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Reactions of Salicylaldehydes with Bromonitromethane

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Various salicylaldehydes were treated with bromonitromethane in the presence of an inorganic base to give 2-nitrobenzo[*b*]furan derivatives, and the reaction mechanisms were investigated. The most remarkable feature of the reactions is that 3-hydroxysalicylaldehyde (**1k**) alone among various hydroxysalicylaldehydes (**1b**, **k**, **n**, **r**) gave 2-nitro-7-hydroxybenzo[*b*]furan in good yield. Bromonitromethane reacted with salicylaldehydes at the aldehyde group exclusively to give 1-(2-hydroxyphenyl)-2-bromo-2-nitroethanols (**14**), followed by cyclization to produce mixtures consisting of *cis*- and *trans*-2-nitro-3-hydroxy-2,3-dihydrobenzo[*b*]furans (**8a**, **b**; **9a**, **b**; **10a**, **b**). The stereochemistry of these products is discussed on the basis of the spectral data and chemical reactivities. The intermediates, 2,3-dihydrobenzo[*b*]furans, underwent dehydration smoothly to give 2-nitrobenzo[*b*]furans.

Keywords——bromonitromethane; salicylaldehyde derivative; ring closure; 2-nitrobenzo[*b*]furan derivative; *cis*-2-nitro-3-hydroxy-2,3-dihydrobenzo[*b*]furan derivative; *trans*-2-nitro-3-hydroxy-2,3-dihydrobenzo[*b*]furan derivative; ^{13}C-NMR; stereochemistry; reaction mechanism

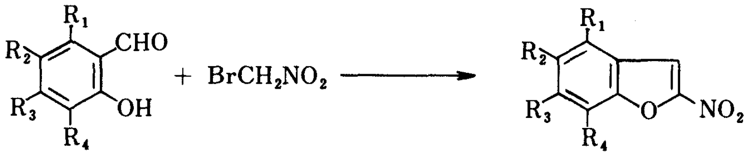
Many kinds of benzo[*b*]furan derivatives have been isolated, chiefly from plants, and some of them show interesting biological activities such as antitumorigenic,[1a)] antimicrobial,[1b)] antifungal[1c)] and bacteriostatic activity[1d)] and toxicity to goldfish.[1e)] Natural benzo[*b*]furan derivatives do not have any nitro groups in their structures, so the biological activities of nitrobenzo[*b*]furans are of interest. In this paper, we describe the preparation of some 2-nitrobenzo[*b*]furan derivatives by condensation of salicylaldehydes with bromonitromethane and present evidence relating to the reaction mechanism.

2-Nitrobenzo[*b*]furans have been prepared by several methods as follows: nitration[2)] of benzo[*b*]furans, replacements of an acetyl group,[2a,b)] bromine[3)] or a carboxyl group[4)] at C-2 of benzo[*b*]furans by a nitro group, and the condensation[5)] of salicylaldehydes with bromonitromethane. Although the condensation reaction may be the most convenient for preparation of 2-nitrobenzo[*b*]furans, little is known about the mechanism. It is well known that nitromethane reacts with aromatic aldehydes to give the corresponding nitroolefins in the presence of primary amines[6)] but when similar reaction conditions were applied to the condensation, 2-nitrobenzo[*b*]furans were obtained in poor yields, probably because of amination of bromonitromethane.

Salicylaldehyde (**1a**) was treated with bromonitromethane in the presence of an inorganic base such as potassium carbonate, sodium hydroxide or potassium hydroxide in such polar solvents[7)] as dimethylsulfoxide, acetone, or water to give 2-nitrobenzo[*b*]furan (**2a**). These conditions were applied to various salicylaldehydes as follows. Various alkyloxy-, 3-hydroxy and bromosalicylaldehydes gave the corresponding 2-nitrobenzo[*b*]furans (**2e**—**f**, **l**, **m**, **o**, **p**, **t**—**w**) in moderate yields as shown in Table I.[8)] However, the salicylaldehydes with a hydroxy group (except for 3-hydroxy), amino group or nitro group did not condense with bromonitromethane under these conditions.

Compounds which could not be prepared directly by ring closure were obtained as

Table I. Condensation Reactions of Salicylaldehydes with Bromonitromethane



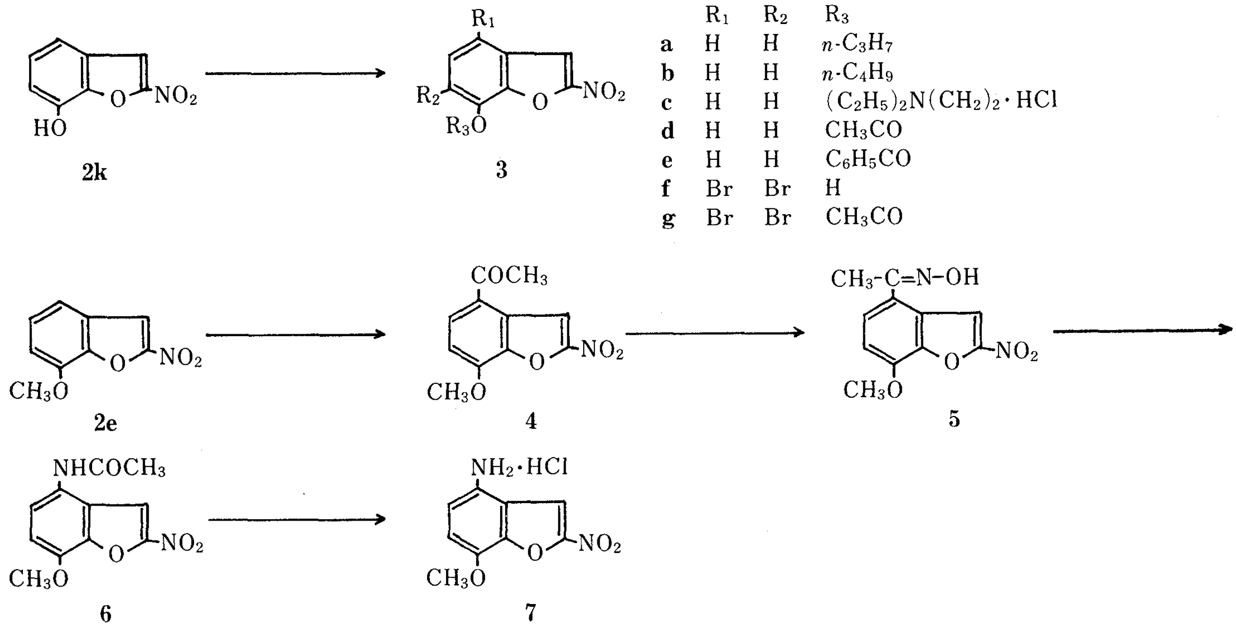
	1					2					
	R_1	R_2	R_3	R_4		R_1	R_2	R_3	R_4	Procedure	Yield (%)
a	H	H	H	H	**a**	H	H	H	H	A	37
b	H	H	HO	H	**b**	H	H	HO	H	A, B	0
c	H	H	$(CH_3)_2N$	H	**c**					A, B	0
d	H	H	$(C_2H_5)_2N(CH_2)_2O$	H	**d**					A, B	0
e	H	H	CH_3O	H	**e**	H	H	CH_3O	H	A	29
f	H	H	C_2H_5O	H	**f**	H	H	C_2H_5O	H	A	26
g	H	H	n-C_3H_7O	H	**g**	H	H	n-C_3H_7O	H	A	24
h	H	H	n-C_4H_9O	H	**h**	H	H	n-C_4H_9O	H	A	25
i	H	H	Geranyloxy	H	**i**	H	H	Geranyloxy	H	A	42
j	H	H	$C_2H_5OOCCH_2O$	H	**j**	H	H	$C_2H_5OOCCH_2O$	H	A	47
k	H	H	H	HO	**k**	H	H	H	HO	B	79
l	H	H	H	CH_3O	**l**	H	H	H	CH_3O	A	31
m	H	H	H	C_2H_5O	**m**	H	H	H	C_2H_5O	A	36
n	H	HO	H	H	**n**	H	HO	H	H	A, B	0
o	H	CH_3O	H	H	**o**	H	CH_3O	H	H	A	45
p	H	Br	H	H	**p**	H	Br	H	H	A	39
q	H	NO_2	H	H	**q**	H	NO_2	H	H	A, B	0
r	H	H	HO	HO	**r**					A, B	0
s	HO	C_2H_5OOC	H	H	**s**					A, B	0
t	H	CH_3O	H	Br	**t**	H	CH_3O	H	Br	A	40
u	H	H	CH_3O	CH_3O	**u**	H	H	CH_3O	CH_3O	A	48
v	CH_3O	H	CH_3O	H	**v**	CH_3O	H	CH_3O	H	A	31
w	H	Br	H	Br	**w**	H	Br	H	Br	A	44
					x	H	H	$HOOCCH_2O$	H		

