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Condensation of Diethyl Acetonedicarboxylate. II[1]

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Selfcondensation of diethyl acetonedicarboxylate (DADC) gave two types of products and the six kinds of the products were formed by using various catalysts.

In order to elucidate the reaction mechanism of DADC for giving these products, the roles of catalysts were investigated. The formation mechanism of the orsellinic acid derivatives (**1**, **2**, **3**, and **4**) was proposed, and the magnesium-DADC chelated complex (*B*) was recommended for the intermediate of these products. Furthermore, the mechanisms giving the coumarin derivatives (**5** and **6**) were discussed.

Keywords——condensation; diethyl acetonedicarboxylate; reaction mechanism; magnesium as catalyst; metal chelated complex; orsellinic acids; coumarin derivatives

As reported previously, two types of product, orsellinic acid derivatives and coumarin derivatives, were obtained from diethyl acetonedicarboxylate (DADC) by using various catalysts (Chart 1).

The present studies were undertaken to elucidate the mechanism of bimolecular condensation of DADC. On the basis of previous data, following assumptions were made. (a) The mechanism of formation of ethyl 4-carboxy-3,5-dihydroxy-2-ethoxycarbonylphenylacetate (**1**) and/or ethyl 4-carboxyorsellinate (**3**) may be different from that of ethyl 2,4-diethoxycarbonyl-3,5-dihydroxyphenylacetate (**2**) and/or ethyl 3,5-dihydroxy-2-ethoxycarbonylphenylacetate (**4**). This assumption was inferred from the fact that the yield of oresellinic acid derivatives (**1**, **2**, **3**, and **4**) was governed by the amount of magnesium and ethyl chloroacetate (ECA) used as a catalyst for a definite amount of DADC, and that the sum of yield of **2** and **4** decreased with increase of that of **1** and **3**. (b) The role of ECA for this condensation seems to be to dissolve magnesium, to facilitate the formation of magnesium-DADC chelated complex, and to stabilize the complex. This assumption is proposed from the fact that α-chlorocarbonyl group of alkyl halides used as a catalyst is indispensable for the selective formation of **1** and/or **3**.

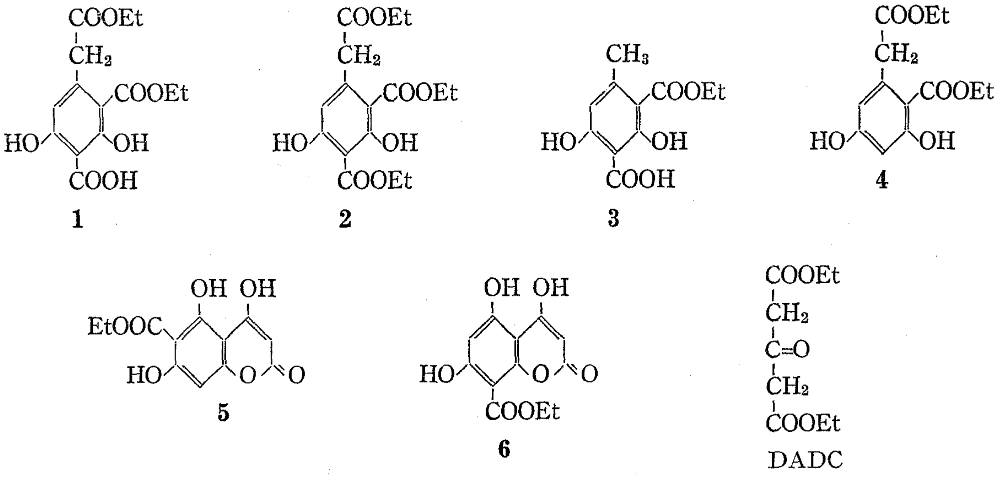

Chart 1

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[1] M. Yamato, J. Uenishi, and K. Hashigaki, *Chem. Pharm. Bull.* (Tokyo), **26**, 1459 (1978).

[2] Location: *Tsushima-naka 1-1-1, Okayama 700, Japan.*

When a mixture of magnesium and ECA was heated at the boiling point of ECA (140°), vigorous reaction set in and the reactant polymerized immediately. On the other hand, when the mixture of magnesium and ECA was heated in the presence of an excess of DADC, gentle dissolution of magnesium was observed.

