Condensation of the Triad System with Carbonyl Compounds. I. Condensation of Ethyl Itaconate with Ketones*[1]

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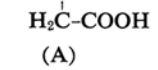
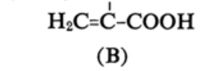
Although the chemical behavior of itaconic acid has already been studied in detail, there has yet been no report on the condensation of its active methylene group with carbonyl compounds other than the classical paper by Fittig and Bock¹⁾; this lack is a result of the isomerisation of the ester in a strongly basic media to a mixture of its isomers²⁾.

From the close structural resemblance of the acid to succinic acid and alkylidenesuccinic acid (A) the ethyl ester of itaconic acid(I) was expected to condense with carbonyl compounds by Stobbe condensation³⁾ and to afford new fulgenic acids (B). However, Fittig et al. obtained, by condensation of I (a molecule) with benzaldehyde (two molecules) in the presence of



$$\begin{array}{l}(R_1R_2)C{=}\underset{|}{C}\text{-COOH,}\\ \qquad H_2C\text{-COOH}\end{array}$$

(A)



$$\begin{array}{l}(R_1R_2)C{=}\underset{|}{C}\text{-COOH}\\ \qquad H_2C{=}C\text{-COOH}\end{array}$$

(B)

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*[1] This paper is a part of a doctoral thesis and was partly presented at the Symposium of the Organic Reaction Mechanism, Shirahama, October, 1960.

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1) R. Fittig, *Ann.*, 331, 151 (1904); R. Fittig and K. Bock, ibid., 331, 174 (1904).

2) E. R. Alexander, "Principles of Ionic Organic Reactions", John Wiley & Sons, Inc., New York (1950), p. 286.

3) W. S. Johnson and C. H. Daub, "Organic Reactions", 6, 1 (1951).

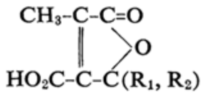
sodium ethoxide, two isomeric heptenedilactones which can not be explained by Stobbe condensation in a straightforward manner. Their findings supported the possibility of the condensation of I with other carbonyl compounds and suggested that I behaves quite differently from ethyl alkylidenesuccinats (A).

In this paper, the novel reactions of I with ketones are described.

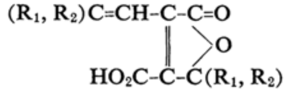
Results and Discussion

The condensation of I with acetone was conducted in the presence of alcohol-free sodium ethoxide in an ice bath or an ice-salt bath. In the ice bath, the condensation reaction afforded two acidic products, II (R_1=R_2=CH_3) and III(R_1=R_2=CH_3), while in the ice-salt bath the reaction gave only III(R_1=R_2=CH_3).

I also condensed with cyclohexanone. The reaction afforded an acid, II[R_1, R_2=$-(CH_2)_5-$], in the ice bath, and, in the ice-salt bath, two acidic products, II[R_1, R_2=$-(CH_2)_5-$] and III [R_1, R_2=$-(CH_2)_5-$].



II



III

The yields, properties and analytical data of these products are shown in Tables IV, V and VI.

The II products were monobasic acids and gave methyl esters and anilides by ordinary procedures.

Structures.—The structures of the II products were determined to be as follows:

i) The analytical data (Table VII) showed that they were condensation products of I(C_5)

Table I. Infrared absorption spectra (in KBr)

Compound	γ-Lactone C=O	Carboxyl C=O	C=C
α, γ, γ-Trimethylaconic acid (II, R_1=R_2=CH_3)	1725	1700(sh)	1650
Methyl α, γ, γ-trimethylaconate	1765	1720[a]	1650
Anilide of α, γ, γ-trimethylaconic acid	1755	1693[b] 1540	1664
α-Methyl-γ, γ-pentamethyleneaconic acid (II, R_1, R_2=$-(CH_2)_5-$)	1725	1690(sh)	1650
Methyl α-methyl-γ, γ-pentamethyleneaconate	1745	1706[a]	1640
Anilide of α-methyl-γ, γ-pentamethyleneaconic acid	1750	1690[b] 1550	1660
Aconic acid	1723	1706(sh)	1640
Lichesterinic acid*	1740	1705(sh)	1650

(sh) Shoulder, a) Ester C=O band, b) Amide bands

Table II. Ultraviolet absorption (in EtOH)

Compound	log ε/mμ 210	220	230	240
α, γ, γ-Trimethylaconic acid (II, R_1=R_2=CH_3)	3.93	4.04	4.03	3.85
Methyl α, γ, γ-trimethylaconate	—	4.05	4.12	4.00
α-Methyl-γ, γ-pentamethyleneaconic acid (II, R_1, R_2=$-(CH_2)_5-$)	3.93	4.04	4.07	3.99
Methyl α-methyl-γ, γ-pentamethyleneaconic acid	—	4.06	4.14	4.11
Lichesterinic acid[5] (II, R_1=H, R_2=n-$C_{13}H_{27}$)	3.82	4.02	4.07	3.80
Methyl α-methylaconate (II, R_1=R_2=H)	3.87	4.01	4.04	3.88

* The Sample was given by Professor Shoji Shibata. The authors want to appreciate him.

