The Reactions of Ester with Acyl Chloride in the Presence of Aluminum Chloride. III. Formation of Dibenzoylmethane and Ethyl Dibenzoylacetate

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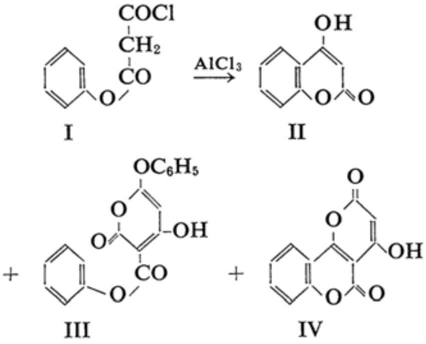
Nakata has reported that acetonetricarboxylic acid derivative III and 3-acyl-4-hydroxycoumarin derivative IV were obtained as by-products in the synthesis[1] of 4-hydroxycoumarin (II) by the action of aluminum chloride on the acid chloride of monophenyl malonate (I) as follows[2]:



The formation of III and IV suggests that the active methylene group of I can be acylated with acid chloride in the presence of aluminum chloride. The acylation of the active methylene group is usually accomplished with a basic reagent such as metallic sodium or sodium alcoholate. With reference to the acylation of the active methylene group in the presence of an acidic reagent, only the synthesis of β-diketones by the acetylation of ketones with acetic anhydride in the presence of boron trifluoride has been studied by Meerwein and Vossen[3] and by Hauser and Adams[4]. Recently, Azatyan[5] has reported that some aromatic ketones were prepared by heating aromatic hydrocarbon and acid chloride in the presence of a small amount of metallic aluminum, and that under similar condition diethyl benzoylmalonate was obtained from diethyl malonate and benzoyl chloride.

The present paper describes the study of the reactions of diethyl malonate with one molecular equivalent of benzoyl chloride, *p*-chlorobenzoyl chloride, *p*-nitrobenzoyl chloride and acetylsalicylic acid chloride in the presence of different amounts of aluminum chloride.

Acylation of Diethyl Malonate with Benzoyl Chloride.—The treatment of diethyl malonate with one molecular equivalent of benzoyl chloride and of aluminum chloride afforded diethyl benzoylmalonate (V) and dibenzoylmethane (VII). When three molecular equivalents of aluminum chloride were used, VII and ethyl dibenzoylacetate (VI) were obtained. It was found that carbon dioxide and ethyl chloride are evolved in the course of the reactions. In these reactions, aluminum chloride reacts not only to give benzoyl derivatives, but also to accelerate the decarbethoxylation of the ester.

$$\begin{aligned}&CH_2(COOC_2H_5)_2+C_6H_5COCl\\&\xrightarrow{AlCl_3} C_6H_5COCH(COOC_2H_5)_2\\&\quad+(C_6H_5CO)_2CHCOOC_2H_5+(C_6H_5CO)_2CH_2\end{aligned}$$

Acylation of Diethyl Malonate with *p*-Chlorobenzoyl Chloride.—The products of the reactions of diethyl malonate with *p*-chlorobenzoyl chloride were diethyl *p*-chlorobenzoylmalonate (VIII), ethyl di-*p*-chlorobenzoylacetate (IX) and di-*p*-chlorobenzoylmethane (X). The relation between amounts of aluminum chloride and reaction products was similar to that of the acylation with benzoyl chloride.

Acylation of Diethyl Malonate with *p*-Nitrobenzoyl Chloride.—When one molecular equivalent of *p*-nitrobenzoyl chloride was used as an acylating agent, *p*-nitroacetophenone (XI) and ethyl *p*-nitrobenzoylacetate (XII) were obtained. By the use of three molecular equivalents of aluminum chloride at a higher reaction temperature, di-*p*-nitrobenzoylmethane (XIII) was obtained as the main product.

$$\begin{aligned}&CH_2(COOC_2H_5)_2+NO_2C_6H_4COCl\\&\xrightarrow{AlCl_3} NO_2C_6H_4COCH_3\\&\qquad\qquad+NO_2C_6H_4COCH_2COOC_2H_5\\&NO_2C_6H_4COCH_2COOC_2H_5+NO_2C_6H_4COCl\\&\xrightarrow{AlCl_3} (NO_2C_6H_4CO)_2CH_2\end{aligned}$$

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[1] K. Matsui and M. Ota, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **78**, 517 (1957).