With regard to an intermediate in this reaction, a chelated compound with magnesium was isolated from the reaction mixture obtained under the following condition: A mixture of magnesium powder (1.25 g, 51.44 mmol), ECA (1.0 g, 8.16 mmol), and DADC (5.0 g, 24.75

Table I. Yields of Orsellinic Acid Derivatives from DADC–Magnesium Chelated Compound (D)

Compound D[a] (mmol)	Catalyst (mmol)		Temp. (°C)	Time	Yield of products[b] (%)			
					1	**2**	**3**	**4**
12.33			140—150	30 min	9.9	2.7	3.5	3.2
12.33			180—190	30 min	4.3	—	4.8	—
12.33	DADC 10.9		180	3 hr	19.1	4.3	4.2	6.5
12.33	Mg 1.2		180	20 min	10.5	2.4	4.6	—
0.11	DADC 24.75		180	3 hr	2.7	7.7	—	8.4
0·11	DADC 24.75	Mg 1.2	180	2.5 hr	3.9	10.7	—	7.2
12.33[c]			140	2 hr	1.2	3.4	—	1.6
12.33	ECA 8.16	Mg 1.2	140	2 hr	0.9	3.0	—	2.1

[a] DADC–Mg chelated compound, 12.33 mmol of D corresponds to 24.75 mmol of DADC.
[b] Each yield was calculated from 24.75 mmol of DADC.
[c] In xylene 30 ml.

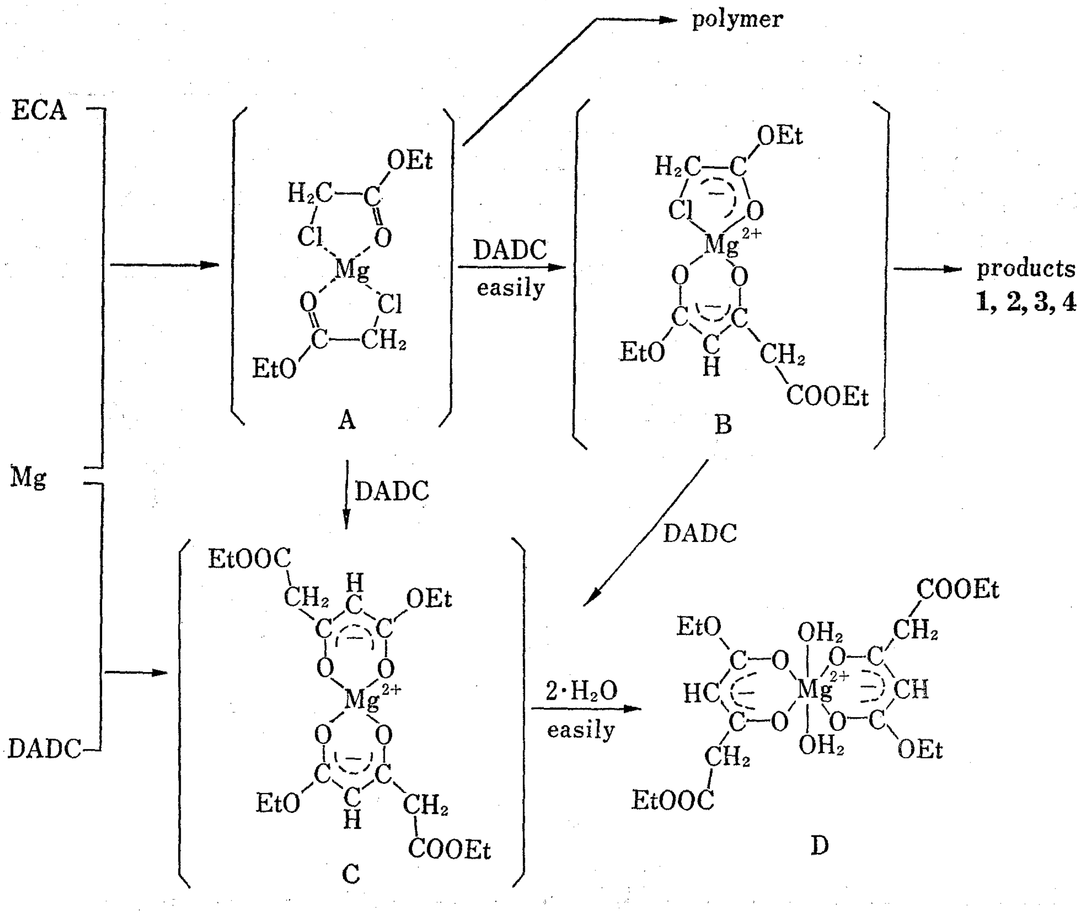

Chart 2

mmol) was heated to 140° with stirring for 5 min and the reaction mixture was crystallized from methanol to a colorless powder (D). The compound D was identified as a magnesium-DADC chelated complex with six number of coordination (in Chart 2), in which two moles of water coordinated assuming from the data of elementary analysis and from nuclear magnetic resonance (NMR) spectra. The compound D was also identified with the product synthesized by other methods mentioned in the experimental part. We considered at first that D might be an intermediate of the formation of **1** and **3**. Therefore, D was heated at

