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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,[1] 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:

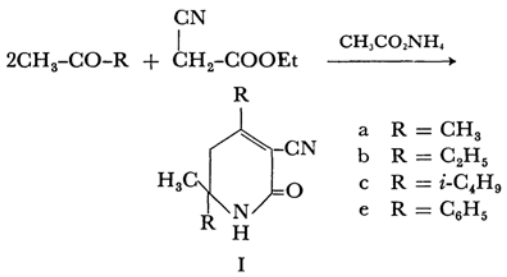
(1) This compound is also obtained by the reaction of cyclohexanone with ethyl cyclohexylidenecyanoacetate in the presence of ammonium acetate. (2) The infrared absorption spectrum (Fig. 1) of compound II showed an absorption at 3200 $cm^{-1}$ for the imino group, one at 2220 $cm^{-1}$ due to the presence of a conjugated cyano group, and one at 1660 $cm^{-1}$ 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 α,β-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:



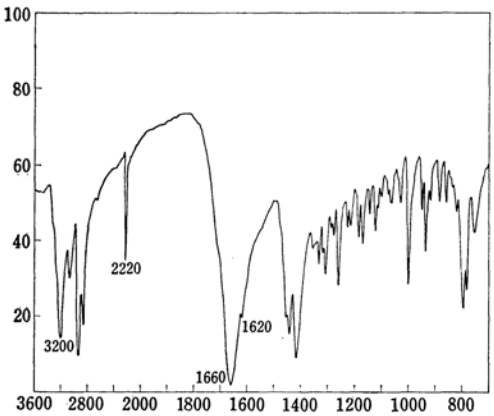
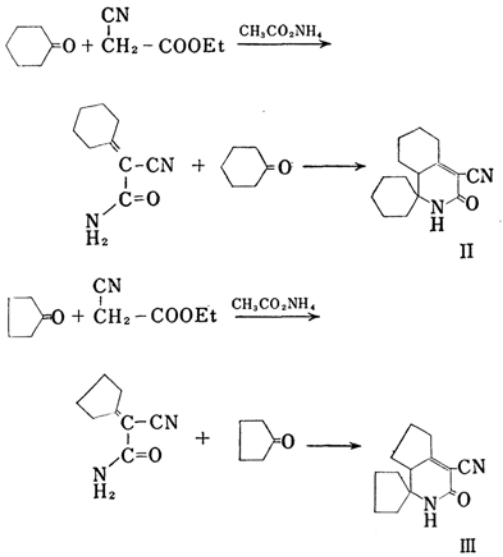
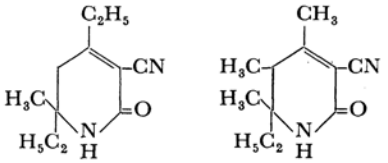




Fig. 1. Infrared spectrum of II.

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[2] and Mcelvain[3] respectively.



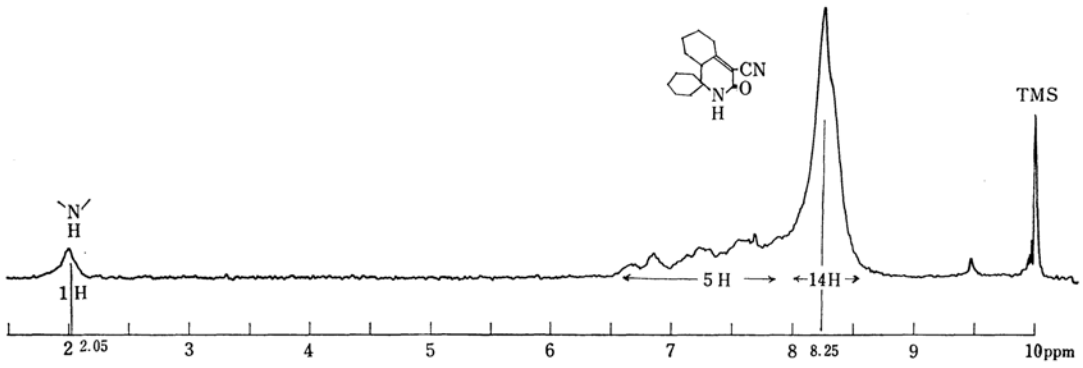




Fig. 2. NMR spectrum of II in $CF_3CO_2H$.

