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## The Cyclization of Ethyl Cyanoacetate and Ketones by Ammonium Acetate

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It was found that a cyclized product containing one nitrogen atom could be obtained by the reaction of ethyl cyanoacetate with various ketones in the presence of excessive ammonium acetate. On the basis of this experiment, pyridone derivatives such as 3-cyano-5,6-dihydro-4,6-dialkyl-6-methyl-2-pyridones (I), pyridine derivatives such as 3-cyano-4,6-dialkyl-2-hydroxypyridines (IV), quinoline derivatives such as 4-alkyl-3-cyano-2-hydroxy-5,6,7,8-tetrahydroquinolines (VII), and related heterocyclic compounds were prepared.

A Knoevenagel reaction by Cope's method often gives some by-products in the presence of excessive ammonium acetate.

In the condensation between cyclohexanone and ethyl cyanoacetate by excessive ammonium acetate,<sup>1)</sup> a compound melting at 241—242°C is obtained, this has been considered as dicyclohexenecyanoacetamide. It seems reasonable, however, to say that the structure of this compound is that of the type II in view of the following facts:

(1) This compound is also obtained by the reaction of cyclohexanone with ethyl cyclohexylidenecy-

anoacetate in the presence of ammonium acetate.

(2) The infrared absorption spectrum (Fig. 1) of compound II showed an absorption at  $3200\text{ cm}^{-1}$  for the imino group, one at  $2220\text{ cm}^{-1}$  due to the presence of a conjugated cyano group, and one at  $1660\text{ cm}^{-1}$  for the carbonyl group of the pyridone type. However, there are no absorption bands of the amino group. (3) The NMR spectrum (Fig. 2) of II revealed an imino proton singlet at  $2.05\tau$ , but no signals of olefinic protons for dicyclohexenecyanoacetamide are observed.

The present paper will deal with the synthesis of pyridone derivatives and related heterocyclic compounds by the reaction of ethyl cyanoacetate and

1) M. Nakamura, *Yakugaku Kenkyu*, **33**, 99 (1961).

ammonium acetate with a variety of ketones, such as methyl ketones, cyclic ketones, and  $\alpha,\beta$ -unsaturated ketones. The condensation was carried out by heating a mixture of ethyl cyanoacetate, ketone, and ammonium acetate (molar ratio: 1:1:0.8 or 1:2:0.8) at 120–150°C for 6–12 hr.

**The Reaction with Saturated Ketones.** The condensation between ethyl cyanoacetate and saturated methyl ketones or methyl aryl ketones in a 1:2 molar ratio took place and dihydropyridone derivatives were obtained through a Knoevenagel reaction, with the elimination of two moles of water and one mole of alcohol as is indicated in the following scheme:

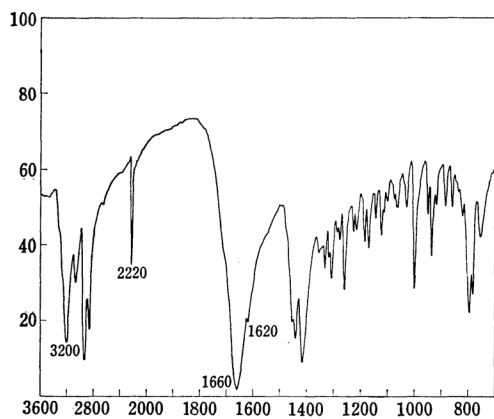
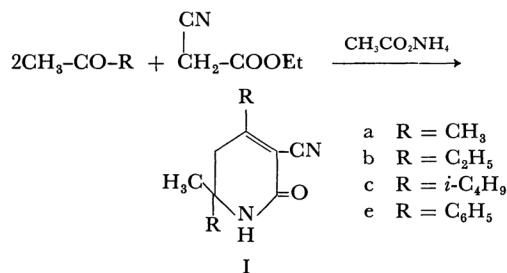
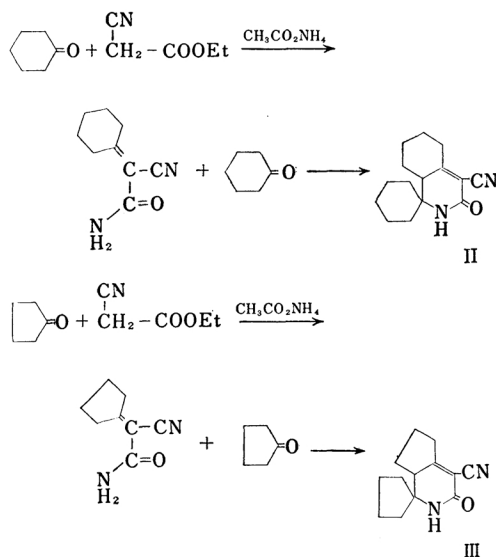


