Syntheses of Aryl Glyoxylate. I. The Reaction of Alkyl Dichloro(alkoxy)acetates with Aromatics in the Presence of Lewis Acid

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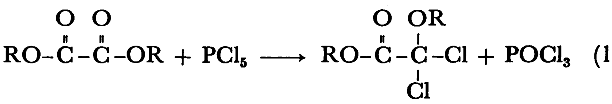
Ethyl dichloro(ethoxy)acetate (**1**) and methyl dichloro(methoxy)acetate (**2**) were characterized. The reaction of **1** and **2** with aromatics in the presence of $AlCl_3$ gave a considerable yield of aromatic α-keto ester. The aromatics included mono- and polymethylbenzene and anisol. The reaction was studied under various conditions and the results were compared with the acylation by ethoxalyl or methoxalyl chloride. The reaction mechanism was also discussed.

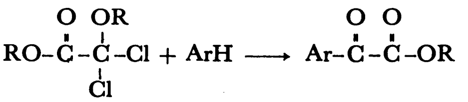
The chemical properties of ethyl dichloro(ethoxy)acetate (**1**) and methyl dichloro(methoxy)acetate (**2**) which are prepared by the reactions of dialkyl oxalate and phosphorus pentachloride[1] appear to have not been fully studied, in spite of their potential wide usability in organic synthesis.



$$\mathrm{RO{-}\overset{O}{C}{-}\overset{O}{C}{-}OR} + \mathrm{PCl_5} \longrightarrow \mathrm{RO{-}\overset{O}{C}{-}\underset{Cl}{\overset{OR}{C}}{-}Cl} + \mathrm{POCl_3} \quad (1)$$

1: R=Et, **2**: R=Me

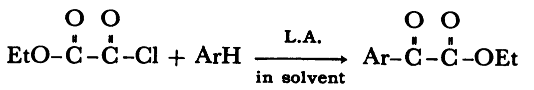
In this paper we wish to report the syntheses of aromatic α-keto esters by the reactions of **1** and **2** with aromatics in the presence of Lewis acids.



$$\mathrm{RO{-}\overset{O}{C}{-}\underset{Cl}{\overset{OR}{C}}{-}Cl} + \mathrm{ArH} \longrightarrow \mathrm{Ar{-}\overset{O}{C}{-}\overset{O}{C}{-}OR} \quad (2)$$

3: R=Et, **4**: R=Me

Needless to say, aromatic α-keto esters can be prepared by the Friedel-Crafts acylation of aromatics with ethoxalyl chloride.[2]



$$\mathrm{EtO{-}\overset{O}{C}{-}\overset{O}{C}{-}Cl} + \mathrm{ArH} \xrightarrow[\text{in solvent}]{\text{L.A.}} \mathrm{Ar{-}\overset{O}{C}{-}\overset{O}{C}{-}OEt} \quad (3)$$

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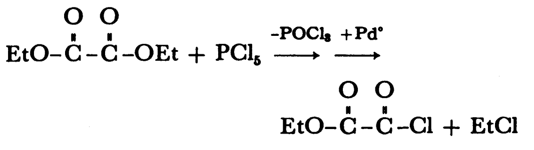
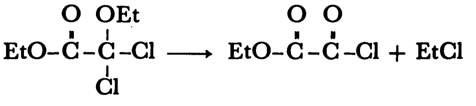
Ethoxalyl chloride is usualy prepared by two-step reactions of diethyl oxalate with phosphorus pentachloride.[3]



$$\mathrm{EtO{-}\overset{O}{C}{-}\overset{O}{C}{-}OEt} + \mathrm{PCl_5} \xrightarrow{-\mathrm{POCl_3}} \xrightarrow{+\mathrm{Pd}^{\circ}} \mathrm{EtO{-}\overset{O}{C}{-}\overset{O}{C}{-}Cl} + \mathrm{EtCl} \quad (4)$$

