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The Acetylation of 2,3-Dimethyl-*bz*-halobenzofurans and Some Reactions of the Products*[1]

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The acetylation of *bz*-chloro- and *bz*-bromo-2,3-dimethylbenzofurans with acetyl chloride and aluminum chloride in carbon disulfide at room temperature was studied; it was found that the acetylation occurred at the 6- or 4-position, which is activated by the furan ring, regardless of whether the halogen atom is at the *o*-, the *m*-, or the *p*-position. In the cases of 7-halo compounds, diacetylation occurred to give the 4,6-diacetyl compounds, and the migration of the bromine atom of 6-acetyl-5-bromo-2,3-dimethylbenzofuran and of the methyl ester of the corresponding carboxylic acid occurred, as a result of the action of aluminum bromide in carbon disulfide at room temperature, to give the 4-bromo compounds. The haloketones thus obtained were then converted to the corresponding carboxylic acids by the bromoform reaction.

The acetylation of 2,3-dimethylbenzofuran and its derivatives, which have various substituents, *e.g.*, hydroxyl,[1] methoxyl,[2] alkyl,[3-5] acetamide,[6] methoxycarbonyl,[7] and acetyl[7-9] groups on the benzene ring, has previously been reported. It has been reported that the acetylation of 7-chloro-2,3-dimethylbenzofuran (**18a**) afforded the 4-acetyl compound[10] (**19a**).

Now, in the present experiments, the acetylation of several halo-2,3-dimethylbenzofurans (**5a**, **8a**, **11a**, **11b**, **18a**, and **18b**) was carried out, the acetyl group of the compounds was converted to the carboxyl group, and the bromine atom of 5-bromo-6-acetyl and -6-methoxycarbonyl compounds (**12b** and **16**) migrated to the 4-position as a result of the action of aluminum bromide.

2,3-Dimethyl-5-[11] and -7-halobenzofurans[10,12] (**11a, 11b, 18a,** and **18b**) were prepared readily by the reported method through the cyclodehydration of 3-aryloxybutanones, but the 4- and 6-halo compounds (**5a, 5b, 8a,** and **8b**) could not be prepared by a similar procedure; the cyclization of 3-(*m*-halophenoxy)butanones (**2a** and **2b**) by sulfuric acid or polyphosphoric acid afforded only crude products, which were found by NMR spectroscopy to be mixtures of the 4- and 6-halo compounds (**5a** and **8a** or **5b** and **8b**). Therefore, the pure 4- and 6-chloro-2,3-dimethylbenzofurans (**5a** and **8a**) were prepared by the Sandmeyer reaction of the corresponding amino compounds[13] (**1** and **3**) (see Chart 1). In the NMR spectra, the 4-halo compounds have the peaks corresponding to the 3-methyl protons in the field lower by about 0.3 ppm than the isomeric 6-halo compounds have; the ratio of the 4- and 6-halo compounds of the mixtures was determined by estimating areas of the peaks.

The acetylation of 4- and 6-chlorobenzofurans (**5a** and **8a**) with acetyl chloride and aluminum chloride in carbon disulfide at room temperature afforded the 6- and 4-acetyl compounds (**6** and **9**) respectively, in which the positions of the acetyl groups were determined by NMR spectroscopy. They have two doublets of $J=1$—3 Hz corresponding to aromatic, two-meta protons. The

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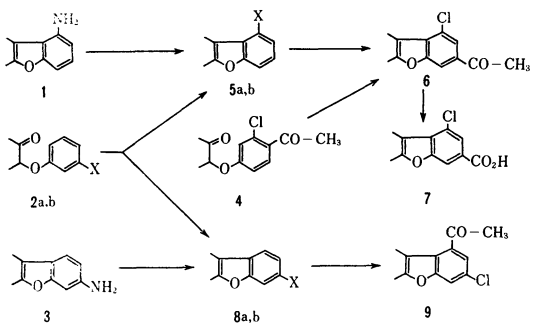
chloroketone **6** was also unexpectedly obtained from 3-(*p*-acetyl-*m*-chlorophenoxy)butanone (**4**) by cyclization with polyphosphoric acid; this also caused a migration of the acetyl group (see Chart 1).