Table III. Infrared spectra of α-alkylidenemethylaconic acids (III) (cm^{-1})

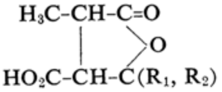
Compound	γ-Lactone C=C	COOH C=O	C=C
α-Isopropylidenemethyl-γ, γ-dimethylaconic acid (in KBr)	1720	—	1660 1610
α-Isopropylidenemethyl-γ, γ-dimethylaconic acid (chloroform solution)	1753	1690	1650 1610
α-Cyclohexylidenemethyl-γ, γ-pentamethyleneaconic acid (in KBr)	1772	1710	1685 1620

with molecules of acetone and cyclohexanone respectively.

ii) The infrared spectrum of these methyl esters and anilides indicated the presence of C=C and of α,β-unsaturated γ-lactone C=O bands (Table I). In free acids, II showed broad bands with a shoulder near 1725 cm^{-1}, bands which were attributable to α,β-unsaturated γ-lactone C=O[4] and carboxyl C=O.

iii) The close resemblance of ultraviolet spectrum of II and of their methyl esters to those of metaconic acid, aconic acid, and more especially, lichesterinic acid (II, R_1=H, R_2=n-$C_{13}H_{27}$)[5] and ethyl ester of α-methylaconic acid (II, R_1=R_2=H)[5] tended to confirm the presence of a substituted O=C–C=C–C=O (trans) conjugated system (Table II).

iv) II [R_1=R_2=CH_3 and R_1, R_2=–$(CH_2)_5$–] afforded a corresponding paraconic acid (IV) by reduction with a sodium amalgam. The infrared spectrum of IV [R_1=R_2=CH_3 and R_1, R_2=–$(CH_2)_5$–] well agreed with those of γ,γ-dimethyl paraconic acid and γ,γ-pentamethyleneparaconic acid.


IV

v) The NMR spectrum of the methyl ester of II(R_1=R_2=CH_3) showed three peaks, corresponding to $COOCH_3$, =C–CH_3 and $C(CH_3)_2$[6] (Fig. 1).

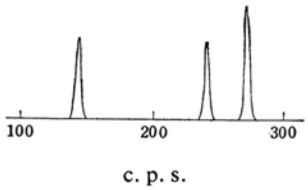


Fig. 1. NMR of methyl α,γ,γ-trimethylaconate.

From the following evidence, the structures of the III products were determined:

i) The analytical data of the III products [R_1=R_2=–CH_3 and R_1, R_2=–$(CH_2)_5$–] showed that I condensed with two molecules of the corresponding ketone.

ii) The infrared spectrum of the III products suggested that they were conjugated dienoic acid, which has an α,β-unsaturated γ-lactone ring (Table III).

iii) The ultraviolet spectrum of the III products showed end absorption and broad bands near 277 mμ (both log ε = 3.67). This suggested

TABLE IV. CONDENSATION REACTIONS

Exp.	Ester, g.	Ketone, g.	Cooling media	Time[a]
a	I, 13.6	Acetone, 8.8	Ice bath	Overnight
b	V, 13.6	Acetone, 8.8	Ice bath	Overnight
c	VI, 13.6	Acetone, 8.8	Ice bath	Overnight
d	I, 18.6	Acetone, 11.6	Ice-salt bath	Overnight
e	I, 18.6	Cyclohexanone, 19.6	Ice-bath	Overnight
f	I, 18.6	Cyclohexanone, 22.5	Ice-salt bath	Overnight[b]

a) Times for keeping at room temperature.
b) The reaction mixture was allowed to stand overnight in ice-salt bath.