However the reaction intermediate should be one of the titled compounds. The reaction mixture of Eq. 1 or Eq. 4 (for 4 d at 95—100 °C) was subjected to a fractional distillation and the higher boiling fractions were found to be a mixture of **1** and diethyl oxalate. One more careful fractional distillation gave the fraction which consisted of 80% of **1** and 20% of diethyl oxalate. It was very difficult to obtain a fraction of more than 95% in purity. This fraction was heated at 180—200 °C for 6 h and then pure ethoxalyl chloride was obtained in 58% (corr. value; 70%). The conversion of **1** to ethoxalyl chloride was followed by GLC and ^{13}C NMR spectra. The evolved gas was partially trapped by Dry Ice–methanol and was identified to be ethyl chloride by ^{1}H NMR (CH_3: 3.55, CH_2: 1.50 in $CDCl_3$ *cf.* CH_3: 3.57. CH_2: 1.48 in CCl_4).



$$\mathrm{EtO{-}\overset{O}{C}{-}\underset{Cl}{\overset{OEt}{C}}{-}Cl} \longrightarrow \mathrm{EtO{-}\overset{O}{C}{-}\overset{O}{C}{-}Cl} + \mathrm{EtCl} \quad (5)$$

1 could not be purified to 100%, but the analogue, methyl dichloro(methoxy)acetate (**2**) was purified by two fractional distillations. The elemental analysis of the most purified fraction coincided with the calculated value for $C_4H_6O_3Cl_2$.

Syntheses of Aromatic α-Keto Esters. Compounds **1** and **2** in $CHCl_3$ reacted with the aromatics (ArH) in the precence of $AlCl_3$, $FeCl_3$, and $TiCl_4$ to form aromatic α-keto esters. To the $CHCl_3$ solution of an equivalent mole of **1** and ArH, powdered $AlCl_3$ (2 equiv mol) was added in parts with constant stirring, keeping the temperature under 5 °C (Method A). After 2 h, the reaction mixture was poured into ice water. The products were distilled out and analyzed by GLC, ^{1}H and ^{13}C NMR. Once **1** and **2** were treated with $AlCl_3$ or $FeCl_3$, **1** and **2** could not be recovered, and then the end point of the reaction could not precisely be detected. Although these reactions were very rapid, 2 h were too short to complete the reaction. However the isolated yields under such reaction conditions were fairly good; they are shown in the first column of Table 1.

The numbers of the yields could indicate a relative rate of the reaction, from the point of view as mentioned above, though the reaction mixture was heterogeneous. The numbers within parentheses were corrected values based on the purity of **1**, and the contaminated diethyl oxalate had no effect on the reaction.

In the reaction of **1** with benzene at bp of $CHCl_3$, ethyl phenylglyoxylate (20%) and a little (3.6%) ethyl *p*-ethylphenylglyoxylate were obtained. The latter was obtained through a fast ethylation of benzene with ethyl chloride and $AlCl_3$, followed by acylation of ethylbenzene. When **1** was treated with $AlCl_3$ or $FeCl_3$ at bp of CH_2Cl_2 or $CHCl_3$, it rapidly decomposed to eliminate ethyl chloride gas. So **1** reacted in two ways: the acylation of ArH and the decomposition, depending upon the reaction conditions. At a lower temperature, the rate of the decomposition might be much slower than that of the acylation. These reactions were

