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The Cyclization Products from Acetone with Cyanoacetic Esters

Minoru Igarashi*,** and Hiroshi Midorikawa**
*Department of Chemistry, Faculty of Science, Ibaraki University, Mito, Ibaraki
**The Institute of Physical and Chemical Research, Wako, Saitama

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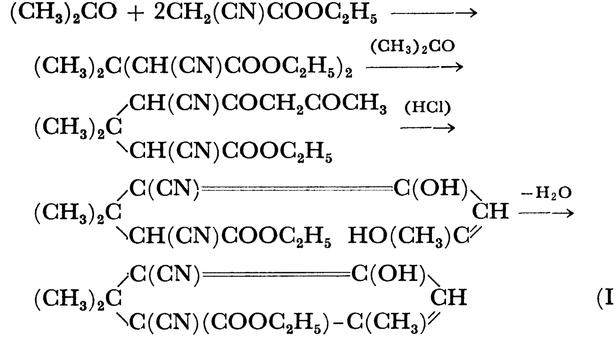
The structure of the cyclization product from acetone with the cyanoacetic ester has been established as 3-alkoxycarbonyl(cyano)methylene-6-cyano-5,5-dimethyl-1-cyclohexene-1-ol by means of infrared and NMR spectroscopic determinations and by successive degradations.

A cyclic compound, $C_{14}H_{16}O_3N_2$, regarded as 4,6-dicyano-4-ethoxycarbonyl-3,5,5-trimethyl-$\Delta^{2,6}$-cyclohexadien-1-ol (I), was first obtained by Gardner and Haworth¹⁾ by the condensatioln of acetone with a sodium derivative of ethyl cyanoacetate. The reaction course was inferred to be as follows.



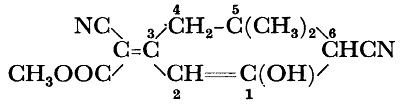
$$\begin{array}{l}
(CH_3)_2CO + 2CH_2(CN)COOC_2H_5 \xrightarrow{NaOC_2H_5} \\
(CH_3)_2C(CH(CN)COOC_2H_5)_2 \xrightarrow{(CH_3)_2CO} \\
(CH_3)_2C\begin{array}{l}\diagup CH(CN)COCH_2COCH_3 \\ \diagdown CH(CN)COOC_2H_5\end{array} \xrightarrow{(HCl)} \\
(CH_3)_2C\begin{array}{l}\diagup C(CN){=\!=\!=}C(OH)\diagdown \\ \diagdown CH(CN)COOC_2H_5\ HO(CH_3)C\diagup\end{array}\!CH \xrightarrow{-H_2O} \\
(CH_3)_2C\begin{array}{l}\diagup C(CN){=\!=\!=}C(OH)\diagdown \\ \diagdown C(CN)(COOC_2H_5)\text{-}C(CH_3)\diagup\end{array}\!CH
\end{array}$$

(I)

They claimed that the product afforded a benzoyl derivative, but no rigorous proof for the structure was presented. The same product was obtained by us from acetone with ethyl cyanoacetate in the presence of potassium fluoride.²⁾ In view of the existing uncertainty of the structure of the product and our interest in the analogous cyclization reaction, it seemed worth while to reinvestigate the condensation product of acetone and cyanoacetic ester.

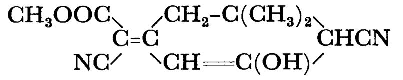
We prepared a compound, $C_{13}H_{14}O_3N_2$, by the condensation of acetone with methyl cyanoacetate in the presence of anhydrous potassium fluoride. After purification by recrystallizations, the product was obtained as pale yellow plates, mp 175°C, which were turned green by the action of ferric chloride in an alcoholic solution and which dissolved readily in an aqueous sodium carbonate solution. The reaction of the product with an excess of alcoholic 2,4-dinitrophenylhydrazine gave no precipitates, but the product became slightly reddish-yellow after standing for several days. These results indicated the structure of the product to be the enol-form rather than the tautomeric keto-form.