TABLE V. CONDENSATION PRODUCTS

Exp.	Products	Yields, %	M. p., °C	Properties
a	II	65.6	231～232	Colorless acid, sublimable
	III	23.0	131～132	Colorless acid, sublimable
b	II	9.7		
c	II	13.7		
d	III	62.0		
e	II	47.2	276 (decomp.)	Colorless acid, sublimable
f	II	40.1		
	III	11.9	137～138	Colorless acid

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[4] The C=O bands of saturated or α,β-unsaturated γ-lactone β-carboxylic acids were of exceptionally lower frequencies than those acids in the normal saturated or α,β-unsaturated γ-lactone C=O region. This spectral behavior may be attributed to intermolecular hydrogen bonding between carboxyl OH and lactone C=O (cf. L. J. Haynes and J. R. Plimmer, *Quart. Revs.*, 14, 307 (1960); Y. Hirata, *J. Japan. Chem.* (*Kagaku-no-Ryoiki*), Supplement, 42, 76 (1961).

[5] E. E. Van Tamelen, C. E. Osborne and S. R. Bach, *J. Am. Chem. Soc.*, 77, 4625 (1955).

[6] N. F. Chemberlain, *Anal. Chem.*, 31, 56 (1959).

[7] The normal frequencies of the lactone C=O(1772 cm^{-1}) of III[R_1, R_2=-$(CH_2)_5$-] suggested the absence of intermolecular hydrogen bonding between carboxyl OH and lactone C=O by bulky substituents.

TABLE VI. ANALYTICAL DATA*

Compound	Formula	Found, % C	Found, % H	Calcd., % C	Calcd., % H
II, R_1=R_2=CH_3	$C_8H_{10}O_4$	56.52	5.94	56.47	5.88
Methyl ester of II	$C_9H_{12}O_4$	58.85	6.55	58.69	6.57
Anilide of II	$C_{14}H_{15}O_3N$	68.53	6.04	58.55	6.16
		N 5.70		N 5.71	
III, R_1=R_2=CH_3	$C_{11}H_{14}O_4$	62.80	6.54	62.84	6.71
II, R_1, R_2=-$(CH_2)_5$-	$C_{11}H_{14}O_4$	62.65	6.68	62.84	6.71
Methyl ester of II	$C_{12}H_{16}O_4$	64.22	7.01	64.27	7.19
Anilide of II	$C_{17}H_{19}O_3N$	N 4.91		N 4.91	
III, R_1, R_2=-$(CH_2)_5$-	$C_{17}H_{22}O_4$	70.19	7.56	70.32	7.64

* We are indebted to Dr. Haruo Homma of the Institute of Physical and Chemical Research for these analyses.

that they were mostly substituted conjugated dienoic acids[8].

iv) The NMR spectrum of III [R_1=R_2=CH_3] showed the presence of COOH, $C(CH_3)_2$ and CH=$C(CH_3)_2$[9] (Fig. 2).

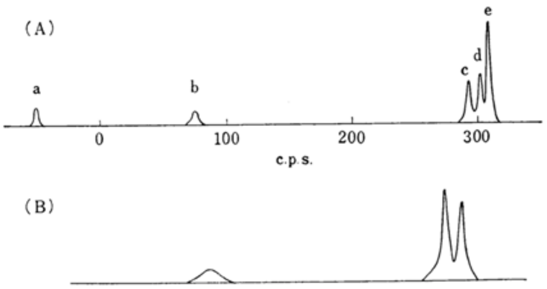
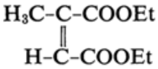


Fig. 2. NMR spectrum

(A) α-Isopropylidenemethyl-γ, γ-dimethylaconic acid (III)

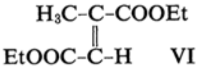
(B) β-Methylcrotonic acid

Reaction Mechanism.—However, I condensed readily with the ketones, its isomerides, ethyl citraconate (V) and ethyl mesaconate (VI), which were expected to be produced from I by a prototropic change of its triad system (CH-C=CH) in the reaction condition; it also dully condensed with acetone and afforded II(R_1=R_2=CH_3) in poor yields. From this fact and the structure of II, it is clear that I condensed with ketones at its active methylene group and that the isomerisation of I to the isomerides is negligible under the reaction conditions.



$$\begin{array}{c} H_3C\text{-}C\text{-}COOEt \\ \| \\ H\text{-}C\text{-}COOEt \end{array}$$

