BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 40 1224—1231 (1967)

The Syntheses of Benzofuran-carboxylic Acids and the Acetylation of Their Esters*[1]

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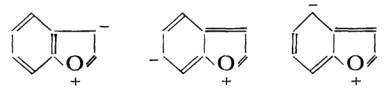
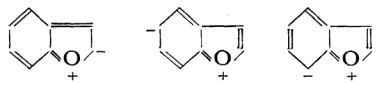
(Received October 8, 1966)

Acetyl derivatives of 2, 3-dimethylbenzofuran and their methyl homologs were derived into the corresponding carboxylic acids by the haloform reaction, and the acetylation of thier esters by the Friedel-Crafts reaction was studied. The keto-esters obtained were hydrolyzed to give keto-acids, which were then further oxidized into dicarboxylic acids by the haloform reaction and decarboxylated to acetylbenzofurans. On the other hand, the dicarboxylic acids were also obtained by the oxidation of diacetylbenzofurans. By the haloform reaction of hindered acetyl compounds, we obtained only halogenated ketones, which it was difficult to hydrolyze to give carboxylic acids. After the structures of these products had been determined and compared, it became clear that the acetylation of 5-alkoxycarbonyl-2, 3-dimethylbenzofurans furnished the 6-acetylated compounds, while that of 6-alkoxycarbonyl compounds and their methyl homologs furnished the 4-acetylated compounds.

It has been reported that alkylbenzofurans are readily acylated in the furan ring[1] and also in the benzene ring when the furan ring is fully substituted, the 6-position being the most reactive site in the benzene ring,[2] and that the further acetylation of acetyl-alkylbenzofurans or the direct diacetylation of alkylbenzofurans readily furnishes diacetyl-alkylbenzofurans.[3] These acylation patterns of alkylbenzofurans seem to be due to the great contributions of extreme resonance structures A—F especially A—D



A B C



D E F

Now in this paper, acetyl or diacetyl derivatives of alkyl-2, 3-dimethylbenzofurans are derived into the corresponding carboxylic acids by the haloform reaction, and the acetylation of their esters is studied.

The 6-acetyl-2, 3-dimethylbenzofuran and its 7- or 5-methyl homologs (2a, b, c), prepared[2b,c] by the acetylation of the corresponding benzofurans (1a, b, c), were treated with aqueous sodium hypobromide to give the corresponding carboxylic acids (3a, b, c) in good yields with the addition of dioxane or tetrahydrofuran as the solvent, and in lower yields with aqueous sodium hypochloride. A similar haloform reaction of 5- or 6-acetyl-2, 3-dimethylbenzofuran (19 or 2a respectively) to give the corresponding acids (20 or 3a respectively) was reported by Bisagni *et al.*, but they obtained them only in low yields without the addition of an organic solvent.[4]

The acids (3a, b, c) were esterified, and the esters (4a, b, c) were acetylated, by the action of acetyl chloride and aluminum chloride in carbon disulfide at room temperature to give keto-esters (5a, b, c); the procedure used was similar to that of the acetylation of the acetylbenzofurans.[3] To determine the position of the acetyl group of the keto-esters (5a and 5b), they were hydrolyzed to keto-acids (6a and 6b), and were then further oxidized to dicarboxylic acids by the bromoform reaction. On the other hand, the oxidation of

*1 Read before the 19th Annual Meeting of the Chemical Society of Japan, April, 1966.

1) a) A. Hantzsch, *Ber.*, **19**, 1294 (1886). b) R. Stoermer, *ibid.*, **28**, 1254 (1895); *Ann.*, **312**, 274 (1900). c) E. W. Smith, *Chem. Abstr.*, **32**, 2938 (1938). d) H. F. Birch and A. Robertson, *J. Chem. Soc.*, **1938**, 306. e) W. B. Whalley, *ibid.*, **1953**, 3479. f) E. Bisagni, N. P. Buu-Hoi and R. Royer, *ibid.*, **1955**, 3688, 3693. g) N. P. Buu-Hoi, E. Bisagni, R. Royer and C. Routier, *ibid.*, **1956**, 625. h) J. N. Chatterjea, *J. Indian Chem. Soc.*, **34**, 347 (1957). i) R. Royer, P. Domerseman and E. Bisagni, *Bull. Soc. Chim. France*, **1960**, 685. j) E. Bisagni and R. Royer, *ibid.*, **1960**, 1968.

2) a) H. Gilman, E. W. Smith and L. C. Cheney, *J. Am. Chem. Soc.*, **57**, 2095 (1935). b) E. Bisagni and R. Royer, *Bull. Soc. Chim. France*, **1962**, 925. C) R. Royer, M. Hubert-Habart, L. Rene and A. Cheutin, *ibid.*, **1964**, 1259. d) Y. Kawase, R. Royer, M. Hubert-Habart, A. Cheutin, L. Rene and J.-P. Buisson, *ibid.*, **1964**, 3131. e) R. Royer, E. Bisagni, M. Hubert-Habart, L. Rene and J.-P. Marquet, *ibid.*, **1965**, 1794.

3) a) Y. Kawase, M. Hubert-Habart, J.-P. Buisson and R. Royer, *Compt. Rend.*, **258**, 5007 (1964). b) R. Royer, Y. Kawase, M. Hubert-Habart, L. Rene and A. Cheutin, *Bull. Soc. Chim. France*, **1966**, 211.

4) E. Bisagni, J.-P. Marquet, A. Cheutin and R. Royer, *ibid.*, **1965**, 1464.