The acetylation of 5-chloro- and 5-bromo-2,3-dimethylbenzofurans (**11a** and **11b**) afforded the 6-acetyl compounds (**12a** and **12b**), while that of 7-chloro- and 7-bromobenzofurans (**18a** and **18b**) afforded the 4-acetyl compounds (**19a** and **19b**) (see Charts 2 and 3). The positions of the acetyl groups were determined by NMR and UV spectroscopy. In the NMR spectra, **12a** and **12b** have two singlets corresponding to aromatic, two-para protons, while **19a** and **19b** have two doublets of $J=7$ Hz corresponding to aromatic, two-ortho protons. However, the positions of the acetyl groups of **19a** and **19b** were not clear from the NMR data; they might be at the 4- or 6-positions, although they seemed to be at the 4-positions, judging from the patterns of the UV spectra, which were comparable to each other and to that of 4-acetyl-2,3-dimethylbenzofuran[14] (see Table 4). The isomeric 5-acetyl-2,3-dimethyl-7-halobenzofurans (**24a** and **24b**) were also prepared by the cyclization of 3-(*p*-acetyl-*o*-halophenoxy)butanones (**23a** and **23b**), which had been prepared by the action of 3-chlorobutanone on *m*-halo-*p*-hydroxyacetophenones (**22a** and **22b**). In the case of the acetylation of the 7-halobenzofurans (**18a** and **18b**), diacetylation occurred to give 4,6-diacetyl compounds (**21a** and **21b**) when double amounts of the reagents were used, analogously to the case of 7-alkyl compounds.[5,8,9] The diacetyl, compound **21a** was also obtained by the acetylation of the ketone **19a**.



For all chart: a) X=Cl, b) X=Br

Chart 1

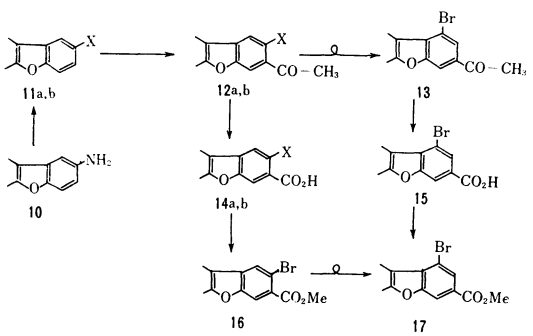


Chart 2

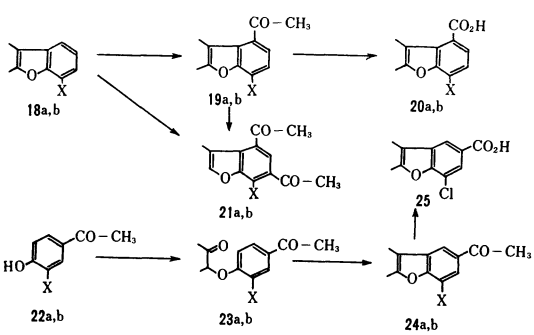


Chart 3

It is found from these results that, in the electrophilic substitution, all the positions on the benzene ring of 2,3-dimethylbenzofuran, especially the 6- and then 4-positions, are activated by the furan ring, and that the acetylation occurs at the 6- or 4-position, regardless of the position of the halogen atom.