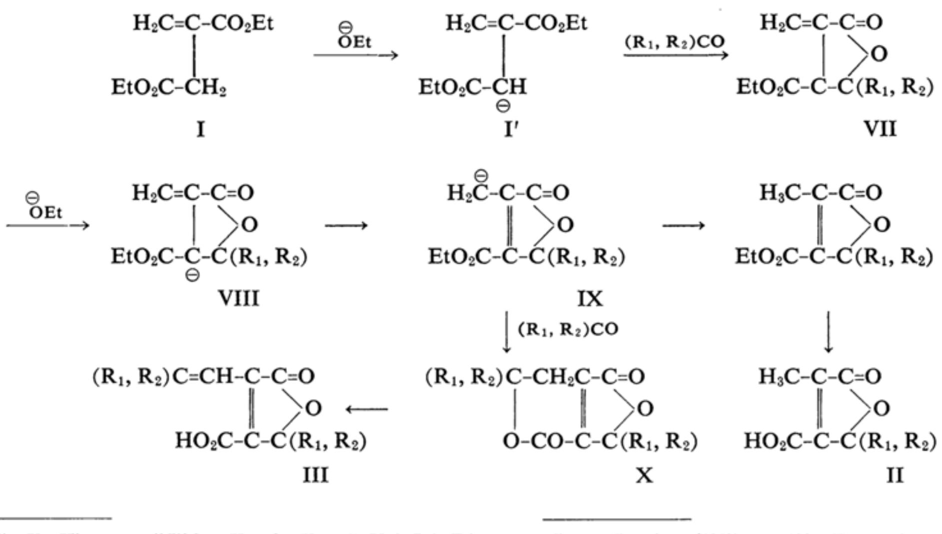
V



$$\begin{array}{c} H_3C\text{-}C\text{-}COOEt \\ \| \\ EtOOC\text{-}C\text{-}H \end{array}$$

VI

The formation of II and III can not simply be explained by Stobbe condensation but only by the following mechanism:



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[8] K. Hirayama, "Jikken Kagaku Koza", Vol. I-1, Ed. by Chem. Soc. of Japan, Maruzen Co., Tokyo, (1957) p. 125.

[9] L. M. Jackman, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press, London (1959), p. 120. From the resemblance of this NMR to that of β-crotonic acid [S. Fujiwara et al., This Bulletin, 33, 428 (1960)], the peaks b(broad), c and d are attributed to protons of =CH-, cis-methyl and trans-methyl of $=C\text{-}CH=C(CH_3)_2$ respectively.

In this process, the formation of II is explained by a mechanism similar to that employed by Stacy et al.[10] to account for the condensation of ethyl oxaloacetate with carbonyl compounds. The change of anion VIII to anion IX is a tautomerism of the triad system. Moreover, the formation of III was explained by the extended Stobbe condensation[11] of anion IX with the ketones.

By this reaction mechanism, the formation of Fittig's heptenedilactones may be explained. The dilactone X and Fittig's heptenedilactone will be reported on in the near future.

Experiments

Ethyl Itaconate (I).—I was prepared by the conventional procedure from itaconic acid, using hydroquinone as a polymerisation inhibitor without isomerisation[12]; b. p., 118°C/20 mmHg and $n_D^{20}=1.4383$ (b.p. 117.5°C/20 mmHg, and $n_D^{20}=1.4377$[12]).

Ethyl Citraconate (V).—V was prepared from citraconic anhydride[13] by the ordinary procedure without isomerisation; b. p., 121°C/20 mmHg and $n_D^{20}=1.4440$ (b. p. 122°C/20 mmHg, and $n_D^{20}=1.4442$[12]).

Ethyl Mesaconate (VI).—VI was prepared from mesaconic acid[14] by the ordinary procedure without isomerisation; b. p., 118°C/20 mmHg and $n_D^{20}=1.4485$ (b.p. 118°C/20 mmHg, and $n_D^{20}=1.4488$[12]).

Condensation of the Esters with Ketone. General Procedure.—Alcohol-free sodium ethoxide was prepared by Fittig's method[15] in a 300 ml. three-necked flask. The flask was fitted with a dropping funnel and a reflux condenser, each protected by calcium chloride tubes, and with a mercury-sealed mechanical stirrer. The molar ratio of the sodium ethoxide, the ester and the ketone was 2 : 1 : 2. The flask was cooled in an ice or ice-salt bath. The mixture of the ester and the ketone was dropped from the funnel into the stirred suspension of sodium ethoxide in ether over a period of one hour. After the addition of the mixture and an additional two hours' cooling, the flask was allowed to stand overnight at room temperature. The reaction mixture was dissolved in water (150 ml.), and the resulting aqueous solution was extracted with ether (50 ml.) several times. The aqueous layer was acidified with excess hydrochloric acid (1 : 1); then the condensation products, which separated as an oil or slurry, were extracted by ether and purified according to the usual procedure. The details of these reactions, products and analytical data are shown in Tables 4, 5 and 6.

Aconic Acid.—Aconic acid was prepared from itaconic acid by the method of Champbell[16].