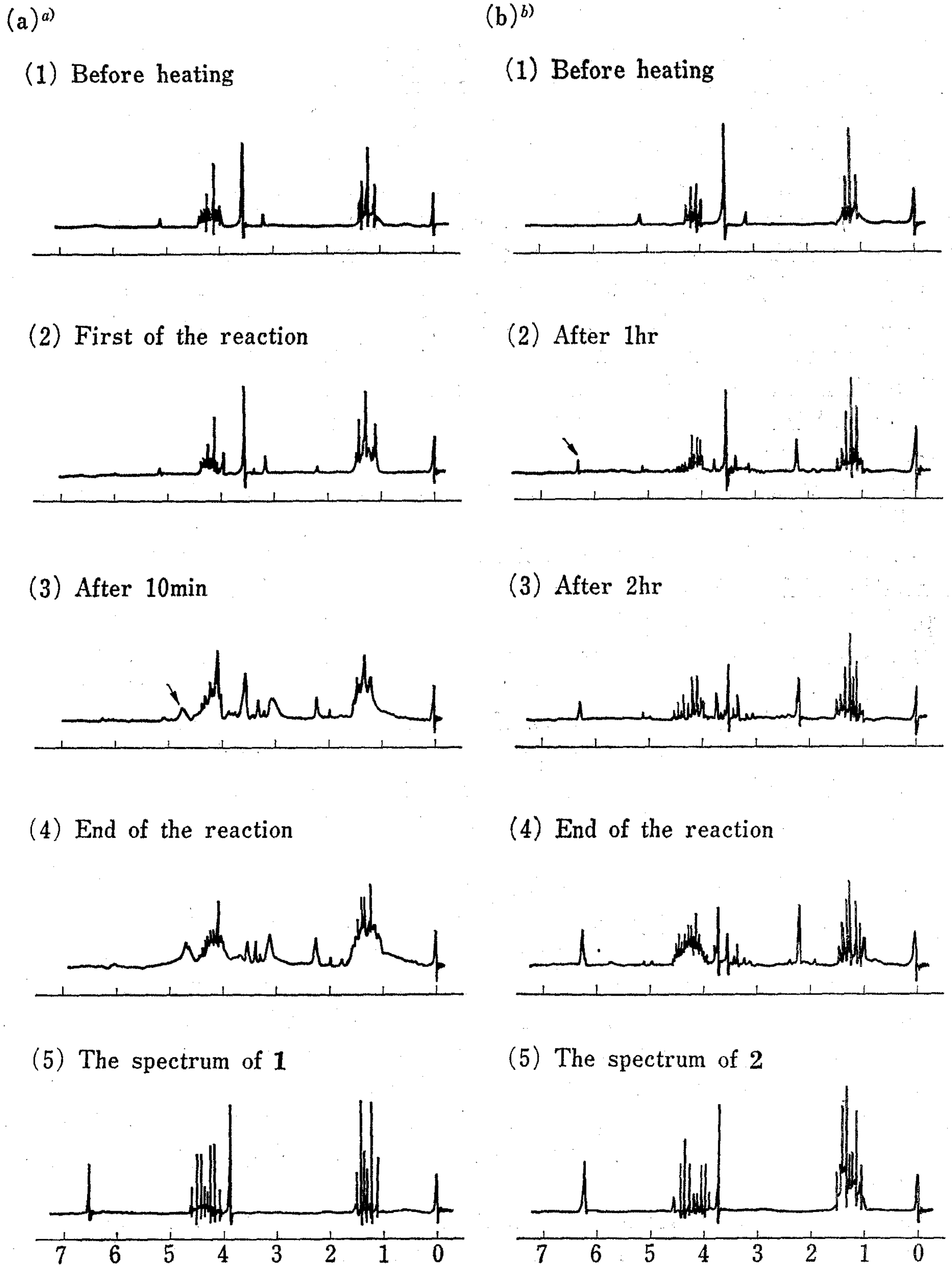

Fig. 1. NMR Spectrums of the Reaction Mixture with Passage of the Reaction Time

All samples were dissolved in $CDCl_3$.

a) The condition used for the formation of 1 and/or 3: DADC 5.0 g, Mg 1.25 g, and ECA 1.0 g, 160—180°, 20 min.

b) The condition used for the formation of 2 and/or 4: DADC 5.0 g, Mg 0.03 g, and ECA 1.0 g, 180°, 3 hr.

140—190° and the products formed were analyzed by gas chromatography (GC) as shown in Table I. Contrary to our expection, the yield of **1** and/or **3** was very poor. Therefore, D was ascertained to be not the true intermediate for the formation of **1** and/or **3**. We propose the mechanism of the formation of D as shown in Chart 2. That is, the compound (C) may be a plane chelated complex, a precursor of D, but it seems that C and D are poor reactants for the formation of **1** and/or **3**. Therefore, we assumed that B might be the true intermediate of orsellinic acid derivatives, although B and C could not be isolated due to their instability.