Fig. 1. Infrared spectrum of II.

The condensations with such cyclic ketones as cyclohexanone and cyclopentanone were considered to proceed through the following pathway, as in the case of the reaction with methyl ketones:



However, attempts to prepare the dihydropyridone derivatives by condensation with diethyl ketone or propiophenone were unsuccessful under similar conditions. It was concluded from these facts that only methyl ketones could be involved in this condensation. The dihydropyridone derivatives, Ia and Id, were identical in their melting points with those obtained by Guareschi<sup>2)</sup> and Mcelvain<sup>3)</sup> respectively.

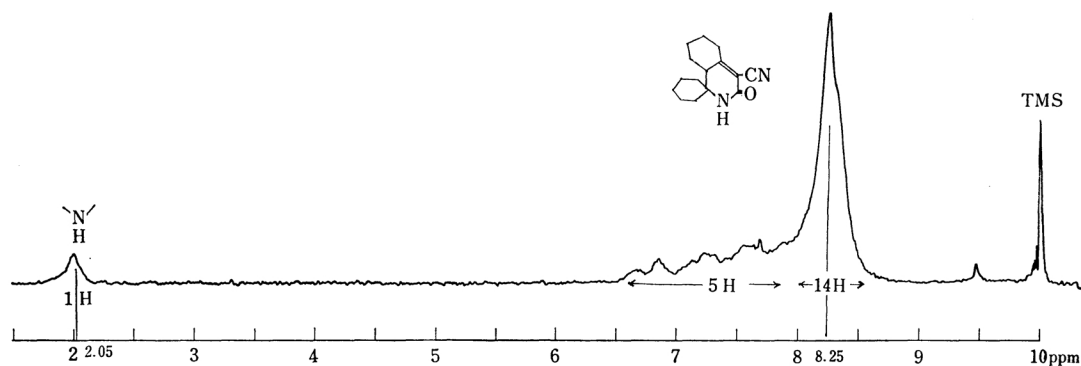
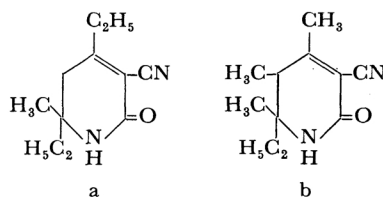


Fig. 2. NMR spectrum of II in  $\text{CF}_3\text{CO}_2\text{H}$ .

2) J. Guareschi *Atti. R. Accad. Sci. Torino*, **1893**, 28.

3) S. M. Mcelvain and D. H. Clemens, *J. Am. Chem. Soc.*, **80**, 3915 (1958).