Procedure A, K_2CO_3–acetone; B, K_2CO_3–DMSO.

follows. 5-Hydroxy-2-nitrobenzo[*b*]furan (**2n**) was obtained by heating the methoxy compound (**2o**) with pyridinium chloride at 180 °C. 2,5-Dinitrobenzo[*b*]furan (**2q**) was obtained by nitration of 2-acetylbenzo[*b*]furan[9] with fuming nitric acid, and the ester (**2j**) was hydrolyzed to give the corresponding carboxylic acid (**2x**). The O-alkyl (**3a**—**c**) and O-acyl derivatives (**3d**, **e**) were obtained by usual alkylation from the phenol (**2k**). Further, the phenol (**2k**) was brominated to give the dibromo derivative (**3f**), which was acetylated to give the dibromo acetate (**3g**). Acetylation of the methoxy derivative (**2e**) gave 2-nitro-4-acetyl-7-methoxybenzo[*b*]furan (**4**). Beckmann rearrangement of the oxime (**5**) of **4** proceeded on treatment of **5** with polyphosphoric acid to yield the acetylamino derivative (**6**), which was hydrolyzed in 10% hydrochloric acid to give 2-nitro-4-amino-7-methoxybenzo[*b*]furan hydrochloride (**7**) (Chart 1). Table II shows physical data for these 2-nitrobenzo[*b*]furans.

It is noteworthy that the position of the hydroxy group on salicylaldehydes apparently influences the progress of the condensation reactions. Namely, 3-hydroxysalicylaldehyde (**1k**) gave the phenol (**2k**) in good yield but 6- and 5-hydroxysalicylaldehyde (**1b**, **n**) did not; this is reminiscent of the reactions of hydroxy aromatic aldehydes with nitromethane.[6c,10)]

When 5-bromosalicylaldehyde (**1p**) was treated with bromonitromethane in the presence of potassium carbonate in acetone at 20—25 °C, an interesting intermediate, which was



	R1	R2	R3
a	H	H	n-C_3H_7
b	H	H	n-C_4H_9
c	H	H	$(C_2H_5)_2N(CH_2)_2 \cdot HCl$
d	H	H	CH_3CO
e	H	H	C_6H_5CO
f	Br	Br	H
g	Br	Br	CH_3CO

Chart 1

converted into 2-nitro-5-bromobenzo[*b*]furan (**2p**) by warming on a silica gel plate, was obtained from the reaction mixture. From the spectral data, it was assumed that the intermediate was a stereoisomeric mixture[11] of *cis*- and *trans*-2-nitro-3-hydroxy-5-bromo-2,3-dihydrobenzo[*b*]furan. Separation of the two isomers (**8a** and **8b**) was carried out by fractional recrystallizations. In the proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **8a** in dimethylsulfoxide-d_6 (DMSO-d_6), three kinds of signals other than those of phenyl protons were detected. The signals at 5.90, 6.66 and 6.96 ppm were reasonably assigned to 3-H, 2-H and 3-OH, respectively, because the signal at 5.90 ppm (dd, 7.0, 7.0 Hz) changed into a doublet ($J_{2H-3H}=7.0$ Hz), the signal at 6.96 ppm disappeared and the peak at 6.66 ppm ($J_{2H-3H}=7.0$ Hz) was unchanged on treatment of **8a** with deuterium oxide. Thus, **8a** was confirmed to be 2-nitro-3-hydroxy-5-bromo-2,3-dihydrobenzo[*b*]furan based on the ^{1}H-NMR, mass and infrared (IR) spectra. Compound **8b** was confirmed to be the diastereomer of **8a**. Figure 1 shows the ^{1}H-NMR spectra of **8a** and **8b**. Stereoisomeric mixtures of *cis*- and *trans*-2-nitro-3-hydroxy-6-ethoxy-2,3-dihydrobenzo[*b*]furan (**9**) and *cis*- and *trans*-2-nitro-3-hydroxy-7-methoxy-2,3-dihydrobenzo[*b*]furan (**10**) were also obtained from alkyloxysalicylaldehydes (**1f** and **1l**, respectively) in a similar manner. These mixtures (**9** and **10**) were each separated into the two isomers (**9a** and **9b**, **10a** and **10b**) respectively. On the other hand, only one stereoisomer (**11b**) of 2-nitro-3-hydroxy-4,6-dimethoxy-2,3-dihydrobenzo[*b*]furan was obtained from **1v**.