Methyl α,γ,γ-Trimethylaconate.—α,γ,γ-Trimethylaconic acid (II, $R_1=R_2=CH_3$) 1.70 g. was esterified by diazomethane[17], and the ester was obtained in the form of colorless prisms (1.45 g.) (from light petroleum); m. p., 30~31°C.

Methyl α-Methyl-γ,γ-pentamethyleneaconate.—The ester was prepared from α-methyl-γ,γ-pentamethyleneaconic acid (II, $R_1, R_2=-(CH_2)_5-$) 0.51 g. and diazomethane, in the form of colorless prisms (from light petroleum), 0.45 g., m. p., 93~94°C.

Anilide of α,γ,γ-Trimethyl Aconic Acid.—The acid (1.05 g.) was converted to the anilide by the ordinary procedure. Colorless prisms (from ethanol), 0.92 g.; m. p., 187~188°C.

Anilide of α-Methyl-γ,γ-pentamethyleneaconic Acid.—From the acid (1.00 g.), the anilide (0.73 g.) was obtained in the form of colorless prisms (from ethanol); m. p., 182~183°C.

α,γ,γ-Trimethylparaconic Acid (IV, $R_1=R_2=CH_3$).—α,γ,γ-Trimethylaconic acid (1.54 g.) was suspended in water (20 ml.), dissolved by neutralization with a 10% sodium hydroxide solution, and then stirred with a 1% sodium amalgam (53 g.) for 10 hr. at room temperature. The aqueous layer was separated and was acidified with cold 1 : 1 hydrochloric acid in ice bath, and then extracted with three portions (10 ml.) of ether. The acidic products were thoroughly extracted with a saturated sodium bicarbonate solution. After careful acidification, extraction with ether yielded the acid as a colorless solid (0.77 g.) (m. p., 186~189°C) that crystallized from acetonitrile as colorless scales; m. p., 191~192°C.

α-Methyl-γ,γ-pentamethyleneparaconic Acid.—This acid was obtained by reduction of α-methyl-γ,γ-pentamethyleneaconic acid (II) (0.52 g.) as above; 0.38 g.; in the form of colorless scales (from ethyl acetate); m. p., 196~197°C.

γ,γ-Dimethylparaconic acid.—This acid was prepared by the lactonization[18] of teraconic acid, obtained by Stobbe condensation of ethyl succinate and acetone[19]. Colorless scales (from acetonitrile); m. p., 173~174°C.

γ,γ-Pentamethyleneparaconic acid.—This acid was prepared by the method of Robinson[20] from the Stobbe condensation of ethyl succinate with cyclohexanone. Colorless scales (from acetonitrile); m. p., 184~185°C.

Measurements.—The ultraviolet spectra were determined with a Hitachi ESP-2 spectrophotometer. Infrared measurements were made with a Nihon Bunko IR-S and a 301 spectrophotometer. NMR measurements were made with a Varian V 4300 spectrometer (56.4 Mc) using a 10% chloroform solution with toluene as the internal standard.

Summary

In the presence of sodium ethoxide, ethyl itaconate condensed with ketones (acetone and cyclohexanone) at the terminal carbon atoms of its triad system without any appreciable

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[10] G. W. Stacy et al., *J. Am. Chem. Soc.*, **74**, 999 (1952); **79**, 1451 (1957).

[11] H. J. F. Loewenthal and R. Pappo, *J. Chem. Soc.*, **1952**, 4799.

[12] E. H. Coulson and G. A. R. Kon, ibid., **1932**, 2568.

[13] "Organic Syntheses", Col. Vol., 2, (1948), p. 140.

[14] Ibid., Col. Vol. 2 (1948), p. 382.

[15] R. Fittig and N. Petkow, *Ber.*, **35**, 4322 (1909).

[16] N. R. Champbell and J. H. Hunt, *J. Chem. Soc.*, **1947**, 1176.

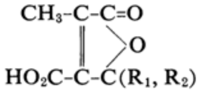
[17] "Organic Syntheses", Vol. 36, (1956), p. 16.

[18] R. Fittig and B. Frost, *Ann.*, **226**, 365 (1884).

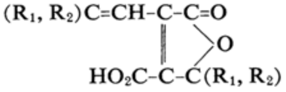
[19] W. Rose, ibid., **220**, 254 (1883).

[20] R. Robinson et al., *J. Chem. Soc.*, **1941**, 582.

isomerisation and afforded novel compounds, α-methyl-γ, γ-disubstituted aconic acids (C) and α-alkylidenemethyl-γ, γ-disubstituted aconic acids (D).



C



D

The chemical structures of C and D were determined by ultraviolet, infrared, NMR spectra etc.

A reaction mechanism has been proposed (p. 1197).

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