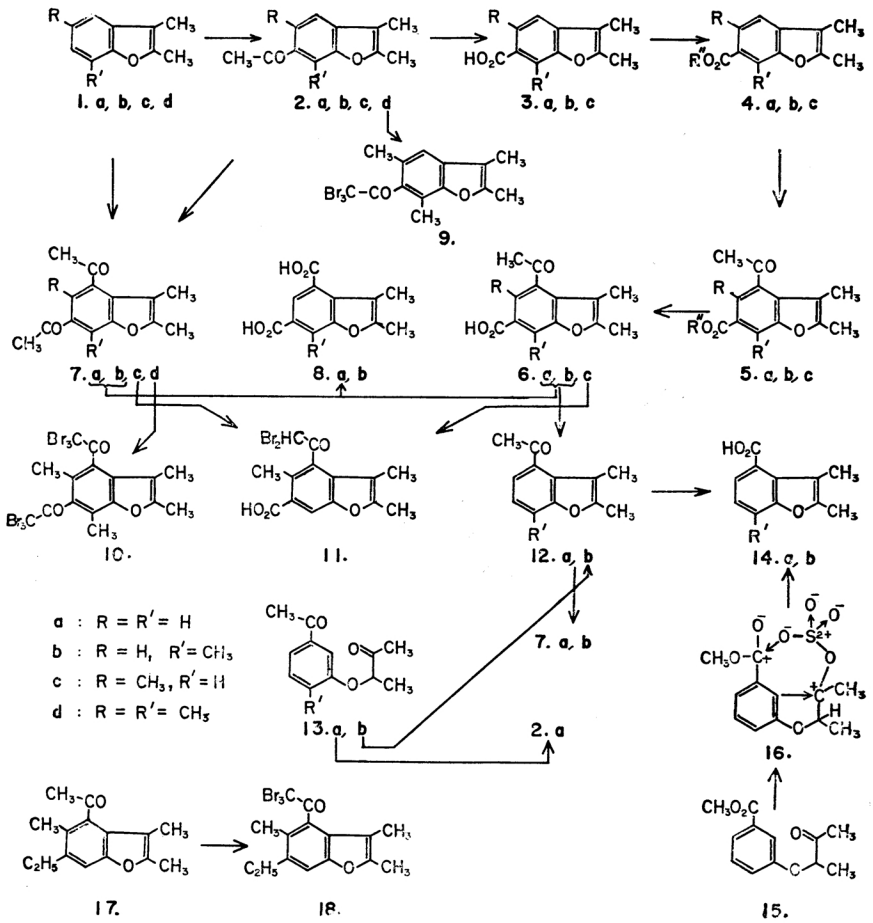


Chart 1

4, 6-diacetyl-2, 3-dimethylbenzofuran and its 7-methyl homolog (7a and 7b)[3] by the bromoform reaction gave 4, 6-dicarboxylic acids (8a and 8b), which were proved to be identical with the previously-mentioned dicarboxylic acids. Therefore, it has become clear that the direction of the acetylation of the esters, 4a and 4b, was similar to that of the ketones, 2a and 2b, and that the acetyl group did enter into the 4-position, as the structures of the diketones, 7a and 7b, had been defined.[3] This pattern of acetylation seems to be due to the strong activation by the furan ring oxygen surpassing the weak deactivation by the *m*-alkoxycarbonyl group at the 4-position.

In the normal course of the haloform reaction, the intermediate trihalo-ketone is readily hydrolyzed by alkali to give a carboxylic acid, but in the cases of 6-acetyl- and 4, 6-diacetyl-2, 3, 5, 7-tetramethylbenzofuran, 2d and 7d respectively, bromoketones were obtained; their structures were decided to be 6-(tribromoacetyl)- and 4, 6-di-(tribromoacetyl)-2, 3, 5, 7-tetramethylbenzofuran (9 and 10) respectively in view of their positive Beilstein Test, the results of analyses, their IR spectra, and the analogous reaction reported by Fuson and Walker[5] in the case of acetomesitylene. Therefore, it seems that the ketone, 2d or 7d, was only brominated to give the bromo-ketone, which it was difficult to hydrolyze to an acid because of the hindrance by both ortho methyl groups. The analogous reaction of 4, 6-diacetyl-2, 3, 5-trimethylbenzofuran (7c) furnished a bromoketo-acid, which was also obtained from the keto-acid 6c (prepared by the hydrolysis of the keto-ester 5c) by the bromoform reaction. The structure of the bromoketo-acid seems to be 4-(dibromoacetyl)-2,3,5-trimethylbenzofuran-6-carboxylic acid (11), because the carboxyl group of the bromoketo-acid is clearly at the 6-position; therefore, the unhindered 6-acetyl group of the diketone 7c undergoes the normal haloform reaction to give the carboxyl group, and the hindered 4-acetyl group only is dibrominated.

The keto-acids, 6a and 6b, were decarboxylated to give 4-acetyl-2, 3-dimethylbenzofuran (12a) and

5) R. C. Fuson and J. T. Walker, *J. Am. Chem. Soc.*, **52**, 3269 (1930).

its 7-methyl homolog (12b) respectively, by heating them in quinoline with copper powder. The acetylation of the ketones, 12a and 12b, afforded the diacetylbenzofurans, which were identical with the diketones, 7a and 7b; the ketone 12b was also synthesized through the authentic route from 3-hydroxy-4-methylacetophenone by the dehydro-cyclization of derived 3-(5-acetyl-2-methylphenoxy)-butanone-2 (13b). These results offer positive proof that the structure of 7b is 4, 6-diacetyl compound. The analogous cyclization of 3-(3-acetylphenoxy)-butanone-2 (13 a) furnished the 6-acetylbenzofuran (2a).