The coupling constants (J_{2H-3H}) were calculated based on the Karplus equations, using the dihedral angle (ϕ) of 2-H and 3-H found to be optimum from an examination of Dreiding molecular models.[12] J_{2H-3H} calculated for the *cis* isomer ($\phi \fallingdotseq 25°$) was 6.5 Hz and for the *trans* ($\phi \fallingdotseq 100°$), 1.0 Hz. The observed coupling constants (J_{2H-3H}) were approximately 7 Hz in **8a**, **9a** and **10a** and 1 Hz in **8b**, **9b**, **10b** and **11b**. ^{1}H-NMR studies utilizing the relative magnitude of the coupling constants have been applied to assign the stereochemistry of many 2,3-dihydrobenzo[*b*]furans,[11,13] and therefore the **a** series (**8a**, **9a**, **10a**) can be presumed to have *cis* configuration and the **b** series (**8b**, **9b**, **10b**, **11b**), *trans* configuration.

Table III shows physical constants and spectral data for the *cis*- and *trans*-2-nitro-3-hydroxy-2,3-dihydrobenzo[*b*]furans (**8a**—**10a** and **8b**—**11b**).

It is known that the substituent groups at C-2 exert anisotropic effects on *cis* groups at C-

TABLE II. Physical Properties of 2-Nitrobenzo[*b*]furans (**2**, **3**, **4**, **5**, **6**, **7**)

Compd. No.	mp (°C)	Formula and Analysis Calcd (Found) %		¹H-NMR (ppm)
		C	H	
2a	157	$C_8H_5NO_3$ 58.90 (59.02)	 3.09 (3.07)	7.24—7.80 (aromatic protons, m) (A)
2e	130	$C_9H_7NO_4$ 55.96 (55.73)	 3.65 (3.56)	3.93 (3H, s, CH_3), 7.08 (1H, dd, 5-H), 7.26 (1H, br d, 7-H), 7.55 (1H, d, 4-H), 7.87 (1H, s, 3-H) (A)
2f	131	$C_{10}H_9NO_4$ 57.97 (58.03)	 4.38 (4.58)	1.40 (3H, t, CH_3), 4.05 (2H, q, CH_2), 6.94 (1H, dd, 5-H), 7.10 (1H, br d, 7-H), 7.64 (1H, d, 4-H), 7.73 (1H, s, 3-H) (A)
2g	83	$C_{11}H_{11}NO_4$ 59.73 (59.72)	 5.01 (5.07)	1.03 (3H, t, CH_3), 1.80 (2H, m, $CH_3C\underline{H}_2-$), 3.97 (2H, t, $-C\underline{H}_2O-$), 6.93 (1H, dd, 5-H), 7.09 (1H, br d, 7-H), 7.58 (1H, d, 4-H), 7.69 (1H, s, 3-H) (A)
2h	61	$C_{12}H_{13}NO_4$ 61.27 (61.09)	 5.57 (5.46)	0.97 (3H, t, CH_3), 1.30—1.88 (4H, m, $CH_3C\underline{H}_2C\underline{H}_2-$), 4.06 (2H, t, $-CH_2O-$), 7.00 (1H, dd, 5-H), 7.17 (1H, br d, 7-H), 7.68 (1H, d, 4-H), 7.78 (1H, s, 3-H) (A)
2i	73	$C_{18}H_{21}NO_4$ 68.55 (68.76)	 6.71 (6.95)	1.58 (3H, s, CH_3), 1.61 (3H, s, CH_3), 1.77 (3H, s, CH_3), 2.08 (4H, m, $-CH_2-CH_2-$), 4.67 (2H, d, $-CH_2O-$), 5.05 (1H, m, $(CH_3)_2C=C\underline{H}-$), 5.46 (1H, br t, $=C\underline{H}-CH_2O-$), 7.01 (1H, dd, 5-H), 7.19 (1H, br s, 7-H), 7.68 (1H, d, 4-H), 7.79 (1H, s, 3-H) (A)
2j	128	$C_{12}H_{11}NO_6$ 54.34 (54.18)	 4.18 (3.97)	1.23 (3H, t, CH_3), 4.14 (2H, q, $CH_3C\underline{H}_2-$), 4.79 (2H, s, $-CH_2COO-$), 7.05 (1H, dd, 5-H), 7.18 (1H, br d, 7-H), 7.70 (1H, d, 4-H), 7.77 (1H, s, 3-H) (A)
2k	157	$C_8H_5NO_4$ 53.64 (53.79)	 2.81 (2.66)	6.84—7.24 (3H, m, benzene ring protons), 7.66 (1H, s, 3-H), 9.36 (1H, br s, OH) (A)
2l	131	$C_9H_7NO_4$ 55.96 (55.69)	 3.65 (3.68)	3.92 (3H, s, CH_3), 6.90—7.24 (3H, m, benzene ring protons), 7.64 (1H, s, 3-H) (A)
2m	87	$C_{10}H_9NO_4$ 57.97 (57.85)	 4.38 (4.34)	1.47 (3H, t, CH_3), 4.19 (2H, q, CH_2), 6.90—7.24 (3H, m, benzene ring protons), 7.66 (1H, s, 3-H) (A)
2n	160	$C_8H_5NO_4$ 53.64 (53.26)	 2.81 (2.72)	7.12 (1H, dd, 6-H), 7.17 (1H, br s, 4-H), 7.48 (1H, d, 7-H), 7.71 (1H, br s, 3-H), 8.60 (1H, s, OH) (A)
2o	131	$C_9H_7NO_4$ 55.96 (55.94)	 3.65 (3.53)	3.81 (3H, s, CH_3), 7.20 (1H, dd, 6-H), 7.26 (1H, d, 4-H), 7.54 (1H, d, 7-H), 7.76 (1H, s, 3-H) (A)
2p	168	$C_8H_4BrNO_3$ 39.70 (39.45)	 1.67 (2.00)	7.40—8.00 (aromatic protons, m) (A)
2q	173	$C_8H_4N_2O_5$ 46.16 (45.87)	 1.94 (1.88)	7.98 (1H, dd, 7-H), 8.12 (1H, d, 3-H), 8.49 (1H, dd, 6-H), 8.84 (1H, d, 4-H) (A)
2t	158	$C_9H_6BrNO_4$ 39.73 (39.69)	 2.22 (2.15)	3.87 (1H, s, CH_3), 7.38 (1H, d, 4-H), 7.43 (1H, d, 6-H), 7.89 (1H, s, 3-H) (A)

Table II. (continued)