The action of aluminum bromide in carbon disulfide at room temperature on the 5-bromoketone (**12b**) thus obtained caused a migration of the bromine atom to the 4-position to give 4-bromoketone (**13**), analogously to the case of 6-acetyl-5-alkyl-2,3-dimethylbenzofurans.[5,8,14] The structure of the migrated compound (**13**) was confirmed by NMR and UV spectroscopy. In the NMR spectra, it has two doublets of $J=2$ Hz corresponding to aromatic, two-meta protons, and the peak corresponding to the 3-methyl protons is in a low field, indicating that the halogen atom is at the 4-position. In the UV spectra, the haloketones (**12a** and **12b**) have two peaks, at around 225 and 290 mμ, while the haloketones (**6** and **13**) have additional peaks at around 240 mμ, such as do 6-acetyl-4- and -5-alkylbenzofurans.[14]

Further, the haloketones (**6**, **12a**, **12b**, **13**, **19a**, **19b**, and **24a**) thus obtained were converted to the corresponding carboxylic acids (**7**, **14a**, **14b**, **15**, **20a**, **20b**, and **25** respectively) by the bromoform reaction. The bromine atom of the methyl ester (**16**) of 5-bromo-6-carboxylic acid (**14b**) also migrated, as a result of the action of aluminum bromide, to the 4-position, to give methyl 4-bromobenzofuran-6-carboxylate (**17**), which was identical with the sample obtained by the esterification of the acid (**15**).

Experimental

All the melting points and boiling points are uncorrected, the UV spectra were measured on a Hitachi

TABLE 1. SUMMARIZED DATA OF REACTIONS

Start	Reagent[a]	Prod	Mp°C (solv.[b]) or bp° C/mmHg n (°C)	Yield %
		Aryloxybutanones		
c)	Cl-butanone	**2a**	136—143/18 1.5200 (26.5)	53
d)	Cl-butanone	**2b**	144—150/20 1.5415 (20)	79
e)	Cl-butanone	**4**	192—195/18 1.5420 (26)	56
22a	Cl-butanone	**23a**	205—209/23 1.5439 (27)	49
22b	Cl-butanone	**23b**	55—57 (Cy)	36
		Halobenzofurans		
2a	H_2SO_4	**5a**+**8a**	135—138/27	75[f]
2a	PPA	**5a**+**8a**	132—135/19	70[f]
2b	H_2SO_4	**5b**+**8b**	140—143/21	79[g]
2b	PPA	**5b**+**8b**	140—143/21	75[h]
1	Sandmeyer	**5a**	120—130/19	35
3	Sandmeyer	**8a**	35— 36 (Pe)	22.5
10	Sandmeyer	**11a**	40— 41 (Pe)[i]	12.5
		Haloketones		
4	PPA	**6**	89.5—90 (Cy)	5
5a	AcCl+$AlCl_3$	**6**	89.5—90 (Cy)	58.5
8a	AcCl+$AlCl_3$	**9**	76—78 (Cy)	50
11a	AcCl+$AlCl_3$	**12a**	36—38 (Cy)	50.5
11b	AcCl+$AlCl_3$	**12b**	59—61 (Cy)	74
12b	$AlBr_3$	**13**	98—99.5 (Cy)	38.5
18a	AcCl+$AlCl_3$	**19a**	105—106 (Cy)[j]	75
18b	AcCl+$AlCl_3$	**19b**	113—115 (Cy)	11.5
18a	AcCl+$AlCl_3$	**21a**	100—101 (Cy)	34
19a	AcCl+$AlCl_3$	**21a**	100—101 (Cy)	75
18b	AcCl+$AlCl_3$	**21b**	119—120.5 (Cy)	11
23a	PPA	**24a**	112—113 (Cy)	11
23b	PPA	**24b**	127—128 (Cy)	6
		Haloacids		
6	NaOBr	**7**	220—221 (Me)	63
12a	NaOBr	**14a**	237.5—239 (Me)	66
12b	NaOBr	**14b**	233—235 (Me)	84
13	NaOBr	**15**	255—256 (Me)	75
19a	NaOBr	**20a**	203—205 (Me)	80
19b	NaOBr	**20b**	199.5—200.5 (Me)	40
24a	NaOBr	**25**	246—247 (Me)	63
		Haloesters		
14b	Me_2SO_4	**16**	96—98 (Cy)	84
15	Me_2SO_4	**17**	119—120 (Cy)	60
16	$AlBr_3$	**17**	119—120 (Cy)	20

a) PPA: polyphosphoric acid. b) Cy: cyclohexane, Pe: petroleum ether, Me: methanol. c) *m*-Chlorophenol. d) *m*-Bromophenol. e) *o*-Chloro-*p*-hydroxyacetophenone. f) A mixture of 67% of **5a** and 33% of **8a**. g) A mixture of 46% of **5b** and 54% of **8b**. h) A mixture of 58% of **5b** and 42% of **8b**. i) Lit mp 42°C (Ref. 11). j) Lit mp 102°C (Ref. 10).

