AcOH. The crystals began to separate out from dil. AcOH solution. Recrystallization from MeOH afforded 0.4 g. (85%) of 4-quinazolinol (XIV), m.p. 216~218°. (XIV) was identified on admixture with an authentic sample prepared by another method.[2]

The author expresses his deep gratitude to Prof. Emeritus E. Ochiai of University of Tokyo, to Dr. T. Ukai, Dean of this College, and to Prof. E. Hayashi of this College for their unfailing guidances and encouragements throughout the course of this work. The author is also indebted to Miss. Y. Saito of this College for microanalytical data. Part of the expenses for this work was defrayed by a Grant-in-Aid of Scientific Research for 1960 from the Ministry of Education, which is gratefully acknowledged.

## Summary

Reactions of 4-quinazolinecarbonitrile (I) with ketones in the presence of 50% sodium hydroxide were carried out in order to elucidate the chemical properties of (I).

With acetone afforded 1-(4-quinazolinyl)-2-propanone (II), with 2-butanone, 1-(4-quinazolinyl)-2-butanone (III) and 4-ethylquinazoline (IV), with 3-pentanone (IV), with 3-methyl-2-butanone, 1-(4-quinazolinyl)-3-methyl-2-butanone (V) and 4-isopropylquinazoline (VI), with acetophenone, 2-(4-quinazolinyl)acetophenone (VII), with propiophenone, (IV) and benzoic acid (VIII), with cyclohexanone, 4-quinazolinehexanoic acid (IX), and with cyclopentanone, 2-(4-quinazolinyl)cyclopentanone (X).

The foregoing experiments showed that the 4-position in (I) was very reactive to anionoid reagents, as already demonstrated in Part I[2] and II[1] of this series.

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*UDC 547.859.1.07*

## 169. Takeo Higashino: On the Reaction of 4-Quinazolinecabonitrile with Nucleophilic Reagents. IV. Reaction of 4-Quinazolinecarbonitrile with Active Methylene Compounds.

(*Shizuoka College of Pharmacy*[*1])

In the previous papers,[1~3] it was reported that the 4-position in 4-quinazolinecarbonitrile (I) was very reactive to anionoid reagents.

In this paper, the reaction of (I) with active methylene compounds was studied in order to elucidate the chemical properties of (I).

In benzene, reaction of (I) with ethyl acetoacetate or diethyl malonate in the presence of sodium amide gave ethyl 4-quinazolineacetate (II).

(II) was identified by admixture with an authentic sample prepared by Y. Mizuno, *et al.*[4] by reaction of 4-chloroquinazoline with acetoacetate.

Treatment of (I) with ethyl cyanoacetate in place of ethyl acetoacetate gave ethyl α-cyano-4-quinazolineacetate (III).

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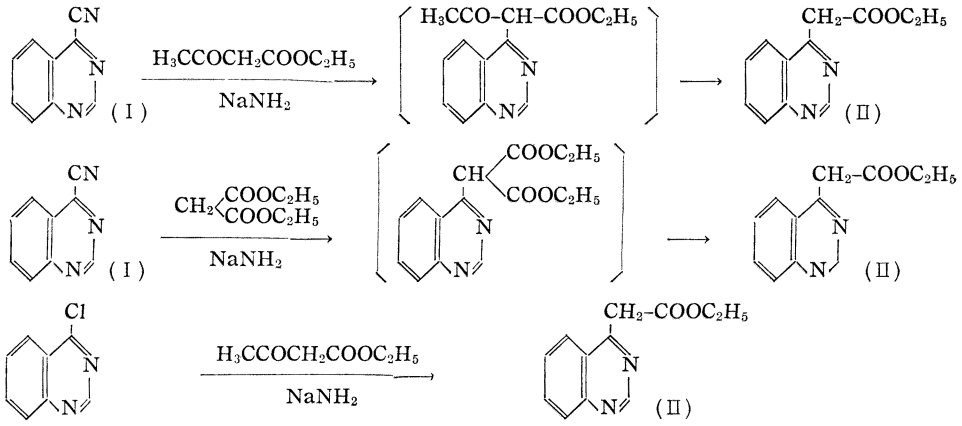
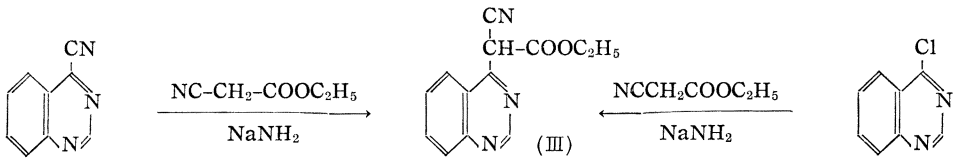
*1 Oshika, Shizuoka (東野武郎).

