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The Friedel-Crafts Reaction of 2,3-Dimethylbenzofuranyl Ketones and the Corresponding Carboxylic Esters[*1]

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The acetylation of methyl 2,3-dimethyl-4- and -7-benzofurancarboxylates was carried out by the action of acetyl chloride and aluminum chloride in carbon disulfide at room temperature to afford the 6-acetyl compounds; these compounds were converted to keto-acids by hydrolysis, and then to the known dicarboxylic acid or to the known 6-acetylbenzofuran. The alkylation of acetyl and methoxycarbonyl derivatives of 2,3-dimethylbenzofuran was carried out by the action of *n*- or iso-propyl bromide and aluminum chloride in carbon disulfide at reflux temperature, both the bromides furnishing the same isopropylated product. The crude products from the 4-acetyl- and 4-methoxycarbonyl-benzofurans could not be purified, but 2,3-dimethyl-6-isopropyl-4-benzofurancarboxylic acid was obtained by the hydrolysis of the product from the latter. In the cases of 5-acetyl- and 5-methoxycarbonyl-benzofurans, the isopropylation occurred at the 7-position and the products were converted to the same carboxylic acids, while the isopropylation occurred at the 4-position in the cases of 6-acetyl- and 6-methoxycarbonylbenzofurans, and diisopropylation occurred in the case of 7-methoxycarbonylbenzofuran.

In previous papers, one of the present authors and others reported that acetylation by the Fridel-Crafts reaction of acetyl-[1—4] and methoxycarbonyl-2,3-dimethylbenzofurans[4] afforded the acetylated compounds, generally in the *m*-position to the acetyl or methoxycarbonyl group except that methyl 2,3-dimethyl-5-benzofurancarboxylate (**9b**) afforded the 6-acetylated compound; they also reported that the isopropylation of the 2,3-dimethyl-6-benzofuranyl methyl ketone (**5**) furnished the 4-isopropyl compound[1,2] (**18**).

In connection with this, the acetylation of other isomeric methyl benzofurancarboxylates (**8b** and **23b**) and the alkylation of benzofuranyl methyl ketones (**3**, **4** and **5**) by the Friedel-Crafts reaction have been studied further; also, extended studies of the alkylation of methyl benzofurancarboxylates (**8b**, **9b**, **10b** and **23b**) have been carried out.

At first, some examinations of the preparation of starting compounds were carried out[5] (Chart 1);

[*1] A major part of this paper was presented at the 21st Annual Meeting of the Chemical Society of Japan, Osaka, March, 1968.

[1] Y. Kawase, M. Hubert-Habart, J.-P. Buisson and R. Royer, *Compt. Rend.*, **258**, 5007 (1964).

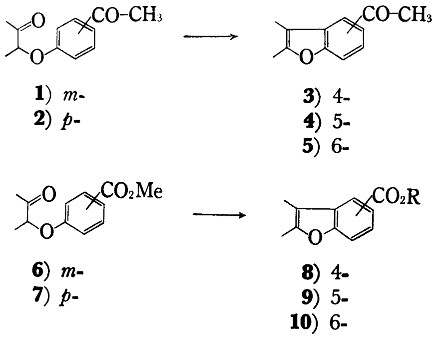
[2] Y. Kawase, R. Royer, M. Hubert-Habart, A. Cheutin, L. René and J.-P. Buisson, *Bull. Soc. Chim. Fr.*, **1964**, 3131.

[3] R. Royer, Y. Kawase, M. Hubert-Habart, L. René and A. Cheutin, *ibid.*, **1966**, 211.

[4] Y. Kawase and M. Takashima, This Bulletin, **40**, 1224 (1967).

[5] Preliminary report: Y. Kawase, *Chem. Ind.* (London), **1970**, 687.

