	9.65 9.72	19.17 18.85)
PHBN	C_3H_7	$(CH_2)_4OH$	63[a]	154—156 (4)	$C_7H_{16}N_2O_2$	52.47 (52.53	10.07 10.04	17.49 17.19)
BBN	C_4H_9	$(CH_2)_4OH$	80[a]	165—167 (5)	$C_8H_{18}N_2O_2$	55.14 (55.09	10.41 10.63	16.08 16.19)
t-BBN	*tert*-C_4H_9	$(CH_2)_4OH$	72[a]	130—131 (3)	$C_8H_{18}N_2O_2$	55.14 (55.44	10.41 10.41	16.08 15.88)
AHBN	C_5H_{11}	$(CH_2)_4OH$	80[a]	164—167 (5)	$C_9H_{20}N_2O_2$	57.41 (57.25	10.71 10.81	14.88 14.69)
EHPN	C_2H_5	$(CH_2)_3OH$	45[a]	129—130 (4)	$C_5H_{12}N_2O_2$	45.44 (45.69	9.15 9.42	21.20 20.60)
PHPN	C_3H_7	$(CH_2)_3OH$	52[a]	n.d.[c]	$C_6H_{14}N_2O_2$	49.30 (49.18	9.65 9.76	19.17 19.14)
BHPN	C_4H_9	$(CH_2)_3OH$	44[a]	144—146 (3)	$C_7H_{16}N_2O_2$	52.47 (52.05	10.07 10.07	17.49 17.11)
AHPH	C_5H_{11}	$(CH_2)_3OH$	58[a]	n.d.	$C_8H_{18}N_2O_2$	55.14 (54.99	10.41 10.23	16.08 15.83)
BHEN	C_4H_9	$(CH_2)_2OH$	45[a]	146—148 (7)	$C_6H_{14}N_2O_2$	49.30 (49.05	9.65 9.74	19.17 18.89)
AHEN	C_5H_{11}	$(CH_2)_2OH$	80[a]	n.d.	$C_7H_{16}N_2O_2$	52.47 (52.71	10.07 9.94	17.49 17.33)
BHBN-3	C_4H_9	$(CH_2)_2CHCH_3$ OH	79[a]	143—146 (5)	$C_8H_{18}N_2O_2$	55.14 (55.37	10.41 10.38	16.08 15.90)
BHBN-2	C_4H_9	$CH_2CHC_2H_5$ OH	73[a]	137—139 (5)	$C_8H_{18}N_2O_2$	55.14 (55.00	10.41 10.68	16.08 15.92)
BHPN-2	C_4H_9	CH_2CHCH_3 OH	55[a]	n.d.	$C_7H_{16}N_2O_2$	52.47 (52.30	10.07 10.37	17.49 17.75)
BOBN-3	C_4H_9	$(CH_2)_2COCH_3$	76[b]	123 (3)	$C_8H_{16}N_2O_2$	55.79 (55.79	9.36 9.45	16.27 16.30)
BOBN-2	C_4H_9	$CH_2COC_2H_5$	58[b]	102 (0.15)	$C_8H_{16}N_2O_2$	55.79 (56.07	9.36 9.61	16.27 16.28)
BOPN	C_4H_9	CH_2COCH_3	41[b]	124—125 (4)	$C_7H_{14}N_2O_2$	53.14 (53.25	8.92 8.94	17.71 17.34)
AOPN	C_5H_{11}	CH_2COCH_3	75[b]	n.d.	$C_8H_{16}N_2O_2$	55.79 (56.00	9.36 9.45	16.27 16.24)

a) Yield of nitrosation.
b) Yield of oxidation.
c) Not distilled.

by its homologs, MHBN, EHBN, and PHBN. No bladder cancer was induced, however, by AHBN and *t*-BBN, although induction of papilloma in the bladder was observed by AHBN. EHPN and BHPN which have a 3-hydroxypropyl chain induced neither bladder tumors nor any tumors in other organs. On the other hand, BHEN having a 2-hydroxyethyl group induced hepatoma as well as papilloma in the esophagus, as did N-ethyl-N-(2-hydroxyethyl)-nitrosamine.[3] BHBN-3 produced no tumors, although degenerative changes in the liver were noticed histologically. BOBN-3, BOBN-2 and BOPN which have an oxo group induced hepatoma.

