BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 43 2176—2181 (1970)

A Study of Acyl Migration in Gallacetophenones

Kazu KUROSAWA

Department of Chemistry, Faculty of Science, Kumamoto University, Kurokami-machi, Kumamoto

(Received December 13, 1969)

3,4-Diacetoxy-2-hydroxyacetophenone, 3,4-dibenzoyloxy-2-hydroxyacetophenone and 3,4-bis(*p*-nitrobenzoyloxy)-2-hydroxyacetophenone gave corresponding 2,3-diacyl-4-methoxyacetophenones on treatment either with diazomethane or with dimethyl sulfate in the presence of potassium carbonate in acetone. Structure determination of the methylation product and also the methylation reaction of 3,4-dimethanesulfonyloxy-2-hydroxyacetophenone and 3,4-bis(*p*-toluenesulfonyloxy)-2-hydroxyacetophenone are reported.

In the course of synthetic studies of isoflavans, Gallacetophenone diacetate, mp 106—107°C,[1] was prepared as a synthetic intermediate material.[1] The structure of the diacetate was first elucidated by Perkin and Storey[1] as 2,4-diacetate on the basis of alkaline degradation of the gallacetophenone mono methyl ether, mp 132—133°C, derived from the diacetate. This ether, they claimed, afforded 2-methylpyrogallol (**6**), indicating the position of the hydroxyl group at 3. The identification, however, had been made by comparison of the melting point of the "2-methylpyrogallol diacetate" (60—63°C) only, whereas an authentic 2-methylpyrogallol diacetate has a mp 51—54°C and 1-methylpyrogallol diacetate has a mp 91—93°C.[3]

The IR spectrum of the diacetate showed a carbonyl absorption at 1648 cm^{-1}, which is slightly higher than those of other *o*-hydroxyacetophenones such as 3-acetoxy-2-hydroxy-4-methoxyacetophenone (**2b**) and 2,3-dihydroxy-4-methoxyacetophenone (**9**). Nevertheless, it is obviously a hydrogen bonded carbonyl when compared with the carbonyl absorptions of 2,3-diacetoxy-4-methoxyacetophenone (**3a**), 3-hydroxy-2,4-dimethoxyacetophenone (**10**) and 3-acetoxy-2,4-dimethoxyacetophenone (**4b**), in which *o*-hydroxyl group is absent (see Table 1). On the other hand, the NMR spectrum of the diacetate exhibited a proton signal at a lower field (δ 12.10)

1) A. G. Perkin and R. C. Storey, *J. Chem. Soc.*, **1928**, 229.

2) Beilstein's Handbuch der Organischen Chemie, Vol. 6, p. 1083 (1923).

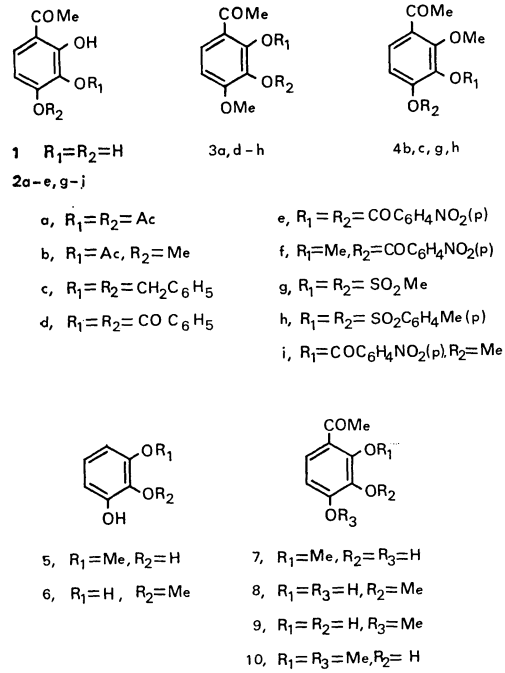

Fig. 1

which disappeared on deutration. The chemical shift is also characteristic to a hydrogen bonded *o*-hydroxyl proton as observed on *o*-hydroxyacetophenones, **9** and **2b**, while a *m*-hydroxyl proton in the compounds, **9** and **10**, appeared at a higher field (see Table 2). From this spectroscopic evidence, it is quite clear that the structure of the diacetate is neither 2,4-diacetate nor 2,3-diacetate, but undoubtedly 3,4-diacetate (**2a**) (see Fig. 1).