[2] T. Nakata, ibid., **78**, 1780 (1957).

[3] H. Meerwein and D. Vossen, *J. prakt. Chem.*, **141**, 149 (1934).

[4] R. Hauser and T. Adams, *J. Am. Chem. Soc.*, **66**, 345 (1944).

[5] V. D. Azatyan, *Daklady Akad. Nauk Armyan. S. S. R.*, **29**, No. 3, 111 (1959); *Chem. Abstr.*, **54**, 12044 (1960).

TABLE I. ACYLATION OF DIETHYL MALONATE WITH BENZOYL CHLORIDE AND *p*-SUBSTITUTED BENZOYL CHLORIDES

Reaction condition: 65°C, * 90°C; 8 hr. Solvent: Nitrobenzene 15 ml.

Substituent	Reactant			Product and yield					
X	X-C_6H_4COCl mol. ×10^2	$CH_2(COOC_2H_5)_2$ mol. ×10^2	$AlCl_3$ mol. ×10^2	X-BME[a] %	X-DBA[b] %	X-DBM[c] %	X-AP[d] %	X-BAE[e] %	X-C_6H_4COOH %
H	2.1	2.1	2.1	59		8			15
	2.1	2.1	6.3		31	16			23
Cl	1.7	1.7	1.7	59					19
	1.7	1.7	5.1		4	33			43
NO_2	1.6	1.6	1.6				26	10	56
	1.6	1.6	3.2			31	29	8	28
	1.6	1.6	4.8			47	14	8	28
	1.6	1.6	1.6*			58	7	26	7
	1.6	1.6	4.8*			74	7	3	14

Yield: Calculated from X-C_6H_4COCl (X=H, Cl, NO_2).

a) X-BME(V, VIII); X-$C_6H_4COCH(COOC_2H_5)_2$

b) X-DBA(VI, IX); (X-$C_6H_4CO)_2CHCOOC_2H_5$

c) X-DBM(VII, X, XIII); (X-$C_6H_4CO)_2CH_2$

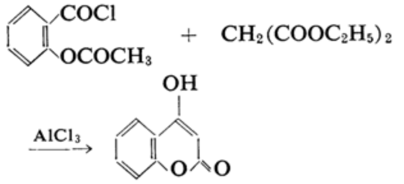
d) X-AP(XI); X-$C_6H_4COCH_3$

e) X-BAE(XII); X-$C_6H_4COCH_2COOC_2H_5$

It can be deduced that the formation of XI and XIII in good yields results in the facilitation of decarbethoxylation by the driving force of the nitro group in the *p*-position.

The reaction conditions and the products of these acylation reactions are summarized in Table I.

Acylation of Diethyl Malonate with Acetylsalicylic Acid Chloride.—Reactions carried out with different amount of aluminum chloride all gave only 4-hydroxycoumarin (II), which may have been formed by decarbethoxylation and intramolecular condensation. The results of these reactions are given in Table II.



The aromatic acids, which should be derived from unreacted acid chlorides, were obtained, and their yields generally increased with the amount of aluminum chloride used.

TABLE II. ACYLATION OF DIETHYL MALONATE WITH ACETYLSALICYLIC ACID CHLORIDE

Solvent: Nitrobenzene 25 ml.

Reaction condition: 95∼100°C, 8 hr.

Reactant			Product and yield	
Acetylsalicylic acid mol. ×10^2	Diethyl malonate mol. ×10^2	$AlCl_3$ mol. ×10^2	II %	Salicylic acid %
1.7	3.3	1.7	56	13
1.7	1.7	1.7	52	17
1.7	1.7	5.1	7	57

Yield: Calculated from acetylsalicylic acid.