Table III. UV and IR Spectral Data

Compound[9]	UV $\lambda_{max}^{95\%\ EtOH}$ nm (ε)		IR ν_{max}^{film} cm^{-1}		
			OH or C=O	N=O	N–N
MHBN	230.5(7900)	346.5(91)	3380	1420	1037
EHBN	233(7400)	351(86)	3420	1450	1060
PHBN	234.5(7000)	351(85)	3420	1455	1058
BBN	234.5(7500)	351.5(86)	3420	1454	1059
t-BBN	231.5(7300)	353(60)	3430	1435	1043
AHBN	234(7000)	350(84)	3400	1455	1064
EHPN	233(7100)	351(86)	3410	1446	1058
PHPN	234(7300)	351.5(88)	3410	1453	1055
BHPN	234.5(7200)	350(88)	3410	1451	1058
AHPN	234.5(7200)	350.5(88)	3410	1452	1059
BHEN	235(7000)	351(89)	3400	1451	1051
AHEN	235(7000)	351(87)	3420	1451	1050
BHBN-3	234(6800)	350(81)	3420	1452	1080
BHBN-2	236.5(7100)	350.5(92)	3410	1452	1055
BHPN-2	236(6900)	352(86)	3430	1450	1058
BOBN-3	234(7000)	351(84)	1718	1451	1083
BOBN-2	240(5500)	349(84)	1729	1449	1084
BOPN	240(5700)	350(85)	1733	1449	1084
AOPN	240.5(5600)	350.5(79)	1732	1450	1090

Twelve compounds except *t*-BBN of the above 13 nitrosamines were shown to be mutagenic to *Salmonella typhimurium* strain TA 1535 in the presence of an S-9 mix prepared from the liver of rats treated with polychlorinated biphenyl.[16]

Experimental[17]

Color Reaction——The N-nitroso compound in CH_2Cl_2 was spotted on a thin-layer plate of Silica gel HF_{254} (E. Merck AG). After spraying reagent A or B followed by irradiation of UV light for *ca.* 10 min, the N-nitroso compound was revealed as a blue violet or pink spot respectively.

Reagent A: 150 mg of diphenylamine in 10 ml of EtOH–AcOH (9: 1).

Reagent B[11]: A mixture (1: 1) of 1% sulfanilic acid in 30% AcOH and 0.1% N-[α-naphthyl]ethylenediammonium dichloride in 30% AcOH (Bratton-Marshall reagent).

General Procedure for the Preparation of N-Alkyl-N-(ω-hydroxyalkyl)amine (I) and N-Alkyl-N-(hydroxyalkyl)amine with a Secondary Hydroxyl Group——To chloroalkanol (0.1 mol) was added alkylamine (0.4 mol) under ice-cooling and the mixture was allowed to stand for 2—3 days at room temperature. The mixture was then refluxed for 3—5 hr. The reflux was performed under pressure when methyl- or ethylamines were used. After evaporation of the excess of the alkylamine *in vacuo*, 40% NaOH solution was added to the residue and the resulting solution was extracted with ether. The organic layer was washed with a small volume of water and dried over anhyd. Na_2SO_4. After evaporation of the solvent, the residue was distilled. The yield and bp of the N-alkyl-N-(hydroxyalkyl)amines are listed in Table I.

N-Butyl-N-(2-hydroxybutyl)amine——To a solution of butylamine (2 mol) in MeOH (150 ml) containing NaOH (0.2 mol) was added dropwise a solution of 1,2-epoxybutane (1 mol) in MeOH (75 ml) under stirring at room temperature and the mixture solution was refluxed for 3 hr. After evaporating MeOH and butylamine the residue was distilled *in vacuo*. The yield and bp of N-butyl-N-(2-hydroxybutyl)amine is indicated in Table I.