1) Part I. T. Higashino: Yakugaku Zasshi, **80**, 1404 (1960).
2) Part II. *Idem*: This Bulletin, **10**, 1043 (1962).
3) Part III. *Idem*: *Ibid.*, **10**, 1048 (1962).
4) Y. Mizuno, K. Adachi, K. Ikeda: *Ibid.*, **2**, 225 (1954).

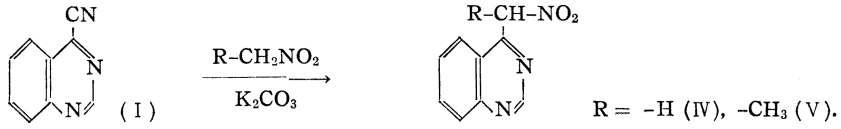


The structure of (III) was established by admixture with authentic sample prepared by Y. Mizuno, *et al.*[4] from 4-chloroquinazoline.



Also, reaction of (I) with nitromethane or nitroethane gave 4-nitromethylquinazoline (IV) and 4-(1-nitroethyl)-quinazoline (V), respectively.

The structures of (IV) and (V) were deduced from the analytical data, by formation of the potassium salts by potassium carbonate solution, and also by analogy with the reaction of (I) with ethyl cyanoacetate and diethyl malonate.



The mechanism of these reactions may be assumed as follows.

For example, the carbanion which may be formed by the action of nitromethane on potassium carbonate, attacks the 4-position of (I) which is liable to anionoid reagents.[2,3]

Consequently, the substituted compound (IV) is formed via an intermediate complex of type (IVa), as shown in Chart 1.

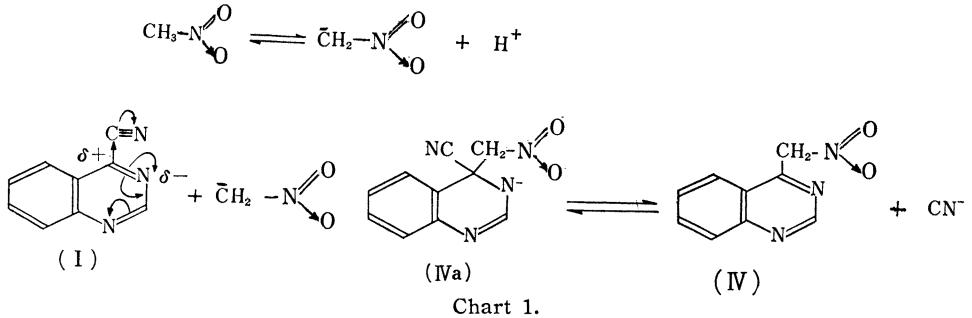


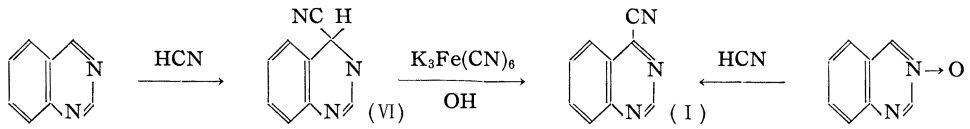
Chart 1.

The above experimental results demonstrate that the chemical properties of the cyano group in compound (I) are different from those in other aromatic heterocyclic compounds.

The extraordinary chemical properties of the cyano group in (I) were shown by the nucleophillic activity of the 4-position in (I) as reported Part I,[1] II,[2] and III[3] of this series.

(I), used throughout the course of this series[1,3] was synthesized by oxidation of 4-cyano-3,4-dihydroquinazoline (VI) with potassium ferricyanide in alkaline medium,[5] which was prepared by reaction of quinazoline with hydrogen cyanide.[5]

As an alternative method, (I) was prepared by the reaction of quinazoline 3-oxide, which was obtained by condensation cyclization of *o*-aminobenzaldehyde oxime and ethyl orthoformate,[6] with hydrogen cyanide.[7]




## Experimental

**Reaction of 4-Quinazolinecarbonitrile (I) with Ethyl Acetoacetate**——A mixture of 0.5 g. of (I), 1.8 g. of ethyl acetoacetate, and 0.5 g. of $NaNH_2$ in 15 cc. of benzene was refluxed for 12 hr. After cool, $H_2O$ was added to the reaction mixture and the benzene layer was separated from the $H_2O$ layer. The benzene solution was extracted with 2*N* HCl, the HCl layer was neutralized with $K_2CO_3$, and extracted with benzene. The benzene solution was dried over anhyd. $Na_2SO_4$. Evaporation of benzene affored 0.1 g. (14%) of ethyl 4-quinazolineacetate (II), as white needles, m.p. 102~103°, from petr. benzin (b.p. 60~80°). *Anal.* Calcd. for $C_{12}H_{12}O_2N_2$ (ethyl 4-quinazolineacetate): C, 66.65; H, 5.59; N, 12.96. Found: C, 66.68; H, 5.69; N, 12.99.