The infrared spectrum (Nujol) (Fig. 1) of the product showed an OH stretching band at 3110 cm^{-1} and a band located at 3530 cm^{-1} in an acetone solution. Other prominent bands were observed at 2270 cm^{-1} (very weak) and 2220 cm^{-1} (strong), corresponding to the presence of unconjugated and conjugated nitrile groups respectively. Absorption bands characteristic of the carbonyl group (1720 cm^{-1}) and the C=C group (1590 cm^{-1}) were observed. These infrared spectrum data render the formula I untenable and suggest that formula II or III is more plausible:



$$\begin{array}{l} NC\diagdown \\ C{=}C \\ CH_3OOC\diagup \end{array}\!\begin{array}{l} {}_3\diagup\overset{4}{C}H_2\text{-}\overset{5}{C}(CH_3)_2\diagdown_6 \\ \\ \diagdown\underset{2}{C}H{=\!=}\underset{1}{C}(OH)\diagup \end{array}\!CHCN$$

(II)



$$\begin{array}{l} CH_3OOC\diagdown \\ C{=}C \\ NC\diagup \end{array}\!\begin{array}{l} \diagup CH_2\text{-}C(CH_3)_2\diagdown \\ \\ \diagdown CH{=\!=}C(OH)\diagup \end{array}\!CHCN$$

(III)

The structure could also be deduced from the NMR spectrum, and a complete assignment could be made in terms of a mixture of two geometrical isomers, II and III.

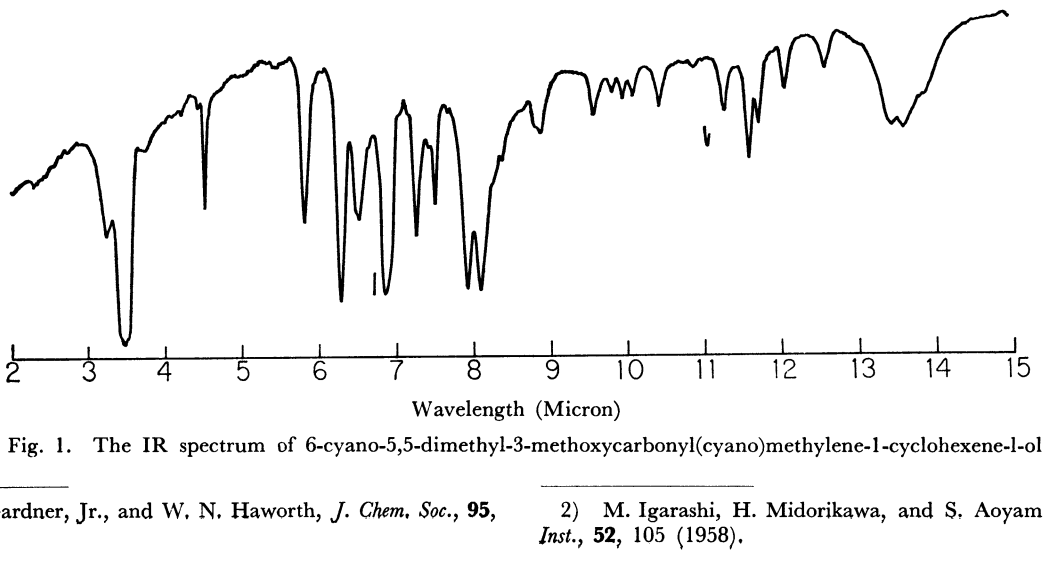


Fig. 1. The IR spectrum of 6-cyano-5,5-dimethyl-3-methoxycarbonyl(cyano)methylene-1-cyclohexene-1-ol.

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1) H. D. Gardner, Jr., and W. N. Haworth, *J. Chem. Soc.*, **95**, 1955 (1909).

2) M. Igarashi, H. Midorikawa, and S. Aoyama, *J. Sci. Res. Inst.*, **52**, 105 (1958).

