

## Studies on Kojic Acid and its Related $\gamma$ -Pyrone Compounds

\*Part V. Synthesis of Chelidonic Acid and its Alkylesters

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The present work represents a continuation of our interest in preparing and investigating  $\gamma$ -pyrone derivatives which might have some potential biological activity. A good many derivatives of kojic acid (5-hydroxy-2-hydroxymethyl- $\gamma$ -pyrone) were discussed in the previous articles from this laboratory<sup>1,2,3,4</sup>.

The present paper describes the new methods for the preparation of the monoalkylester and dialkylester of chelidonic acid ( $\gamma$ -pyrone-2,6-dicarboxylic acid).

Chelidonic acid was first isolated from *Chelidonium majus* by Probst<sup>5</sup>), and was thoroughly investigated by Lieben and Haitinger<sup>6</sup>). They have deduced the structure of chelidonic acid which was later confirmed by synthesis and degradation with alkali. The acid was first prepared by Claisen<sup>7</sup>) by ring-closure of acetoneoxalate with hydrochloric acid and the method was subsequently improved by Willstätter<sup>8</sup>) and Ruzicka.<sup>9</sup>)

In our experiments, a modification of Ruzicka's method was used and it gave more satis-

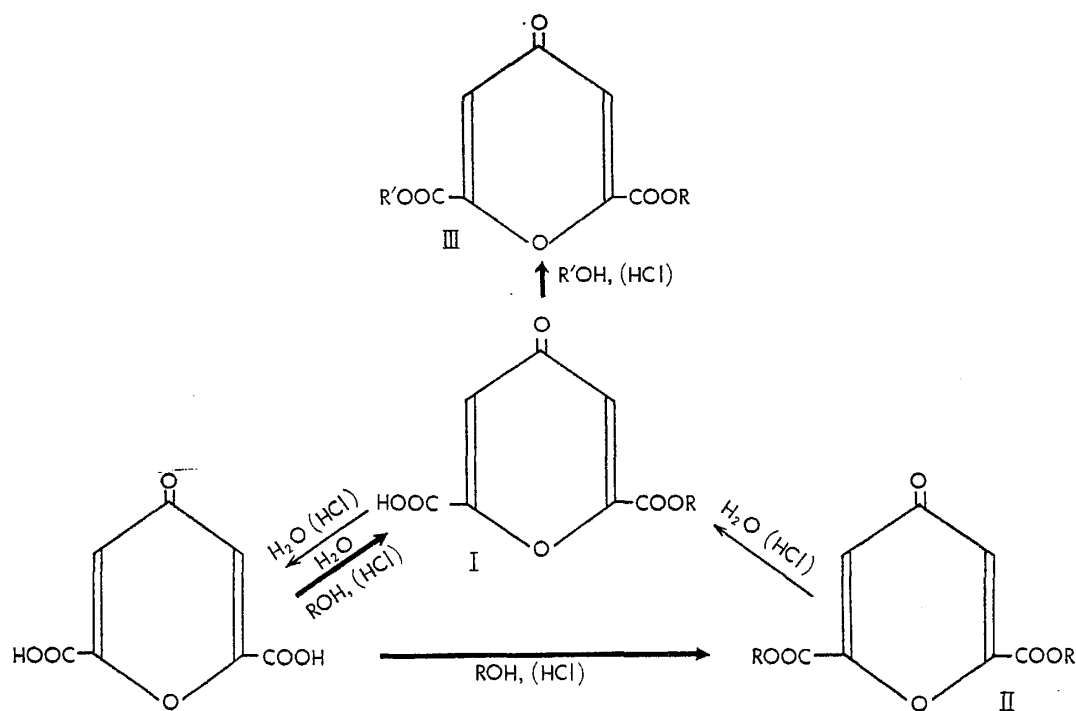


Fig. 1. Synthesis of Chelidonic Acid Alkylester.

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factory results for the synthesis of chelidonic acid. Furthermore, the authors devised new methods for the alkylation of chelidonic acid which gave the corresponding monoalkylesters and dialkylesters.

As chelidonic acid has two carboxyl groups in symmetrical positions (2 or 6) for  $\gamma$ -pyrone ring, the esterification in the usual procedure by the use of alcohol ( $C_1 \sim C_4$ ) gave the corresponding dialkyl esters (II) in good yield (see Table 2).