Experimental*

Materials.—Benzoyl chloride⁶⁾ (b. p. 192°C), *p*-chlorobenzoyl chloride⁷⁾ (b. p. 112°C/23 mmHg) and *p*-nitrobenzoyl chloride⁸⁾ (b. p. 160°C/26 mmHg) were prepared from benzoic acid, *p*-chlorobenzoic acid and *p*-nitrobenzoic acid with phosphorus pentachloride respectively in 65, 96 and 92% yields. Acetylsalicylic acid⁹⁾ was prepared from salicylic acid and acetic anhydride, m. p. 137∼138°C., 82% theoretical yield. Anhydrous aluminum chloride¹⁰⁾ was prepared by passing a stream of dry hydrogen chloride over aluminum (99.99%) heated in a furnace. The diethyl malonate used was a commercial product purified by distillation.

Acylation of Diethyl Malonate with Benzoyl Chloride.—Diethyl malonte was added to benzoyl chloride and aluminum chloride dissolved in nitrobenzene, and the reaction mixture was kept at 65°C for 8 hr. After cooling, the reaction mixture was poured into crushed ice and extracted with ether. The ethereal solution was successively extracted with a saturated sodium bicarbonate solution, with a sodium hydroxide solution (15%) and then with water. After the aqueous layer, which contained aluminum chloride, was heated on a water bath and left for a few days, solid VII was produced. A precipitate was obtained by acidifying the sodium bicarbonate solution with hydrochloric acid and was identified as benzoic acid by the mixed melting point method (m. p. 118∼121°C). The sodium hydroxide solution and the water extract were acidified to give solid VI and oil V respectively. The ether solution was evaporated and the residual solution

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* The boiling and melting points are uncorrected.

6) J. B. Cohen, "Practical Organic Chemistry", Macmillan and Co., Ltd., London (1926), p. 254

7) "Organic Syntheses", Coll. Vol. 3 (1955), p. 29.

8) Ibid., Coll. Vol. 1 (1948), p. 394.

9) L. F. Fieser, "Experiments in Organic Chemistry", D. C. Heath & Co., Boston (1955), p. 204.

10) L. Gattermann, "Laboratory Method of Organic Chemistry", Macmillan and Co., Ltd., London (1952), p. 342.

subjected to distillation with water under reduced pressure in order to remove nitrobenzene. Residue VIIa was obtained.

Diethyl Benzoylmalonate (V).—The ethereal solution of the oil V was shaken with a copper acetate solution. The solid obtained on evaporating the ether was crystallized from ethanol as green needles, 3.8 g. (3.3 g. as V), m. p. 180~181°C.

Found: C, 56.90; H, 5.00; Cu, 10.52. Calcd. for $C_{28}H_{30}O_{10}Cu$: C, 56.99; H, 5.12; Cu, 10.76%.

No depression of the melting point was observed on the admixture of this crystalline with copper chelate of diethyl benzoylmalonate (m. p. 180°C) prepared by the method of the literature[11].

Ethyl Dibenzoylacetate (VI).—The solid VI crystallized from ethanol as colorless needles, m. p. 108~111°C, reported m. p. 112°C[12].

Found: C, 72.86; H, 5.52. Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44%.

This substance gave copper chelate, which was crystallized from ethanol in the form of light green needles, m. p. 218~220°C, reported m. p. 221°C[12]. The product obtained by boiling the solid VI (0.3 g.) with sulfuric acid (15%) for 15 hr. crystallized from methanol to give light yellow needles, 0.1 g., m. p. 78~79°C. Melting point and mixed melting point with dibenzoylmethane proved the identity of this material.

Dibenzoylmethane (VII).—The solid VII crystallized from methanol as light yellow needles, m. p. 78~79°C. A mixed melting point with dibenzoylmethane prepared by the method of the literature[13] showed no depression.