Diacetate (**2a**) gave a diacetyl mono methylgallacetophenone, mp 150—151°C,[1] on treatment with diazomethane, structure of which had been shown as 2,4-diacetoxy-3-methoxyacetophenone. However, this structure is also incorrect and should be revised as 2,3-diacetoxy-4-methoxyacetophenone (**3a**) by the following evidence. Diacetyl mono methylgallacetophenone was hydrolyzed to give gallacetophenone mono methyl ether, mp 132—133°C,[1] which was considered to be "2,4-dihydroxy-3-methoxyacetophenone." However, this ether was, in fact, 2,3-dihydroxy-4-methoxyacetophenone (**9**), being identical with an authentic sample, mp 132—133°C,[4] and differs from 2,4-dihydroxy-3-methoxyacetpohenone (**8**), mp 75—76°C,[5] and 3,4-dihydroxy-2-methoxyacetophenone (**7**), mp 84—85°C. It follows therefore that the two acetyl groups can be located at the position-2 and -3 in **3a**. This was further confirmed by acetylation of **9**, which gave an identical acetate, mp 150—151°C, with **3a**. The reaction could be explained in terms of a double acetyl migration during methylation. Acyl migration is fairly frequently observed in alicyclic and polyaromatic system[1,6] and extensively reviewed by Akahori[7] recently.

Various gallacetophenone 3,4-diesters (**2d, 2e, 2g, 2h**) (Fig. 1) were prepared by partial esterification of Gallacetophenone (**1**) with acid anhydride or with acid chloride in pyridine (see Table 3). The position of the hydroxyl group is confirmed as ortho to the carbonyl by the presence of a hydrogen bonded carbonyl in the IR spectra and the presence of the proton signal at a lower field in the NMR spectra (see Tables 1 and 2).

Methylation of 3,4-dibenzoyloxy-2-hydroxyacetophenone (**2d**), mp 108—109°C, and 3,4-bis(*p*-nitrobenzoyloxy)-2-hydroxyacetophenone (**2e**), mp 208—209°C, gave mono methyl ethers (**3d**), mp 186—187°C,[8] and **3e**, mp 181—182°C, which were

Table 1. The carbonyl absorption bands of Gallacetophenones in IR spectra (cm^{-1})

Galloacetophenone	-COMe Free	-COMe Hydrogen bonded	-OCOR
1		1628[a]	
2a		1648[b]	1779
2b		1644[b]	1768
2c		1628[a]	
2d		1640[a]	1735
2e		1638[a]	1757
2g		1643[a]	
2h		1650[a]	
2i		1640[b]	1750
3a	1681[b]		1776
3d	1673[a]		1751
3e	1674[a]		1759
3f	1692[a]		1754
3g	1700[a]		
3h	1695[a]		
4b	1673[b]		1770
4c	1668[a]		
4g	1673[a]		
4h	1679[a]		
7	1670[b]		
8		1630[b]	
9		1643[b]	
10	1672[b]		

IR spectra were determined in KBr disk (a) and in chloroform (b).

3) W. Baker, L. V. Montgomery and H. A. Smith, *J. Chem. Soc.*, **1932**, 1282.

4) W. Baker, F. H. T. Jukes and C. A. Subrahmanyan, *ibid.*, **1934**, 1683.

5) R. N. Kanna and T. S. Seshadri, *Indian J. Chem.*, **1**(9), 385 (1963); *Chem. Abstr.*, **60**, 1724h (1964).

6) A. G. Perkin and C. W. H. Story, *J. Chem. Soc.*, **1929**, 1399.

7) Y. Akahori, *Kagaku no Ryoiki*, **19**, 270 (1965).

8) Ishwar-Dass, N. Narasimhachari and T. R. Seshadri, *Proc. Indian Acad. Si.*, **37A**, 599 (1953); *Chem. Abstr.*, **48**, 7604d (1954).

