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Reaction of Aliphatic Ketones with α-Cyano-α, β-unsaturated Acid Derivatives[1]

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The reaction of several aliphatic ketones with α-cyano-α, β-unsaturated acid derivatives has been studied. Ethylidenecyanoacetic acid reacted with a large excess of acetone in an autoclave at 150—160°C to give 3-methyl-5-oxohexanonitrile, which was considered to be produced by the decarboxylation of the Michael-type adduct of acetone onto the acid. Similar adducts were obtained by the reaction of the acid with methyl ethyl ketone, cyclohexanone, and ethyl laevulinate. The reaction of ketones with ethyl ethylidenecyanoacetate did not afford Knövenagel-type condensates, but Michael-type adducts in appreciable yields, for example, ethyl 2-cyano-3, 4-dimethyl-5-oxohexanoate from methyl ethyl ketone. Diethyl ethylidenemalonate also gave Michael-type adducts. These results seem to suggest that the γ-methyl group of ethylidenecyanoacetic acid or its ester is not active enough to give Knövenagel-type condensates with aliphatic ketones, and that, therefore, the Knövenagel-type reaction is preceded by the Michael-type addition reaction of ketones onto the activated carbon-carbon double bond.

In the course of an investigation of the synthesis of phytol and its related compounds,[3] it became desirable to examine the reaction of aliphatic ketones with α-cyano-α, β-unsaturated acid derivatives. The great majority of studies of the reaction of this sort of acid derivative with carbonyl compounds have dealt only with that reaction on such aromatic aldehydes as carbonyl compounds, giving Knövenagel-type condensation products. Thus Wittig and Hartmann[4] reported the reaction of methyl isopropylidenecyanoacetate with benzaldehyde in the presence of piperidine and acetic acid at room temperature to give methyl 2-cyano-3-methyl-5-phenyl-2, 4-pentadienoate. The ethylidenemalonic ester had previously been condensed with several aromatic aldehydes by means of concentrated sulfuric acid.[5] The saponification of the condensation products gave cinnamylidenemalonic acids. Afterwards Gardner and his co-workers[6] found that potassium hydroxide in absolute alcohol, benzyltrimethylammonium hydroxide in methanol, or choline in methanol could replace sulfuric acid in this reaction. Robeson[7] synthesized an isoprene skeleton by a base-catalyzed reaction between diethyl isopropylidenemalonate and such an aldehyde as β-ionylideneacetaldhyde or benzaldehyde. Little attention has thus been paid to the reaction of aliphatic ketones with such acid derivatives, the key intermediates for the synthetic organic materials. The present investigation was undertaken to see what kind of product might be obtained in the reaction of aliphatic ketones with ethylidenecyanoacetic acid (I), its ethyl ester (II), or diethyl ethylidenemalonate (III).

Most experiments were carried out at temperatures between 120 and 160°C in an autoclave, using an excess of ketone as reactant and solvent and, as catalyst, a small amount of ammonium carbonate or acetate, which is known to promote the Knövenagel reaction.

The reaction of the I acid with acetone in an autoclave at 150—160°C for 5 hr gave a liquid which boiled at 74—76°C/2 mmHg. The two structures (IV, R=CH_3, R'=H; Va) shown below are possible, *i. e.*, one formed by the Knövenagel-type condensation reaction, and the other by the Michael-type addition reaction. The former was eliminated by the infrared spectrum examination of the product, which showed the absence of conjugated double bonds and even of a sole double bond in the molecule; the product was assigned to the Michael-type adduct with concurrent decarboxylation, 3-methyl-5-oxohexanonitrile (Va), through elemental analysis and infrared spectroscopy.

Similar adducts were obtained by the reaction of I with methyl ethyl ketone, cyclohexanone, or

1) Presented in part at the 17th and 19th Annual Meeting of the Chemical Society of Japan, April, 1964 and 1966, respectively.

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3) K. Sato, Y. Kurihara and S. Abe, *J. Org. Chem.*, **28**, 45 (1962).