Compd. No.	mp (°C)	Formula and Analysis Calcd (Found) %			^{1}H-NMR (ppm)
			C	H	
2u	122	$C_{10}H_9NO_5$	53.82 (53.56)	4.06 (4.02)	3.92 (3H, s, 7 or 6-OCH_3), 4.00 (3H, s, 6 or 7-OCH_3), 7.17 (1H, d, 5 or 4-H), 7.46 (1H, d, 4 or 5-H), 7.79 (1H, s, 3-H) (A)
2v	189	$C_{10}H_9NO_5$	53.82 (54.08)	4.06 (3.90)	3.87 (3H, s, 4 or 6-OCH_3), 3.92 (3H, s, 6 or 4-OCH_3), 6.57 (1H, d, 5-H), 7.10 (1H, d, 7-H), 8.02 (1H, s, 3-H) (DMSO-d_6)
2w	145	$C_8H_3Br_2NO_4$	28.52 (28.72)	0.90 (0.92)	7.87 (1H, d, 4 or 6-H), 7.88 (1H, s, 3-H), 8.02 (1H, d, 6 or 4-H) (A)
2x	190	$C_{10}H_7NO_6$	50.64 (50.39)	2.98 (2.71)	4.59 (2H, s, –OCH_2–), 6.84 (1H, dd, 5-H), 7.10 (1H, d, 7-H), 7.52 (1H, d, 4-H), 7.76 (1H, s, 3-H) (A)
3a	64	$C_{11}H_{11}NO_4$	59.73 (59.92)	5.01 (4.99)	1.08 (3H, t, CH_3), 1.88 (2H, m, $CH_3C\underline{H}_2$–), 4.15 (2H, t, –CH_2O–), 7.01—7.40 (3H, m, benzene ring protons), 7.79 (1H, s, 3-H) (A)
3b	49	$C_{12}H_{13}NO_4$	61.27 (61.81)	5.57 (5.51)	0.99 (3H, t, CH_3), 1.20—2.00 (4H, m, $CH_3C\underline{H}_2C\underline{H}_2$–), 4.16 (2H, t, –$CH_2O$–), 7.00—7.40 (3H, m, benzene ring protons), 7.75 (1H, s, 3-H) (A)
3c	233 (dec.)	$C_{14}H_{19}ClN_2O_4$	53.42 (53.46)	6.08 (6.34)	1.42 (6H, t, $CH_3 \times 2$), 3.38 (4H, q, –$C\underline{H}_2CH_3 \times 2$), 3.70 (2H, t, $>N–CH_2$–), 4.54 (2H, t, –CH_2O–), 7.08—7.50 (3H, m, benzene ring protons), 7.77 (1H, s, 3-H) (D_2O)
3d	143	$C_{10}H_7NO_5$	54.30 (54.23)	3.19 (3.01)	2.40 (3H, s, CH_3), 7.24—7.70 (3H, m, benzene ring protons), 7.80 (1H, s, 3-H) (A)
3e	128	$C_{15}H_{10}NO_5$	63.61 (63.45)	3.20 (3.43)	7.12—7.96 (aromatic protons, m) (A)
3f	145	$C_8H_3Br_2NO_4$	28.52 (28.71)	0.90 (0.92)	7.56 (1H, s, ring proton), 7.63 (1H, s, ring proton), 10.1 (1H, br s, OH) (A)
3g	135	$C_{10}H_5Br_2NO_5$	31.69 (31.51)	1.33 (1.35)	2.44 (3H, s, CH_3), 7.80 (1H, s, ring proton), 7.85 (1H, s, ring proton) (A)
4	194	$C_{11}H_9NO_5$	56.17 (55.91)	3.86 (4.14)	2.66 (3H, s, –OCH_3), 4.12 (3H, s, –$COCH_3$), 7.06 (1H, d, 6-H), 7.96 (1H, d, 5-H), 8.41 (1H, s, 3-H) ($CDCl_3$)
5	241	$C_{11}H_{10}N_2O_5$	52.80 (52.80)	4.03 (3.87)	2.20 (3H, s, $CH_3–C=N$–), 3.94 (3H, s, CH_3O–), 7.20 (1H, d, 6 or 5-H), 7.49 (1H, d, 5 or 6-H), 8.08 (1H, s, 3-H), 11.29 (1H, s, OH) (DMSO-d_6)
6	251	$C_{11}H_{10}N_2O_5$	52.80 (52.96)	4.03 (3.85)	2.10 (3H, s, –$COCH_3$), 3.86 (3H, s, –OCH_3), 7.14 (1H, d, 6 or 5-H), 7.71 1H, d, 5 or 6-H), 8.14 (1H, s, 3-H), 9.85 (1H, br s, NH) (DMSO-d_6)
7	215 (dec.)	$C_9H_9ClN_2O_4$	44.19 (44.30)	3.71 (3.75)	3.84 (3H, s, OCH_3), 6.32 (1H, d, 4 or 5-H), 7.12 (1H, d, 5 or 4-H), 7.76 (1H, s, 3-H) (D_2O)

Acetone-d_6 = A.

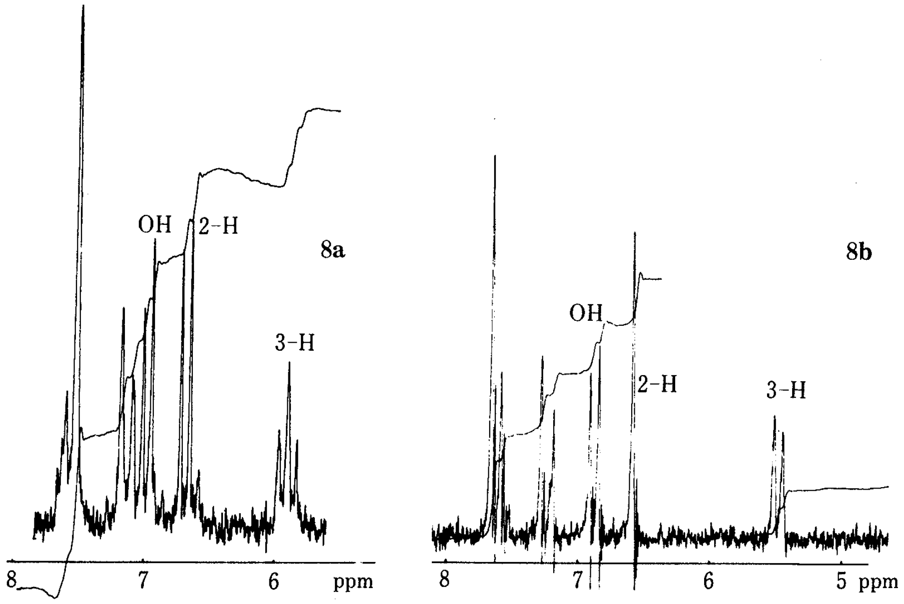


Fig. 1. ^{1}H-NMR Spectra of *cis*- and *trans*-2-Nitro-3-hydroxy-5-bromo-2,3-dihydrobenzo[*b*]furan (**8a**, **8b**) (in DMSO-d_6)

3 in 2,3-dihydrobenzo[*b*]furans.[14] The 3-H signals of the *trans* isomers (**8b**, **9b**, **10b**) in the ^{1}H-NMR spectra were about 0.3—0.4 ppm upfield from those of the *cis* isomers (**8a**, **9a**, **10a**) because they were in the shielding region[15] of the C-2 nitro group.