Table 2. NMR spectral data for Gallacetophenones (δ value in ppm) in $CDCl_3$

Gallacetophenone	OH (s.)		H_6 (d.)[a]	H_5 (d.)[a]	Phenyl or *p*-substituted phenyl	OMe (s.)	COMe (s.)	Other signal	
	o-	*m*- and *p*-						δ	Assignment
2a	12.10		7.67	6.80			2.62	2.32 (s., 3H) 2.34 (s., 3H)	-OCOMe
2b	11.56		7.65	6.54		3.90	2.53	2.33 (s., 3H)	-OCOMe
2c	12.68		*ca.* 7.6	6.43	7.31 (m., 10H)		2.45	5.08 (m., 4H)	$-CH_2-$
2d	12.68		7.73	6.95	7.2—8.2(m., 10H)		2.62		
2e	12.67		7.69	6.80	6.88 (d., 2H) 6.59 (d., 2H) 7.98 (d., 2H) 8.09 (d., 2H)		2.59		
2g	12.91		7.73	7.05			2.64	3.33 (s., 3H) 3.44 (s., 3H)	$-OSO_2Me$
2h	12.65		7.69	7.06	7.25 (d., 2H) 7.35 (d., 2H) 7.60 (d., 2H) 7.81 (d., 2H)		2.60	2.46 (s., 3H) 2.40 (s., 3H)	Aromatic Me
3a			7.78	6.90		3.97	2.63	2.28 (s., 3H) 2.32 (s., 3H)	-OCOMe
4b			7.70	6.78		3.87(6H)	2.58	2.35 (s., 3H)	-OCOMe
7		5.90(2H)	7.29	6.75		3.88	2.59		
9	11.77	4.57(1H)	7.33	6.53		3.97	2.57		
10		5.87(1H)	7.38	6.74		3.75 3.97	2.62		

a) $J_{5,6}$=9.0 Hz.

Table 3. Esterification of Gallacetophenones

Gallacetophenone	Reaction conditions: Reagent	Molar ratio of gallacetophenone: acylating reagent	Time (hr)	Temp. (°C)	Product	Yield (%)	Mp (°C)	Lit, mp (°C)
1	Ac_2O, AcOH, pyr.	1 : 3	12	R.T.[a]	**2a**	59	106—107	106—107[1]
1	AcCl, pyr.	1 : 3	2	0	**2a**	29	106—107	
1	C_6H_5COCl, pyr.	1 : 3	3	100	**2d**	21	108—109	
1	*p*-$NO_2C_6H_4COCl$, pyr.	1 : 2.4	20	100	**2e**[b]	42	208—209	
1	$MeSO_2Cl$, pyr.	1 : 2.1	5	100	**2g**	23	142—143	
1	*p*-$MeC_6H_4SO_2Cl$, pyr.	1 : 3.5	19	50	**2h**	25	151—152	152—153[1]
7	$MeSO_2Cl$, pyr.	1 : 4.1	24	R.T.	**4g**	81	116—117	
7	*p*-$MeC_6H_4SO_2Cl$, pyr.	1 : 3.5	23	R.T.	**4h**	86	118—119	
9	AcCl, pyr.	1 : 1.3	2	0	**2b**	52	122—123	123.4—125.0[9]
9	*p*-$NO_2C_6H_4COCl$, pyr.	1 : 1.6	3	R.T.	**2i**[b]	20	193—194	
9	Ac_2O, pyr.	1 : 19	18	R.T.	**3a**	79	150—151	
9	C_6H_5COCl, pyr.	1 : 4.3	3.5	100	**3d**	60	186—187	185—186[8]
9	*p*-$NO_2C_6H_4COCl$, pyr.	1 : 4.8	20	120	**3e**[b]	42	181—182	
9	$MeSO_2Cl$, pyr.	1 : 11	48	100	**3g**	18	169—170	
9	*p*-$MeC_6H_4SO_2Cl$, pyr.	1 : 2.9	3	120	**3h**	34	154—155	

a) R.T. means room temperature.
b) Recrystallized from ethanol-chloroform.