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

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

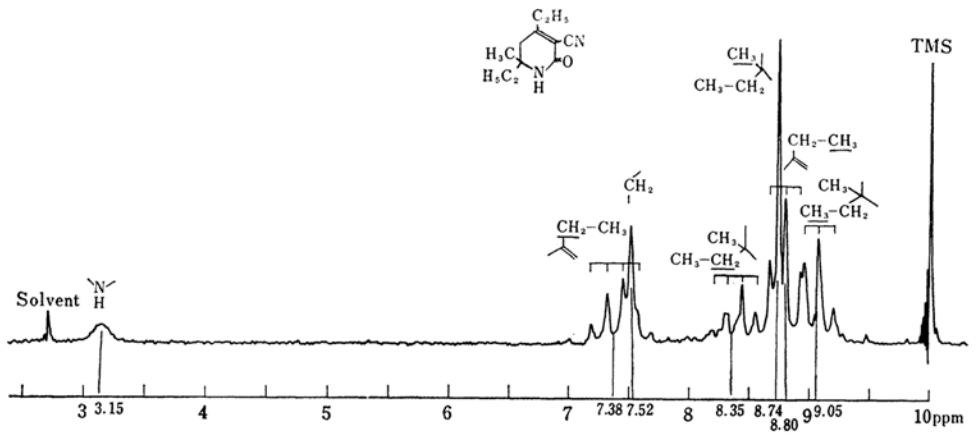
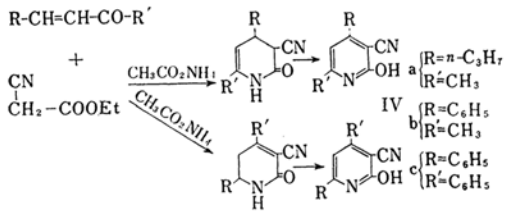



Fig. 3. NMR spectrum of the product obtained by the reaction with methyl ethyl ketone (in $CDCl_3$).

In the case of the reaction with methyl ethyl ketone, the expected product has the structure a or b, as is indicated below. The NMR spectrum ($CDCl_3$), shown in Fig. 3, showed complicated signals at 7.2—7.6 $\tau$ (4H) and 8.2—9.2 $\tau$ (11H). The signals of the higher field showed a pair of overlapping methyl triplets, centered at 8.80 ($J$=7.5 cps, 4-ethyl) and 9.05 $\tau$ ($J$=7.5 cps, 6-ethyl) and a methyl singlet at 8.74 $\tau$ (6-methyl). The signal of the crumbling quartet centered at 8.35 $\tau$ ($J$=7.5 cps) is assigned to the methylene proton of the 6-ethyl group. The signals of the lower field are ascribed to methylene protons of the cyclic (singlet, 7.52 $\tau$) and the 4-ethyl groups (quartet centered at 7.38, $J$=7.5 cps). This methylene quartet is coupled with the methyl proton at 8.80 $\tau$. This is confirmed by the spin-spin decoupling. The imino proton showed a broad signal at 3.15 $\tau$ (1H). On the other hand, the signal of the methine group of the structure b is absent, and the proton ratio of methyl signals is not in agreement with that of the structure b. Consequently, the NMR spectrum supported the structure a.

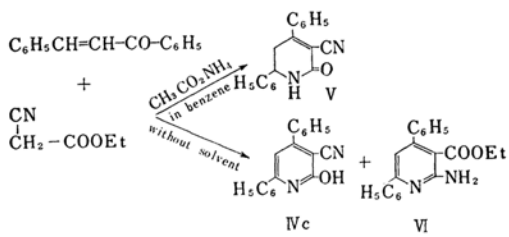
**The Reaction with $\alpha,\beta$-Unsaturated Ketones.** The condensations of ethyl cyanoacetate with $\alpha,\beta$-unsaturated ketones were carried out with them in a 1 : 1 molar ratio. In these reactions, there are two ways to obtain pyridone derivatives. One is through a Michael-type condensation, while the other is through a Knoevenagel-type condensation, as is illustrated below.

On the other hand, the products were identical with those formed through a Michael reaction by Kohler[4] and Issoglio.[5] These facts indicated that in the reaction with $\alpha,\beta$-unsaturated ketones the reactants underwent Michael addition and then cyclization to form pyridone derivatives. Moreover, these reactions accompanied dehydrogenation




except for the reaction of benzalacetophenone in benzene.

The constitution of compound IVb[5-7] was further proved by the fact that it gave the known 4-phenyl-6-methyl-2-pyridone on hydrolysis.[8] An interesting observation was made in the case of the reaction with benzalacetophenone. When the reaction was carried out in benzene, only the tetrahydropyridine derivative V was isolated. The reaction without a solvent, however, gave the dehydrogenated product (IVc) of V and the 2-amino-4,6-diphenylnicotinic acid ester VI as follows.




V and its hydrolysed product were identical with those obtained by Kohler and Barat.[9] Moreover, V was dehydrogenated to IVc by refluxing it in acetone. These phenomena were observed only in the reaction of benzalacetophenone.