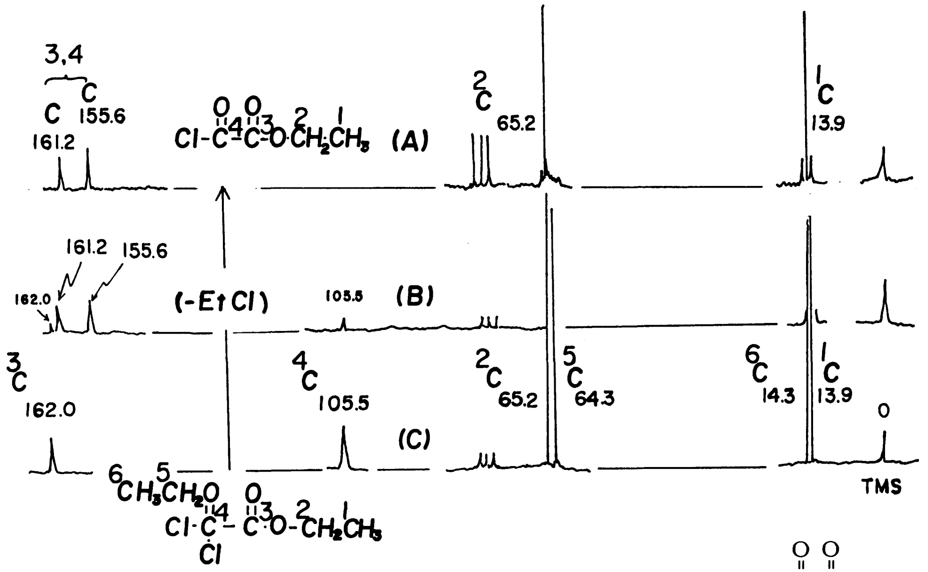


Fig. 1. C-13 NMR spectral change in the decomposition of **2** to $\mathrm{EtO{-}\overset{\overset{O}{\|}}{C}{-}\overset{\overset{O}{\|}}{C}{-}Cl}$. (A) After 2 h at 200 °C, spectrum of $\mathrm{EtO{-}\overset{\overset{O}{\|}}{C}{-}\overset{\overset{O}{\|}}{C}{-}Cl}$. (B) Spectrum of mixtures. (C) Spectrum of **2**; before heating.

Table 1. Yields of substituted phenylglyoxylates[a)]

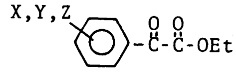
Starting materials	**3**	Column No.	1	2	3	4
		Products Substituents	**1** (%) (Corr. value)	**1** or **11** (%) Max. value	Ethoxalyl chloride (%)	(%)
Mesitylene	**3a**	2, 4, 6-Me_3	53.0 (74)	90[b)] (**4a**)	47.9	—
o-xylene	**3b**	3, 4-Me_2	57.0 (88)	—	76	—
m-xylene	**3c**	2, 4-Me_2	50	—	56	—
p-xylene	**3d**	2, 5-Me_2	41 (61)	—	48.3	—
Toluene	**3e**	2-or 4-Me	43.2 (64.5) *o*/*p*=0.09	50[c)] (**4e**) *o*/*p*=0.18	31.6 *o*/*p*=0.01	79[g)]
Anisole	**3f**	2-or 4-MeO	27 (32) only *p*-	65[d)] *o*/*p*=0.23	63.4	79[g)]
Benzene	**3g**	H	—	20[e)]+3.6[f)]	13.6	50[h)]

a) All compounds recorded in this table gave satisfactory analysis. Isolated yields in all cases. Method A: ArH (0.05 mol) and **1** (0.05 mol) were dissolved in 100 ml of $CHCl_3$ at 0—5 °C. Powdered $AlCl_3$ (0.1 mol) was added into the well-stirring reaction mixture for 20—40 min. The reaction time is 80—120 min. b) CH_2Cl_2 solvent; mesitylene (0.50 mol), $AlCl_3$ (0.10 mol), **2** (0.05 mol). c) Reaction time is 1 day at r.t. d) **1** was added to the CH_2Cl_2 solution. e) Benzene (0.24 mol), $AlCl_3$ (0.2 mol), **1** (0.1 mol). f) Another compound=ethyl *p*-ethylphenylglyoxylate. g) Ref. 2; solvent is $C_6H_5NO_2$. h) Ref. 2; solvent is C_6H_6. In our case (Table 2), the yields is 47%.

dependent on the following three factors: the solvents, the catalysts, and the reagent ratio. 1) The best solvent is CH_2Cl_2. Other usable solvents are $CHCl_3$ and CH_3NO_2, but CS_2, Et_2O, and $C_6H_5NO_2$ are not good solvents. 2) The best catalysts are $AlCl_3$, $TiCl_4$, and $SnCl_4$. When $TiCl_4$ was used, the reaction worked well in a homogeneous state. This reaction will be reported in future. 3) The reagent ratio of ArH, $AlCl_3$, and **1** or **2** must be the most suitable value in response to the reactivity of ArH; the ratios of 1:2:1 and 10:2:1 were generally used.

In the cases of mesitylene, toluene, benzene, and anisol, the reactions under the optimum conditions were tried; the maximum yields are shown in the second column of Table 1.