139 spectrophotometer, and the NMR spectra were measured on a JEOL JNM-C-60H (60 MHz) spectrometer. Detailed data are summarized in Tables 1—4.

Aryloxybutanones (2a, 2b, 4, 23a, and 23b). Potassium carbonate (80 g) was added to a solution of *m*-chlorophenol (25 g) and 3-chlorobutanone (22.7 g) in acetone (200 ml), and the mixture was refluxed for 8 hr. Most of the acetone was distilled off, and the residue was treated with water and then extracted with ether. The ethereal solution was washed with an aqueous sodium hydroxide solution, and the residual product from the ether solution was distilled to give 3-(*m*-chlorophenoxy)butanone (**2a**), bp 136—143°C/18 mmHg, 20.5 g (53%). Similarly, 3-(*m*-bromophenoxy)butanone (**2b**), 3-(*p*-acetyl-*m*-chlorophenoxy)butanone (**4**), and 3-(*p*-acetyl-*o*-chloro- and -bromophenoxy)butanones (**23a** and **23b**) were also prepared by this procedure.

Cyclization of the Aryloxybutanones. *a) By Sulfuric Acid.* Concentrated sulfuric acid (10 g) was stirred into **2a** (10 g) with cooling below 30°C, and the mixture was kept at 30°C for 1 hr. The cooled mixture was then poured into ice water and extracted with ether, and the residual product from the

Table 2. Analyses of the new compounds

Compd	Formula	Found C%	Found H%	Calcd C%	Calcd H%
	Aryloxybutanones				
2a	$C_{10}H_{11}O_2Cl$	60.49	5.64	60.48	5.58
2b	$C_{10}H_{11}O_2Br$	49.69	4.50	49.40	4.56
4	$C_{12}H_{13}O_3Cl$	60.15	5.72	59.88	5.45
23a	$C_{12}H_{13}O_3Cl$	60.51	5.65	59.88	5.45
23b	$C_{12}H_{13}O_3Br$	50.67	4.60	50.54	4.60
	Halobenzofurans				
5a	$C_{10}H_9OCl$	66.74	5.11	66.51	5.02
8a	$C_{10}H_9OCl$	66.41	4.92	66.51	5.02
	Haloketones				
6	$C_{12}H_{12}O_2Cl$	64.71	4.91	64.73	4.98
9	$C_{12}H_{12}O_2Cl$	64.49	4.74	64.73	4.98
12a	$C_{12}H_{12}O_2Cl$	64.79	5.10	64.73	4.98
12b	$C_{12}H_{12}O_2Br$	53.79	4.05	53.95	4.15
13	$C_{12}H_{12}O_2Br$	54.22	3.93	53.95	4.15
19b	$C_{12}H_{12}O_2Br$	54.11	4.11	53.95	4.15
21a	$C_{12}H_7O_2Cl_2$	63.36	4.94	63.52	4.95
21b	$C_{12}H_7O_2Br_2$	54.53	4.38	54.39	4.24
24a	$C_{12}H_{12}O_2Cl$	64.73	4.95	64.73	4.98
24b	$C_{12}H_{12}O_2Br$	53.88	3.88	53.95	4.15
	Haloacids				
7	$C_{11}H_9O_3Cl$	58.61	4.15	58.81	4.04
14a	$C_{11}H_9O_3Cl$	58.62	4.09	58.81	4.04
14b	$C_{11}H_9O_3Br$	49.04	3.25	49.09	3.37
15	$C_{11}H_9O_3Br$	49.33	3.22	49.09	3.37
20a	$C_{11}H_9O_3Cl$	58.57	4.00	58.81	4.04
20b	$C_{11}H_9O_3Br$	48.99	3.53	49.09	3.37
25	$C_{11}H_9O_3Cl$	59.03	3.81	58.81	4.04
	Haloesters				
16	$C_{12}H_{11}O_3Br$	51.17	3.80	50.90	3.92
17	$C_{12}H_{11}O_3Br$	50.64	3.72	50.90	3.92