The condensation with an alkylidenecyclohexa-

4) E. P. Kohler and B. L. Souther, *ibid.*, **44**, 2903 (1922).
5) G. Issoglio, *Atti. R. Accad. Sci. Torino*, **40**, 495 (1905).
6) J. C. Bardhan, *J. Chem. Soc.*, **1929**, 2223.
7) U. Bazu, *J. Indian Chem. Soc.*, **7**, 481 (1930).
8) S. Ruheman, *J. Chem. Soc.*, **75**, 413 (1899).
9) C. Barat, *J. Indian Chem. Soc.*, **7**, 321 (1930).

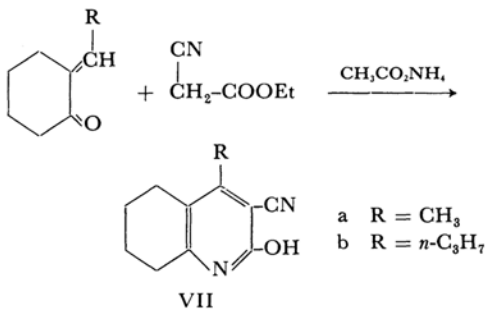
Table 1. Heterocyclic compounds obtained by the reaction with saturated ketones

| Ketone | Product | Reaction time hr | Mp, °C | Crystn. solv. | Yield % | Formula | Anal., % Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Acetone | Ia | 12 | 194—195[2] | Alcohol | 22 | $C_9H_{12}ON_2$ | 65.83 | 7.37 | 17.06 | 66.27 | 7·18 | 17.11 |
| Methyl ethyl ketone | Ib | 8 | 147—148 | Methanol +water | 10 | $C_{11}H_{16}ON_2$ | 68.72 | 8.39 | 14.57 | 69.04 | 8.26 | 14.79 |
| Methyl isobutyl ketone | Ic | 12 | 108—109 | Methanol +water | 4 | $C_{15}H_{24}ON_2$ | 72.54 | 9.74 | 11.28 | 72.41 | 9.28 | 11.43 |
| Acetophenone | Id | 12 | 211—212[3] | Acetic acid +water | 14 | $C_{19}H_{16}ON_2$ | 79.14 | 5.59 | 9.72 | 79.61 | 5.50 | 9.84 |
| Cyclohexanone | II | 8 | 241—242 | Acetic acid | 19 | $C_{15}H_{20}ON_2$ | 73.77 | 8.20 | 11.47 | 73.73 | 7.79 | 11.52 |
| Cyclopentanone | III | 8 | 229—232 | Alcohol+ acetic acid | 12 | $C_{13}H_{16}ON_2$ | 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. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Butylidene-acetone | IVa | 7 | 223—224 | Methanol | 10 | $C_{10}H_{12}ON_2$ | 68.16 | 6.86 | 15.90 | 67.90 | 6.76 | 16.07 |
| Benzalacetone | IVb | 7 | 274—275[5-7] | Acetic acid | 20 | $C_{13}H_{10}ON_2$ | 74.28 | 4.76 | 13.33 | 74.14 | 4.29 | 13.36 |
| Benzal-acetophenone | IVc | 5 | 313—315[4,9] | Acetic acid | 30 | $C_{18}H_{12}ON_2$ | 79.41 | 4.41 | 10.30 | 78.79 | 4.18 | 10.17 |
| | V | 7 | 222—224[4,9] | Acetic acid | 17 | $C_{18}H_{14}ON_2$ | 78.83 | 5.11 | 10.22 | 78.76 | 5.12 | 10.67 |
| | VI | 5 | 144—145 | Methanol +water | 13 | $C_{20}H_{18}O_2N_2$ | 75.45 | 5.70 | 8.80 | 75.55 | 5.74 | 8.97 |
| Ethylidene-cyclohexanone | VIIa | 8 | 308—310 | Acetic acid | 23 | $C_{11}H_{12}ON_2$ | 70.21 | 6.38 | 14.89 | 70.17 | 6.30 | 15.17 |
| Butylidene-cyclohexanone | VIIb | 8 | 242—243 | Alcohol | 14 | $C_{13}H_{16}ON_2$ | 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*1 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.




a R = $CH_3$
b R = $n$-$C_3H_7$

VII

*1 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 $cm^{-1}$ ($\nu_{NH}$), 2220—2230 $cm^{-1}$ (conjugated $\nu_{C\equiv N}$), 1660—1670 $cm^{-1}$ ($\nu_{C=O}$), and 1615—1630 $cm^{-1}$ ($\nu_{C=C}$).

**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 m*l* 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 m*l* 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 conplicated 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 m*l* 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,[8] 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 m*l* 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.[10] 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%.

The authors wish to express their hearty thanks to Dr. Taro Hayashi and Dr. Tatsuo Takeshima for their kind advice. Thanks are also to Dr. Haruo Homma and his staff for their microanalyses.

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