The configuration of the Aromatic α-Keto Esters. The aromatic α-keto esters (**3e**—**g**) were identified with the authentic samples obtained by the known methods as mentioned above Eq. 3 and in Ref. 3 (*cf.* footnote of Table 1). By using ^1H and ^{13}C NMR spectra of each compound, we were able to assign their configurations.



3a; 2,4,6-Me_3

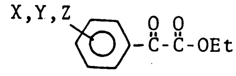
3b; 3,4-Me_2

3c; 2,4-Me_2

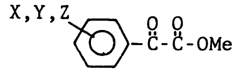
3d; 2,5-Me_2

3e; 2-or 4-Me

3f; 2-or 4-MeO



3g; unsubstituted



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There were many other compounds (**3a**—**d**) which could not be found in the literature, but these configurations were determined by ^{13}C NMR spectra. The observed chemical shifts were compared with the calculated values; the values almost coincided.

In the case of toluene, the product was a mixture whose composition were variable with the reaction conditions; it always included two compounds. The C, H analysis of the mixture coincided with the calculated values for $C_{11}H_{12}O_3$. The isolation of one of the mixtures was very difficult. From the reaction of toluene with methoxalyl chloride (*cf*; Table 2), an almost pure compound (95%), one of the two compounds, was obtained; its configuration was determined to be methyl *p*-methylphenylglyoxylate. The other compound, therefore, was deduced to be methyl *o*-methylphenylglyoxylate.

In the case of anisole, the same method was applied.

Table 2. Yields of substituted phenylglyoxylates[a)]

Starting materials		Column 1 Reagent **2**	Column 2 Reagent $MeO\text{-}\overset{O}{C}\text{-}\overset{O}{C}\text{-}Cl$
Mesitylene	**4a**	15	18
Toluene	**4e**	0[b)]	50 (*o*/*p*=0.05)
Anisole	**4f**	0[c)]	50 (*o*-: trace)
Benzene	**4g**	38 and 47[d)]	62

a) Method B: mole ratio of ArH: $AlCl_3$: **2** or $MeO\text{-}\overset{O}{C}\text{-}\overset{O}{C}\text{-}Cl$ was about 30:2:1. An acylating reagent was added at the end. b) No distillable product was obtained. c) Some other product was obtained. d) To the cooled mixture of ArH and an acylating reagent, $AlCl_3$ was added.

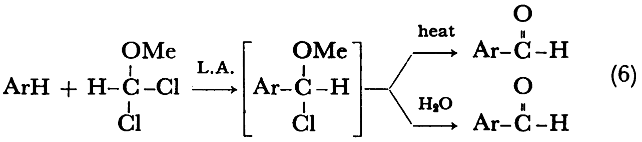
The Reaction of Ethoxalyl Chloride with ArH in $CHCl_3$. The yields of classical Friedel-Crafts reaction using ethoxalyl chloride as an acylating reagent are shown in column 4. These values were very large, in comparison with our data, although the reaction conditions were very severe, at higher temperature for longer reaction time in CH_2Cl_2 or in nitrobenzene. We also reexamined this reaction under our reaction conditions (0 °C, 80 min, in $CHCl_3$); the available data are tabulated in the column 3.

These values in the columns 1 and 3 show only small differences. However, under the reaction without solvents, great diffrences were observed between the reaction of **2** with ArH and that of methoxalyl chloride with ArH (Columns 1 and 2 in Table 2).

*The Reaction of **2** and Methoxalyl Chloride with ArH without a Solvent.* Compounds **2** was a little more stable under these reaction conditions than **1** was, although **2** decomposed to eliminate methyl chloride under more severe conditions (*e.g.*, at bp of CH_2Cl_2). The reaction of **2** with ArH at 0 °C was studied in detail. To an aromatic hydrocarbon containing 2 equivs of $AlCl_3$, 1 equiv of **2** was added with good stirring and cooling with ice. The results with respect to mesitylene, toluene, anisole, and benzene are shown in the first column of Table 2. In the second column, the yields of aromatic α-keto esters obtained by the reaction of methoxalyl chloride with ArH without solvent are shown. The yield of the reaction of **2** with mesitylene decreased from 53% (in the case of **1**) to 15%. In the case of anisole, an aromatic α-keto ester was not obtained, but some other compound[4)] was obtained. In the case of toluene, none of the product could be distilled out. Only when $AlCl_3$ was added to the toluene solution of **2**, a little amount of α-keto ester and some other product happened to be obtained. We can not yet explain why the reaction in toluene did not work well.