Table 4. Methylation of Gallacetophenones

Gallaceto-phenone	Reagent	Reaction conditions: Molar ratio of gallaceto-phenone: methylating reagent	Time (hr)	Temp. (°C)	Product	Yield (%)	Mp (°C)	Lit, mp (°C)
2a	Me_2SO_4, K_2CO_3, Me_2CO	1 : 1.8	3.5	reflux	**3a**	59	150—151	
2a	CH_2N_2	excess	12	0	**3a**	59	150—151	150—155[1]
2d	Me_2SO_4, K_2CO_3, Me_2CO	1 : 4.5	7	reflux	**3d**	52	186—187	
2b	CH_2N_2	excess	12	0	**3d**	47	186—187	
2e	Me_2SO_4, K_2CO_3, Me_2CO	1 : 9.9	7	reflux	**3e**	6.5	181—182	
					3f	29	151—152	
2b	Me_2SO_4, K_2CO_3, Me_2CO	1 : 1.6	6	reflux	**4b**	93	112—113	110—111[10]
2i	Me_2SO_4, K_2CO_3, Me_2CO	1 : 11.5	3	reflux	**3f**	71	151—152	
2g	Me_2SO_4, K_2CO_3, Me_2CO	1 : 6.9	3	reflux	**4g**	87	116—117	
2h	Me_2SO_4, K_2CO_3, Me_2CO	1 : 9.5	14	reflux	**4h**	86	118—119	
2h	CH_2N_2	excess	12	0	**4h**	86	118—119	111—113[1]

Table 5. Analytical data for Gallacetophenones

Gallaceto-phenone	Formula	Found (%) C	Found (%) H	Found (%) N	Calcd (%) C	Calcd (%) H	Calcd (%) N
2d	$C_{22}H_{16}O_6$	69.96	4.25	—	70.21	4.29	—
2e	$C_{22}H_{14}O_{10}N_2$	56.49	3.00	5.99	56.66	3.03	6.01
2g	$C_{10}H_{12}O_8S_2$	36.91	3.73	—	37.03	3.70	—
2h	$C_{22}H_{20}O_8S_2$	55.42	4.31	—	55.46	4.23	—
2i	$C_{16}H_{13}O_7N$	57.72	3.97	4.06	58.01	3.96	4.23
3c	$C_{23}H_{22}O_4$	76.30	6.20	—	76.22	6.12	—
3d	$C_{23}H_{18}O_6$	a) 70.66	4.76	—	70.76	4.65	—
		b) 70.58	4.74	—			
3e	$C_{23}H_{16}O_{10}N_2$	a) 57.22	3.28	5.80	57.50	3.36	5.83
		b) 57.12	3.26	5.75			
3f	$C_{17}H_{15}O_7N$	a) 59.01	4.45	4.00	59.13	4.38	4.06
		b) 59.16	4.43	3.92			
3g	$C_{11}H_{14}O_8S_2$	38.99	4.17	—	39.04	4.17	—
3h	$C_{23}H_{22}O_8S_2$	56.14	4.56	—	56.31	4.52	—
4g	$C_{11}H_{14}O_8S_2$	a) 38.86	4.19	—	39.04	4.17	—
		b) 38.96	4.19	—			
4h	$C_{23}H_{22}O_8S_2$	a) 56.43	4.54	—	56.31	4.52	—
		b) 56.24	4.54	—			
7	$C_9H_{10}O_4$	59.14	5.59	—	59.33	5.53	—

a) Obtained by methylation.
b) Obtained by the esterification of corresponding monomethyl gallacetophenone.

found to be identical with those obtained by benzoylation of **9**. This indicates that the same type of benzoyl migration did occur in the reaction. In the case of **2e**, another product, mp 151—152°C, was isolated and found to be 2,4-dimethoxy-3-(*p*-nitrobenzoyloxy)acetophenone (**3f**), structure of which was confirmed by the independent synthesis of **3f** from **9**. 3-Acetoxy-2-hydroxy-4-methoxyacetophenone (**2b**), mp 122—123°C,[9] gave 3-acetoxy-2,4-dimethoxyacetophenone (**4b**), mp 112—113°C,[10] which was hydrolyzed to 3-hydroxy-2,4-dimethoxyacetophenone (**10**), mp 79—80°C,[11] indicating that the acetyl group could not migrate unless another acetyl group was present at the position-4. 3,4-Dimethanesulfonyloxy-2-hydroxyacetophenone (**2g**), mp 142—143°C, and 3,4-bis(*p*-

9) W. J. Horton and M. G. Scott, *J. Org. Chem.*, **20**, 1221 (1961).

10) W. Bradley and R. Robinson, *J. Chem. Soc.*, **1928**, 1565.