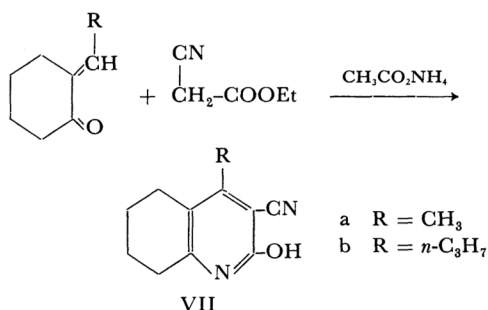
TABLE 1. HETEROCYCLIC COMPOUNDS OBTAINED BY THE REACTION WITH SATURATED KETONES

Ketone	Product	Reaction time, hr	Mp, °C	Crystn. solv.	Yield %	Formula	Anal., %					
							Calcd.			Found		
							C	H	N	C	H	N
Acetone	Ia	12	194—195 <sup>2)</sup>	Alcohol	22	C <sub>9</sub> H <sub>12</sub> ON <sub>2</sub>	65.83	7.37	17.06	66.27	7.18	17.11
Methyl ethyl ketone	Ib	8	147—148	Methanol + water	10	C <sub>11</sub> H <sub>16</sub> ON <sub>2</sub>	68.72	8.39	14.57	69.04	8.26	14.79
Methyl isobutyl ketone	Ic	12	108—109	Methanol + water	4	C <sub>15</sub> H <sub>24</sub> ON <sub>2</sub>	72.54	9.74	11.28	72.41	9.28	11.43
Acetophenone	Id	12	211—212 <sup>3)</sup>	Acetic acid + water	14	C <sub>19</sub> H <sub>16</sub> ON <sub>2</sub>	79.14	5.59	9.72	79.61	5.50	9.84
Cyclohexanone	II	8	241—242	Acetic acid	19	C <sub>15</sub> H <sub>20</sub> ON <sub>2</sub>	73.77	8.20	11.47	73.73	7.79	11.52
Cyclopentanone	III	8	229—232	Alcohol + acetic acid	12	C <sub>13</sub> H <sub>16</sub> ON <sub>2</sub>	72.19	7.46	12.95	72.23	7.26	13.07

TABLE 2. HETEROCYCLIC COMPOUNDS OBTAINED BY THE REACTION WITH UNSATURATED KETONES

Ketone	Product	Reaction time, hr	Mp, °C	Crystn. solv.	Yield %	Formula	Anal., %					
							Calcd.			Found		
							C	H	N	C	H	N
Butylideneacetone	IVa	7	223—224	Methanol	10	C <sub>10</sub> H <sub>12</sub> ON <sub>2</sub>	68.16	6.86	15.90	67.90	6.76	16.07
Benzalacetone	IVb	7	274—275 <sup>5-7)</sup>	Acetic acid	20	C <sub>13</sub> H <sub>10</sub> ON <sub>2</sub>	74.28	4.76	13.33	74.14	4.29	13.36
Benzalacetophenone	IVc	5	313—315 <sup>4,9)</sup>	Acetic acid	30	C <sub>18</sub> H <sub>12</sub> ON <sub>2</sub>	79.41	4.41	10.30	78.79	4.18	10.17
	V	7	222—224 <sup>4,9)</sup>	Acetic acid	17	C <sub>18</sub> H <sub>14</sub> ON <sub>2</sub>	78.83	5.11	10.22	78.76	5.12	10.67
	VI	5	144—145	Methanol + water	13	C <sub>20</sub> H <sub>18</sub> O <sub>2</sub> N <sub>2</sub>	75.45	5.70	8.80	75.55	5.74	8.97
Ethylidene-cyclohexanone	VIIa	8	308—310	Acetic acid	23	C <sub>11</sub> H <sub>12</sub> ON <sub>2</sub>	70.21	6.38	14.89	70.17	6.30	15.17
Butylidene-cyclohexanone	VIIb	8	242—243	Alcohol	14	C <sub>13</sub> H <sub>16</sub> ON <sub>2</sub>	72.19	7.46	12.95	72.13	7.39	13.23

none such as ethylidene and butylidenecyclohexanone was normal, with the elimination of water, alcohol, and hydrogen. The condensation product of ethylidenecyclohexanone with ethyl cyanoacetate has the structure VIIa. By the hydrolysis of the cyano group and subsequent decarboxylation, the product gave the same compound\*<sup>1</sup> as was prepared by the condensation of cyclohexanone with ethyl acetoacetate. In this case, a Michael reaction seemed to be preferred over a Knoevenagel reaction, as is illustrated below.