General Procedure for Nitrosation——To a 40% N-alkyl-N-(ω-hydroxyalkyl)amine (I) solution (1 mol) was added 10 N HCl (0.9 mol) and a 40% $NaNO_2$ solution (1.2—1.3 mol). After warming the mixture solution at 50°, further addition of HCl was made dropwise under stirring until the pH of the solution turned to

16) M. Nagao, E. Suzuki, K. Yasuo, T. Yahagi, Y. Seino, T. Sugimura, and M. Okada, *Cancer Res.*, **37**, 399 (1977).

17) UV spectra were measured in 95% EtOH solution. IR spectra were determined on Hitachi EPI-S2 spectrophotometer.

4—5. After stirring for 30 min at 70—80°, the solution was cooled and extracted with $CHCl_3$ or AcOEt. The organic layer was washed with water and dried over anhyd. Na_2SO_4. Evaporation of the solvent gave a yellow residue which was purified by distillation *in vacuo*. The nitrosation of N-butyl-N-(2-hydroxybutyl)amine and other amines with a secondary hydroxyl group was carried out in the same manner.

For elemental analysis and UV, IR or NMR spectral measurements, the compounds were further purified by column chromatography of Silica gel (E. Merck AG) using hexane–ether–CH_2Cl_2 (4 : 3 : 2) as eluting solvent. The yield, bp, and data of elemental analysis are indicated in Table II, and UV and IR spectral data are listed in Table III. Purification of the nitrosamines which were not distilled was made by column chromatography in the similar way.

Oxidation of N-Alkyl-N-(hydroxyalkyl)nitrosamine with a Secondary Hydroxyl Group to the Corresponding Oxo Compound——The oxidation was performed in the usual way using CrO_3–pyridine complex or CrO_3–AcOH. For example, BOBN-3 was prepared from BHBN-3 as follows: To a solution of BHBN-3 (10 g) in anhyd. CH_2Cl_2 (50 ml) was added a solution of CrO_3-pyridine complex (100 g) in the same solvent (1700 ml), and the mixture was allowed to stand at room temperature for 20 hr. After filtration of the precipitate, the solvent was removed under reduced pressure. The residue was extracted with EtOAc, and the organic layer was washed successively with 10% HCl, 5% Na_2CO_3 and water, and then dried over anhyd. Na_2SO_4. After evaporation of the solvent, an oily residue was distilled to give BOBN-3 as a pale yellow oil.

For elemental analysis and UV, IR or NMR spectral measurements, the compounds were further purified by column chromatography as described above. Purification of AOPN which was not distilled was also performed by column chromatography. Yield of the oxidation, bp, and data of elemental analysis are given in Table II, and UV and IR spectral data are shown in Table III.

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Synthesis and Reaction of Furazanobenzothiadiazole and Related Compounds

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Furazanobenzothiadiazole and related compounds were prepared by a new synthetic route starting from 4,7-dibromo-5-nitrobenzo-2,1,3-thiadiazole, which was obtained in good yield by nitration of 4,7-dibromobenzo-2,1,3-thiadiazole easily acessible. Some chemical reactions of this tricyclic ring system—ring opening reaction, photo-cleavage reaction, bromination and reduction—were discussed.

Keywords——furazanobenzothiadiazole; furoxanobenzothiadiazole; tricyclic ring system; vasodilatory and hypotensive activities; mass spectrum;

Synthesis of furazanobenzothiadiazole (I) and its N-oxide (furoxanobenzothiadiazole) (II) having vasodilatory and hypotensive activities[2] was reported by Ghosh.[3] His method consists of two independent routes, starting in each case from the appropriately substituted benzothiadiazole (Chart 1). We now describe a new synthetic route to I starting from easily ac-

1) Location: *a) 1-3-80, Tomobuchi-cho, Miyakojima-ku, Osaka; b) 4, Koishikawa, Bunkyo-ku, Tokyo.*
2) P.B. Ghosh and B.J. Everitt, *J. Med. Chem.*, **17**, 203 (1974).
3) P.B. Ghosh, *Tetrahedron Lett.*, **32**, 2999 (1971).