The 4-acetyl compounds, 12a and 12b, were also oxidized into the carboxylic acids (14a and 14b) by the bromoform reaction. The acid 14a was also obtained by the dehydro-cyclization of 3-(3-methoxycarbonylphenoxy)-butanone-2 (15) with sulfuric acid, cyclization having occurred in the *o*-position of the ester group, accompanied by the simultaneous hydrolysis of the ester group. It seems that this reaction proceeded through an intermediate (16), in which the intramolecular reaction between the ester group and the carbonyl group bounding with the sulfuric acid occurred, because the cyclization occurred exclusively in the ortho position of the ester group, because the ester group was easily hydrolyzed, and because the cyclization with polyphosphoric acid furnished a mixture of acids. The hindered 4-acetyl compound, 4-acetyl-6-ethyl-2, 3, 5-trimethylbenzofuran (17), prepared[3b] by the acetylation of the corresponding benzofuran or by the partial reduction of the 4, 6-diacetyl compound 7c, was also derived to a tribromoacetyl compound (18) by the bromoform reaction (See Chart 1).

The 5-acetyl-2, 3-dimethylbenzofuran (19), prepared[3a] by the dehydro-cyclization of 3-(4-acetylphenoxy)-butanone-2, was also oxidized to give an acid (20). Esterification furnished the ester (21), which was also obtained by the dehydro-cyclization of 3-(4-alkoxycarbonylphenoxy)-butanone-2 (22), accompanied by a small amount of the acid 20. The acetylation of the ester 21 also afforded a keto-ester, which was hydrolyzed to a keto-acid and was then decarboxylated to give the 6-acetyl compound (2a). Therefore, the keto-ester was proved to be alkyl 6-acetyl-2, 3-dimethylbenzofuran-5-carboxylate (23), the acetylation having occurred at the 6-position, and the keto-acid to be 6-acetyl-2, 3-dimethylbenzofuran-5-carboxylic acid (24). The oxidation of the keto-acid 24 by the bromoform reaction afforded 2, 3-dimethylbenzofuran-5, 6-dicarboxylic acid (25),

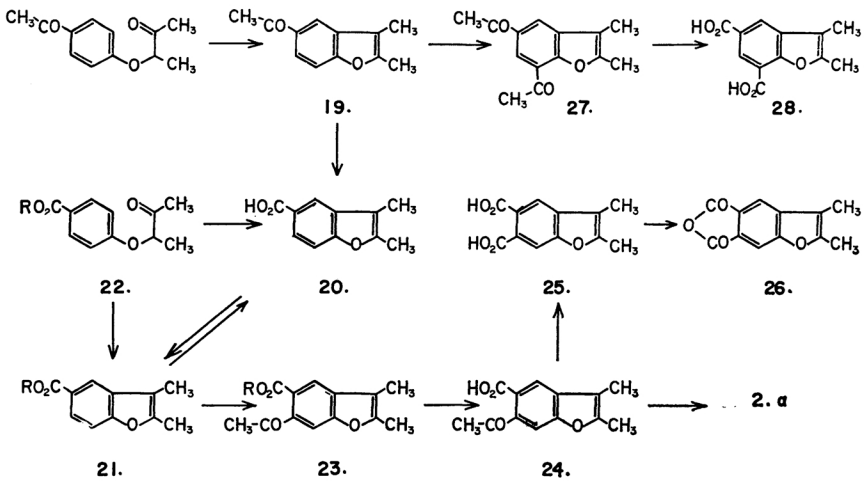


Chart 2

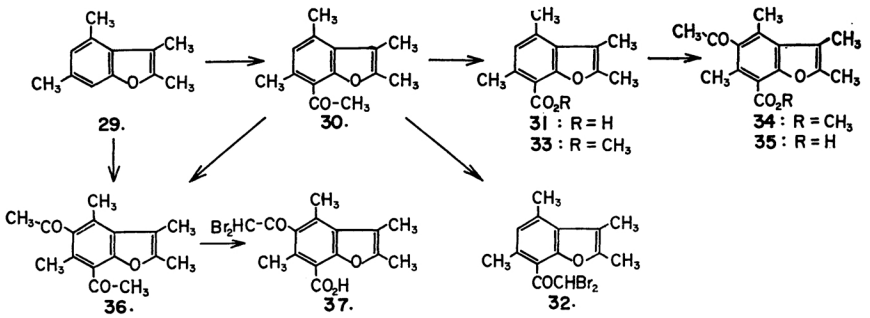


Chart 3

which was readily converted into an anhydride (26) by the action of acetic anhydride. The anhydride was readily brought back to the acid 25 by hydrolysis. On the other hand, the oxidation of the 5, 7-diacetyl compound (27), prepared[3a] by the acetylation of the 5-acetyl compound 19, furnished another dicarboxylic acid, 2, 3-dimethylbenzofuran-5, 7-dicarboxylic acid (28). It seems that in the case of the acetylation of the 5-acetyl compound 19, the 6-position is more deactivated by the *o*-carbonyl group than it is activated by the furan ring, and that the reaction occurs at the 7-position. On the other hand, the 6-position of the 5-alkoxycarbonyl compound 21 is less deactivated by the *o*-alkoxycarbonyl group, because the electron-attractive character of the ester group is weaker than that of the carbonyl group, and the acetylation occurs at the 6-position (See Chart 2).