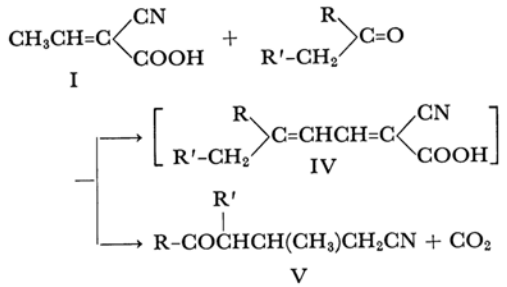
4) G. Wittig and H. Hartmann, *Ber.*, **72**, 1387 (1939).

5) L. Higginbotham and A. Lapworth, *J. Chem. Soc.*, **121**, 2823 (1922).

6) P. D. Gardner, W. J. Horton, G. Thompson and R. R. Twelves, *J. Am. Chem. Soc.*, **74**, 5527 (1952) and their subsequent papers.

7) C. D. Robeson, U. S. Pat. 2662914 (1953).

ethyl laevulinate.



Va $R=CH_3$, $R'=H$ Vb $R=R'=CH_3$
Vc $R-R'=-(CH_2)_4-$
Vd $R=CH_3$, $R'=CH_2COOC_2H_5$

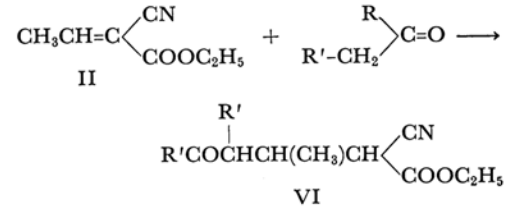
The reaction of methyl ethyl ketone with I might also possibly proceed in such a manner that either the reactive methyl group adjacent to the carbonyl group or the reactive methylene group is added onto the activated carbon-carbon double bond of the I acid.

A decision between the two possible courses of the reaction could be made on the basis of NMR spectroscopy. This spectroscopy showed that the latter was the case and that 3, 4-dimethyl-5-oxohexanonitrile (Vb) was produced in this reaction; the NMR spectrum of the product exhibited a singlet at τ 7.81 due to three acetyl protons, along with other singals due to the remaining protons.

A mechanism consistent with the results obtained thus far may reasonably be described as follows: (1) the addition of ketone to the I acid, after which decarboxylation takes place, or (2) first decarboxylation is caused, giving crotononitrile, to which the ketone is then added.

The fact that the reaction of I with aliphatic ketones under the typical conditions of a Knövenagel reaction gave the Michael-type adducts is attributable either to an originally lower reactivity of the γ-methyl group of I or to the decreased reactivity of this group caused by the decarboxylation. Therefore, the reaction of ethyl ethylidenecyanoacetate (II), in which the decarboxylation was suppressed, was examined.

The reaction of II with ketones, however, was found by gas chromatographic analyses to give a mixture of several components, and a combination of infrared spectroscopy, elemental analysis, and, in one specific case, NMR spectroscopy showed that the main component was not the expected Knövenagel-type condensation product, but the similar Michael-type addition product. The presence of both carbonyl and ethoxycarbonyl groups is shown by the appearance of two absorption bands in the infrared spectrum due to the C=O stretching vibration in the region between 1710 and 1740 cm^{-1}. The reaction can be described as follows:



VIa $R=CH_3$, $R'=H$ VIb $R=R'=CH_3$
VIc $R-R'=-(CH_2)_4-$
VId $R=CH_3$, $R'=CH_2COOC_2H_5$

Table 1. Reaction of aliphatic ketones with ethylidenecyanoacetic acid (I), its ethyl ester (II) or ethyl ethylidenemalonate (III)

Compd.	Ketone	Reaction Temp. °C	Reaction Time hr	Product	Yield %
I					
	Acetone	150—160	5	Va	56
	Methyl ethyl ketone	150—160	8	Vb	30
	Cyclohexanone	150—160	5	Vc	22
	Ethyl laevulinate	250—260	8	Vd	20
II					
	Acetone	150—160	5	VIa	60
	Methyl ethyl ketone	120—130	5	VIb	21
	Cyclohexanone	127—129	6	VIc	29
	Ethyl laevulinate	148—149	5.5	VId	16
III					
	Acetone	110—120	5	VIIa	44
	Methyl ethyl ketone	120—130	5	VIIb	34