On the other hand, Heyns<sup>10)</sup> has shown that the monoethyl ester was obtained from chelidonic acid diethylester by using hydrochloric acid and water in the alcohol solution. From this fact, it may be expected that the monoalkyl ester is produced when chelidonic acid is esterified with alcohol by using hydrochloric acid and water. With this in mind, we have made a comparative study of the relative ratio of esterification in the presence of water. The water contents used in this experiments were 10 % and 20 % for the alcohol, respectively.

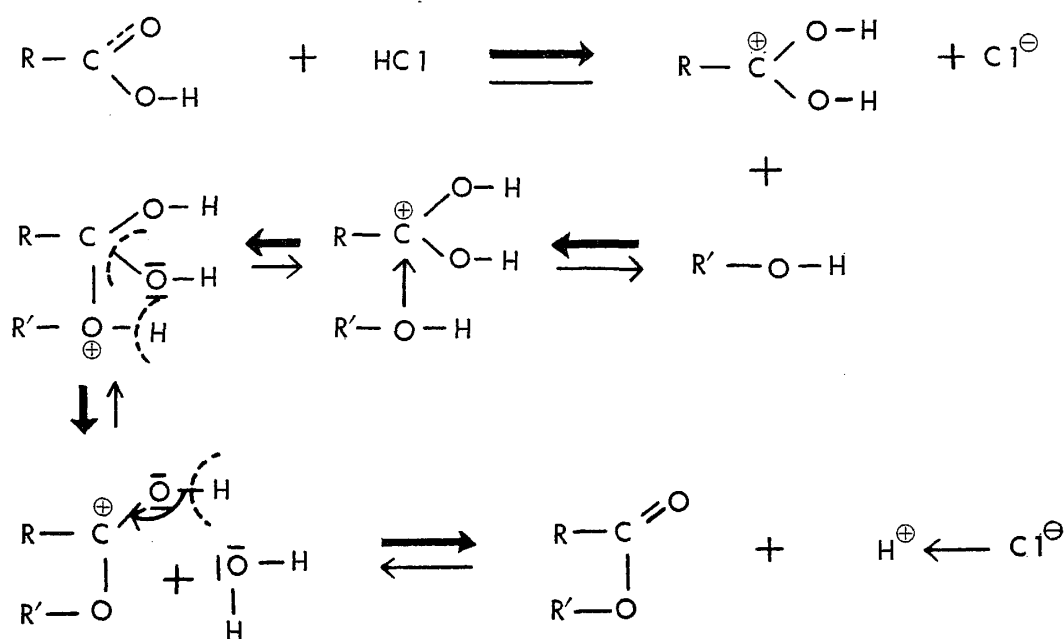
TABLE 1. THE RATIO OF MONOALKYLESTER AND DIALKYLESTER BY THE ESTERIFICATION OF CHELIDONIC ACID USING  $H_2O$

Added $H_2O$	Produced Monoalkylester	Produced Dialkylester
10 %	40 %	43 %
20 %	80 %	11 %

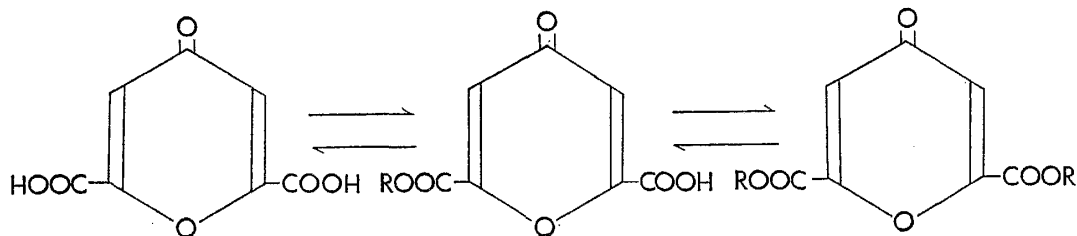
In this experiment, ethanol was used as alkyl group. 14g of chelidonic acid was refluxed with alcoholic hydrogen chloride (100ml, 5%) and  $H_2O$  for 3 hrs.

As shown in Table I, 43% of dialkylester and 40% of monoalkylester were produced when 10% of water was added to the reaction mixture. Whereas, with 20% of water, the monoalkylester and dialkylester were obtained, in 80% and 11%, respectively.