3-(*m*- and *p*-acetylphenoxy)butanones[4,6] (**1** and **2**) were treated with concentrated sulfuric acid at 45 or 60°C for 30 min to give 2,3-dimethyl-4- and -5-benzofuranyl methyl ketones (**3** and **4**) respectively, while **1** and **2** afforded 2,3-dimethyl-6- and -5-benzofuranyl methyl ketones (**5** and **4**) by means of the action of polyphosphoric acid.[4,5] Therefore, the almost pure ketone **3** could be prepared much more easily than by the reported method;[4] however, the product was found by the NMR spectroscopy to contain only a small amount (*ca.* 1%) of the isomeric ketone (**5**). On the other hand, 3-(*m*- and *p*-methoxycarbonylphenoxy)-butanones[4] (**6** and **7**) were treated with polyphosphoric acid at 100°C for 1 hr to give a mixture of 2,3-dimethyl-4- and -6-benzofurancarboxylic acids (**8a** and **10a**) and 2,3-dimethyl-5-benzofurancarboxylic acid (**9a**) respectively, the ester group having been hydrolyzed, while **6** and **7** afforded 4-benzofurancarboxylic acid (**8a**) and methyl 5-benzofurancarboxylate (**9b**) respectively, by the action of concentrated sulfuric acid.[4]



In all charts: a) R=H, b) R=Me

Chart 1

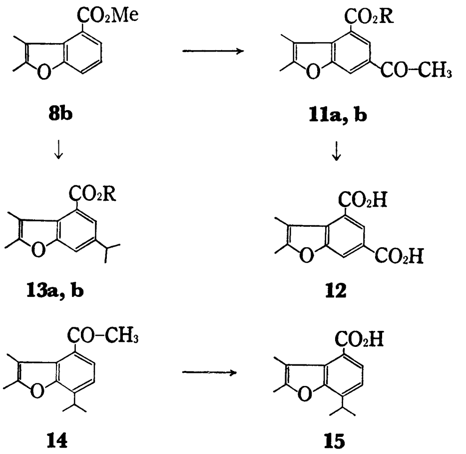


Chart 2

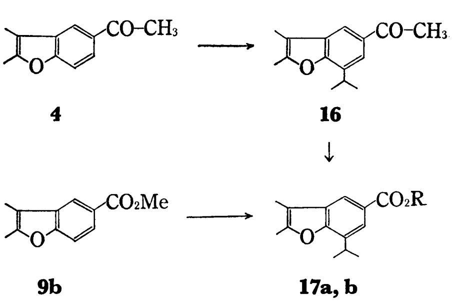


Chart 3

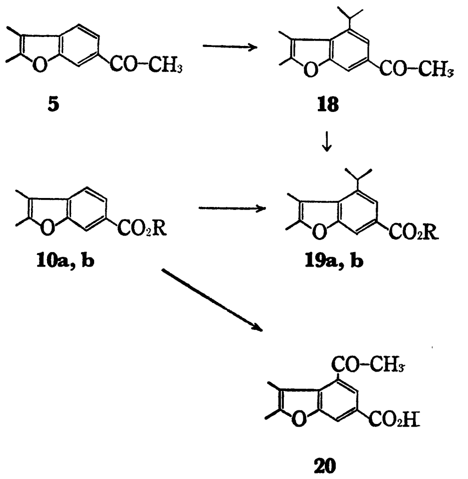


Chart 4

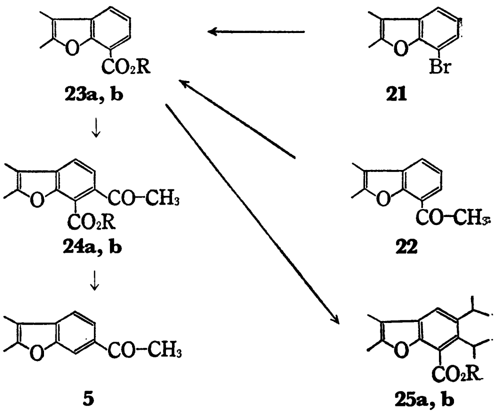


Chart 5

The mixture of 4- and 6-carboxylic acids (**8a** and **10a**) described above could not be separated by crystallization or chromatography, but the ratio of the components was determined by estimating the areas of the peaks corresponding to the 3-methyl protons of **8a** and **10a** (δ=2.22 and 2.17 ppm respectively) in the NMR spectrum of the mixture. The ring closure of **1** and **6** occurred at the ortho position of the acetyl or methoxy-

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6) E. Bisagni, J. -P. Marquet, A. Cheutin, R. Royer and M. L. Desvoye, *Bull. Soc. Chim. Fr.*, **1965**, 1466.

carbonyl group by means of sulfuric acid and mainly at the para position by means of polyphosphoric acid. 2,3-Dimethyl-7-benzofurancarboxylic acid (**23b**) was prepared by the action of carbon dioxide on the Grignard reagent prepared from 7-bromobenzofuran[7] (**21**) or by the bromoform reaction of the 7-benzofuranyl methyl ketone[7] (**22**), and methyl 4- and 7-benzofurancarboxylates (**8b** and **23b**) were prepared by the esterification of the corresponding carboxylic acids (**8a** and **23a**).