Found: C, 80.37; H, 5.54. Calcd. for $C_{15}H_{12}O_2$: C, 80.34; H, 5.39%.

This crystalline (0.2 g.) was boiled with semicarbazide hydrochloride (0.2 g.) in methanol (10 ml.) for 4 hr. Water was added to the methanol solution, and the separated crystal was crystallized from ethanol to give colorless plates, 0.19 g., m. p. 199.5 ~200.5°C. The recorded melting point for 3,5-diphenylpyrazol is 200°C[14]. A few drops of concentrated hydrochloric acid was added to the solid VIIa (0.1 g., m. p. above 270°) dissolved in a small amount of tetrahydrofuran, and the solution was kept at room temperature for 1 hr. The precipitated crystal was washed with water and crystallized from methanol, 0.09 g., m. p. 77~78°C. This substance was identified as VII by the mixed melting point method. The yields of products were listed in Table I.

Carbon Dioxide and Ethyl Chloride.—The gas evolved during the reaction was absorbed by a potassium hydroxide solution (30%) and toluene cooled with ice. The alkali solution was analyzed by differential titration with a standard acid solution to determine the amount of carbon dioxide evolved. The obtained value was about 70% of the amount of carbon dioxide which was estimated from the yields of VI and VII. The gas absorbed in toluene was distilled into aniline cooled with ice. The aniline placed in a sealed tube was heated for 7 hr. at 130°C, and then the reaction product was treated with *p*-toluenesulfonyl chloride by the Hinsberg method. The resulting product was crystallized from ethanol to give colorless crystals, m. p. 68~69°C, which agreed with the melting point in the literature[15] for *N*-ethyl-*N*-phenyl-*p*-toluenesulfonamide. The melting point was not depressed on admixture with an authentic sample prepared by the method of the literature.

Acylation of Diethyl Malonate with *p*-Chlorobenzoyl Chloride.—The reaction conditions and treatments of reaction mixture are quite the same as that described for acylation with benzoyl chloride. When the aqueous layer which contained aluminum chloride was heated on a water bath and left to stand for a few days, a solid precipitated. When this solid was collected, washed with water, and extracted with hot ethanol, insoluble solid Xa remained. On cooling the ethanol solution, solid X was obtained. The sodium bicarbonate solution was acidified to give a crystalline substance which gave no depression of melting point on mixture with *p*-chlorobenzoic acid. Nothing was obtained when the sodium hydroxide solution was acidified. The water extract was acidified to give solid IX. The removal of ether and nitrobenzene gave solid Xb. In the experiment used, one molecular equivalent of aluminum chloride, solid VIII, was obtained from the aqueous layer and the water extract.

Diethyl *p*-Chlorobenzoylmalonate (VIII).—The solid VIII crystallized from ethanol in the form of colorless needles, m. p. 52.5~53°C.

Found: C, 56.30; H, 5.05; Cl, 11.73. Calcd. for $C_{14}H_{15}O_5Cl$: C, 56.29; H, 5.06; Cl, 11.87%.

A suspension of the solid VIII in sulfuric acid (30%) was refluxed for 6 hr. The oily substance produced solidified on cooling and crystallized from ethanol as colorless needles, m. p. 20.5~21°C. A mixed melting point with *p*-chloroacetophenone prepared according to the literature[16] showed no depression.

Ethyl Di-*p*-chlorobenzoylacetate (IX).—The solid IX crystallized from ethanol in the form of colorless leaflets, m. p. 127.5~128.5°C.

Found: C, 59.12; H, 3.90; Cl, 19.30. Calcd. for $C_{18}H_{14}O_4Cl_2$: C, 59.20; H, 3.80; Cl, 19.42%.

A suspension of the solid IX (1 g.) in sulfuric acid (30%, 20 ml.) was refluxed for 4 hr., and the resulting product was crystallized from ethanol to give colorless needles, 0.6 g., m. p. 160~160.5°C. This product gave no depression of melting point on mixture with di-*p*-chlorobenzoylmethane.