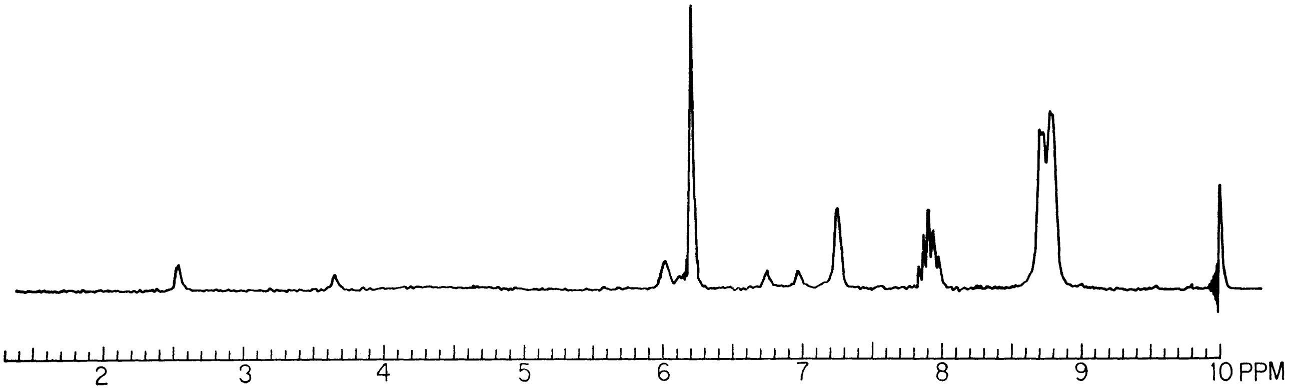
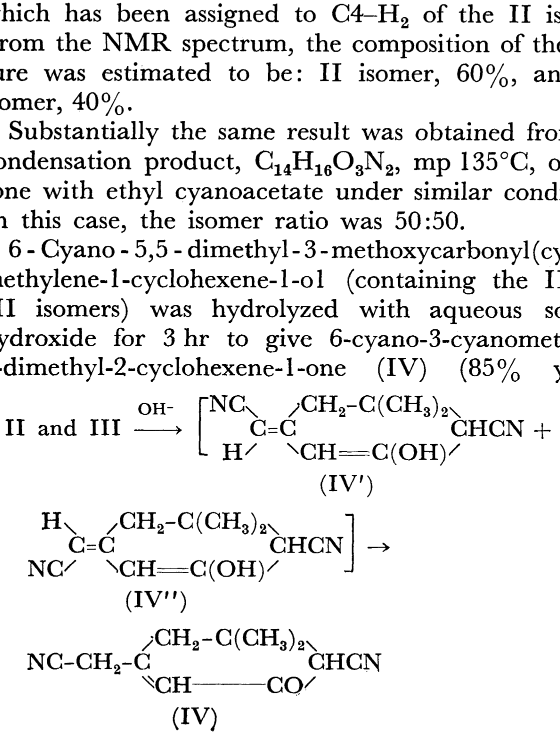


Fig. 2. The NMR spectrum of 6-cyano-5,5-dimethyl-3-methoxycarbonyl(cyano)methylene-1-cyclohexene-1-ol.

The spectrum (deuterioacetone) (Fig. 2) contained two doublets, (each 3H) at 1.22 and 1.29 ppm, which can be ascribed to the C5–dimethyl groups. The methylene group gave rise to a singlet and a doublet at 2.75 and 3.14 ppm respectively. C4–(axial)H and (equatorial)H of the III isomer would be expected to give more separated signals than those of the II isomer because of the marked interaction with the ester carbonyl group. Molecular-model considerations supported this effectation. On the basis of this assumption, the singlet was assigned to the C4–H_2 protons of the II isomer, and the doublet, to those of the III isomer. In both isomers, the O–CH_3 signal of the ester group appeared at 3.80 ppm as a sharp singlet. The singlet (1H) at 4.00 ppm was assignable to the C6–H since it would be expected to appear at a higher field than the olefinic C2–H. Two signals (1H), at 6.35 and 7.46 ppm, were assigned to the C2–H proton. One of these (7.46 ppm) was indicative of C2–H in the II isomer, since the isomeric composition estimated on the basis of the integration of the area under this signal was consistent with that estimated on the basis of a signal at 2.75 ppm, which has been assigned to C4–H_2 of the II isomer. From the NMR spectrum, the composition of the mixture was estimated to be: II isomer, 60%, and III isomer, 40%.