Table 3. The NMR spectra[a)]

Compd	Ph-H[b)]	-COMe	2-Me	3-Me
	Halobenzofurans			
5a			2.35	2.35
8a			2.25	2.02
11a			2.28	2.01
11b			2.29	2.03
18a			2.31	2.04
18b			2.32	2.03
	Haloketones			
6	7.55(d) 7.60(d) J=1 Hz	2.51	2.36	2.33
9	7.36(d) J=3 Hz	2.55	2.34	2.09
12a	7.43 7.22	2.54	2.31	2.04
12b	7.48 7.41	2.57	2.34	2.07
13	7.67(d) 7.75(d) J=2 Hz	2.48	2.31	2.27
19a	7.04(d) 7.33(d) J=7 Hz	2.50	2.38	2.10
19b	7.24(d) J=7 Hz	2.54	2.42	2.12
21a	7.84	2.69, 2.62	2.47	2.16
21b[b)]	7.75	2.74, 2.66	2.46	2.17
24a	7.92(d) J=1 Hz	2.62	2.50	2.24
24b[c)]	8.03(d) 7.99(d) J=1 Hz	2.63	2.44	2.18

a) δ(ppm) values in CCl_4 solution (about 5%), with TMS as the internal standard. b) d: Doublet. c) In $CDCl_3$.

Table 4. The UV spectra

Compd.	λ_{max}^{EtOH} mμ[a)] (log ε)
	Halobenzofurans
5a	218(4.37), 260(4.07), 288(3.34)
8a	220(4.35), 256(4.13), 261(4.12), 286(3.66), 294(3.56)
11a	215(4.55), 257(4.06), 287(3.63), 295(3.62)
11b	216(4.44), 258(4.06), 287(3.65), 295(3.65)
18a	217(4.30), 256(4.07), 287(3.30)
18b	219(4.30), 257(4.01), 286(3.25)
	Haloketones
6	211.5(4.23), 237(4.18), 292.5(4.17)
12a	225(4.28), 291(4.11)
12b	224(4.27), 290(4.07)
13	217.5(4.27), 241(4.25), 294(4.24)
19a	237.5(4.37), 285(3.98), 315[s](3.76)
19b	239(4.34), 285.5 (4.00), 314[s](3.75)

a) s: Shoulder.

ether solution was distilled to give a crude product, bp 135—138°C/27 mmHg, 6.8 g (75%), which was found by the NMR spectrum to be a mixture of 4- and 6-chlorobenzofurans (**5a** and **8a**). Analogously, the product from **2b** was also a mixture of 4- and 6-bromo compounds (**5b** and **8b**).

b) By Polyphosphoric Acid. A mixture of **2a** (10 g) and polyphosphoric acid (n=2.5, 200 g) was heated at 100°C for 1.5 hr. The cooled mixture was poured into ice water and extracted with ether, and the residual product from the ether solution was distilled to give a mixture of the 4- and 6-chloro compounds (**5a** and **8a**), bp 132—135°C/19 mmHg, 6.4 g (70%). Analogously, a mixture of **5b** and **8b** was also obtained from **2b.** 6-Acetyl-2,3-dimethyl-7-halobenzofurans (**24a** and **24b**) were obtained from **23a** and **23b** by the same procedure; in the case of the aryloxybutanone (**4**), there was also a migration of the acetyl group to give 6-acetyl-4-chloro-2,3-dimethylbenzofuran (**6**).