The compounds of the **b** series (*trans* form) were always obtained in preference to the corresponding compounds of the **a** series (*cis* form); the isomer ratios of **8a**/**8b**, **9a**/**9b** and **10a**/**10b** in the reaction mixtures were 1/3, 1/5 and 1/6, respectively, as determined by ^{1}H-NMR spectrometry (Table III).

Both the *cis* isomer **8a** and the *trans* isomer **8b** were transformed into a stereoisomeric mixture by equilibration in the presence of potassium hydroxide, giving **8a**/**8b** = 1/3, as determined by ^{1}H-NMR. The predominant isomer (**8b**) in the equilibrium mixtures could be assigned the *trans* configuration on the grounds that the *trans* isomer, with less interaction between the C-2 nitro group and the C-3 hydroxy group, should be thermodynamically more stable than the *cis* isomer[11,13d,16] and by consideration of the coupling constants.

However, further chemical evidence is need to confirm the configuration assignment of the stereoisomers, especially in view of the findings that $J_{trans\,2H\text{-}3H} > J_{cis\,2H\text{-}3H}$ in 2-isopropyl-3-acetoxy-5-bromo-2,3-dihydrobenzo[*b*]furan[16] and that $J_{trans\,2H\text{-}3H} = J_{cic\,2H\text{-}3H}$ in 2,3-dimethoxy-2,3-dihydrobenzo[*b*]furan.[17]

There are no reports of a comparison of the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra of stereoisomers of 2,3-dihydrobenzo[*b*]furan derivatives. In the ^{13}C-NMR spectra of the stereoisomeric pairs (**8a** and **8b**, **9a** and **9b**), the assignments of C-2 and C-3 were made based on the one-bond coupling constant ($^1J_{C-H}$) and the chemical shift values. The assignments of the ring carbons are shown in Table IV.[18,19]

Although intra- and intermolecular hydrogen bonding in chloroform solutions of acyclic nitroalcohols at concentrations of 0.001—0.1 M have been studied,[20] there has been no IR study on fused five-membered β-nitroalcohols. Therefore we performed the IR spectroscopic studies of **8a**, **8b**, **9a** and **9b** at concentrations of 0.0015 M (cell length: 5 mm) and 0.1 M (cell length: 0.1 mm). It is interesting that intramolecular hydrogen bonds were not observed in *cis* (**8a**, **9a**) or *trans* isomers (**8b**, **9b**). Free hydroxy stretching bands (at about 3565 cm^{-1}, sharp band) were detected in the solutions of 0.0015 M and both free hydroxy stretching and intermolecular stretching bands (at about 3300 cm^{-1}, broad band) were seen in the solutions

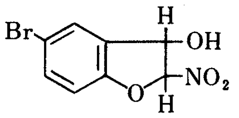
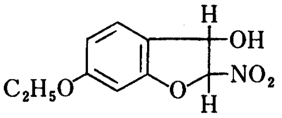
Table III. Physical Data for *cis*- and *trans*-2-Nitro-3-hydroxy-2,3-dihydrobenzo[*b*]furans (**8a**—**10a** and **8b**—**11b**)

Compd. No.	Ratio of *cis*/*trans*	Stereo-isomer	mp (°C)	^{1}H-NMR				MS (M^+)	IR ($\nu_{\max}^{\mathrm{KBr}}$ cm^{-1})
				2-H (ppm)	3-H (ppm)	$J_{2H\text{-}3H}$ (Hz)	Other protons (ppm)		
8	1:3	*cis* (**8a**)	147	6.66 (6.22)	5.90 (5.74)	7.0 (7.0)	7.14 (1H, d, 7-H), 7.54 (1H, br d, 4-H), 7.58 (1H, dd, 6-H), 6.96 (1H, d, OH) DMSO-d_6 (Acetone-d_6)	261	3615, 3475, 3150, 1563, 1471, 1384
		trans (**8b**)	103	6.59 (6.11)	5.47 (5.30)	1.0 (1.0)	7.23 (1H, d, 7-H), 7.60 (1H, dd, 6-H), 7.66 (1H, br d, 4-H), 6.87 (1H, d, OH) DMSO-d_6 (Acetone-d_6)	261	3495, 1566, 1467, 1350
9	1:5	*cis* (**9a**)	154	6.56 (6.60)	5.96 (5.75)	6.5 (6.5)	6.65 (1H, d, 7-H), 6.68 (1H, dd, 5-H), 7.32 (1H, d, 4-H), 5.64 (1H, br s, OH) Acetone-d_6 (DMSO-d_6)	225	3605, 3440, 1558, 1383
		trans (**9b**)	86	6.34 (6.46)	5.42 (5.30)	1.0 (1.0)	6.63 (1H, dd, 5-H), 6.68 (1H, d, 7-H), 7.34 (1H, d, 4-H), 5.53 (1H, br s, OH) Acetone-d_6 (DMSO-d_6)	225	3490, 1555 1395
10	1:6	*cis* (**10a**)	116	6.22	5.76	7.0	7.00—7.12 (3H, m, phenyl protons), 3.94 (3H, s, OCH_3), 2.66 (1H, br s, OH) $CDCl_3$	211	3260, 1566, 1453, 1373
		trans (**10b**)	76	6.12	5.47	1.0	7.00—7.12 (3H, m, phenyl protons), 3.94 (3H, s, OCH_3), 2.68 (1H, br s, OH) $CDCl_3$	211	3350, 1568, 1458, 1376
11		*trans* (**11b**)	115	6.11	5.56	1.0	6.20 (1H, d, 7 or 5-H), 6.34 (1H, d, 5 or 7-H), 3.87 (6H, s, $OCH_3 \times 2$), 2.35 (1H, br s, OH) $CDCl_3$	241	3490, 1567, 1458, 1373

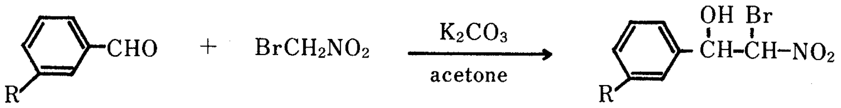
of 0.01 M. This is probably because the nitro group and the hydroxy group in *cis* isomers (**8a**, **9a**) may be in closer proximity than in *o*-nitrophenol (based on Dreiding molecular models).