Substantially the same result was obtained from the condensation product, $C_{14}H_{16}O_3N_2$, mp 135°C, of acetone with ethyl cyanoacetate under similar conditions. In this case, the isomer ratio was 50:50.

6-Cyano-5,5-dimethyl-3-methoxycarbonyl(cyano)-methylene-1-cyclohexene-1-ol (containing the II and III isomers) was hydrolyzed with aqueous sodium hydroxide for 3 hr to give 6-cyano-3-cyanomethyl-5,5-dimethyl-2-cyclohexene-1-one (IV) (85% yield).



$$\text{II and III}\xrightarrow{\text{OH}^-}\left[\begin{array}{lll}\text{NC}\diagdown & \diagup\text{CH}_2\text{-C(CH}_3)_2\diagdown & \\ \quad\text{C=C} & & \text{CHCN} \\ \text{H}\diagup & \diagdown\text{CH=C(OH)}\diagup & \end{array}\right.+$$

(IV′)

$$\left.\begin{array}{lll}\text{H}\diagdown & \diagup\text{CH}_2\text{-C(CH}_3)_2\diagdown & \\ \quad\text{C=C} & & \text{CHCN} \\ \text{NC}\diagup & \diagdown\text{CH=C(OH)}\diagup & \end{array}\right]\rightarrow$$

(IV″)

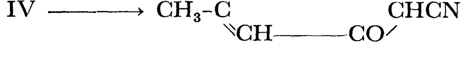
$$\begin{array}{lll} & \diagup\text{CH}_2\text{-C(CH}_3)_2\diagdown & \\ \text{NC-CH}_2\text{-C} & & \text{CHCN} \\ & \diagdown\text{CH}\text{———}\text{CO}\diagup & \end{array}$$

(IV)

We had expected to obtain a mixture of two isomeric compounds, IV′ and IV″. However, the product obtained gave no evidence of being a mixture (tlc, IR, and NMR). The structure of IV was confirmed as follows.

The product readily afforded the corresponding hydrazone, in contrast to the case when the starting materials were II and III, when it was treated with 2,4-dinitrophenylhydrazine in ethanol. The infrared spectrum of the product revealed a band at 2270 cm^{-1} characteristic of the unconjugated nitrile group, and none due to the conjugated one. Other prominent bands observed at 1680 and 1640 cm^{-1}, which may be assigned to the stretchings of C=O (conjugated) and C=C (conjugated) groups respectively, suggest the presence of the keto-form structure, IV.

The NMR spectrum (deuteriochloroform) showed signals at 1.19 and 1.33 ppm (singlets) due to the two methyl groups. The singlet at 2.45 ppm (2H) was assignable to the ring methylene protons (C4–H_2), and the singlet at 3.35 ppm (2H), to the side-chain protons (C3–CH_2–CN), because the latter disappeared completely when IV was converted into V. Two signals were observed for the methine protons. We attribute the signal at 3.45 ppm to the C6–H proton, and the signal at 6.30 ppm to the C2–H proton, on the general ground that the olefinic proton is more deshielded than the paraffinic proton.



$$\text{IV}\xrightarrow{\text{conc. HCl}}\begin{array}{lll} & \diagup\text{CH}_2\text{-C(CH}_3)_2\diagdown & \\ \text{CH}_3\text{-C} & & \text{CHCN} \\ & \diagdown\text{CH}\text{———}\text{CO}\diagup & \end{array}$$

(V)

The hydrolysis and subsequent decarboxylation of IV yielded a ketone (yield 80%). Microanalysis supported the formula of $C_{10}H_{13}ON$. The infrared spectrum revealed a band at 2270 cm^{-1} attributable to a unconjugated nitrile group, a strong carbonyl band at 1675 cm^{-1}, and a conjugated C=C band at 1635 cm^{-1}.