Chlorobenzofurans (5a, 8a, and 11a) by the Sandmeyer Reaction. 4-Amino-2,3-dimethylbenzofuran[13] (**1**) (3 g) was diazotized and then treated with cuprous chloride in the usual manner[15] to give **5a**, bp 120—130°C/20 mmHg, 1.2 g (35%). Similarly, 5- and 6-chloro-2,3-dimethylbenzofurans (**11a** and **8a**) were also prepared from amines (**10** and **3**).

Acetylation of Halobenzofurans (5a, 8a, 11a, 11b, 18a, and 18b) and Chloroketone (19a). Anhydrous aluminum chloride (1 g) was stirred, with cooling, into a solution of **5a** (1 g) and acetyl chloride (0.5 g) in carbon disulfide (50 m*l*); after the mixture had then been stirred at room temperature for 4 hr, it was poured into ice water. The resulting mixture was extracted with chloroform, and the chloroform solution was washed with an aqueous sodium hydroxide solution. The residual product from the chloroform solution was distilled and then crystallized from cyclohexane to give 6-acetyl-4-chloro-2,3-dimethylbenzofuran (**6**), mp 89.5—90°C, 0.7 g (58%). Similarly, 4-acetyl-6-chloro-, -7-chloro-, and -7-bromo-2,3-dimethylbenzofurans (**9**, **19a**, and **19b**), and 6-acetyl-5-chloro- and -5-bromo-2,3-dimethylbenzofurans (**12a** and **12b**) were also obtained. The acetylation of 7-chloro- and 7-bromobenzofurans (**18a** and **18b**) by double amounts of reagents afforded 7-chloro- and 7-bromo-4,6-diacetyl-2,3-dimethylbenzofurans (**21a** and **21b**); **21a** was also obtained by the acetylation of the haloketone **19a**.

Migration of the Bromine Atom of Bromoketone (12b) and Bromoester (16). Anhydrous aluminum bromide (10.4 g) was stirred into a solution of **12b** (5.2 g) in carbon disulfide (70 m*l*); after the mixture had been stirred for 4 hr, it was then treated such as has been described for the acetylation. The product was distilled and crystallized from cyclohexane to give 6-acetyl-4-bromo-2,3-dimethylbenzofuran (**13**), mp 98—99.5°C. 2 g (38.5%). Similarly, methyl 4-bromo-2,3-dimethylbenzofuran-6-carboxylate (**17**) was obtained from **16**.

Haloacids (7, 14a, 14b, 15, 20a, 20b, and 25) by the Bromoform Reaction. A solution of the chloroketone **6** (1 g) in dioxane (20 m*l*) was stirred, with cooling, into an aqueous sodium hypobromite solution, prepared by the addition of bromine (3.4 g) to a cold mixture of sodium hydroxide (2 g), water (6 m*l*), and ice (6 g); the mixture was stirred for 30 min at 15°C and then for 1.5 hr at 45°C. The cooled solution was extracted with ether, and the aqueous layer was acidified after the addition of a small amount of sodium sulfite. The precipitates thus formed were crystallized from methanol to give 4-chloro-2,3-dimethylbenzofuran-6-carboxylic acid (**7**), mp 220—221°C, 0.7 g (63%). Similarly, 4-bromo-, 5-chloro-, 5-bromo-, and 7-chloro-2,3-dimethylbenzofuran-6-carboxylic acids (**15**, **14a**, **14b**, **and 25**) and 7-chloro- and 7-bromo-2,3-dimethylbenzofuran-4-carboxylic acids (**20a** and **20b**) were also prepared.

Esterification of the Acids (14b and 15). The acids were esterified by refluxing them for 8 hr with methyl sulfate and sodium carbonate in acetone; the product was crystallized from cyclohexane to give two esters (**16** and **17**).

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15) Cf. W. W. Hartman and M. R. Brethen, "Org. Synth.," Coll. Vol. 1, p. 162 (1956).