In order to elucidate the role of magnesium as a catalyst in this condensation, NMR spectra of the reaction mixture was measured at regular time intervals.

Fig. 1-a is the NMR charts of the reaction mixture obtained under the condition for the formation of **1** and/or **3**. A characteristic peak at 4.72 ppm (in Fig. 1-a-3) suggests the presence of a methine proton of magnesium-DADC chelated complex, such as the type of β-dicarbonyl-metal chelated compound. Because the methine proton in an enol form of DADC appears as a single peak at 5.12 ppm (in Fig. 1-a-1), while that of D appears at 4.80 ppm, the characteristic peak at 4.72 ppm of the reaction mixture seems to be the peak of a methine proton of the magnesium chelated complex. The peak at 4.72 ppm becomes broader with passage of reaction time, probably due to heterogeneous phase formed by increase in the amount of condensed organometallo-chelated compound in this reaction mixture. Although no aromatic proton is observed in these NMR charts, the sample obtained by acidification of the reaction mixture with dil. hydrochloric acid has a peak of aromatic proton of **1** at 6.50 ppm.

From these facts, it is imaginable that the products do not exist in an aromatic form but in an aliphatic form chelated with magnesium in this reaction mixture.

Fig. 1-b is the NMR charts of the reaction mixture obtained under the reaction condition for the formation of **2** and/or **4**. New peaks appear as the reaction time passes. The height of some peaks increases little by little with decrease of the peak height of DADC in these spectra (Fig. 1-b-2, 3, and 4). A new peak at 6.28 ppm may be assigned to the aromatic proton of the product **2**, and a new peak at 2.20 ppm is probably that of a methyl proton of ethyl acetoacetate formed by pyrolysis of DADC. The main product **2** can be detected in the NMR spectrum at the end of the reaction (Fig. 1-b-4) without treatment with dil. hydrochloric acid. Therefore it becomes apparent that the product **2** exists in an aromatic form in this reaction mixture. Especially, all the peaks appear sharp and contrast to those in Fig. 1-a.

On the basis of these facts, the formation mechanism of the intermediate giving orsellinic acid derivatives is suggested as shown in Chart 2. Magnesium is dissolved by the reaction with ECA to form an intermediate (**A**). When an excess of DADC is present in the reaction, the next intermediate B is smoothly formed. The compound B may be formed at the reaction temperature of 160—180°, and acts as a transition intermediate. To date, many studies on the reactivity of metal-chelated compounds have been reported[3]; the Friedel-Crafts type acylation, bromination, and nitration of methine carbon of metal acetyl acetonate, and, especially, the Knoevenagel type reaction of glycin-copper compound, which reacts with aldehyde,[4] and the bimolecular condensation of DADC using magnesium may be similar to this reaction.

The compound B may react as a nucleophile because the structure of B is one of metal chelated complexes of an acetyl acetonate type and the methine carbon is known to be electron rich.[5]