The NMR spectrum (Fig. 3) of the product showed three singlets (each 3H), at 1.08, 1.23, and 1.98 ppm. The two higher-field singlets were ascribed to the C5–dimethyl groups by analogy with those of compounds II—IV. Then, the remaining lower field singlet was ascribed to the C3–methyl group. The methylene protons in the ring (C4–H_2) gave a singlet at 2.35 ppm; this was consistent with that of the compound IV. The singlets at 3.38 (1H) and 5.88 (1H) ppm were

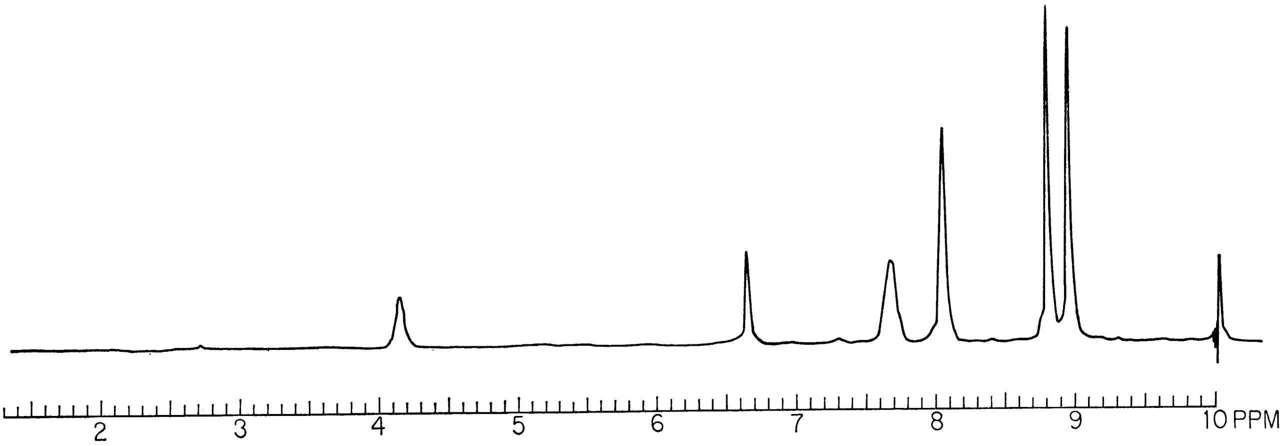


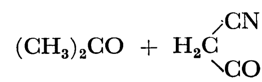
Fig. 3. The NMR spectrum of 6-cyanoisophorone.

assigned to the C6–H and C2–H protons respectively by a comparison with those of the other, known 2-cyclohexene-1-one systems.[3]

From the above data, we assign the product to the V structure, 6-cyanoisophorone.

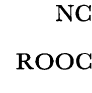
6-Cyanoisophorone (V) was converted into 6-carbamoylisophorone (VI) with 75% sulfuric acid at 70—80°C for 2 hr. The infrared spectrum of the product showed the two bands at 3355 and 3135 cm^{-1} characteristic of the NH_2 group. The remainder of the spectrum was consistent with the presence of a $CONH_2$ group. These bands disappeared from the spectrum when the compound was hydrolyzed and subjected to decarboxylation.