In contrast to this reaction, the reaction of methoxyalyl chloride with ArH was a normal reaction and the yields increased except only the case of mesitylene.

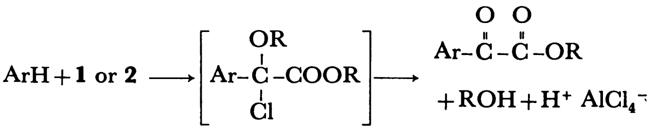
The Reaction Mechnism. An analogous reaction to this was reported earlier by Riech and Gross:[5)] the formylation of ArH by dichloro(methoxy)methane in the presence of $AlCl_3$, $TiCl_4$, and $SnCl_4$ (Eq. 6). They explained the reaction route through the parenthesized intermediate.



$$ArH + H\text{-}\overset{OMe}{\underset{Cl}{C}}\text{-}Cl \xrightarrow{L.A.} \left[Ar\text{-}\overset{OMe}{\underset{Cl}{C}}\text{-}H\right] \begin{cases} \xrightarrow{heat} Ar\text{-}\overset{O}{C}\text{-}H \\ \xrightarrow{H_2O} Ar\text{-}\overset{O}{C}\text{-}H \end{cases} \quad (6)$$

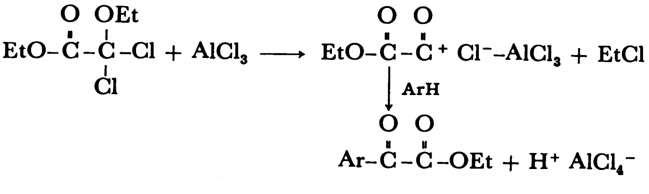
The parenthesized compound was not the final product, but the reaction product, which was labile to heat or to work-up condition.

The same mechanism was most probable for the aromatic α-keto ester reaction.



$$ArH + \mathbf{1} \text{ or } \mathbf{2} \longrightarrow \left[Ar\text{-}\overset{OR}{\underset{Cl}{C}}\text{-}COOR\right] \longrightarrow Ar\text{-}\overset{O}{C}\text{-}\overset{O}{C}\text{-}OR + ROH + H^+ AlCl_4^-$$

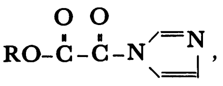
In the case of **1**, another mechanism could be as follows:



$$EtO\text{-}\overset{O}{C}\text{-}\overset{OEt}{\underset{Cl}{C}}\text{-}Cl + AlCl_3 \longrightarrow EtO\text{-}\overset{O}{C}\text{-}\overset{O}{C}^+ \; Cl^-\text{-}AlCl_3 + EtCl \xrightarrow{ArH} Ar\text{-}\overset{O}{C}\text{-}\overset{O}{C}\text{-}OEt + H^+ AlCl_4^-$$

When ArH was added after the treatment of **1** or **2** with $AlCl_3$ in a solvent, the yield of the product greatly decreased or reduced to zero. Thus, the latter mechanism is not probable. The parenthesized compound of this reaction $Ar\text{-}\overset{OR}{\underset{Cl}{C}}\text{—}\overset{O}{C}\text{-}OR$, is more stable than $Ar\text{-}\overset{OMe}{\underset{Cl}{C}}\text{-}H$, that of the formylation reaction. The parenthesized compound was the reaction product, and then it changed to aromatic α-keto esters under work-up.