11) Beilstein's Handbuch der Organischen Chemie, **8**, II, 440 (1948).

toluenesulfonyloxy)-2-hydroxyacetophenone (**2h**), mp 151—152°C,[1] yielded 3,4-dimethanesulfonyloxy-2-methoxyacetophenone (**4g**), mp 116—117°C, and 3,4-bis(*p*-toluenesulfonyloxy)-2-methoxyacetophenone (**4h**), mp 118—119°C,[1] respectively. These sulfonates were found to be identical with those prepared from 3,4-dihydroxy-2-methoxyacetophenone (**7**), mp 84—85°C. These experiments showed that the sulfonate group did not migrate in the reaction. The results are summarized in Tables 3 and 4.

It is interesting to note that acyl migration did occur not in the sulfonates but in the carboxylic esters in the methylation. It is presumably due to the fact that O–CO bond is readily cleaved by the participation of the hydroxyl group at the neighboring position, whereas O–SO_2 bond cannot be cleaved under the condition used. Although an intermolecular reaction mechanism could not be ruled out,[12] the methylation reaction seems to proceed *via* cyclic intermediates (II and IV in Fig. 2). Anion (I) can be in equilibrium with anion (III) and anion (V) *via* the cyclic intermediates in the cases R are acetyl, benzoyl and *p*-nitrobenzoyl, and V is then methylated preferentially, as it is sterically less hindered. On the other hand, when methanesulfonyl and *p*-toluenesulfonyl groups are involved, the neighboring hydroxyl group cannot attack them and I is directly methylated. Methylation with diazomethane can also be accounted for by the same mechanism: the first step of the reaction is the capture of the proton on the hydroxyl group with diazomethane molecule, providing the anion (I), and then I is rearranged to anion (V) which is methylated.

The fact that the mono *p*-nitrobenzoate (**3f**) was obtained in the methylation of **2e** is queer. It seems that the bis-*p*-nitrobenzoate (**3e**) could be hydrolyzed with moisture and then methylated with excess dimethylsulfate present. Further investigation on this point is necessary.

Methylation of 3,4-bis(*p*-methoxybenzoyloxy)-2-hydroxyacetophenone was examined under similar conditions. However, the product has not been isolated in crystalline form as yet.

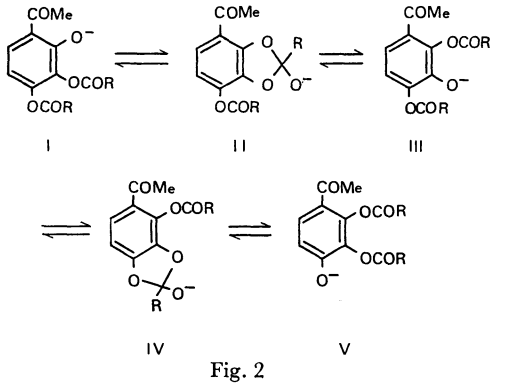

Fig. 2

Experimental

Measurements. IR spectra were recorded with JASCO Model DS 403G, a grating infrared spectrometer. Melting points were determined with Yanagimoto melting point apparatus. NMR spectra were obtained on a Varian A60 NMR spectrometer and JEOL JNM C 60H spectrometer using TMS as an internal standard.

Esterification of Gallacetophenones. a) Gallacetophenone (1 mmol) was treated with a mixture of acid anhydride (from 3 to 11 mmol) and pyridine (from 1 to 3 m*l*) at temperatures, room temperature — 120°C, for 3—24 hr. The reaction mixture was poured into ice water and the precipitates were collected. The crude ester was recrystallized from ethanol. b) Gallacetophenone (1 mmol) was dissolved in pyridine (from 1 to 3 m*l*) and treated with acid chloride (from 2 to 4.1 mmol) at temperatures 0—120°C for a period of time shown in Table 3. Working up in a similar manner to the above, a pure ester was obtained.

Methylation of Gallacetophenone. a) Gallacetophenone (1 mmol) was treated with a mixture of dimethyl sulfate (from 1.6 to 11.5 mmol) and potassium carbonate in acetone (30 to 40 m*l*). The reaction mixture was heated under reflux for a period of time shown in Table 4. After acetone was distilled off, the residue was triturated with water and the solid was collected. It was recrystallized from ethanol.

b) Gallacetophenone (1 mmol) was treated with distilled diazomethane at 0°C for 12 hr. After removal of the excess diazomethane and ether, the resulting solid was recrystallized from ethanol (see Table 4).