The bromoform reaction of 7-acetyl-2, 3, 4, 6-tetramethylbenzofuran (30) furnished, analogously, the corresponding 7-carboxylic acid (31), accompanied by a small amount of a bromoketone (32). The esterification of the acid 31 was carried out to give an ester 33 in a good yield when it was refluxed with dimethyl sulfate and potassium carbonate in acetone, but in only a low yield when Fischer's method was used, this is probably because the carboxyl group is hindered by the ortho methyl group and the furan ring. The acetylation of the ester 33 afforded a keto-ester (34), which was hydrolyzed to a keto-acid (35). The 5, 7-diacetyl compound (36), prepared by the acetylation of the ketone 30 or by the diacetylation[3b] of the benzofuran 29, was also oxidized by the bromoform reaction to furnish a bromoketo-acid (37) in a low yield, the less hindered 7-acetyl group being oxidized to the carboxyl group and the hindered 5-acetyl group only being brominated (See Chart 3).

The unhindered acetyl groups of the ketones, diketones, keto-acids, and keto-esters have their ν_{CO}^{max} at 1670 cm^{-1}, while *o*, *o'*-substituted ones have them at 1690—1710 cm^{-1}, and the bromoacetyl groups, at 1715—1735 cm^{-1}. Similarly, the unhindered carboxyl groups of the acids, diacids, and keto-acids have their ν_{CO}^{max} at 1670—1680 cm^{-1}, and the ester groups, at 1700—1710 cm^{-1}. The 4-acetyl or 4-carboxyl groups seem to be somewhat hindered, even when the 5-positions are free, because their ν_{CO}^{max} are at 1680 cm^{-1} or 1685—1690 cm^{-1} respectively, while the 7-acetyl or 7-carboxyl group is less hindered even when the 6-position is methylated. The ortho keto-acid, keto-ester, and diacid have the ν_{CO}^{max} greatly shifted to a high wave number (See the table).

In conclusion, the patterns of the electrophilic substitutions in the benzene ring of alkylbenzofurans can be determined by studying the total effects of the furan ring and substituents on the benzene ring.

Experimental*2

3-Phenoxybutanones. Anhydrous potassium carbonate (52 g, 3 mol equivalents) and potassium iodide (5 g) were added to a solution of 3-hydroxyacetophenone (17 g) and 3-chlorobutanone-2 (15 g, 1 mol equivalent) in anhydrous acetone (200 m*l*), and the mixture was refluxed for 10 hr. The cooled mixture was then treated with water and extracted with ether, and the ethereal layer was washed with dilute aqueous sodium hydroxide and with water, and then dried. The ether was distilled off, and the residue was distilled to give 3-(3-acetylphenoxy)-butanone-2 (13a). By similar procedures, 3-(5-acetyl-2-methylphenoxy)-butanone-2 (13b), 3-(3-methoxycarbonylphenoxy)-butanone-2 (15), 3-(4-methoxycarbonylphenoxy)-butanone-2 (22, R=CH_3), and 3-(4-ethoxycarbonylphenoxy)-butanone-2 (22, R=C_2H_5) were also prepared, as is shown in the table.

Acetylbenzofurans. *a) By the Acetylation of Benzofurans.* 6-Acetyl-2, 3-dimethylbenzofuran (2a), 6-acetyl-2, 3, 7-trimethylbenzofuran (2b), 6-acetyl-2, 3, 5-trimethylbenzofuran (2c), 6-acetyl-2, 3, 5, 7-tetramethylbenzofuran (2d), 4-acetyl-6-ethyl-2, 3, 5-trimethylbenzofuran (17), and 7-acetyl-2, 3, 4, 6-tetramethylbenzofuran (30) were prepared by the methods of Refs. 2b, 2c, and 3b.

b) By the Dehydro-cyclization of Phenoxybutanones. i) With Polyphosphoric Acid (PPA): A mixture of 13a (5 g) and PPA (n=2.5, 100 g) was heated at 100°C for 1.5 hr; then the cooled mixture obtained was poured onto ice water and extracted with ether. The ethereal layer was washed with dilute aqueous sodium hydroxide and with water, and dried, and then the ether was distilled off. The residual product was distilled and then crystallized from petroleum ether to give 2a. This was identical with the sample described above.

ii) With Concentrated Sulfuric Acid: Concentrated sulfuric acid (15 g) was stirred, drop by drop, into 13b (15 g) under 30°C, after which the mixture was left for 1 hr at that temperature. The cooled mixture was then poured onto ice water and treated similarly as has been described in the case with polyphosphoric acid, thus giving 4-acetyl-2, 3, 7-trimethylbenzofuran (12b).

c) By the Decarboxylation of Keto-acids. A mixture of 4-acetyl-2, 3-dimethylbenzofuran-6-carboxylic acid (6a, 5.5 g), copper powder (5.5 g), and quinoline (100 m*l*) was refluxed for 3 hr; the cooled mixture was then filtered from the copper, and the filtrate was diluted with ether. The ethereal solution was washed with dilute hydrochloric acid to remove the quinoline, and with dilute aqueous sodium hydroxide. The ether was distilled off, and the residual product was distilled to give 4-acetyl-2, 3-dimethylbenzofuran (12a). Similarly, 2a and 12b were also obtained from the keto-acids 24 and 6b respectively.

Diacetylbenzofurans. *a) By the Diacetylation of Benzofurans.* Following the procedure described in Refs. 3a and 3b, 4, 6-diacetyl-2, 3-dimethylbenzofuran (7a), 4, 6-diacetyl-2, 3, 7-trimethylbenzofuran (7b), 4, 6-diacetyl-2, 3, 5-trimethylbenzofuran (7c), 4, 6-diacetyl-2, 3, 5, 7-tetramethylbenzofuran (7d), and 5, 7-diacetyl-2, 3, 4, 6-tetramethylbenzofuran (36) were prepared.

*2 The detailed data are listed in the table, in which the melting points and boiling points are uncorrected; the infrared spectra were measured by the KBr method.