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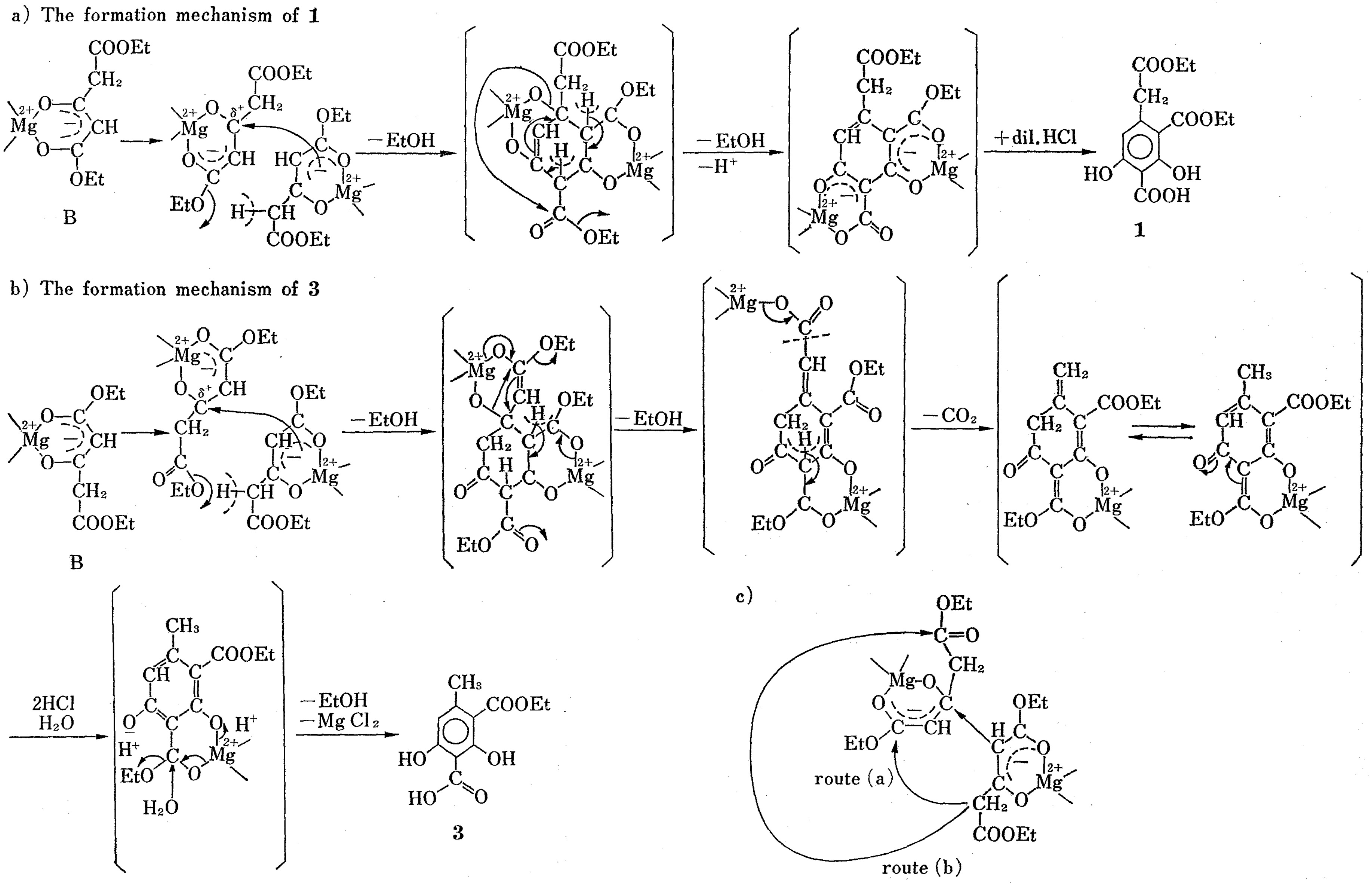
[3] *a*) J.P. Collman, *Inorg. Chem.* ,4, 1273 (1965); *b*) R.W. Kluiber, *J. Am. Chem. Soc.*, **82**, 4839 (1960); *c*) P.R. Singh and R. Sahai, *Aust. J. Chem.*, **20**, 649 (1967).

[4] J.C. Hammel and J.A. Smith, *J. Chem. Soc.*, **1970**, 1855.

[5] M. Sato, K. Okawa, and S. Akabori, *Chem. Pharm. Bull.* (Tokyo), **30**, 937 (1957).



a) The formation mechanism of **1**

b) The formation mechanism of **3**

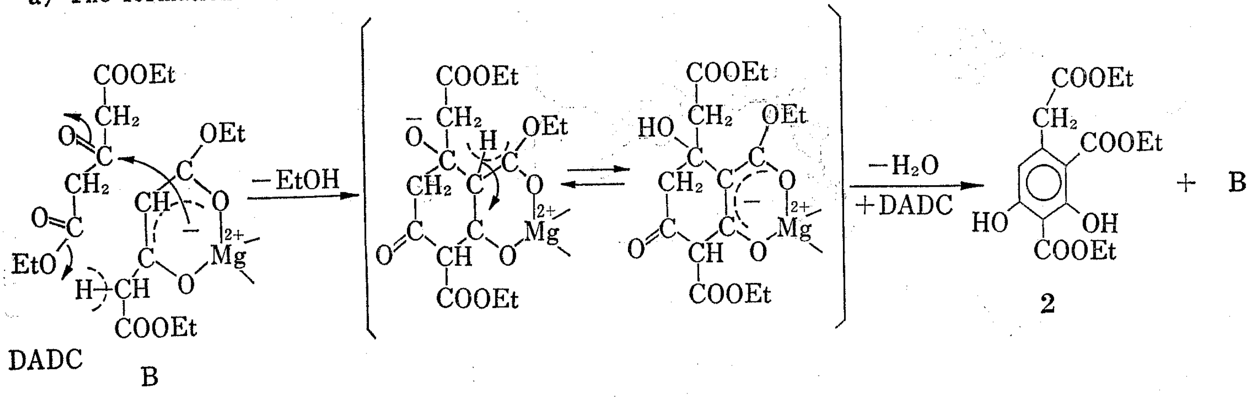
c)

Chart 3

The mechanisms for the formation of **1** and **3** are suggested in schemes (**a**), (**b**), and (**c**) in Chart 3. Chart 3-a is the reaction mechanism for the formation of **1**. The electron-rich methine carbon of B attacks the inductively polarized carbon of another B which is regarded as a kind of *α*,*β*-unsaturated ester in the Michael type reaction, and ester condensation occurs in another part concomitantly. In addition, a cleavage of the carbon-oxygen bond in the chelate ring occurs and the oxygen atom attacks the ester carbonyl group of another B. In this stage, structure of the product may be an aliphatic intermediary complex chelated with magnesium. When the reaction mixture is acidified with dil. hydrochloric acid, the magnesium atom in the chelated complex is eliminated and aliphatic complex is changed into the aromatic compound **1**.