Finally, the hydrolysis of the amide VI with 75% sulfuric acid at 130—150°C for 3 hr yielded isophorone (VII). The infrared spectrum and the mp (144°C) of its 2,4-dinitrophenylhydrazone were identical with those of an authentic sample.



$$V \rightarrow CH_3\text{-}C\begin{matrix}\nearrow CH_2\text{-}C(CH_3)_2\searrow \\ \searrow CH\text{———}CO\swarrow\end{matrix}CHCONH_2 \rightarrow$$

(VI)



$$CH_3\text{-}C\begin{matrix}\nearrow CH_2\text{-}C(CH_3)_2\searrow \\ \searrow CH\text{———}CO\swarrow\end{matrix}CH_2$$

(VII)

From the facts that the cyclic products (II and III) were obtained from only the isopropylidenecyanoacetic ester and that its dimer was isolated as the intermediate,[2] the reaction course may be concluded to be as shown in Scheme I.

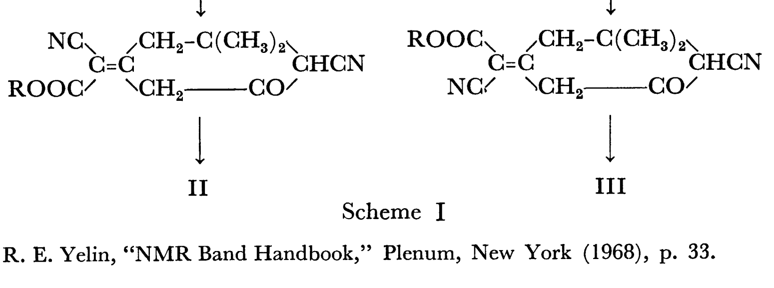
Experimental

The infrared spectra were recorded on a Shimadzu model IR-27G infrared spectrophotometer. The NMR spectra were measured on a JNM-60 high-resolution NMR spectrometer operating at 60 MHz. The chemical shifts are given as ppm downfield from tetramethylsilane as the internal standard.

6-Cyano-5,5-dimethyl-3-methoxycarbonyl(cyano)methylene-1-cyclohexene-1-ol. The condensation was carried out according to the method previously used.[2]

Acetone (11.6 g) and methyl cyanoacetate (9.9 g) were mixed, and then anhydrous potassium fluoride (5.8 g) was added to the mixture. After refluxing for 10 hr on a water bath, the reaction mixture was cooled, dissolved in water, acidified with hydrochloric acid, and extracted with ether. The ethereal solution was washed several times with water and shaken with an aqueous sodium carbonate solution. When the alkaline solution was acidified with hydrochloric acid, a yellowish oil separated. After a while, the oil solidified to a hard cake. The yield was 13.6 g (55%). It was crystallized from acetone-water to slight yellow needles melting at 177—178°C (decomp).

The compound dissolved readily in an aqueous sodium carbonate solution, and it gave a green coloration with ferric



Scheme I

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[3] H. A. Szymanski and R. E. Yelin, "NMR Band Handbook," Plenum, New York (1968), p. 33.

chloride in an alcoholic solution. The reaction of the product with 2,4-dinitrophenylhydrazine in an ethanolic solution gave no crystalline material; it only turned slightly reddish-yellow after standing for several days.

Found: C, 63.60; H, 5.72; N, 11.48%; mol wt, 242. Calcd for $C_{13}H_{14}O_3N_2$: C, 63.40; H, 5.73; N, 11.38%; mol wt, 246.

IR(Nujol): 3110 (OH), 2270 (very weak) (unconjugated CN), 2220 (strong) (conjugated CN), 1725 (CO), 1590 (side chain C=C), 1540 (ring C=C) cm^{-1}.

NMR (deuterioacetone): 1.22 (doublet) (CH_3), 1.29 (doublet) (CH_3), 2.75 (singlet) and 3.15 (doublet) (CH_2), 4.00 (singlet) (C6–H), 6.35 (singlet) and 7.46 (singlet) (C2–H) ppm.

6-Cyano-3-cyanomethyl-5,5-dimethyl-2-cyclohexene-1-one (IV). A mixture of the unsaturated ester (II and III) (0.1 mol) and a 0.2 N sodium hydroxide solution (0.2 mol) was allowed to saponify for 3 hr on a water bath. The alkaline solution was cooled. When it was acidified with dilute hydrochloric acid, a yellowish oil separated from the aqueous solution. The oil solidified when it was allowed to stand in an ice-box. The yield was 83%. Recrystallizations from water gave slightly yellow needles; mp 111—113°C.