Aromatic α-keto esters were generally synthesized through the oxidation of mandelic acid derivatives,[6)] but the yield of oxidation was generally low. Recently a new synthesis of α-keto esters and acids was reported by Mosher and *et al.*[7)] The acylating reagents was


, which was prepared by the reaction between ethoxalyl chloride and imidazole. This method is the best method on laboratory scale. In comparison to these methods, **1** and **2** are easily prepared in large scale and the cost to prepare **1** and **2** is most inexpensive. In addition, **1** and **2** have other usabilities in organic synthesis. The other kinds of aromatic α-keto esters could be synthesized using **1**, **2**, ethoxalyl and methoxalyl chloride. The application of this reaction to halobenzenes, biphenyl, and naphthalene will be reported in future.

Experimental

Measuremets. Melting and boiling points were uncorrected. ^{1}H NMR spectra were measured on a JEOL-60 (60 MHz) spectrometer with tetramethylsilane as an internal standard, and IR spectra on a Hitachi EPI-G2 infrared spectrometer. ^{13}C NMR spectra were measured on a JEOL-PFT-100 spectrometer.

Materials. The following materials were synthesized according to the reported method[1] and an improved one.

1. An equivalent mole of diethyl oxalate (2mol) and PCl_5 (2mol) were mixed and then heated at 105—115 °C for 6—10 h. The reaction mixture was distilled through a Vigrew column by a water pump. The amounts of the third, fourth and fifth fraction (bp of them, 80—92 °C/18 mmHg, 92—98 °C/18 mmHg and 99 °C/18 mmHg—104 °C/24 mmHg) were 79, 44, and 194 g; their purities were 76, 88, and 95%. These fractions was further subjected to efficient fractional distillation. The total yield amounted to 67% (1.35 mol), as found by GLC analyses.

2. Dimethyl oxalate (236 g, 2.0 mol) and PCl_5 (417 g, 2.0 mol) were mixed in a solid state and heated at 110 ± 5 °C for 10—15 h. An aliquot was analyzed by GLC. After dimethyl oxalate of more than 80% converted to **2**, oxyphosphoryl chloride and then **2** were distilled off from the reaction mixture. The first fraction (bp 35 °C/49 mmHg) and the second fraction (bp 44 °C/36 mmHg—50 °C/36 mmHg) were composed of oxyphosphoryl chloride and a little dimethyl oxalate. The third fraction (bp 77 °C/34 mmHg—87 °C/32 mmHg) was composed of 60% of **2** and 40% of dimethyl oxalate. The GLC analysis gave the total yield as 190 g, 55%. The third and fourth fractions were combined and this was subjected to efficient distillation. The fraction of constant bp, 80 °C/22 mmHg (98 g, 28%) was analyzed as shown below. Calcd for $C_4H_6O_3Cl_2$: C, 27.77; H, 3.49; Cl, 40.98%. Found: C, 27.96; H, 3.42; Cl, 40.83%. ^{1}H NMR δ=3.82 (s, 3H) 3.93 (s, 3H). IR: $\nu_{C=O}$ 1770 cm^{-1}: $\delta_{C=O\ or\ C=O}$ 1285, 1200, and 1150 cm^{-1}: ν_{C-Cl} 660 cm^{-1}.

Reaction of Substituted Benzene with 1 or 2 in $CHCl_3$. The substituted benzene (0.05 mol) and **1** or **2** (0.05 mol) were dissolved in 100 ml of $CHCl_3$ and kept at 0—5 °C on the ice bath. Powdered $AlCl_3$ (0.1 mol) was added into the well-stirred reaction mixture for 20—40 min. Then it was kept at 0—5 °C for 80 min. The reaction mixture was

Table 3. C and H Analyses of substituted' phenylglyoxylates

Products	Bp θ_b/°C(mmHg) Mp θ_m/°C	Obsd (Calcd) (%)	
		C	H
4a	129—131(3)	69.87(69.89)	7.00(6.84)
3e	148—149(10)[a]	68.46(68.43)	6.26(6.29)
4e	122(5)[a]	67.68(67.41)	5.66(5.66)
3f	140(5)[a]	63.44(63.45)	5.99(5.81)
4f	150(4)[a]	61.97(61.85)	5.14(5.19)
3g	—	—	—
4g	120—123(6)[b]	65.96(65.84)	4.92(4.92)
3b	140(4)	69.74(69.89)	7.12(6.84)
3c	53	69.61(69.89)	6.78(6.84)
3d	135(5)	70.11(69.89)	6.88(6.84)
3h[c]	122(5)	69.96(69.89)	6.93(6.84)

a) Bp of a mixture of *o*- and *p*-isomer. b) 250—255 °C/760 mmHg; R.B.Corson *et al. Org. Synth.* Coll. Vol. I, 241 (1955). c) **3h**=Ethyl *p*-ethylphenylglyoxylate prepared by Eq. 3.