Chart 3-b is the reaction mechanism for the formation of **3**. Similarly to that of Chart 3-a, the Michael type reaction takes place at first. Ester condensation will be set in between the activated methylene of B and ethoxyl group of another B. This process is different from that of the formation of **1** in Chart 3-c. The chelated ring is cleaved in the course of electron transfer in Chart 3-b, and hydrolyzed with dil. hydrochloric acid to give **3**. Actually, **1** was obtained much more than **3**, because the ester condensation of the route (a) may take

a) The formation mechanism of 2



b) The formation mechanism of 4

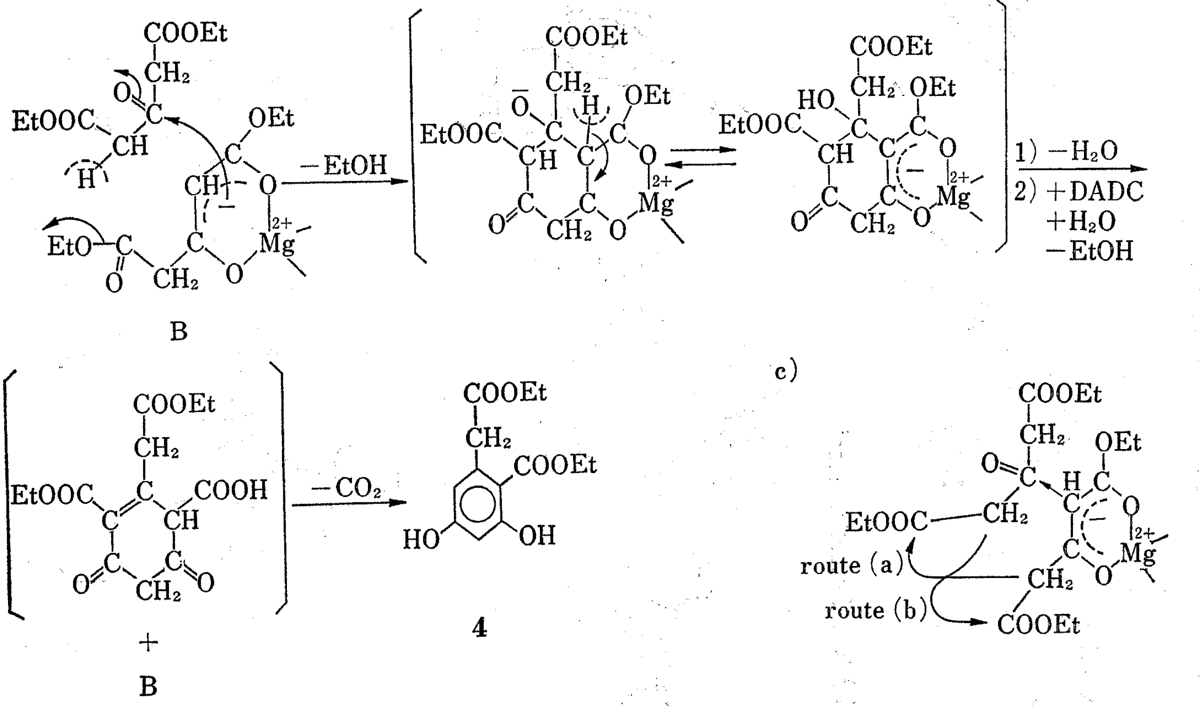


Chart 4

place more easily than that of the route (b).

The mechanisms for the formation of **2** and **4** are suggested in schemes (a), (b), and (c) in Chart 4. Whenever a small amount of magnesium and ECA are used as a catalyst for the condensation, the products **2** and/or **4** are formed selectively. In this case, B will be formed only a little, and will act catalytically. DADC reacts with B by the addition and by ester condensation to give a chelated complex which is assumed to be unstable. This complex is broken readily by transport of magnesium to another DADC present in a large quantity and is dehydrated to give **2**. The magnesium atom in the unstable chelated complex is interchanged with other DADC molecules and renewed B will be formed, and this process will be repeated. Whether **2** or **4** is formed in the reaction is a matter of the course of ester condensation in Chart 4-c. The ester condensation of the route (a) may take place more easily than that of the route (b), because the methylene of the route (a) may be more activated than that of the route (b).