Therefore, the actylation of the esters **8b** and **23b** was carried out much as has been reported before[4] by the action of acetyl chloride and aluminum chloride in carbon disulfide at room temperature; this gave the acetylated compounds (**11b** and **24b**) (Charts 2 and 5). The position of the acetyl group was determined by NMR spectroscopy and also by converting the keto-esters to known compounds; the keto-esters (**11b** and **24b**) were converted to the corresponding keto-acids (**11a** and **24a**). The keto-acid **11a** was oxidized by the bromoform reaction to the known 2,3-dimethyl 4,6-dicarboxylic acid[4] (**12**); this indicated that the acetylation occurred at the 6-position of the ester **8b**, similarly to the case of the 4-benzofuranyl methyl ketone[4] (**4**). The keto-acid **24a** was decarboxylated to the ketone **5**;[6] this indicated that the acetylation occurred at the 6-position of the ester, **23b**, as in the case of methyl 2,3-dimethyl-5-benzofurancarboxylate[4] (**9b**). The analogous acetylation of 6-carboxylic acid (**10b**) furnished the 4-acetyl compound (**20**), which was identical with the authentic sample prepared by the acetylation of the 6-carboxylic ester (**10b**), followed by hydrolysis[4] (Chart 4).

Next, the alkylation of the ketones (**3**, **4** and **5**) and the esters (**8b**, **9b**, **10b** and **23b**) was carried out by the use of *n*- or iso-propyl bromide and alminum chloride in carbon disulfide at the reflux temperature, whereas the alkylation occurred at room temperature in the cases of the 6-substituted compounds (**5** and **10b**). Normal- and iso-propyl bromide gave the same isopropylated products, probably through the isomerization of the *n*-propyl group, while ethyl bromide or iodide and aluminum chloride or bromide gave no alkylation products.

In the cases of the ketone **3** and the ester **8b** (Chart 2), the crude products could not be purified by usual methods; it was confirmed by gas chromatography that they contained some recovery compounds and two other compounds in each case. The crude product from the ester **8b** was hydrolyzed and then crystallized to give pure 2,3-dimethyl-6-isopropyl-4-benzofurancarboxylic acid (**13b**). The position of the isopropyl group was determined from the fact that the compound was not identical with 2,3-dimethyl-7-isopropyl-4-benzofurancarboxylic acid (**15**), which had itself been prepared by the bromoform reaction of the corresponding ketone[2] (**14**), and from the pattern of the NMR spectrum.

The alkylation of the ketone **4** and the ester **9b** was carried out similarly to give the isopropylated ketone (**16**) and ester (**17b**) (Chart 3); these products were then both converted to the same 2,3-dimethyl-7-isopropyl-5-benzofurancarboxylic acid (**17a**) by the bromoform reaction or by hydrolysis respectively. The ketone **16** was identical with an authentic sample[2] prepared from the 4-hydroxy-3-isopropylphenyl methyl ketone, and the NMR spectra of **16** and **17b** had two doublets (J=2 Hz) corresponding to the aromatic protons, indicating that the two aromatic hydrogens were at positions meta to each other.

The alkylation of the ketone **5** and the ester **10b** afforded the known 4-isopropyl compounds (**18** and **19b**)[2,8] (Chart 4).

The alkylation of the ester **23b** by a similar procedure afforded a mixture which was proved by gas chromatography to contain the recovery compound and four other compounds. The crude product was hydrolyzed and then crystallized from ethanol to give an acid, the structure of which was confirmed to be 2,3-dimethyl-5,6-diisopropyl-7-benzofurancarboxylic acid (**25a**) from the data of microanalysis and the NMR spectrum (Chart 5). The NMR spectrum of **25a** had a peak corresponding to one aromatic proton and two doublets corresponding to two isopropyl methyl protons, plus a peak corresponding to 3-methyl protons which was in a higher field than in the cases of 4-substituted compounds,[5,8] indicating that **25a** had no substituent in the 4-position.