Moreover, the reaction mechanism was checked as followed. Phenol (pK_a 10) and bromonitromethane (pK_a 8.20[21]) under similar conditions did not give any product. In contrast, the benzaldehydes reacted with bromonitromethane to give a mixture consisting of *erythro*- and *threo*-1-phenyl-2-bromo-2-nitroethanol[22] (**12a** and **12b**) and of *erythro*- and *threo*-1-(3-hydroxyphenyl)-2-bromo-2-nitroethanol[22] (**13a** and **13b**) respectively (Chart 2). The structure of the nitroalcohols was supported by the ^{1}H-NMR,[23] IR and mass spectra (MS). As mentioned above, acidic bromonitromethane reacted with the aromatic aldehyde group under mild conditions to give the nitroalcohols. It can therefore be presumed that bromonitromethane would react with the aldehyde group of salicylaldehydes[24] to give mixtures consisting of *erythro*- and *threo*-1-(2-hydroxyphenyl)-2-bromo-2-nitroethanols[25] (**14**), because the aldehyde group of the salicylaldehydes is more activated than that of the benzaldehydes due to the chelation. If the nitroalcohols (**14**) were converted to 2-nitro-3-

Table IV. ^{13}C-NMR Chemical Shifts and One-Bond Coupling Constants ($^1J_{C-H}$) of 2-Nitro-3-hydroxy-2,3-dihydrobenzo[*b*]furans (**8a**, **8b**, **9a**, **9b**) in Acetone-d_6

Carbon number	Compounds 			
	cis Isomer (**8a**)	*trans* Isomer (**8b**)	*cis* Isomer (**9a**)	*trans* Isomer (**9b**)
C-2	109.3 $^1J=187.3$	113.0 $^1J=184.6$	109.8 $^1J=186.0$	113.8 $^1J=183.9$
C-3	73.4 $^1J=155.4$	78.0 $^1J=157.1$	73.3 $^1J=154.4$	78.2 $^1J=155.8$
C-4	113.0 $^1J=168.2$	113.6 $^1J=168.5$	110.3[c] $^1J=166.5$	110.9[d] $^1J=163.1$
C-5	129.6	129.9	97.7[c] $^1J=163.8$	97.2[d] $^1J=163.8$
C-6	134.1[a] $^1J=168.1$	134.8[b] $^1J=168.5$	160.2[e]	161.6[f]
C-7	129.2[a] $^1J=168.8$	129.9[b] $^1J=168.8$	126.6 $^1J=162.4$	127.2 $^1J=163.9$
C-3a	115.3	115.6	118.3	118.8
C-7a	158.0	159.1	162.5[e]	162.9[f]

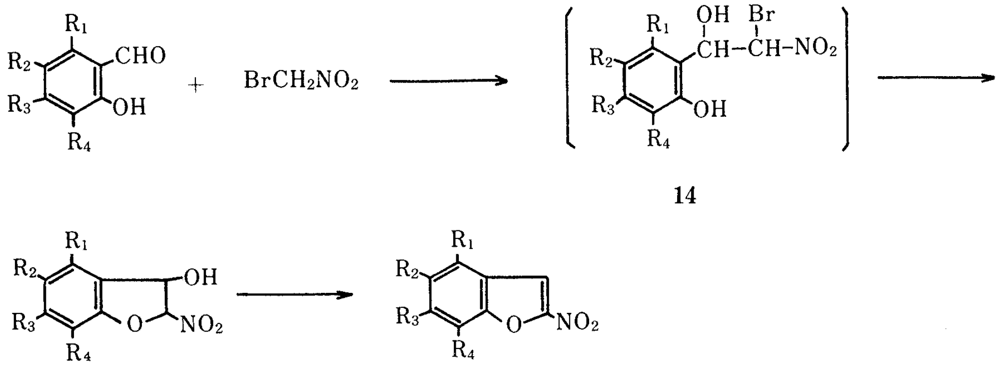
The chemical shifts are expressed in ppm downfield from TMS and the coupling constants ($^1J_{C-H}$) are given in Hz.
a—*f*) Assignments may be interchanged.



R=H
R=OH

12a+**12b** : R=H
13a+**13b** : R=OH

Chart 2



14

8: $R_2=Br$, $R_1=R_3=R_4=H$
9: $R_3=C_2H_5O$, $R_1=R_2=R_4=H$
10: $R_4=CH_3O$, $R_1=R_2=R_3=H$
11: $R_1=R_3=CH_3O$, $R_2=R_4=H$

Chart 3

hydroxy-2,3-dihydrobenzo[*b*]furans in the following ring closure step according to Zalkow's discussion,[16] *i.e.*, *erythro*-1-(2-hydroxy-5-bromophenyl)-2-bromo-3-methylbutanol is converted to the *cis*-2,3-dihydrobenzo[*b*]furan derivative exclusively, the *erythro* isomers and *threo* isomers of the nitroalcohols (**14**) should give corresponding *cis*- and *trans*-2-nitro-3-hydroxy-2,3-dihydrobenzo[*b*]furans, respectively. However, the 2-nitro-3-hydroxy-2,3-dihydrobenzo[*b*]furans were obtained as equilibrium mixtures with the *trans* isomers predominating due to the effect of the C-2 nitro group. These products were subsequently dehydrated to the corresponding 2-nitrobenzo[*b*]furans (Chart 3).

Experimental

All melting points were measured with a Thomas Hoover capillary melting point apparatus, and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded with JEOL PS-100 and JEOL FX-100 (25 MHz) spectrometers. Chemical shifts are given in ppm (δ) with tetramethylsilane (TMS) as an internal standard and the following abbreviations are used: s, singlet; br s, broad singlet; d, doublet; dd, double doublet; br d, broad doublet; t, triplet; m, multiplet. Low-resolution MS were obtained with a Hitachi M-52 instrument, with a direct inlet system. IR spectra were measured on a Shimadzu IR-430 grating infrared spectrometer.