Di-*p*-chlorobenzoylmethane (X).—The solid X crystallized from ethanol in the form of colorless leaflets, m. p. 160~160.5°C. The literature values for di-*p*-chlorobenzoylmethane are: m. p. 159°C[17], 160~161°C[18].

Found: C, 61.34; H, 3.51; Cl, 24.08. Calcd. for $C_{15}H_{10}O_2Cl$: C, 61.46; H, 3.44; Cl, 24.19%.

A suspension of the solid X (0.5 g.) in a mixture of sulfuric acid (60%, 50 ml.) and ethanol (5 ml.)

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11) C. Bülow and E. Hailen, *Ber.*, **35**, 934 (1902).

12) "Beilsteins Handbuch der organischen Chemie", H., **10**, 830 (1927).

13) "Organic Syntheses", Coll. Vol. 1 (1948), p. 199.

14) T. Posner, *Ber.*, **34**, 3984 (1901).

15) "Beilsteins Handbuch der organischen Chemie", Z., **12**, 306 (1950).

16) "Organic Syntheses", Coll. Vol. 1 (1948), p. 105.

17) A. Sieglitz and O. Horn, *Ber.*, **84**, 607 (1951).

18) G. S. Hammond et al., *J. Am. Chem. Soc.*, **81**, 7682 (1959).

was heated under reflux for 15 hr., and the resulting solution was extracted with ether. The ethereal solution was further extracted with a sodium hydroxide solution. With removal of the ether, an oily product (0.2 g.) was obtained. Semicarbazone prepared from this oily product melted at 202～203°C, which was not depressed on admixture with an authentic sample of semicarbazone[19] prepared from *p*-chloroacetophenone. The sodium hydroxide solution was acidified with hydrochloric acid to give a crystalline, 0.2 g., m. p. 236～237°C, which showed no depression on admixture with *p*-chlorobenzoic acid. The solid Xa (0.2 g., m. p. above 270°C) treated by the same merhod as described in the case of solid VIIa gave X, 0.19 g., m. p. 16°C. The solid Xb crystallized from ethanol to afford a crystalline, m. p. 160°C, and was identified as X by the mixed melting point method. The yields of products have been listed in Table I.

Acylation of Diethyl Malonate with *p*-Nitrobenzoyl Chloride.—The reaction conditions and treatments of reaction mixture are quite the same as that described above. The orange-red colored crystalline mass formed when the ethereal solution extracted with a sodium hydroxide solution was collected and washed with ether. The aqueous layer which contained aluminum chloride was heated on a water bath to form a precipitate. The precipitate was collected, washed with water and extracted with hot ethanol and then with cold ethanol-tetrahydrofuran (1 : 2) ; an insoluble solid XIII remained. On cooling the ethanol solution, solid XI precipitated. Upon evaporating the ethanol-tetrahydrofuran solution, solid XIIIa was obtained. The sodium bicarbonate solution was acidified to give a crystalline substance, which was crystallized from ethanol as yellowish white colored crystals and was identified as *p*-nitrobenzoic acid by the mixed melting point method. Nothing was obtained when the sodium hydroxide solution was acidified. When the above-mentioned orange-red colored crystalline was treated with hydrochloric acid and washed with water, it turned into yellow-colored crystalline XIIIb. The water extract was acidified to give solid XII. When the ethereal solution was evaporated and then distilled with water under reduced pressure, solid XIIa was obtained.

***p*-Nitroacetophenone (XI)**.—The solid XI crystallized from ethanol in the form of light yellow prisms, m. p. 80～81°C.

Found : C, 58.25 ; H, 4.21 ; N, 8.40. Calcd. for $C_8H_7O_3N$: C, 58.15 ; H, 4.28 ; N, 8.48%.

Phenylhydrazone prepared from the solid XI (0.2 g.) crystallized from ethanol in the form of red needles, 0.2 g., m. p. 133.5～134.5°C.