\*<sup>1</sup> The details of the synthesis of this compound will be reported later.

## Experimental

All melting points are uncorrected.

The infrared spectra were determined by means of pressed potassium bromide disks.

The NMR spectra were determined in deuteriochloroform of trifluoroacetic acid at a frequency of 60 Mc, using tetramethylsilane as an internal standard. The peak positions are expressed in  $\tau$  values.

### The Reaction of Ethyl Cyanoacetate with Saturated Methyl Ketones and with Cyclic Ketones.

A mixture of ethyl cyanoacetate (0.1 mol), ketone (0.2 mol), and ammonium acetate (0.08 mol) was refluxed in benzene or without a solvent for 8—12 hr. After cooling, the reaction mixture, to which water had been added, was allowed to stand in a refrigerator overnight. A colorless crystalline matter was thus obtained. The results are summarized in Table 1.

The infrared spectra of the resulting products showed absorptions at 3200—3250 cm<sup>-1</sup> ( $\nu_{NH}$ ), 2220—2230 cm<sup>-1</sup> (conjugated  $\nu_{C\equiv N}$ ), 1660—1670 cm<sup>-1</sup> ( $\nu_{C=O}$ ), and 1615—1630 cm<sup>-1</sup> ( $\nu_{C=C}$ ).

**The Reaction of Cyclohexanone with Cyanoacetamide.** A mixture of cyclohexanone (4.9 g, 0.05 mol), cyanoacetamide (4.2 g, 0.05 mol), and ammonium acetate (1.2 g, 0.015 mol) was refluxed in 20 ml of



benzene for 7 hr. After the reaction mixture had then been allowed to stand overnight, a crystalline matter was precipitated. Recrystallization from glacial acetic acid gave colorless crystals, mp 240–242°C. (II A)

Found: C, 73.64; H, 8.19; N, 11.32%. Calcd for  $C_{15}H_{20}ON_2$ : C, 73.77; H, 8.20; N, 11.47%.

**The Reaction of Cyclohexanone with Ethyl Cyclohexylidenecyanoacetate.** A mixture of cyclohexanone (2.9 g, 0.03 mol), ethyl cyclohexylidenecyanoacetate (5.8 g, 0.03 mol), and ammonium acetate (1.5 g, 0.02 mol) was refluxed in 20 ml of benzene for 7 hr. The reaction mixture gave a colorless crystalline matter, mp 241–242°C (II B), when treated as above. The products, II A and II B, were identical with II in elemental analysis and in infrared spectra. The NMR spectrum of II in trifluoroacetic acid showed complicated signals at 6.6–9  $\tau$  (cyclic methine and methylene, 19 H). The broad signal at 2.05  $\tau$  was assigned to the imino proton (singlet, 1 H).

**The Reaction of Ethyl Cyanoacetate with  $\alpha,\beta$ -Unsaturated Ketones and with Alkylidenecyclohexanones.** A mixture of ethyl cyanoacetate (0.05 mol), ketones (0.05 mol), glacial acetic acid (0.025 mol), and ammonium acetate (0.04 mol) was refluxed in 30 ml of benzene for 6–8 hr. After the solvent had been removed under reduced pressure, a crystalline matter was precipitated. The results are summarized in Table 2. The infrared spectra of IV and VII showed absorptions at 3430–3480  $cm^{-1}$  ( $\nu_{OH}$ ), 2220–2230  $cm^{-1}$  (conjugated  $\nu_{C\equiv N}$ ), and 1610–1625  $cm^{-1}$  ( $\nu_{C=C}$ ).

**Hydrolysis of 3-Cyano-6-methyl-4-phenyl-2-pyridone (IV b).** IVb was boiled with 80% sulfuric acid for 1 hr. The cooled mixture was then poured into ice water and filtered. The filtrate, on neutralization with sodium carbonate, gave a solid mass. Recrystallization from dilute alcohol gave 6-methyl-4-phenyl-2-pyridone,<sup>8)</sup> mp 204–205°C.