It has been generally well known that esterification is reversible reaction. The reaction mechanism may be written as follows:



Therefore, our results suggested that the producing ratio of the monoalkylester and dialkylester of chelidonic acid would depend on the relative amount of water which was used for esterification. An equilibrium will be established between the starting material and final products as follows:



Thus obtained monoalkylester (Ib) was further esterified by the use of different alcohols ( $C_1 \sim C_4$ ) and gave the corresponding dialkylesters (IIIa, IIIb, IIIc, IIId, IIIe).

All the products were powdery crystals of which the structures were identified by the following experiments.

As shown in Fig. 2, the typical ultra-violet absorption spectra of these products are similar to each other, whose maxima are at  $225 \text{ m}\mu$  and  $272 \text{ m}\mu$ , respectively. Also their infrared absorption spectra are presented in Fig. 3. The strong peaks which correspond to the OH group ( $3550\text{-}3430 \text{ cm}^{-1}$ ) and COOH group ( $1730, 1417, 1129, 740 \text{ cm}^{-1}$ ) in chelidonic

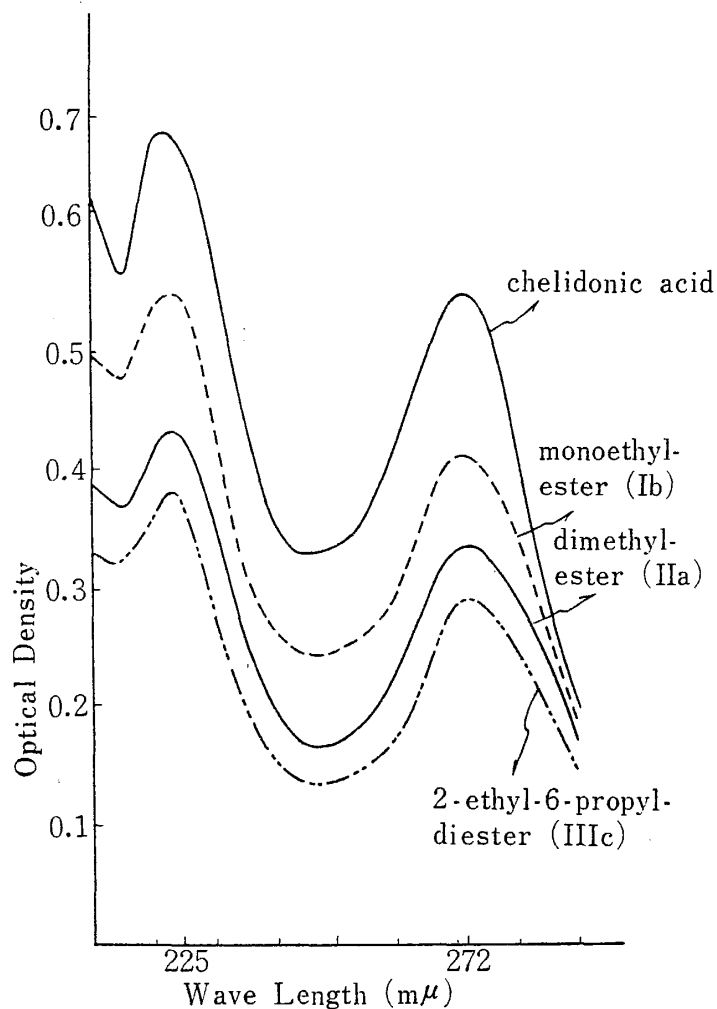


Fig. 2. Ultraviolet Spectra of Chelidonic Acid and its Alkylesters.

acid disappear in these products (dialkylesters), except for monoalkylesters, for which, the relatively weak peaks have remained. Whereas, new intensive peaks of alkylesters are observed at 1750-1740, 1254, 1123-1103  $\text{cm}^{-1}$  (ester, R-COOR) and 2980-2940, 1470-1465, 1378-1345, 720  $\text{cm}^{-1}$  (alkane group,  $\text{CH}_3\text{-C}$ ,  $-\text{CH}_2-$ ), respectively. The specific absorption bands of  $\gamma$ -pyrone ring on the chelidonic acid lie at 1650, 1600 and 1585  $\text{cm}^{-1}$ , while about 10~30  $\text{cm}^{-1}$  shift is observed for its alkylesters. Such a shift is attributed to the

TABLE 2. ALKYLESTERS OF CHELIDONIC ACID

(I)