Found : N, 16.48. Calcd. for $C_{14}H_{13}O_2N_3$: N, 16.46%.

The recorded melting point[20] for *p*-nitroacetophenone and its phenylhydrazone are 80～81°C and 132°C respectively.

Ethyl *p*-Nitrobenzoylacetate (XII).—The solid XII crystallized from ethanol in the form of yellow needles, m. p. 69～72°C. Perkin and Bellenot[21] gave a m. p. of 74～76°C for ethyl *p*-nitrobenzoylacetate.

Found : C, 56.00 ; H, 4.89 ; N, 6.06. Calcd. for $C_{11}H_{11}O_5N$: C, 55.69 ; H, 4.67 ; N, 5.90%.

The solid XII (0.3 g.) was boiled with sulfuric acid (30%) for 8 hr. The separated crystal was crystallized from ethanol as light yellow prisms, 0.1 g., m. p. 80～81°C, and was identified as XI by the mixed melting point method. The solid XIIa which was crystallized from ethanol was determined to be identical with XII by the melting point and mixed melting point, m. p. 69～72°C.

Di-*p*-nitrobenzoylmethane (XIII).—The solid XIII crystallized from ethyl acetate in the form of yellow needles, m. p. 240～243°C, reported m. p. 241～242°C[17].

Found : C, 57.27 ; H, 3.18 ; N, 8.96. Calcd. for $C_{15}H_{10}O_6N_2$: C, 57.33 ; H, 3.21 ; N, 8.91%.

A suspension of the solid XIII (0.4 g.) in a mixture of sulfuric acid (60%, 50 ml.) and glacial acetic acid (4 ml.) was heated at reflux for 17 hr. The reaction mixture diluted with water was extracted with ether. The ethereal solution was extracted with sodium hydroxide solution. Removal of the ether gave a crystalline mass, 0.2 g., m. p. 79～80°C, which showed no depression on admixture with XI. The sodium hydroxide extract was acidified to yield a crystalline substance, 0.2 g., m. p. 234～235°C This substance was identified as *p*-nitrobenzoic acid by the mixed melting point method. XIII was obtained from the solid XIIIa (1 g., m. p. above 270°C) by the same method as has been described in the case of the solid VIIa, 0.97 g., m. p. 240～243°C. The solid XIIIb crystallized from ethyl acetate as yellow needles. The melting point was not depressed on admixture with XIII. The yields of products have been listed in Table I.

Acylation of Diethyl Malonate with Acetylsalicylic Acid Chloride.—Phosphorus pentachloride was added to a solution of acetylsalicylic acid in nitrobenzene, and the solution was warmed at 50～55°C for 3 hr. On cooling, aluminum chloride was added to the solution and dissolved, and then diethyl malonate was added. This solution was kept at 95～100°C for 8 hr. The reaction mixture was poured into crushed ice, and an excess of sodium hydroxide solution (15%) was added until the liquid had a alkaline reaction. The solution was extracted with ether to remove nitrobenzene and stirred into a hydrochloric acid solution (15%). The resulting crystals were crystallized from aqueous ethanol, m. p. 209～210°C. The melting point was not depressed on admixture with an authentic sample of 4-hydroxycoumarin (II)[1]. The filtrate separated from II was extracted with ether. Removal of the solvent from the ether extract gave a crystal. After recrystallization from aqueous ethanol, colorless needles were obtained, m. p. 158～159°C, which showed no depression of melting point on mixture with salicylic acid. The yields of products have been listed in Table II.

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[19] "Beilsteins Handbuch der organischen Chemie", Z., 7, 219 (1948).

[20] I. Heilbron and H. M. Bunburg, "Dictionary of Organic Compounds", Vol. 3, Eyre & Spottiswoode, Ltd., London (1953), p. 608.

[21] H. Perkin and G. Bellenot, *J. Chem. Soc.*, **49**, 447 (1887).

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