The structure of the VIb compound was identified by means of its NMR spectrum. The relatively low yield of VIa-d compounds seems to be the result of several simultaneous side reactions and the brittle property of the complex products during distillation, along with an incomplete reaction because of the low reactivity of II; it should also be noted that the yield of cyanoacetic esters, VI, was nearly equal to that of the corresponding nitriles, V.

In addition to these results, it was found that crotononitrile did not react with acetone under similar conditions. Consequently, it seems reasonable to assume that the addition of ketones to I precedes the decarboxylation in the case of the reaction of I with ketones.

Diethyl ethylidenemalonate (III), the reactivity of which is similar to but somewhat less than II, was also found to react with aliphatic ketones, yielding Michael-type adducts, $R-COCH(R')-CH(CH_3)CH(COOC_2H_5)_2$ (VIIa, $R=CH_3$, $R'=H$, VIIb, $R=R'=CH_3$).

While Michael-type adducts were thus obtained

TABLE 2. PHYSICAL CONSTANTS AND ANALYTICAL CHARACTERISTICS OF PRODUCTS

Compd.	B p °C/mmHg	n_D^{20}	$\nu C=O$ cm^{-1}	Analysis, % Found C	Found H	Found N	Calcd. C	Calcd. H	Calcd. N
Va	74—76/2	1.4432	1720	67.05	9.02	11.49	67.17	8.86	11.19
Vb	73—74/1	1.4478	1715	69.14	9.31	9.74	69.03	9.41	10.06
Vc	111—118/2	1.4848	1720	72.90	8.93	8.68	72.69	9.15	8.48
Vd	143—145/4.5		1730	62.77	7.73		62.54	8.11	
VIa	134—135/3	1.4480	1740 1715	60.80	7.57	7.36	60.89	7.67	7.10
VIb*	112.5/0.7	1.4588	1740 1710	62.68	7.96		62.54	8.11	
VIc	127—129/0.33	1.4759	1740 1705	65.86	7.94	6.20	65.80	8.07	5.90
VId	148—149/0.25	1.4638	1730	59.42	7.23		59.35	7.47	
VIIa	118—121/2	1.4420	1720	59.09	7.92		59.00	8.25	
VIIb	130—132/2	1.4517	1725	59.98	8.37		60.44	8.59	

* The preparation of this compound from ethyl cyanoacetate and 3-methyl-3-penten-2-one by means of a Michael reaction is described in a literature in which the boiling point is reported to be 131—134°C/5 mmHg. H. Yasuda, H. Midorikawa and S. Aoyama, *Sci. Papers Inst. Phys. Chem. Research* (*Tokyo*), **53**, 19 (1959).

when I or II was treated with various aliphatic ketones under the conditions of the Knövenagel reaction, attempts to obtain these adducts by reacting I or II with ketones in the catalysis of sodium hydroxide or methoxide at various temtemperatures were unsuccessful; only a resinous material was produced.

Experimental[8]

Materials. Ethylidenecyanoacetic acid (I) was prepared by the condensation of sodium cyanoacetate[9] and acetaldehyde in an aqueous solution at 3—5°C.

A 60% yield of I was obtained (on the basis of the starting monochloroacetic acid); white plates from benzene, mp 98°C. Ethyl ethylidenecyanoacetate (II) was obtained in a 60% yield according to the procedure of Popp and Catala.[10] Diethyl ethylidenemalonate (III) was successfully prepared in a 50% yield by the least modified procedure of the literature.[11] The other materials were obtained from commercial sources.