TABLE

Compound	Starting compound	Method	Yield %	Mp °C or (bp °C/mmHg) and n (°C)	ν_{CO}^{max} cm^{-1}	Formula	C% Calcd. Found	H% Calcd. Found
3-Phenoxybutanones								
13 a			68	(173—181/20) 1.5262(24.5)	1710 1670	$C_{12}H_{14}O_3$	69.88 69.57	6.84 7.11
13 b			60	(180/20) 1.5288(13)	1715 1675	$C_{13}H_{16}O_3$	70.89 71.75	7.32 7.44
15			74	(173—176/21) 1.5139(25)	1715 (Broad)	$C_{12}H_{14}O_4$	64.85 64.48	6.35 6.48
22(Me)			60	(180—183/20) 1.5310(18)	1710 (Broad)	$C_{12}H_{14}O_4$	64.85 65.01	6.35 6.48
22(Et)			68	39—40	1715 (Broad)	$C_{13}H_{16}O_4$	66.08 65.78	6.83 6.78
Acetylbenzofurans[a]								
2 a	13 a	Cyclization by PPA	44	79—80.5[b]	1670			
2 a	24	Decarboxylation	32	79—80.5[b]				
12 a	6 a	Decarboxylation	54	(150—160/22)[c] 1.5807(27)	1680	$C_{12}H_{12}O_2$	76.57 76.15	6.43 7.08
12 b	13 b	Cyclization by H_2SO_4	47	45—45.5	1680	$C_{13}H_{14}O_2$	77.20 77.26	6.98 7.04
12 b	6 b	Decarboxylation	35	45—45.5				
Bromoacetyl-benzofurans								
9	2 d	NaOBr	47	165—167	1720	$C_{14}H_{13}O_2Br_3$	37.12 37.76	2.89 2.95
18	17	NaOBr	50	98—98.5	1715	$C_{15}H_{15}O_2Br_3$	38.55 38.47	3.24 3.34
32	30	NaOBr	3	104—106	1720	$C_{14}H_{14}O_2Br_2$	44.95 45.24	3.77 3.55
Diacetylbenzofurans[d]								
7 a	12 a	Acetylation	25	99—101[e]	1680 1670			
7 b	2 b	Acetylation	44	80—81.5[f]	1680	$C_{15}H_{16}O_3$	73.75 73.73	6.60 6.58
7 b	12 b	Acetylation	27	80—81.5[f]				
7 d	2 d	Acetylation	84	85.5—86.5[g]	1710 1690	$C_{16}H_{18}O_3$	74.39 74.45	7.02 7.22
36	30	Acetylation	12	98—98.5[h]	1710 1670	$C_{16}H_{12}O_3$	74.39 74.76	7.02 7.22
Di-(bromoacetyl)-benzofuran								
10	7 b	NaOBr	89	208—209	1730	$C_{16}H_{12}O_3Br_6$	26.26 26.31	1.65 1.52
Benzofuran-carboxylic Acids								
3 a	2 a	NaOBr	78	225—226[i]	1670	$C_{11}H_{10}O_3$	69.46 68.90	5.30 5.22
3 a	2 a	NaOCl	38[j]	225—226[i]				
3 b	2 b	NaOBr	66.5	242—243	1670	$C_{12}H_{12}O_3$	70.57 70.03	5.92 5.82
3 c	2 c	NaOBr	81	212—213	1680	$C_{12}H_{12}O_3$	70.57 70.47	5.92 5.86
14 a	12 a	NaOBr	50	171—172	1685	$C_{11}H_{10}O_3$	69.46 69.56	5.30 5.28
〃	15	Cyclization by H_2SO_4	57	171—172				
14 b	12 b	NaOBr	30	177—178	1690	$C_{12}H_{12}O_3$	70.57 70.68	5.92 5.81
20	19	NaOBr	70	241—242[k]	1670	$C_{11}H_{10}O_3$	69.46 69.17	5.30 5.12
20	19	NaOCl	55[l]	241—242[k]				
20	21(Me)	KOH	60	241—242[k]				
20	21(Et)	KOH	69	241—242[k]				
31	30	NaOBr	52	217—218	1670	$C_{13}H_{14}O_3$	71.54 71.51	6.47 6.47

TABLE (Continued)