In conclusion, we can say that in the electrophilic substitution of *bz*-acetyl or *bz*-methoxycarbonyl derivatives of 2,3-dimethylbenzofuran, all position, but especially the 6- and 4-positions, are activated by the effect of the furan ring,[1-4] and that the *m*-position relative to the acetyl or methoxycarbonyl group is less deactivated than the *o*- or *p*-position by the effect of the group. In the cases of the acetylation of **8b** and the alkylation of **5** and **10b**, the reaction occurred at the 6- and 4-positions, favored by both effects, and the effect of the furan ring predominated in the acetylation of **23b**, while the substituent effect dominated in the alkylation of **4** and **9b** and the polyalkylation occurred in the alkylation of **3**, **8b** and **23b**.

Experimental

All the melting points and boiling points are uncorrected, and IR spectra were measured in the form

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[7] C. Pène, P. Demerseman, A. Cheutin and R. Royer, *Bull. Soc. Chim. Fr.*, **1966**, 586.

[8] Y. Kawase, S. Takata and T. Miwa, This Bulletin, **43**, 1796 (1970).

of KBr disks in the case of solid samples, and the gas chromatography was carried out on a Hitachi K23 apparatus, with Silicone DC-11 on Chamelite as a stationary phase, a flow rate, He, of 46 m*l*/min (0.7 kg/cm^3), and a temperature rise of 5°C/min from 180°C. The NMR spectra were measured on a Nihon Denshi 60 MHz spectrometer in carbon tetrachloride (*ca.* 5% solution), unless otherwise noted, with TMS as the internal standard. The detailed data are summarized in the tables.

Materials. *a) Aryloxybutanones.* The 3-(*m*- and *p*-acetyphenoxy)butanones[4,6] (**1** and **2**) and 3-(*m*- and *p*-methoxycarbonylphenoxy)butanones[4] (**6** and **7**) were prepared following the methods in the references.

b) Benzofuranyl Methyl Ketones. 2,3-Dimethyl-6-[9] and -7-benzofuranyl methyl ketones[7] (**5** and **22**) and 2,3-dimethyl-7-isopropyl-4-benzofuranyl methyl ketone[2] (**14**) were prepared following the methods in the references. 2,3-Dimethyl-4- and -5-benzofuranyl methyl ketones (**3** and **4**) were prepared as follows:

Table 1. Reactions other than alkylation

Starting compd.	Reagent	Prod.	Yield %
	Dehydro-cyclization		
1	H_2SO_4	**3**	62[a]
2	H_2SO_4	**4**	33
6	PPA[b]	**8a**+**10a**	43[c]
7	PPA	**9a**	86
	Grignard Reaction		
21	$Mg+CO_2$	**23a**	58
	Esterification		
8a	$Me_2SO_4+K_2CO_3$	**8b**	74.5
8a	$MeOH+H_2SO_4$	**8b**	93
23a	$Me_2SO_4+K_2CO_3$	**23b**	76
	Acetylation		
8b	$AcCl+AlCl_3$	**11b**	37.5
10a	$AcCl+AlCl_3$	**20**	16
23b	$AcCl+AlCl_3$	**24b**	55
	Hydrolysis		
11b	KOH	**11a**	81
13b[d]	KOH	**13a**	27
17b	KOH	**17a**	69
24b	KOH	**24a**	65
25b[d]	KOH	**25a**	20
	Bromoform Reaction		
11a	NaOBr	**12**	49.5
14	NaOBr	**15**	48
16	NaOBr	**17a**	61
22	NaOBr	**23a**	14
	Decarboxylation		
24a	Cu+quinoline	**5**	42.5

a) This contains about 1% of **5**.
b) Polyphosphoric acid.
c) This consists of 77% of **8** and 23% of **10**.
d) The crude compound.