The coumarin derivatives, 6-ethoxycarbonyl-4,5,7-trihydroxycoumarin (**5**) and 8-ethoxycarbonyl-4,5,7-trihydroxycoumarin (**6**), were obtained from DADC in a high yield by using

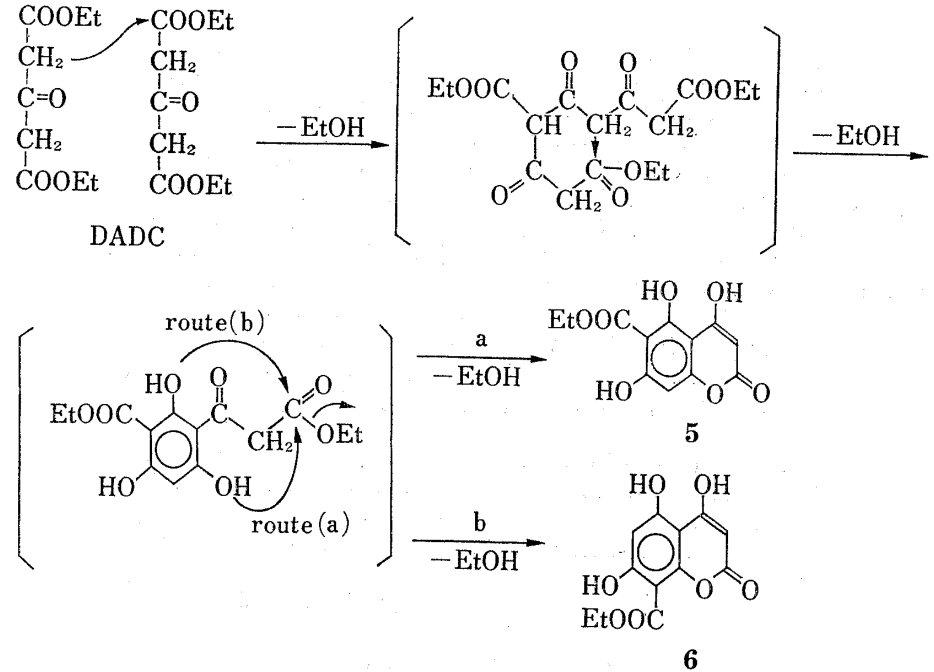
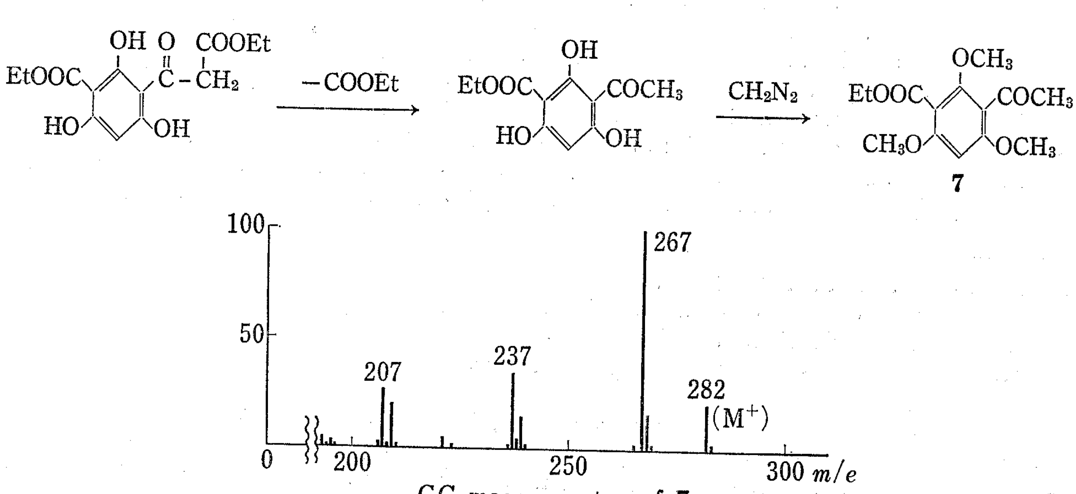


Chart 5



GC–mass spectra of **7**

Chart 6

a catalyst of the Claisen ester condensation in a nonpolar solvent. The mechanism for the formation of the coumarin derivatives, **5** and **6**, is considered as shown in Chart 5. Two possible routes of lactonization are considered, that is, the ester exchange may take place with either of the two *o*-hydroxyl groups (route a or b). The route a may be favored than the route b because hydroxyl group of the route b may form a stronger hydrogen bonding than that of the route a and be more hindered by the presence of the adjacent ethoxycarbonyl group. Therefore, **5** is formed much more than **6**.