Compound	Starting compound	Method	Yield %	Mp °C or (bp °C/mmHg) and n (°C)	ν_{CO}^{max} cm^{-1}	Formula	C% Calcd. Found	H% Calcd. Found
Benzofuran-dicarboxylic Acids								
8 a	6 a	NaOBr	33	326 (decomp.)	1680 (Broad)	$C_{12}H_{10}O_5$	61.54 61.54	4.30 4.28
8 a	7 a	NaOBr	79	326 (decomp.)				
8 b	6 b	NaOBr	40	280—283	1680 (Broad)	$C_{13}H_{12}O_5$	62.90 62.77	4.87 4.64
8 b	7 b	NaOBr	33	280—283				
25	24	NaOBr	33	226—227	1690 (Broad)	$C_{12}H_{10}O_5$	61.54 61.52	4.30 3.62
28	27	NaOBr	60	310 (decomp.)	1685 (Broad)	$C_{12}H_{10}O_5$	61.54 60.72	4.30 3.78
Acetylbenzofuran-carboxylic Acids								
6 a	5a(Me)	KOH	92.5	210—211	1680 (Broad)	$C_{13}H_{12}O_4$	67.23 67.15	5.21 5.30
6 a	5a(Et)	KOH	56	210—211				
6 b	5b(Me)	KOH	89	234—235	1680 (Broad)	$C_{14}H_{14}O_4$	68.28 68.42	5.73 5.86
6 c	5c(Me)	KOH	86	209—210.5	1710 1685	$C_{14}H_{14}O_4$	68.28 68.11	5.73 5.77
24	23(Me)	KOH	50	146—147	1735 (Broad)	$C_{13}H_{12}O_4$	67.23 66.68	5.21 5.04
24	23(Et)	KOH	68	146—147				
35	34	KOH	70	179—180	1710 1670	$C_{15}H_{16}O_4$	69.21 68.94	6.20 6.08
Bromoacetyl-benzofuran-carboxylic Acids								
11	6 c	NaOBr	65	207—208	1725 1680	$C_{14}H_{12}O_4Br_2$	41.22 41.38	2.75 2.67
11	7 c	NaOBr	45	207—208				
37	36	NaOBr	15	198	1720 1700	$C_{15}H_{24}O_4Br_2$	43.10 43.39	3.38 3.06
Esters of Benzofuran-carboxylic Acids								
4a(Me)	3 a	Me_2SO_4-K_2CO_3	87	87.5—88	1700	$C_{12}H_{12}O_3$	70.57 70.67	5.92 5.96
4a(Me)	3 a	MeOH-H_2SO_4	74.5	37.5—88				
4a(Et)	3 a	EtI-K_2CO_3	11.5	48—49	1700	$C_{13}H_{14}O_3$	71.54 71.69	6.47 6.40
4b(Me)	3 b	Me_2SO_4-K_2CO_3	82	88—88.5	1705	$C_{13}H_{14}O_3$	71.54 71.47	6.47 6.66
4c(Me)	3 c	Me_2SO_4-K_2CO_3	77	57.5—58	1710	$C_{13}H_{14}O_3$	71.54 71.33	6.47 6.76
4c(Et)	3 c	EtI-K_2CO_3	62	78.5—80	1720	$C_{14}H_{16}O_3$	72.39 72.42	6.94 7.06
21(Me)	20	Me_2SO_4-K_2CO_3	63	57—58	1710	$C_{12}H_{12}O_3$	70.57 71.17	5.92 6.03
21(Me)	20	MeOH-H_2SO_4	75	57—58				
21(Me)	22(Me)	Cyclization by H_2SO_4	71	57—58				
21(Et)	22(Et)	Cyclization by H_2SO_4	81	(180—183/22) 1.5449(15)	1720	$C_{13}H_{14}O_3$	71.54 71.89	6.47 6.67
33	32	Me_2SO_4-K_2CO_3	85	82.5—84	1715	$C_{14}H_{16}O_3$	72.39 72.12	6.94 7.12
Esters of Acetylbenzofuran-carboxylic Acids								
5a(Me)	4a(Me)	Acetylation	81	78—79.5	1700 1670	$C_{14}H_{14}O_4$	68.28 68.20	5.73 5.49
5a(Et)	4a(Et)	〃	8	67.5—69	1700 1670	$C_{15}H_{16}O_4$	69.21 68.85	6.20 6.30
5b(Me)	4b(Me)	〃	33	120—121	1710 1680	$C_{15}H_{16}O_4$	69.21 68.99	6.20 6.55

TABLE (Continued)

Compound	Starting compound	Method	Yield %	Mp °C or (bp °C/mmHg) and *n* (°C)	ν_{CO}^{max} cm^{-1}	Formula	C% Calcd. Found	H% Calcd. Found
5c(Me)	4c(Me)	Acetylation	16	111—112.5	{1710 1695	$C_{15}H_{16}O_4$	69.21 69.03	6.20 6.40
23(Me)	21(Me)	Acetylation	40	61—63	{1710 1700	$C_{14}H_{14}O_4$	68.28 68.70	5.73 5.93
23(Et)	21(Et)	Acetylation	25	66—68	{1705 1690	$C_{15}H_{16}O_4$	69.21 69.04	6.20 6.28
34	33	Acetylation	34	130—131.5	1720 (Broad)	$C_{16}H_{18}O_4$	70.05 70.25	6.61 6.75

a) The ν_{CO}^{max} of the ketones not listed here are: 2b, 1670; 2c, 1670; 2d, 1710; 17, 1695; 19, 1670; 30, 1670 cm^{-1}, respectively.
b) Reported melting point is 77.5°C (Ref. 2b).
c) 2,4-Dinitrophenylhydrazone, mp 252°C. Found: C, 59.35; H, 4.10; N, 14.52%. Calcd for $C_{18}H_{16}O_5N_4$: C, 58.69; H, 4.38; N, 15.21%.
d) The ν_{CO}^{max} of the diketones not listed here are: 7c, 1710, 1680; 27, 1710, 1670 cm^{-1}, respectively.
e) Reported melting point is 101°C (Ref. 3a).
f) Reported melting point is 76°C (Ref. 3b).
g) Reported melting point is 83—84°C (Ref. 3b).
h) Reported melting point is 98—99°C (Ref. 3b).
i) Reported melting point is 228—229°C (decomp.) and yield is 25% without the addition of a solvent (Ref. 4).
j) Recovery is 49%.
k) Reported melting point is 242°C and yield is 7% without the addition of a solvent (Ref. 4).
l) Recovery is 30%.

b) By the Acetylation of Acetylbenzofurans. Powdered anhydrous aluminum chloride (2.7 g, 3 mol equivalents) was gradually stirred, at room temperature, into a solution of 12a (1.5 g) and acetyl chloride (0.7 g, 1.1 mol equivalents) in carbon disulfide (50 *ml*); the mixture was stirred for 2 more hr at room temperature and then left overnight. The next day, the mixture was poured onto ice water, and then extracted with chloroform. The product, 7a, was obtained from the organic layer through distillation and crystallization from cyclohexane. Similarly, 7b, 7c, 7d, 27, and 36 were prepared, among which the preparations of 7c and 27 have been reported in Refs. 3a and 3b.