The Reaction of Aliphatic Ketones with Ethylidenecyanoacetic Acid (I). To a solution of 11.1 g (0.1 mol) of the I acid dissolved in 100 m*l* of ketone, 0.96 g (0.01 mol) of ammonium carbonate was added; the mixture which resulted was heated in an autoclave and kept for about 5 hr at the temperature shown in Table 1. Thereafter, the reaction mixture was allowed to cool and was distilled under reduced pressure to give the product, V, as a slightly yellowish liquid.

When methyl ethyl ketone was used as an aliphatic ketone, Vb was obtained (bp 73—74°C/1 mmHg); its infrared spectrum included absorption bands at 2500 (νCN), 1715 (νCO), 1460 (δCH_3, CH_2), and 1365 cm^{-1} (δCH_3 of the acetyl group). The NMR spectrum (in CCl_4, TMS standard) contained a sharp three-proton singlet at τ 7.81 due to the acetyl group.

Found: C, 69.14; H, 9.31; N, 9.74%. Calcd for $C_7H_{11}NO$: C, 69.03; H, 9.41; N, 10.06%.

Results with individual compounds are shown in Tables 1 and 2.

The Reaction of Aliphatic Ketones with Ethyl Ethylidenecyanoacetate (II). *With Acetone or Methyl Ethyl Ketone.* A mixture of 10.0 g (0.07 mol) of freshly-distilled ester II, 100 g of the ketone, and 0.8 g (0.01 mol) of ammonium acetate was heated in an autoclave at the temperature described in Table 1 for 6 hr, during which time stirring was continued. After the reaction mixture had then cooled, the excess ketone was removed on a water bath *in vacuo*. The concentrated solution was taken up with ether, and the ethereal solution was washed several times with water, dried over anhydrous sodium sulfate, and distilled under reduced pressure to yield a slightly viscous, pale yellow liquid.

With Cyclohexanone or Ethyl Laevulinate. A mixture of 10.0 g of II, 50 g of the ketone, and 0.8 g of ammonium acetate was heated at the temperature described in Table 1 for 5 hr. To the cooled-down reaction mixture there was then added 50 m*l* of ether, after which the solution was washed with water and dried over anhydrous sodium sulfate. The removal of ether and the ketone *in vacuo* and the distillation of the residue gave a pale yellow, viscous liquid.

Each of these distillate was contaminated by several by-products which could not be identified by analysis by means of vapor phase chromatography.[12] The products were purified by repeated distillations. The

8) All boiling points are uncorrected. Infrared and NMR spectra were recorded on a Hitachi Model EPI-S2 spectrophotometer and a Varian A-60 spectrometer, respectively.

9) J. K. H. Inglis, "Organic Syntheses," Coll. Vol. I, p. 254 (1948).

10) F. D. Popp and A. Catala, *J. Org. Chem.*, **26**, 3738 (1961).

11) W. S. Fones, "Organic Syntheses," Coll. Vol. 4, p. 293 (1963).

12) A 2.25-m vapor phase chromatography column packed with solicon oil (DC 200) absorbed on Celite 545 was employed.

physical and analytical data of individual compounds are shown in Table 2.

The Reaction of Aliphatic Ketones with Diethyl Ethylidenemalonate (III). This reaction was similarly carried out by using 10 g (0.05 mol) of III, 100 g of the ketone, and 0.8 g of ammonium acetate. The results and the characteristics of the individual compounds are summarized in Tables 1 and 2.

Attempts to isolate the Michael-type addition product from the distillate, which showed several peaks in gas chromatography, by means of repeated distillations in the reaction of III with cyclohexanone or ethyl laevulinate were unsuccessful.

The Reaction of Acetone with Ethylidenecyanoacetic Acid (I) or the Ester (II) under Atmospheric Pressure. When a mixture of I (0.1 mol), acetone (100 g), and sodium hydroxide (0.11 mol) was refluxed or allowed to stand at room temperature for several hours, only a dark, high-boiling residue was obtained; the acid I was not recovered. The same result was also obtained when sodium methoxide was used as a catalyst in place of sodium hydroxide. Furthermore, the reaction of II with acetone in the presence of sodium ethoxide in ethanol, Triton B in methanol, piperidine acetate, or sodamide in liquid ammonia gave the same results.

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