Bromonitromethane[26)]——Improved Procedure: Nitromethane (47 g) was added to 2.5% aqueous sodium hydroxide solution (1200 ml) at 5 °C and the mixture was stirred at 5 °C for 0.5 h. Bromine (122 g) was added to the solution at once at 3 °C under vigorous stirring and the mixture was stirred for 1 h at room temperature. The ethereal extract of the reaction mixture was steam-distilled to give pale yellow oily bromonitromethane (87 g). ^{1}H-NMR (CCl_4): 5.45 ppm (s, CH_2). IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 1565, 1370, 1260, 746.

2-Nitro-7-methoxybenzo[*b*]furan (2l)——General Procedure A: A mixture of **1l** (1.5 g, 10 mmol) and K_2CO_3 (3.2 g, 23 mmol) in dry acetone (50 ml) was stirred at 25 °C for 30 min, then bromonitromethane (1.7 g, 12 mmol) was added dropwise at 25 °C. The mixture was refluxed for 5 h then filtered. The filtrate was evaporated to afford crude **2l**, which was chromatographed (10% ethanol–benzene, silica gel) to give pure **2l** (0.6 g, 31%). Physical data, see Table II. Compounds **2a**, **2e**—**2j**, **2m**, **2o**, **2p** and **2t**—**2w** were obtained by the same procedure as described for **2l**, and the yields and physical data are shown in Tables I and II.

2-Nitro-7-hydroxybenzo[*b*]furan (2k)——General Procedure B: A mixture of **1k** (1.4 g, 10 mmol) and K_2CO_3 (3.5 g, 25 mmol) in dry dimethylsulfoxide (25 ml) was stirred at 25 °C for 30 min, then bromonitromethane (1.7 g, 12 mmol) was added dropwise for 5 min, and the mixture was stirred for 30 min at 25 °C. The mixture was poured into water (200 ml) and extracted with ether (200 ml). The ether layer was washed with brine and dried over Na_2SO_4. The product, obtained by removal of the solvent under reduced pressure, was recrystallized from benzene to furnish **2k** (1.4 g, 79%). Physical data, see Table II.

2-Nitro-5-hydroxybenzo[*b*]furan (2n)——A mixture of **2o** (0.4 g) and dry pyridine hydrochloride (2.5 g) was heated at 180 °C for 1 h. The mixture was poured into ice-water to precipitate a yellow solid (250 mg), which was recrystallized from benzene. Yellow fine needles (130 mg). Physical data, see Table II.

2,5-Dinitrobenzo[*b*]furan (2q)——2-Acetylbenzo[*b*]furan (1 g, 6.3 mmol) was added to fuming sulfuric acid (6 ml) at −5 °C under vigorous stirring and the mixture was stirred at 0 °C for 15 min. The reaction mixture was poured slowly into ice-water to give crude **2q** (500 mg), which was purified by column chromatography on silica gel (5% ethanol benzene). Yellow needles (230 mg, 18%). Physical data, see Table II.

2-Nitro-6-carboxymethoxybenzo[*b*]furan (2x)——An ethanol solution of **2j** (350 mg in 11 ml) was treated with aqueous 3 N NaOH solution (3 ml) at room temperature for 20 min. After usual work-up, the product was recrystallized from ethyl acetate to give pale yellow plates (200 mg). Physical data, see Table II.

2-Nitro-7-alkyloxybenzo[*b*]furans (3a—c)——A mixture of **2k** (500 mg, 2.8 mmol), K_2CO_3 (660 mg, 4.8 mmol) in dry acetone (35 ml) was stirred at 25 °C for 0.5 h, and then an alkyl halide (3.6 mmol) was added to the solution. The mixture was refluxed for 3 h with stirring. After filtration, the filtrate was concentrated under reduced pressure to give an oily residue, which was extracted with ethyl acetate. Removal of the ethyl acetate under reduced pressure gave the corresponding crude 7-alkyloxy derivative, which was purified by recrystallization. **3a** (from methanol, 445 mg, 72%), **3b** (from methanol, 450 mg, 69%), **3c** (from ethanol, 451 mg, 61%). Physical data for **3a**, **3b** and **3c** hydrochloride, see Table II.

2-Nitro-7-acetyloxybenzo[*b*]furan (3d)——Concentrated sulfuric acid (1 drop) was added to a solution of **2k** (700 mg, 3.9 mmol) in acetic anhydride (9 ml). The mixture was stirred at 23 °C for 3 h, and then poured into ice-water to give a pale yellow precipitate. Recrystallization from ethanol–benzene gave colorless needles (741 mg, 86%). Physical data, see Table II.

2-Nitro-7-benzoyloxybenzo[*b*]furan (3e)——A mixture of **2k** (700 mg, 3.9 mmol) and benzoyl chloride (655 mg, 4.7 mmol) in dry pyridine (20 ml) was stirred at room temperature for 12 h. After usual work-up, the product was recrystallized from ethanol to give needles (971 mg, 88%). Physical data, see Table II.

2-Nitro-4,6-dibromo-7-hydroxybenzo[*b*]furan (3f)——Bromine (540 mg, 3.4 mmol) was added to a solution of **2k** (500 mg, 2.8 mmol) in carbon tetrachloride (85 ml). The mixture was stirred at 25 °C for 5 h, then the solvent was evaporated off under reduced pressure, and the residue was dissolved in 100 ml of ethyl acetate. The ethyl acetate layer was washed with brine and dried over Na_2SO_4, then concentrated to give the crude crystalline bromide (**3f**). Recrystallization from ethanol gave pale yellow prisms (680 mg, 72%). Physical data, see Table II.

2-Nitro-4,6-dibromo-7-acetoxybenzo[*b*]furan (3g)——Under conditions similar to those used for **2k**, **3f** (500 mg, 1.5 mmol) gave **3g** (from ethyl acetate, pale yellow prisms, 510 mg, 91%). Physical data, see Table II.

2-Nitro-4-acetyl-7-methoxybenzo[*b*]furan (4)——Acetyl chloride (1.5 g, 32.6 mmol) was added to a mixture of **2e** (3 g, 15.5 mmol) and aluminum chloride (3.1 g, 23.3 mmol) in dry carbon disulfide (100 ml) at room temperature. The solution was refluxed under stirring for 5 h and worked up as usual. The product was recrystallized from ethanol to give pale yellow needles (3.2 g, 87%). Physical data, see Table II.

4-(2-Nitro-7-methoxybenzo[*b*]furanyl) Methyl Ketone Oxime (5)——A mixture of hydrazine hydrochloride (1.3 g, 18.7 mmol) and $NaHCO_3$ (1.8 g, 21.3 mmol) in 80% ethanol aqueous solution (20 ml) was added to a solution of **4** (2 g, 8.5 mmol) in ethanol (95 ml) at room temperature under vigorous stirring. The whole was refluxed for 1 h under stirring and then acidified with 2 N HCl. The reaction mixture was evaporated to dryness to give a yellow solid, which was extracted with ethyl acetate. Removal of the ethyl acetate under reduced pressure gave colorless prisms (1.5 g, 71%). Physical data, see Table II.