2,3-Dimethyl-5-benzofuranyl Methyl Ketone (4). Concentrated sulfuric acid (5 g) was stirred, drop by drop, into the 3-aryloxybutanone **2** (3 g) with cooling below 60°C, after which the mixture was stirred at 60°C for 30 min. The cooled mixture was then poured into ice water and extracted with ether. The ethereal solution was washed with an aqueous sodium hydroxide solution, and the ether was distilled off. The residual product was distilled, bp 175—183°C/23 mmHg, 1.2 g (44%), and then crystallized to give the pure ketone **4**, mp 78°C, 0.9 g (33%), which was identical with an authentic sample.[6]

2,3-Dimethyl-4-benzofuranyl Methyl Ketone (3). This was also prepared by the same procedure with a reaction temperature of 45°C; the product, bp 157—160°C/20 mmHg, 1.7 g (62%), was confirmed to be identical with an authentic sample[4] by a study of the IR and NMR spectra, by gas chromatography, and preparing 2,4-dinitrophenylhydrazone. However, it was found to contain a small amount (*ca.* 1%) of the isomeric ketone **5** on the basis of the NMR spectrum, in which a low peak corresponding to the 3-methyl protons of **5** appeared at $\delta=2.14$ in addition to high peak corresponding to those of **3** at $\delta=2.11$.[5,8]

c) Benzofurancarboxylic Acids. 2,3-Dimethyl-4- and -6-benzofurancarboxylic acids[4] (**8a** and **10a**) were prepared following the method in the reference, while 2,3-dimethyl-5- and -7-benzofurancarboxylic acid (**9a** and **23a**) were prepared as follows:

2,3-Dimethyl-5-benzofurancarboxylic Acid (9a). A mixture of 3-aryloxybutanone (**7**) (3 g) and polyphosphoric acid ($n=2.5$, 60 g) was heated at 100°C for 1 hr with stirring, after which the cooled mixture was poured into ice water. The crystalline product thus formed was collected and recrystallized from ethanol to give **9a**, mp 239—240°C, 2.2 g (86%), which was identical with an authentic sample.[4]

The 3-aryloxybutanone (**6**) (1.5 g) was also treated similarly to give a crude crystalline product, mp 151—155°C, 0.55 g (43%), which could not be purified by crystallization; the product was found to be a mixture of **8a** (77%) and **10a** (23%) by estimating the area of the peaks, $\delta=2.22$ and 2.17 ppm (in trifluoroacetic acid), corresponding to the 3-methyl protons of **8a** and **10a** respectively.[5,8]

2,3-Dimethyl-7-benzofurancarboxylic Acid (23a). *i) By the Grignard Reaction of the Bromo Compound 21.* A solution of 2,3-dimethyl-7-bromobenzofuran[7] (**21**) (30 g) in tetrahydrofuran (80 m*l*) was gradually added to a suspension of magnesium (3.3 g) in tetrahydrofuran (30 m*l*), with the addition of a small amount of iodine at first. After all of the magnesium had been dissolved (about 40 min), the solution was cooled to −10°C; then a stream of carbon dioxide from dry ice was passed into it with stirring and cooling. Dilute sulfuric acid was added, and the mixture was extracted with ether. The ether was distilled off, and the residue was crystallized from ethanol to give **23a**; mp 192—193.5°C, 14.6 g (58%). The UV[8] and NMR[5,8] spectra were reported previously.

ii) By the Bromoform Reaction of the Ketone 22. A solution of **22** (0.7 g) in dioxane (30 m*l*) was added with cooling to an aqueous sodium hypobromite solution; this solution had been prepared by adding bromine (0.8 g, 3.8 mol equivalents) to a mixture of sodium hydroxide (1.5 g, 9 mol equivalents), water (5 m*l*),

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[9] E. Bisagni and R. Royer, *Bull. Soc. Chim. Fr.*, **1962**, 925.

and ice (5 g). The mixture was stirred for 30 min with cooling and then for 1.5 hr at 45°C. The cooled mixture was diluted with water, washed with ether, and then acidified after the addition of a small amount of sodium bisulfite. The crystalline product thus formed was collected and recrystallized from ethanol to give **23a**, mp 189—191°C, 0.1 g (14%), which was identical with the other sample.

d) Methyl Benzofurancarboxylates. Methyl 2,3-dimethyl-5- and -6-benzofurancarboxylates[4] (**9b** and **10b**) were prepared following the method of the reference, while the 4- and 7-isomers (**8b** and **23b**) were prepared as follows:

Methyl 2,3-Dimethyl-4- and -7-Benzofurancarboxylates (8b and 23b). *i) By the Action of Dimethyl Sulfate and Potassium Carbonate.* Potassium carbonate (8.5 g, 3 mol equivalents) was added to a solution of the acid **8a** (4 g) and dimethyl sulfate (3.9 g, 1.4 mol equivalents) in acetone (150 m*l*), 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 ether was distilled off. The residual product was distilled to give **8b**, bp 162—165°C/16 mmHg, n=1.5660 (21.5°C), 3.2 g (74.5%). The UV[8] and NMR[5,8] spectra of which have been reported previously. The ester **23b** was prepared by the same procedure; mp 58—59°C (from cyclohexane); yield, 76%; its UV[8] and NMR[5,8] spectra have also been reported previously.

ii) By the Action of Methanol and Sulfuric Acid. A mixture of the acid **8a** (7 g), methanol (40 m*l*), and concentrated sulfuric acid (2 g) was refluxed for 4 hr. A half of the methanol was then distilled off, and the mixture was treated with water and then extracted with ether. The ethereal solution was washed with a 5% aqueous sodium hydroxide solution, and the ether was distilled off. The residual product was distilled to give **8b**, bp 163—164°C/20 mmHg, 7 g (93%).

Acetylation of the Esters (8b and 23b) and the Acid (10a). Powdered aluminum chloride (4.5 g, 2.2 mol equivalents) was gradually added, with cooling, to a solution of the ester **8b** (3.1 g) and acetyl chloride (1.5 g, 1.7 mol equivalents) in carbon disulfide (50 m*l*); the mixture was stirred for 4 hr at room temperature and then allowed to stand overnight. The next day, the mixture was poured into ice water and extracted with chloroform. The organic layer was washed with an aqueous sodium hydroxide solution and the solvent was distilled off. The residual product was crystallized from petroleum ether to give methyl 2,3-dimethyl-6-acetyl-4-benzofurancarboxylate (**11b**), mp 106—107°C, 1.4 g (37.5%).

Methyl 2,3-dimethyl-6-acetyl-7-benzofurancarboxylate (**24b**) was obtained by the same procedure from the ester **23b**, and 2,3-dimethyl-4-acetyl-6-benzofurancarboxylic acid (**20**), mp 211—212°C, which was identical with an authentic sample,[4] was also obtained by the same procedure from the acid **10a** by means of the action of acetyl chloride (1.2 mol equivalents) and aluminum chloride (3 mol equivalents) in carbon di-

Table 2. Alkylation of ketones and esters by AlCl$_3$ in CS$_2$

Starting compd.	RBr	Reac. temp.	Crude product		Pure[b] product (yield %)
			Bp°C/mmHg (yield %)	Peaks in gas chromatogram °C[a] (share %)	
3	*n*-Pr	Reflux	185—190/21(76)	195[c](2), 204(30), 208(50)	—
3	*i*-Pr	Reflux	178—183/20(71)	195[c](2), 204(30), 208(50)	—
4	*n*-Pr	Reflux	185—195/20(74)	193[c](5), 203[d](75), 209(10)	**16**(37)
5	*n*-Pr	Room	180—190/23(67)	—	**18**(15.5)
5	*n*-Pr	Reflux	193—196/21(90)	197[c](2), 205[d](95)	**18**(70)
5	*i*-Pr	Reflux	185—196/19(80)	197[c](2), 205[d](95)	**18**(30.5)
8b	*i*-Pr	Room	Recovery		
8b	*n*-Pr	Reflux	195—198/23(73)	195[c](2), 208[d](95), 211(3)	e)
8b	*i*-Pr	Reflux	180—195/21(57)	195[c](2), 208[d](95), 211(3)	e)
9b	*n*-Pr	Room	Recovery		
9b	*n*-Pr	Reflux	185—190/21(66)	198[c](3), 208[d](90), 213(7)	**17b**(41.5)
9b	*i*-Pr	Reflux	185—189/20(58)	198[c](3), 208[d](90), 213(7)	**17b**(21)
10b	*n*-Pr	Room	~187/20(58)	—	**19b**(16.5)
10b	*i*-Pr	Room	~198/23(66)	—	**19b**(16.5)
10b	*n*-Pr	Reflux	190—200/21(75)	198[c](1), 211[d](85), 214(5), 217(5)	**19b**(25)
10b	*i*-Pr	Reflux	~190/21(75)	—	**19b**(16.5)
23b	*i*-Pr	Room	Recovery		
23b	*i*-Pr	Reflux	190—205/21(35)	198[c](20), 207(17), 210(30), 212(10), 220(15)	e)

a) The gas chromatography was carried out with temperature rise of 5°C/min from 180°C.