Mono-esters	Alkyl group	M.P. °C	Formula	Analyses %	
				Calcd.	Found
Ia	Methyl	220-222	$\text{C}_8\text{H}_8\text{O}_6$	C 48.49	C 48.58
				H 3.05	H 3.19
Ib	Ethyl	218-220	$\text{C}_9\text{H}_8\text{O}_6$	C 50.95	C 50.62
				H 3.80	H 4.16
Ic	n-Propyl	180	$\text{C}_{10}\text{H}_{10}\text{O}_6$	C 53.10	C 52.85
				H 4.46	H 4.45
Id	iso-Propyl	185-187	$\text{C}_{10}\text{H}_{10}\text{O}_6$	C 53.10	C 52.79
				H 4.46	H 4.41
Ie	n-Butyl	162-164	$\text{C}_{11}\text{H}_{12}\text{O}_6$	C 55.00	C 54.98
				H 5.04	H 4.92

(II)

Di-esters	Alkyl group	M.P. °C	Formula	Analyses %	
				Calcd.	Found
IIa	Methyl	116-118	$\text{C}_9\text{H}_8\text{O}_6$	C 50.95	C 50.78
				H 3.80	H 3.70
IIb	Ethyl	63	$\text{C}_{11}\text{H}_{12}\text{O}_6$	C 55.00	C 55.07
				H 5.04	H 5.03
IIc	n-Propyl	51-52	$\text{C}_{13}\text{H}_{16}\text{O}_6$	C 58.20	C 58.51
				H 6.01	H 6.14
IIId	iso-Propyl	58-59	$\text{C}_{13}\text{H}_{16}\text{O}_6$	C 58.20	C 57.86
				H 6.01	H 5.89
IIe	n-Butyl	24.5-25	$\text{C}_{15}\text{H}_{20}\text{O}_6$	C 60.80	C 60.38
				H 6.80	H 6.99

(III)

2-Ethyl-6R-diesters	Alkyl group	M.P. °C	Formula	Analyses %	
				Calcd.	Found
IIIa	Methyl	70	$\text{C}_{10}\text{H}_{10}\text{O}_6$	C 53.10	C 53.65
				H 4.46	H 4.63
IIIb	Ethyl	63	$\text{C}_{11}\text{H}_{12}\text{O}_6$	C 55.00	C 55.07
				H 5.04	H 5.03
IIIc	n-Propyl	46-47	$\text{C}_{12}\text{H}_{14}\text{O}_6$	C 56.69	C 57.10
				H 5.55	H 5.72
IIId	iso-Propyl	52-53	$\text{C}_{12}\text{H}_{14}\text{O}_6$	C 56.69	C 57.09
				H 5.55	H 5.69
IIIe	n-Butyl	22	$\text{C}_{13}\text{H}_{16}\text{O}_6$	C 58.20	C 58.50
				H 6.01	H 6.17

esterification.

Physical properties and analytical data for all products are given in Table II. The analytical data agreed with calcd. values.

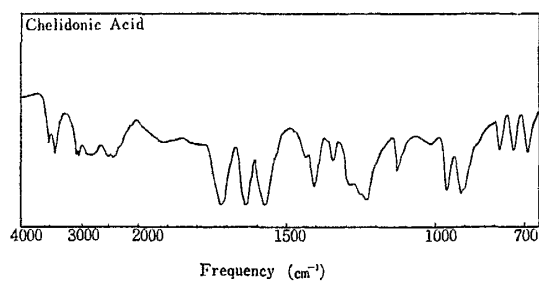


Fig. 3-1.

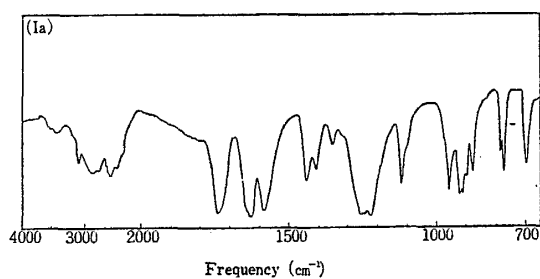


Fig. 3-2.

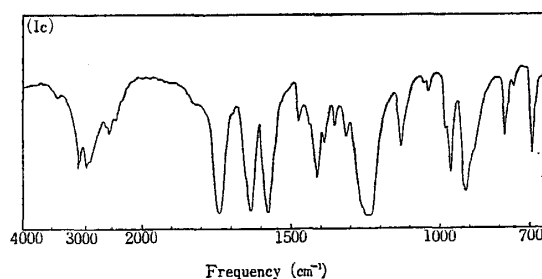


Fig. 3-3.