According to Gruber,[6] the yield of **5** was about 30 times that of **6**. Actually, we also found a similar result. In the qualitative analysis of the reaction mixture obtained under the condition for the formation of coumarin derivatives by GC, an unknown peak was detected, and the GC-mass spectra suggested the structure to be ethyl 3-acetyl-2,4,6-trimethoxybenzoate (**7**), shown in Chart 6. It may be an evidence for the formation of ethyl 3-ethoxycarbonyl-2,4,6-trihydroxybenzoylacetate, which is an intermediate of the coumarin derivatives, **5** and/or **6**.

Experimental[7]

Preparation of Samples for GC Analysis——Five grams of DADC was reacted under the conditions shown in Table I. After the reaction, the reaction mixture was acidified dil. HCl, and extracted with AcOEt. The extract was washed with H_2O and dried over anhyd. $MgSO_4$. The one-fifth of the solutuon was methylated with CH_2N_2 by the usual method, until the reactant gave a negative reaction to the $FeCl_3$ test. The solvent was evaporated and the residue was dissolved in 50 ml of AcOEt. A five ml of the solution and 1 ml of pyren solution (1.5 mg/ml as an internal standard in AcOEt) were pipetted into a 10 ml measuring-flask and the whole was diluted with AcOEt to 10 ml. One μl of this solution was injected into the gas chromatograph.[8]

Synthesis of Magnesium-DADC Chelated Compound (D)——To 150 ml of water, 9.6 g (0.1 mol) of $MgCl_2$ and 20 g (0.1 mol) of DADC were added. Aqueous ammonia was added with stirring till the precipitate was deposited at pH 8—10. After stirring for an hour, the precipitate was collected and washed with water for several times. It was recrystallized from MeOH to give a chelated compound 17 g (75%). mp 72—73°. *Anal.* Calcd. for $C_{18}H_{30}MgO_{10}$: C, 46.29; H, 6.25. Found; C, 46.72; H, 6.54. NMR (in $CDCl_3$) δ; 1.10—1.35 (12H, m, CH_3), 2.45—2.70 (4H, broad, H_2O), 3.09 (4H, s, CH_2COO), 4.18—4.73 (8H, m, $C\underline{H_2}CH_3$), 4.82 (2H, s, CH).

Another Synthetic Method of (D)——To the mixture of 20 g of DADC and 2.4 g of magnesium powder, a few drops of conc. HCl were added with stirring at room temperature. After stirring for 24 hours the precipitate was collected and recrystallized from MeOH to give the chelated compound, 12.0 g (52%). This compound agreed with the magnesium-DADC chelated compound obtained by the above method in all analytical data.

Synthesis of 6-Ethoxycarbonyl-4,5,7-trihydroxycoumarin (5) and 8-Ethoxycarbonyl-4,5,7-trihydroxycoumarin (6)——To the flask containing the sodium ethoxide solution prepared previously by dissolving 9.0 g of sodium in 200 ml of abs. EtOH and 100 ml of dry toluene, 50 g of DADC was dissolved in 100 ml of dry toluene was added from a dropping funnel with stirring at room temperature. The flask was heated while distilling the ethanol and toluene as an azeotropic mixture. In the course of the reaction, dry toluene was added into the flask. When the temperature reached to about 110°, the distillation of the solvent was changed to refluxing and it was continued for 6 hours. After the reaction the mixture was poured into 750 ml of ice water, and the aqueous solution was acidified with dil. HCl to give precipitate, which were collected with suction and recrystallized from acetic acid giving **5** and/or **6** as colorless powder, 27 g (90%), mp 184—186°. *Anal.* Calcd. for $C_{12}H_{10}O_7$: C, 54.14; H, 3.79. Found ; C, 54.09; H, 3.78. NMR (in d_6-DMSO) δ; 1.27 (3H, t, $J=8$ Hz, CH_3), 4.27 (2H, q, $J=8$ Hz, CH_2), 5.00—5.40 (1H, broad, C_3-H), 6.25 (1H, s, aromatic H), 8.50—10.40 (3H, broad, OH). MS *m/e*: 266 (M^+), 220 (M^+-EtOH, base peak), 192, 188.

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[6] W. Gruber, *Chem. Ber.*, **76**, 135 (1943).

[7] Melting points were determined on a Yanagimoto micro-melting point apparatus and were uncorrected. NMR spectra were taken with Hitachi Model R-22 Spectrometer using tetramethylsilane as an internal standard. Mass and GC-mass spectroscopy were measured with Shimadzu Model LKB-9000 Spectrometer.

[8] A Shimadzu Model GC-6AM gas chromatograph equipped with a flame ionization detector was used. The operating condition was as follows. Liquid phase OV-1 (1.5%) on Chromosorb W, AW-DMCS, 60—80 mesh; column, 1.5 m × 3 mm, glass; initial column temp., 175°; final temp., 240°; program rate 5°/min; injection and detector ports temp., 260°; carrier gas (N_2) flow-rate, 40 ml–min; hydrogen flowrate, 50 ml/min; air flow-rate, 0.8 l/min.