Benzofuran-carboxylic Acids. *a) By the Haloform Reaction. i) With Hypobromide:* Aqueous sodium hypobromide was prepared by the gradual stirring of bromine (77 g, 3.5 mol equivalents) into a mixture of aqueous sodium hydroxide (50 g, 8 mol equivalents, in 145 m*l* of water) and ice (145 g). To this solution, 2a (27 g) and dioxane or tetrahydrofuran (150 m*l*) were added at one time, after which the mixture was stirred vigorously at 15°C for 0.5 hr and then at 45°C for 1.5 hr. The resulting mixture was diluted with water and extracted with ether. The aqueous layer was acidified after the addition of an adequate amount of sodium sulfite. The precipitates formed were collected, washed with water, and crystallized from methanol or ethanol to give 2, 3-dimethylbenzofuran-6-carboxylic acid (3a). Similarly, 2, 3, 7-trimethylbenzofuran-6-carboxylic acid (3b), 2, 3, 5-trimethylbenzofuran-6-carboxylic acid (3c), 2, 3-dimethylbenzofuran-4-carboxylic acid (14a), 2, 3, 7-trimethylbenzofuran-4-carboxylic acid (14b), and 2, 3-dimethylbenzofuran-5-carboxylic acid (20) were obtained. In the case of 7-acetyl-2, 3, 4, 6-tetramethylbenzofuran (30), the sodium salt of the resulting acid was produced as a precipitate at the end of the reaction; therefore, the precipitate was collected, washed with ether, and then treated with dilute hydrochloric acid to give prcipitates of the free acid. The aqueous filtrate was washed with ether, and then acidified to give precipitates. Both the ether solutions were concentrated and submitted to steam distillation, and the residues were collected and crystallized from cyclohexane to give 7-(dibromoacetyl)-2, 3, 4, 6-tetramethylbenzofuran (32). The two precipitates were then combined and crystallized from methanol to give 2, 3, 4, 6-tetramethylbenzofuran-7-carboxylic acid (31) as the main product.

ii) With Aqueous Sodium Hyprochloride: 5-Acetyl-2, 3-dimethylbenzofuran (19, 1 g) and dioxane or tetrahydrofuran (10 m*l*) were added to a solution of commercial aqueous sodium hypochloride (active chlorine 10%, 9 g, 5 mol equivalents) and aqueous sodium hydroxide (10%, 10 g), and the mixture was treated much as in the case with sodium hypobromide to give the acid 20. Similarly, 3a was obtained from 2a.

b) By the Dehydro-cyclization of Butanone. 3-(3-Methoxycarbonylphenoxy)-butanone-2 (15, 5 g) was treated with concentrated sulfuric acid (5 g) by much the same method as has been described for 13a. The product, 14a, was obtained from the alkaline-soluble part through crystallization from methanol. It was identical with the sample described above.

c) By the Hydrolysis of Esters. A mixture of methyl or ethyl 2, 3-dimethylbenzofuran-5-carboxylate (21, 1 g), aqueous potassium hydroxide (20%, 10 m*l*), and ethanol (20 m*l*) was refluxed for 3 hr, and then treated as usual to give the acid 20, which was identical with the other sample.

Benzofuran-dicarboxylic Acids. *a) From Diacetylbenzofurans.* 4, 6-Diacetyl-2, 3-dimethylbenzofuran (7a) was treated with aqueous sodium hypobromide (7 mol equivalents), much as has been described for the acetylbenzofurans, to give 2, 3-dimethylbenzofuran-

4, 6-dicarboxylic acid (8a). 2, 3, 7-Trimethylbenzofuran-4, 6-dicarboxylic acid (8b) and 2, 3-dimethylbenzofuran-5, 7-dicarboxylic acid (28) were obtained similarly from 7b and 27 respectively.

b) From Keto-acids. 4-Acetyl-2, 3-dimethylbenzofuran-6-carboxylic acid (6a, 1.2 g) was treated with aqueous sodium hypobromide prepared from sodium hydroxide (3 g, 10 mol equivalents) and bromine (3.2 g, 4 mol equivalents), and then treated much as has been described before to give 8a. Similarly, 8b and 2, 3-dimethylbenzofuran-5, 6-dicarboxylic acid (25) were obtained from the keto-acids, 6b and 24, respectively. The dicarboxylic acid 25 (1 g) was heated with acetic anhydride (5 ml) on a steam bath for 1 hr; the precipitates formed on cooling were collected and crystallized from benzene or chloroform to give the anhydride 26 (0.3 g). Mp 228°C (uncorr.).

Found: C, 67.29; H, 3.16%. Calcd for $C_{12}H_8O_4$: C, 66.67; H, 3.73%.

IR: ν_{CO}^{max} (phthalic anhydride) 1845, 1780 cm^{-1}.

They were insoluble in cold aqueous sodium hydroxide, and dissolved on heating. The acidification of the alkaline solution furnished precipitates which were identical with the acid 25.

Bromoacetyl-benzofurans. The ketone 2d (9 g) was treated with aqueous sodium hypobromide (3.5 mol equivalents) much as when the carboxylic acid was obtained from the ketone. The reaction mixture containing many precipitates was filtered, and the precipitates were washed with water, dried, and then crystallized from cyclohexane or ethanol to give 6-(tribromoacetyl) - 2, 3, 5, 7 - tetramethylbenzofuran (9), which have a positive Beilstein Test. Similarly, 4-(tribromoacetyl)-6-ethyl-2, 3, 5-trimethylbenzofuran (18) was obtained from the ketone 17, and the bromoketone 32 was obtained as a by-product from the ketone 30, as has been described before. In the case of the diacetyl compound 7d, the amount of the reagent was doubled and the product was 4, 6-di(tribromoacetyl)-2, 3, 5, 7-tetramethylbenzofuran (10).