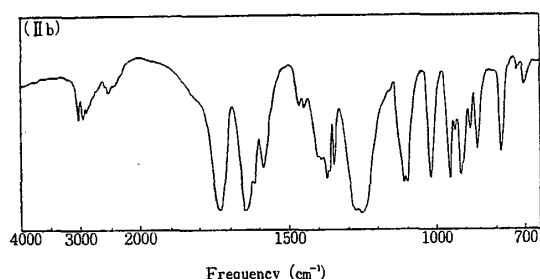


Fig. 3-4.

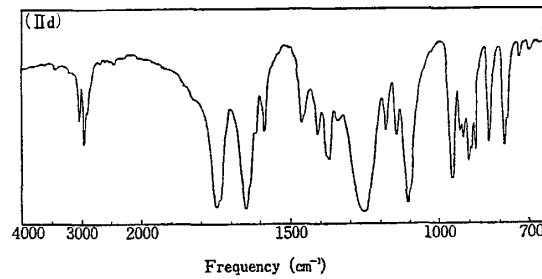


Fig. 3-5.

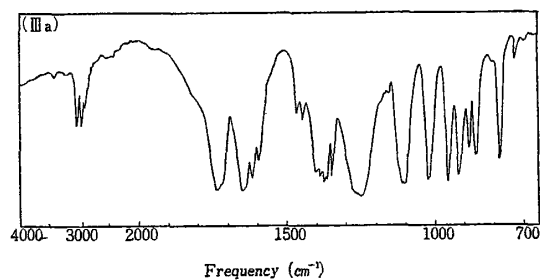


Fig. 3-6.

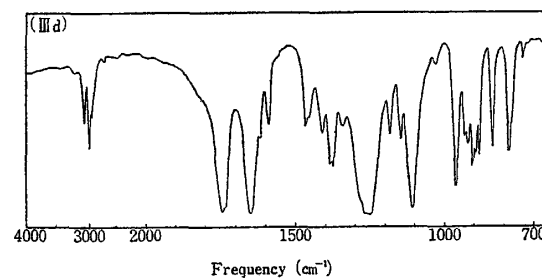


Fig. 3-7.

Fig. 3. Infrared Spectra of Chelidonic Acid and its Alkylesters.

In the case of esterification by using higher alcohol ( $C_5$ ), no crystalline product could be obtained.

### Experimental

All melting points were uncorrected. Infrared absorption spectra were taken on a Hitachi Infrared Spectrophotometer EPI-2 using potassium bromide pellets. Ultraviolet absorption spectra were determined in the ethanol solution with Shimadzu Spectrophotometer QR-50.

*Chelidonic Acid.* Forty and six grams of sodium was carefully dissolved in 600 ml of absolute ethanol. Toward the end of the reaction the flask was heated with a small smoky flame. About half of the sodium ethoxide solution was poured into another flask; the other half was kept warm by a small flame. The first half of the solution was allowed to cool until a solid began to appear, then 58 g of dry acetone mixed with 150 g of ethyl oxalate was added at once and the mixture was stirred. Heat was evolved, and the reaction solution turned brown color. As soon as any turbidity appears, the other half of the hot sodium ethoxide solution was poured into the reaction mixture together with 160 g of ethyl oxalate. After stirring for about thirty minutes the mixture became practically solid. The flask was then heated in an oil