b) Crystallized from the solvent described in references or Table 3.

c) This peak corresponded to the recovery.

d) This peak corresponded to the compound obtained in pure form.

e) The crude product was hydrolyzed to the acid.

TABLE 3. THE mp OR bp, IR AND ANALYSES OF NEW COMPOUNDS

Compd.	Mp°C (solv.)[a] or bp°C/mmHg	$\nu_{\text{CO}}^{\text{max}}$ cm^{-1}	Formula	Found C%	Found H%	Calcd C%	Calcd H%
			Esters				
8b	163—164/20	1724	$C_{12}H_{12}O_3$	70.43	6.07	70.57	5.92
11b	106—107(Pet)	1720 1674	$C_{14}H_{14}O_4$	68.43	5.74	68.28	5.73
17b	84.5—86(Pet)	1715	$C_{15}H_{18}O_3$	73.22	7.39	73.14	7.37
23b	58—59(Cy)	1720	$C_{12}H_{12}O_3$	70.64	5.84	70.57	5.92
24b	124.5—125.5(Cy)	1720 1668	$C_{14}H_{14}O_4$	68.44	5.72	68.28	5.73
			Carboxylic Acids				
11a	178—180(Et)	1710 1680	$C_{13}H_{12}O_4$	66.70	5.56	67.23	5.21
13a	135—137.5(DMe)	1695 1672	$C_{14}H_{16}O_3$	72.61	7.19	72.39	6.94
15	180.5—182(Et)	1700 1685	$C_{14}H_{16}O_3$	72.53	6.73	72.39	6.94
17a	213—215(Me)	1680	$C_{14}H_{16}O_3$	72.12	6.99	72.39	6.94
23a	192—193.5(Et)	1685	$C_{11}H_{10}O_3$	70.05	5.10	69.46	5.30
24a	207—208(Et)	1728 1640	$C_{13}H_{12}O_3$	67.07	5.19	67.23	5.21
25a	242—244(DMe)	1668	$C_{17}H_{22}O_3$	74.07	8.35	74.42	8.08

a) Pet: petroleum ether, Cy: cyclohexane, Et: ethanol, DMe: dilute methanol, Me: methanol.

TABLE 4. THE NMR SPECTRA (δ-VALUE[a] (ppm))

Compd.	Ph-H	$-CO_2CH_3$	Ph-CH<	$-COCH_3$	$2-CH_3$	$3-CH_3$	$\text{Ph-}\overset{}{\underset{\vert}{\text{C}}}{<}^{\text{CH}_3}_{\text{CH}_3}$
b)			3.33(m)		2.28	2.03	1.32(d)
11b	5-H 7-H $\underbrace{8.02(\text{d})\ \ 7.77(\text{d})}_{J=2\text{ Hz}}$	3.83		2.52	2.32	2.19	
13a[c]	5-H 7-H $\underbrace{7.83(\text{d})\ \ 7.45(\text{d})}_{J=2\text{ Hz}}$		3.06(m)		2.42	2.36	1.31(d)
14	5-H 6-H $\underbrace{7.28(\text{d})\ \ 6.33(\text{d})}_{J=7\text{ Hz}}$		3.40(m)	2.47	2.34	2.12	1.30(d)
16	4-H 6-H $\underbrace{7.73(\text{d})\ \ 7.63(\text{d})}_{J=2\text{ Hz}}$		3.40(m)	2.55	2.40	2.15	1.39(d)
17b	4-H 6-H $\underbrace{7.83(\text{d})\ \ 7.67(\text{d})}_{J=2\text{ Hz}}$	3.84	3.39(m)		2.35	2.11	1.36(d)
24b	5-H 4-H $\underbrace{7.41(\text{d})\ \ 7.24(\text{d})}_{J=8\text{ Hz}}$	3.91		2.49	2.39	2.11	
25a	7.54		3.34(m)		2.20	1.80	1.28(d) 1.23(d)

a) Measured on a Nihon Denshi 60 MHz apparatus in CCl_4 (about 5%), unless otherwise noted, using TMS as the internal standard, and (d): doublet and (m): multiplet.

b) 2,3-Dimethyl-7-isopropylbenzofuran. c) In $CDCl_3$.

sulfide.