Found: C, 77.26; H, 5.71; N, 7.57%. Calcd for  $C_{12}H_{11}ON$ : C, 77.84; H, 5.94; N, 7.57%.

**The Reaction of Ethyl Cyanoacetate with Benzalacetophenone in Benzene.** A mixture of ethyl cyanoacetate (5.6 g, 0.05 mol), benzalacetophenone (10.4 g, 0.05 mol), and ammonium acetate (3 g, 0.04 mol) in 30 ml of benzene was refluxed for 7 hr. Water was added to the reaction mixture, and, after it had stood overnight, a crystalline matter was precipitated. Recrystallization from glacial acetic acid gave V as pale yellow needles.

**Reaction without a Solvent.** To a mixture of ethyl cyanoacetate (4.5 g, 0.04 mol) and benzalacetophenone (8.3 g, 0.04 mol), ammonium acetate (2.3 g, 0.03 mol) was added. When the mixture was then heated at 140–150°C for 6 hr, a pale yellow mass was separated. After it had been cooled, the solid was washed with water, dried, and treated with methanol. It was divided to two parts: a methanol-soluble part (A) and a methanol-insoluble part (B). The methanol

solution was concentrated, and water was added to it. After it had then stood overnight at room temperature, pale yellow crystals precipitated. Recrystallization from dilute methanol gave VI as colorless needles. The methanol-insoluble precipitate, B, was recrystallized from glacial acetic acid to afford IVc as colorless needles. The details of these products are summarized in Table 2. The NMR spectrum ( $CDCl_3$ ) of VI had the following peaks: a triplet centered at 9.27  $\tau$  (methyl proton), a quartet centered at 6.05  $\tau$  (methylene proton), 3.85  $\tau$  (broad singlet, amino proton), 2.99  $\tau$  (singlet, olefinic proton), and 2.1 and 2.68  $\tau$  (phenyl protons).

**Hydrolysis of 3-Cyano-4,6-diphenyl-2-oxo-tetrahydropyridine (V).** V was heated with 60% sulfuric acid for 3 hr.

After cooling, the solution was poured into ice water and neutralized with sodium carbonate. The solution separated a crystalline mass. Recrystallization from dilute alcohol gave valeric acid,  $\delta,\delta$ -dihydroxy- $\beta,\delta$ -diphenyl,  $\delta$ -lactone.

Found: C, 76.24; H, 6.21%. Calcd for  $C_{17}H_{16}O_3$ : C, 76.12; H, 5.97%.

**2-Amino-4,6-diphenyl Nicotinic Acid.** Ethyl 2-amino-4,6-diphenyl nicotinic acid (VI) was heated to 10% alcoholic potash over a 3 hr. Period, after the mixture had stood overnight, a crystalline compound separated. When it was dissolved in water and acidified with dilute hydrochloric acid, it rapidly gave a white precipitate. Recrystallization from dilute methanol gave colorless needles, melting at 234–235°C with decomposition.

Found: C, 74.64; H, 4.94; N, 9.96%. Calcd for  $C_{18}H_{14}O_2N_2$ : C, 74.48; H, 4.83; N, 9.66%.

**Hydrolysis of 3-Cyano-2-hydroxy-4-methyl-5,6,7,8-tetrahydroquinoline (VII a).** VIIa was heated with sulfuric acid (60%) for about 1 hr. After the solution had been cooled, it was neutralized with sodium carbonate, and 2-hydroxy-4-methyl-5,6,7,8-tetrahydroquinoline was obtained from the dilute alcohol as colorless needles, mp 251–252°C.<sup>10)</sup> The melting point was not depressed by admixture with the compound obtained by the condensation between cyclohexanone and ethyl acetoacetate described above. It was soluble in a warm alkali solution and was colored reddish orange by alcoholic ferric chloride.

Found: C, 73.28; H, 7.72; N, 8.52%. Calcd for  $C_{10}H_{13}NO$ : C, 73.59; H, 8.02; N, 8.58%.

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10) A. Dornow and E. Neuse, *Arch. Pharm.*, **287**, 361 (1954).