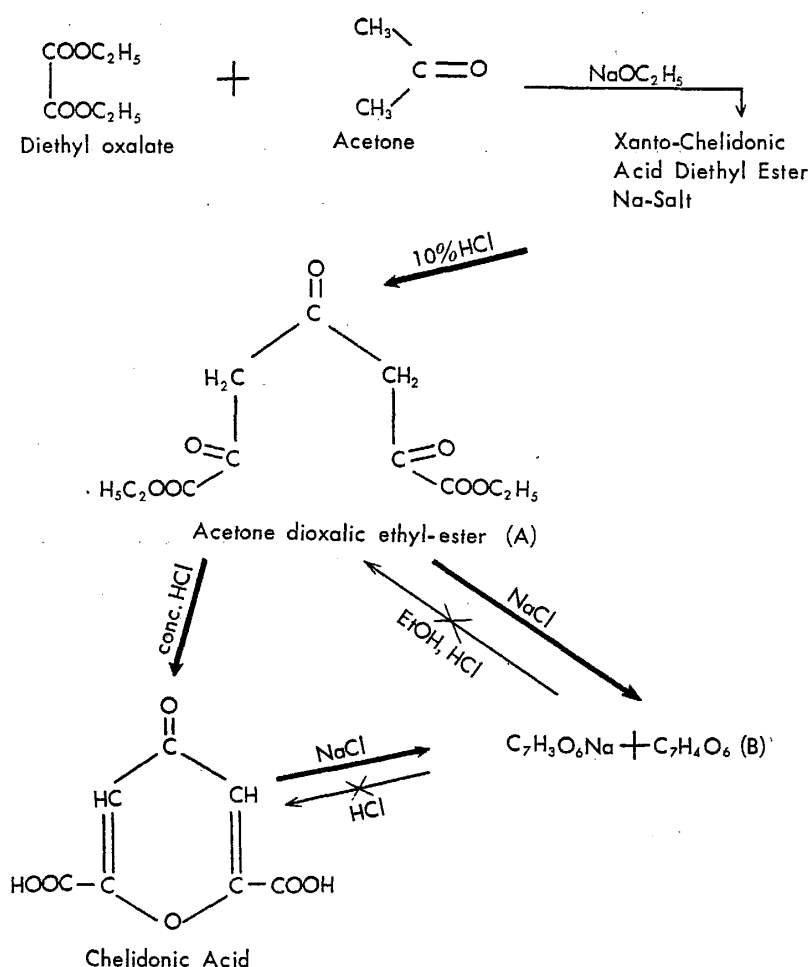


Fig. 4. Synthesis of Chelidonic Acid.

bath at 110°C until 150 ml of alcohol had distilled. The reaction mixture was cooled to 20°C and treated with a mixture of 300 ml of concentrated hydrochloric acid and 800 g of cracked ice. All lumps were carefully crushed and the creamy yellow suspension of acetonedioxalic ethylester (A) was collected on a filter. The ester was washed several times with ice water to remove sodium chloride and dried. For the hydrolysis the ester was heated with 300 ml of concentrated hydrochloric acid on the steam bath for twenty hours. After cooling to room temperature, the solid product was collected on a filter and washed with two 50 ml portion of ice water. Thus obtained crude product was recrystallized from hot water and dried at 160°C to constant weight to remove the water of crystallization. Yield, 116g (65%), m.p. 257°C (dec.).

If the washing of compound (A) is not enough, a complex (B) which can not be converted to chelidonic acid is produced, and therefore, the completely washing to remove sodium chloride needs to be done. (see Fig. 4)

*Monoalkyl Chelidonate (Ia, Ib, Ic, Id, Ie).* Eighteen and four-tenths grams of chelidonic acid was refluxed with the mixture of alcoholic hydrogen chloride (100 ml, 5 %) and 20 ml of water for three hours and the reaction mixture then maintained in refrigerator for over night. The solid product was obtained from the reaction mixture by filtration and well pressed. The filtrate was evaporated in a vacuum at 30°C to small solid obtained from the pasty mass. The combined, moist solids were washed with ether and dried at 80°C. The crude crystalline products were twice recrystallized from hot water and gave the white crystals. Yields were between 68 % and 80 %.

From the combined ethereal washings, dialkyl chelidonates were isolated by evaporation. Yields were less than 20 %.

*Dialkyl Chelidonate (IIIa, IIIb, IIIc, IIId, IIIe).* Monoethyl chelidonate (1.84g) was refluxed with alcoholic hydrogen chloride (10 ml, 5 %) for three hours and the reaction mixture was stood in refrigerator for 24~120 hours. The product was separated on a filter and well pressed. The moist solids were extracted by ether. The ether extract was dried with sodium sulfate. After evaporating of ether under the reduced pressure, crude crystalline product could be obtained. Recrystallization from ethanol gave the white crystals. Yields were between 55 and 78 %.

*Dialkyl Chelidonate (IIa, IIb, IIc, IIId, IIe).* The same procedure as above described was used. Yields were between 60 and 85 %.

### Summary

An extensive study has been made on the esterification of the chelidonic acid. Using the usual method, the dialkylesters of chelidonic acid were obtained. On the other hand, the monoalkylester of chelidonic acid were obtained in good yield by using hydrochloric acid and water in the alcohols. Thus obtained monoalkylester was further esterified by the use of different alcohols and gave the corresponding dialkylesters. The chemical structures of these products were discussed.

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