Alkylation of the Ketones (3, 4, and 5) and the Esters (8b, 9b, 10b and 23b) (Table 2). Powdered aluminum chloride (2.8 g, 2 mol equivalents) was added, with stirring and cooling, to a solution of the ketone **4** (2 g) and *n*-propyl bromide (1.6 g, 1.2 mol equivalents) in carbon disulfide (50 m*l*); the mixture was then refluxed for 3 hr. The cooled mixture was poured into ice water containing some dilute hydrochloride acid and subsequently extracted with chloroform. The organic layer was washed with a dilute aqueous sodium hydroxide solution, and the solvent was distilled off. The residual product was distilled to give a crude product, bp 185—195°C/20 mmHg, 1.8 g; this crude product was crystallized from petroleum ether to give a pure 2,3-dimethyl-7-isopropyl-5-benzofuranyl methyl ketone (**16**), mp 107—108°C, 0.9 g (37%), which was identical with an authentic sample.[2)]

The alkylation was carried out much as in the cases of the ketones (**3** and **5**) and the esters (**8b, 9b, 10b,** and **23b**) as is shown in Table 2, but the products could not be purified by distillation, crystallization, or chromatography on alumina in the cases of **3, 8b,** and **23b**; the crude products from the latter two were directly hydrolyzed to the carboxylic acids. In the cases of the ketone **5** and the ester **10b**, some of the alkylated products were obtained by a reaction at room temperature.

Hydrolysis of the Keto-esters (11b and 24b) and the Esters (13b, 17b and 25b). A mixture of the keto-ester **11b** (1.3 g), methanol (2 m*l*), and a 50% aqueous potassium hydroxide solution (2 m*l*) was refluxed for 3 hr. The cooled mixture was diluted with water and washed with ether. The alkaline solution was then acidified to give a crystalline product; this product was subsequently recrystallized from ethanol to give 2,3-dimethyl-6-acetyl-4-benzofurancarboxylic acid (**11a**), mp 178—180°C, 1 g (81%).

Similarly, 2,3-dimethyl-6-acetyl-7-benzofurancarboxylic acid (**24a**) and 2,3-dimethyl-7-isopropyl-6-benzofurancarboxylic acid (**17a**) were obtained from **24b** and **17b** respectively, and 2,3-dimethyl-6-isopropyl-4-benzofurancarboxylic acid (**13a**) and 2,3-dimethyl-5,6-diisopropyl-7-benzofurancarboxylic acid (**25a**) were obtained from two crude esters, **13b** and **25b** respectively.

The Bromoform Reaction of the Ketones (14 and 16) and of the Keto-acid (11a). In the cases of **14** and **16**, the reaction was carried out to give 2,3-dimethyl-7-isopropyl-4-benzofurancarboxylic acid (**15**) and **17a** respectively, much as has been described for **23a** from **22**. The keto-acid **11a** was treated with an excess of sodium hydroxide to give 2,3-dimethyl-4,6-benzofurandicarboxylic acid (**12**), mp 324°C, which was identical with an authentic sample.[4)]

Decarboxylation of the Keto-acid 24a. A mixture of the keto-acid **24a** (0.29 g), copper powder (0.18 g), and quinoline (5 m*l*) was refluxed under a stream of nitrogen until the evolution of carbon dioxide had ceased. The cooled solution was then acidified by the addition of dilute hydrochloric acid, and the mixture was extracted with ether. The ethereal solution was washed with a 5% auqueous sodium hydroxide solution, and the ether was distilled off. The residual product was crystallized from cyclohexane to give the ketone **5**, mp 79—80°C, 0.034 g (42.5%), which was identical with an authentic sample.[9)]

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