Bromoacetyl-benzofuran-carboxylic Acids. *a) From Diacetylbenzofurans.* The diketone 7c (3 g) was treated with aqueous sodium hypobromide (7 mol equivalents), much as has been described before, to give 4-(dibromoacetyl)-2, 3, 5-trimethylbenzofuran-6-carboxylic acid (11), which gave a positive Beilstein Test. In the case of the diketone 36, the sodium salt of the resulting acid, 4-(dibromoacetyl)-2, 3, 4, 6-tetramethylbenzofuran-7-carboxylic acid (37), was insoluble in water; therefore, it was treated much as has been described in the case of the acid 31.

b) From Keto-acid. 4-Acetyl-2, 3, 5-trimethylbenzofuran-6-carboxylic acid (6 c, 1 g) was treated with aqueous sodium hypobromide, similarly as described in the case of the keto-acid 6a, to give the bromoketo-acid 11, which was identical with the sample described above.

Esters of the Acids. *a) By the Dehydro-cyclization of Phenoxybutanones.* Ten grams of the phenoxybutanone 22 ($R=CH_3$ or C_2H_5) were treated with concentrated sulfuric acid (10 g), much as has been described before for the other phenoxybutanones, to give methyl or ethyl 2, 3-dimethylbenzofuran-5-carboxylate (21, $R=CH_3$ or C_2H_5 respectively), accompanied by a small amount of the free acid (20).

b) By the Esterification of Acids. i) With Diethyl Sulfate and Potassium Carbonate: Anhydrous potassium carbonate (30 g, 4 mol equivalents) was added to a solution of the acid 3a (14 g) and dimethyl sulfate (10 g, 1.5 mol equivalents) in anhydrous acetone (300 ml), after which the mixture was refluxed for 10 hr. The cooled mixture was treated with water and extracted with ether. The ethereal solution was washed with dilute aqueous sodium hydroxide, with water, and dried. The distillation and crystallization (from petroleum ether) of the product furnished methyl 2, 3-dimethylbenzofuran-6-carboxylate (4a, $R''=CH_3$). Similarly, methyl 2, 3, 7-trimethylbenzofuran-6-carboxylate (4b, $R''=CH_3$), methyl 2, 3, 5-trimethylbenzofuran-6-carboxylate (4c, $R''=CH_3$), 21 ($R=CH_3$), and methyl 2, 3, 4, 6-tetramethylbenzofuran - 7 - carboxylate (33) were obtained from the corresponding acids. Two ethyl esters, 4a ($R''=C_2H_5$) and 4c ($R''=C_2H_5$) were also obtained by refluxing the acids with ethyl iodide and potassium carbonate in acetone.

ii) Following Fischer's Method: A solution of the acid 3a (1 g) in methanol (10 ml) containing concentrated sulfuric acid (1 g) was refluxed for 3 hr, and then treated as usual to give the methyl ester 4a ($R''=CH_3$). Two esters, 21 ($R=CH_3$) and 33, were obtained similarly; the yield of the latter ester was not good, however, probably because of the hindrance.

Acetylbenzofuran-carboxylates. Powdered anhydrous aluminum chloride (11 g, 2.5 mol equivalents) was gradually stirred, at room temperature, into a solution of the ester 4a ($R''=CH_3$, 6.5 g) and acetyl chloride (2.8 g, 1.1 mol equivalents) in carbon disulfide (100 ml); after the mixture had then been stirred for 2 more hr, it was left overnight. The next day, the mixture was poured onto ice water and extracted with chloroform. The chloroform solution was treated as usual to give methyl 4-acetyl-2, 3-dimethylbenzofuran-6-carboxylate (5a, $R''=CH_3$) through distillation and crystallization from pertoleum ether. Ethyl 4-acetyl-2, 3-dimethylbenzofuran-6-carboxylate (5a, $R''=C_2H_5$), methyl 4-acetyl-2, 3, 7-trimethylbenzofuran-6-carboxylate (5b, $R''=CH_3$), methyl 4-acetyl-2, 3, 5-trimethylbenzofuran-6-carboxylate (5c, $R''=CH_3$), methyl or ethyl 6-acetyl-2, 3-dimethylbenzofuran-5-carboxylate (23, $R=CH_3$ or C_2H_5), and methyl 5-acetyl-2, 3, 4, 6-tetramethylbenzofuran-7-carboxylate (34) were obtained similarly.

Acetylbenzofuran-carboxylic Acids. A mixture of the keto-ester 5a ($R''=CH_3$, 6 g), aqueous potassium hydroxide (20%, 50 ml), and ethanol (50 ml) was refluxed for 3 hr and then treated as usual to give 4-acetyl-2, 3-dimethylbenzofuran-6-carboxylic acid (6a) through crystallization from methanol or ethanol. 4-Acetyl-2, 3, 7-trimethylbenzofuran-6-carboxylic acid (6b), 4-acetyl-2, 3, 5-trimethylbenzofuran-6-carboxylic acid (6c), 6-acetyl-2, 3-dimethylbenzofuran-5-carboxylic acid (24), and 5-acetyl-2, 3, 4, 6-tetramethylbenzofuran-7-carboxylic acid (35) were also obtained similarly from their esters.

The authors are grateful to the members of the Laboratory of Microanalyses, Faculty of Pharmacology, Toyama University, and the Institute of Industrial Sciences, Osaka University, for their microanalyses. This work was supported in part by a grant from the Ministry of Education, for which the authors are also grateful.