Found: C, 69.85; H, 6.56; N, 14.93%. Calcd for $C_{11}H_{12}ON_2$: C, 70.18; H, 6.43; N, 14.88%.

IR (Nujol): 2270 (CN), 1680 (C=O), 1640 (C=C) cm^{-1}.

NMR (deuteriochloroform): 1.19 (singlet) (CH_3), 1.33 (singlet) (CH_3), 2.45 (singlet) (C4–H_2), 3.35 (singlet) (C3–CH_2–CN), 3.45 (singlet) (C6–H), 6.30 (singlet) (C2–H) ppm.

2,4-Dinitrophenylhydrazone. Mp 212°C.

Found: C, 55.44; H, 4.06; N, 22.99%. Calcd for $C_{17}H_{16}O_4N_6$: C, 55.43; H, 4.38; N, 22.82%.

6-Cyanoisophorone (V). A mixture of IV (4.2 g) and concentrated hydrochloric acid was refluxed for one hour. The reaction mixture was then dissolved in water and extracted with ether. The ether extract on evaporation left an oil distilling at 163—164°C/12 mmHg. The oil solidified when it was allowed to stand overnight in an ice-box. The yield was 2.8 g (77%). Recrystallizations from chloroform - petroleum ether gave colorless plates; mp 56—57°C.

Found: C, 73.51; H, 7.90; N, 8.56%. Calcd for $C_{10}H_{13}ON$: C, 73.59; H, 8.03; N, 8.58%.

IR (Nujol): 2270 (CN), 1670 (C=O), 1635 (C=C) cm^{-1}.

NMR (carbon tetrachloride): 1.08 (singlet) (C5–CH_3), 1.23 (singlet) (C5–CH_3), 1.98 (singlet) (C3–CH_3), 2.35 (singlet) (C4–H_2), 3.38 (singlet) (C6–H), 5.88 (singlet) (C2–H) ppm.

2,4-Dinitrophenylhydrazone. Mp 230°C.

Found: N, 20.24%. Calcd for $C_{16}H_{17}O_4N_5$: N, 20.40%.

6-Carbamoylisophorone (VI). To a solution of 95% sulfuric acid (10 g) and water (2 g), 6-cyanoisophorone (3 g) was added, and then the mixture was heated at 70—80°C for 2 hr. After being cooled, the solution was poured into ice water and extracted with ether. The ethereal solution was repeatedly washed with water, and then the ether was removed. The oily residue solidified when it was allowed to stand overnight in an ice-box. Recrystallizations from methanol gave colorless plates; mp 139—140°C (yield, 75%).

Found: C, 66.05; H, 8.09; N, 7.68%. Calcd for $C_{10}H_{15}O_2N$: C, 66.27; H, 8.34; N, 7.73%.

Isophorone VII . A mixture of 75% sulfuric acid (2 *ml*) and 6-carbamoylisophorone (0.6 g) was heated at 150—160°C for 3 hr. After cooling, the reaction mixture was poured into ice water and extracted with ether. The ethereal solution was washed, dried, and then evaporated. The distillation of the residue gave isophorone; bp 95—100°C/2 mmHg (lit,[4] bp 109°C/32 mmHg).

IR: 1670 (C=O), 1640 (C=C) cm^{-1}.

2,4-Dinitrophenylhydrazone. Mp 144—145°C (lit,[4] mp 146°C).

Found: N, 17.70 %. Calcd for $C_{15}H_{18}O_4N_4$: N, 17.60%.

The authors wish to express their hearty thanks to Professors Taro Hayashi and Tatsuo Takeshima for their kind advice and encouragement, and to Dr. Haruo Homma and his staff for their microanalyses.

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4) A. W. Fort, *J. Org. Chem.*. **26**, 332 (1961).