Table 4. Carbon-13 NMR chemical shifts of 3 and 4[a]

Substituents		C_1	C_2	C_3	C_4	C=O	O–C=O	–CH_2	–CH_3	Me *et al.*
2, 4, 6-Me_3	**3a**	133.0	136.2	129.0	141.0	191.9	162.8			^{2,6}(19.6, ^{4}21.1)
	4a	133.0	136.2	129.0	141.0	191.4	163.6		52.9	
4-Me	**3e**	129.7	(129.8,	129.6)[b]	146.3	185.8	164.3			
	4e									
4-MeO	**3f**	125.4	132.4	114.4	165.2	185.1	164.4	62.1	14.1	
	4f	125.4	132.6	114.2	165.0	184.4	164.3		52.6	$^{MeO-}$55.7
H	**3g**	132.5	129.9	128.9	134.9	186.5	164.0	62.3	14.1	
	4g	132.4	130.0	128.8	134.9	186.0	164.0		52.7	
		C_1	C_2	C_3	C_4	C_5	C_6	C=O	O–C=O	Me *et al.*
3, 4-Me_2	**3b**	130.3	130.1	137.4	145.0	130.7	127.8	186.3	164.2	^{3}19.6, ^{4}20.1
2, 4-Me_2	**3c**	128.4	141.1	133.3	144.9	126.7	132.7	188.5	165.0	^{2,4}21.5
2, 5-Me_2	**3d**	131.0	138.0	132.2	134.5	135.5	132.6	188.9	164.7	^{2,5}20.7, 20.8

a) Samples were 5—10% w/v. Solvent is $CDCl_3$. b) Similar values in paretheses may be interchanged.

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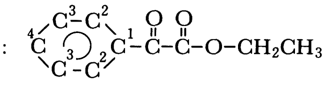

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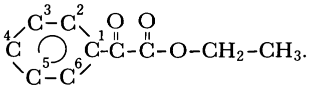

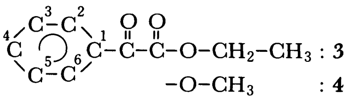
: 3

: 4

poured into ice water and then $CHCl_3$ was added; this mixture was extracted two times and the $CHCl_3$ solution was washed with a 10% solution of sodium hydrogencarbonate and then with water and dried with $MgSO_4$. After distilling off $CHCl_3$, the residue was distilled by an oil pump. The distillates were analyzed by GLC, IR, and NMR. The chemical shift of ^{13}C NMR was compared with the calculated value. The elemental analyses of all of the products showed that the structures were right (see Table 3).

The Reaction of Ethoxalyl Chloride with Aromatics in $CHCl_3$. These reactions were carried out in the same way as above.

*The Reaction of **2** or Methoxalyl Chloride with ArH without Solvents.* Powdered $AlCl_3$ (0.05 mol) was suspended in the cooled aromatics (1.5 mol). Compound **2** or methoxalyl chloride (0.025 mol) was added to the cooled mixture for about 10—25 min. After 2 h the organic layer was washed with 10% sodium hydrogen-carbonate solution and water, and was dried with $MgSO_4$. After distilling off $CHCl_3$, the residue was distilled by an oil pump. All products gave satisfactory analyses of C and H.

*^{13}C NMR Spectra of **3** and **4**.* The chemical shifts of a series of **3** and **4** in $CDCl_3$ solution using TMS as a standard, are summarized in Table 4. The assignments were made with the help of off-resonance decoupling, the comparison of the signal intensity, and the use of the long range coupling constants. Furthermore, the observed chemical shifts were compared with the calculated values. Each signal were reasonably assigned to be due to the corresponding carbon, on the basis of the signals of ethyl phenylglyoxylate and methyl phenylglyoxylate.

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