Preparation of Gallacetophenone (1), Gallacetophenone Monomethyl Ethers (7), (8) and (9), and 2,4-Dimethyl Ether (10). *Gallacetophenone (1).* The modified Nencki reaction of pyrogallol with boron tritrifluoride-acetic acid complex gave colourless needles (90%), mp 173°C.

2,3-Dihydroxy-4-methoxyacetophenone (9). 1-Methylpyrogallol[3] (4.0 g) was heated with boron trifluoride-acetic acid complex (12 m*l*) on a steam bath for an hour. The reaction mixture was poured into hot 2N hydrochloric acid (200 m*l*) and allowed to crystallize. This yielded colourless needles (4.0 g, 77%), mp 132—133°C (after sublimation) (lit,[4] mp 132—133°C).

2,4-Dihydroxy-3-methoxyacetophenone (8). 2-Methylpyrogallol[13] (839 mg) was heated with boron trifluoride-acetic acid complex (3 m*l*) on a steam bath for 30 min. The reaction mixture was poured into ice water and the precipitates were collected. Recrystallization of the crude material from water gave colourless leaves (928 mg, 85%), mp 75—76°C (lit,[5] mp 75°C).

3,4-Dibenzyloxy-2-hydroxyacetophenone (2c). A mixture of Gallacetophenone (**1**) (2 g), benzyl chloride (3.0 g), sodium iodide (4.0 g), and sodium bicarbonate (17 g) in acetone (71 m*l*) containing ethanol (6 m*l*), was heated under reflux for 19 hr. After removal of the acetone and the ethanol under reduced pressure, the residue was

12) T. H. Thompson and R. S. Wright, *J. Org. Chem.*, **26**, 4686 (1961).

13) Beilstein's Handbuch der Organischen Chemie, **6**, 1081 (1923).

triturated with water and then extracted with chloroform. The chloroform evaporated and the resulting liquid was allowed to crystallize in benzene. Recrystallization from ethanol gave colourless needles (2.01 g, 48%), mp 114—115°C (lit,[5] mp 113—114°C).

*3,4-Dibenzyloxy-2-methoxyacetophenone (**4c**).* 3,4-Dibenzyloxy-2-hydroxyacetophenone (**2c**) (4.9 g) was heated with a mixture of dimethyl sulfate (5.0 g) and potassium carbonate (6.0 g) in methyl ethyl ketone (100 m*l*) under reflux for 24 hr. After removal of the methyl ethyl ketone under reduced pressure, the residue extracted with chloroform. The chloroform was removed and the residue was crystallized from ethanol to give colourless plates (4.5 g, 88%), mp 62—63°C.

*3,4-Dihydroxy-2-methoxyacetophenone (**7**).* 3,4-Dibenzyloxy-2-methoxyacetophenone (**4c**) (1.14 g) was debenzylated with 15% hydrogen chloride-ethanol (20 m*l*), heating on a steam bath for an hour. Excess hydrogen chloride-ethanol was removed under reduced pressure and the resulting coloured liquid was separated on a silica column (Wakogel, C100, 100 g) with chloroform as an eluant. From a slow running fraction the required 3,4-dihydroxy-2-methoxyacetophenone (**7**) was crystallized on concentration, which was recrystallized from chloroform to give colourless needles (128 mg, 22%), mp 84—85°C.

*3-Hydroxy-2,4-dimethoxyacetophenone (**10**).* 3-Acetoxy-2,4-dimethoxyacetophenone (**4b**) (200 mg) was hydrolyzed with 2N hydrochloric acid (6 m*l*) in methanol (6 m*l*) under reflux for an hour. After removal of excess acid and methanol, the resulting solid was recrystallized from a mixture of benzene and light petroleum (30/70) to give micro crystals (130 mg, 78%), mp 79—80°C (lit,[11] mp 79—80°C).

The author wishes to thank Professor S. Sasaki, of Miyagi University of Education, JEOL Co., Ltd., and Dr. Y. Nakadaira, of Tohoku University for measuring the NMR spectra.