2-Nitro-4-acetylamino-7-methoxybenzo[*b*]furan (6)——A mixture of **5** (1.2 g) and polyphosphoric acid (55 g) was heated at 90 °C for 30 min. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The ethyl acetate extract was washed with brine and evaporated to dryness. The residue was recrystallized from 50% ethanol–benzene to give needles (1.0 g, 83%). Physical data, see Table II.

2-Nitro-4-amino-7-methoxybenzo[*b*]furan Hydrochloride (7)——A mixture of **7** (900 mg, 3.6 mmol) and 4 N HCl (33 ml) was stirred under reflux for 1 h. After cooling, the reaction mixture was concentrated under reduced pressure to give a yellow solid which was recrystallized from ether–ethanol. Pale yellow plates (668 mg, 76%). Physical data, see Table II.

***cis*- and *trans*-2-Nitro-3-hydroxy-5-bromo-2,3-dihydrobenzo[*b*]furan (8a, 8b)**——General procedure for **9a**, **9b**, **10a**, **10b** and **11b**: A mixture of **1p** (5 g, 25 mmol) and K_2CO_3 (3.5 g, 25 mmol) in dry acetone (70 ml) was stirred for 30 min, then bromonitromethane (3.5 g, 25 mmol) was added slowly at 23 °C and the mixture was stirred at 25 °C for 1 h. After removal of insoluble materials by filtration, the filtrate was concentrated under reduced pressure at 25 °C to afford a red oil. The oil was extracted with ether and the ether layer was washed with brine and dried over Na_2SO_4. The solvent was evaporated off under reduced pressure at 25 °C to give a red oily residue (6.1 g). The residue was a mixture of **8a** and **8b** containing a small amount of **2p**. The mixture was purified by preparative thin layer chromatography (TLC) (on silica gel, 3% ethanol in benzene) to yield a pale yellow powder (4.4 g, 68%). Upon recrystallization from carbon tetrachloride, the *trans* isomer (**8b**) slowly precipitated as colorless prisms, which were recrystallized from 15% carbon tetrachloride in chloroform three times (2.1 g). Concentration and cooling of the mother liquor yielded the crude *cis* isomer (**8a**), which was purified by repeated fractional crystallizations from chloroform and carbon tetrachloride to give colorless fine needles (0.5 g). The other compounds were prepared similarly. Physical properties of **8a**, **8b**, **9a**, **9b**, **10a**, **10b** and **11b** are shown in Table III.

Equilibrium Mixtures from *cis*- 8a and *trans*- 8b——A solution of **8a** (40 mg) in acetone-d_6 (0.4 ml) was treated with 0.41% KOH in ethanol (0.05 ml) at room temperature and the ^{1}H-NMR spectrum of the solution was recorded every six minutes. The ratio of **8a**/**8b** was evaluated based on the intensities of the 3-H and 2-H signals: 2/5 (6 min), 2/5 (12 min), 1/3 (18 min), 1/3 (24 min), 1/3 (30 min). The equilibrium mixture from **8b** was obtained in the same way. Ratios of **8a**/**8b** were determined to be 2/7 (6 min), 2/7 (12 min), 1/3 (18 min), 1/3 (24 min), 1/3 (30 min).

1-Phenyl-2-bromo-2-nitroethanol (12a + 12b) and 1-(3-Hydroxyphenyl)-2-bromo-2-nitroethanol (13a + 13b)——Dried K_2CO_3 (0.7 g, 5 mmol) was added to a mixture of benzaldehyde (1 g, 9 mmol) and bromonitromethane (1.4 g, 10 mmol) in dry acetone (15 ml) at 23 °C and the solution was stirred for 1 h at 23—25 °C. After filtration of the reaction mixture, the filtrate was concentrated under reduced pressure to give a pale yellow oil. An ether solution of the oil was washed with brine and dried over Mg_2SO_4. Removal of the ether under reduced pressure gave a mixture consisting of *erythro*- and *threo*-1-phenyl-2-bromo-2-nitroethanol (**12a**, **b**) as a colorless oil (0.7 g). *Rf* value in TLC 0.37 (on silica gel, benzene). IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 3550, 1565, 1463, 1360. MS *m/z*: 245 (M^+), 198, 119, 107. ^{1}H-NMR (CCl_4) δ: 4.79 (br d, J = 8.8 Hz, 1-H of **12a**), 5.49 (d, J = 8.8 Hz, 2-H of **12a**), 4.87 (br d, J = 5.0 Hz, 1-H of **12b**), 5.59 (d, J = 5.0 Hz, 2-H of **12b**), 3.30 (br s, OH), 6.89 (m, phenyl protons). The ratio of **12a**/**12b** = 4/3 (based on ^{1}H-NMR).

The mixture of *erythro*- and *threo*-1-(3-hydroxyphenyl)-2-bromo-2-nitroethanol (**13a**, **b**) was obtained in the same way. Pale yellow oil. *Rf* value in TLC 0.47 (on silica gel, 10% ethanol in benzene). IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 3533, 3270, 1572, 1460, 1377. MS *m/z*: 261 (M^+), 214. ^{1}H-NMR (CCl_4) δ: 4.98 (dd, J = 8.7, 4.7 Hz, 1-H of **13a**), 6.03 (d, J = 8.7 Hz, 2-H of **13a**), 5.20 (dd, J = 4.5, 4.7 Hz, 1-H of **13b**), 6.26 (d, J = 4.5 Hz, 2-H of **13b**), 3.65 (br s, OH), 6.43—6.90 (m, phenyl protons). The ratio of **13a**/**13b** = 3/2 (based on ^{1}H-NMR).

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7) The mixture of dimethylformamide (DMF) and bromonitromethane turned dark red within one minute, so DMF was unsuitable as a condensation solvent.

8) *a*) By our procedures the 2-nitrobenzo[*b*]furans were easily isolated from the reaction mixtures, and **2l**, **2p** and **2o** were obtained in good yields compared with the procedure given in reference 5. Furthermore, the reaction intermediates, 2,3-dihydrobenzo[*b*]furans, were isolated in our procedure; *b*) Compounds **2b**, **2n**, **2k**, **2e**, **2u** and **2v** have been reported by Royer *et al.* (R. Royer, J.-P. Buisson and L. Rene, *Bull. Soc. Chim. Fr.*, **1972**, 4158; R. Royer and L. Rene, *Eur. J. Med. Chem.*, **1982**, 253).

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