The melting point of (II) was undepressed on admixture with an authentic sample prepared by Y. Mizuno, *et al.*[4]

**Reaction of (I) with Diethyl Malonate**——Treatment of a mixture of 0.5 g. of diethyl malonate and 0.5 g. of $NaNH_2$ by the above described method afforded 0.14 g. (20%) of (II) as white needles, m.p. 102~103°, from petr. benzin (b.p. 60~80°). *Anal.* Calcd. for $C_{12}H_{12}O_2N_2$ (ethyl 4-quinazolineacetate): C, 66.65; H, 5.59; N, 12.96. Found: C, 66.61; H, 5.65; N, 13.02.

The melting point of (II) was undepressed on admixture with an authentic sample prepared by Y. Mizuno, *et al.*[4]

**Reaction of (I) with Ethyl Cyanoacetate**——A mixture of 0.5 g. of (I), 1.4 g. of ethyl cyanoacetate, and 0.5 g. of $NaNH_2$ in 10 cc. of benzene was refluxed for 12 hr. After cool, $H_2O$ was added to the reaction mixture and the benzene layer was separated from the $H_2O$ layer. The benzene solution was dried over anhyd. $Na_2SO_4$. Evaporation of benzene afforded 0.17 g. (22%) of ethyl α-cyano-4-quinazolineacetate (III) as white needles, m.p. 170°, from petr. benzin (b.p. 60~80°). *Anal.* Calcd. for $C_{13}H_{11}O_2N_3$ (ethyl α-cyano-4-quinazolineacetate): C, 64.72; H, 4.60; N, 17.42. Found: C, 64.79; H, 4.63; N, 17.10.

The melting point of (III) was undepressed on admixture with an authentic sample prepared by Y. Mizuno, *et al.*[4]

**Reaction of (I) with Nitromethane**——A mixture of 0.5 g. of (I), 0.5 g. of nitromethane, and 0.5 g. of anhyd. $K_2CO_3$ in 10 cc. of benzene was refluxed for 12 hr. After cool, 10 cc. of $H_2O$ was added to the reaction mixture, and the $H_2O$ layer was neutralized with AcOH carefully. The separated crystals were collected by suction and recrystallization from $H_2O$ afforded 0.14 g. (20%) of 4-nitromethylquinazoline (IV) as pale yellow needles, m.p. 225~228° (decomp). *Anal.* Calcd. for $C_9H_7O_2N_3$ (4-nitromethylquinazoline): C, 57.14; H, 3.73; N, 22.21. Found: C, 57.38; H, 3.81; N, 22.16.

**Reaction of (I) with Nitroethane**——Treatment of 0.5 g. of (I), 0.5 g. of nitroethane by the same

5) T. Higashino: Yakugaku Zasshi, **80**, 245 (1960).
6) K. Adachi: *Ibid.*, **77**, 507 (1957).
7) T. Higashino: This Bulletin, **9**, 635 (1961).

method as described above afforded 0.08 g. (12%) of 4-(1-nitroethyl)quinazoline (V) as pale yellow needles, m.p. 142° from $H_2O$. *Anal.* Calcd. for $C_{10}H_9O_2N_3$ (4-(1-nitroethyl)quinazoline) : C, 59.12; H, 4.46, N, 20.68. Found : C, 59.15; H, 4.29; N, 20.47.

The author expresses his deep gratitude to Prof. Emeritus E. Ochiai of the University of Tokyo, to Dr. T. Ukai, Dean of this College, and to Prof. E. Hayashi of this College, for their unfailing guidance and encouragement throughout the course of this work. The author is indebted to Miss. Y. Saito of this College for microanalytical data.

The expenses for this work was partly defrayed by Grant-in-Aid of Scientific Research for 1961 from the Ministry of Education, which is gratefully acknowledged.

## Summary

The reactions of 4-quinazolinecarbonitrile (I) with active methylene compounds were carried out in order to elucidate the chemical properties of (I).

In the presence of sodium amide, reactions of (I) with ethyl acetoacetate, diethyl malonate, or ethyl cyanoacetate give ethyl 4-quinazolineacetate (II), and ethyl $\alpha$-cyano-4-quinazolineacetate (III), respectively.

In the presence of potassium carbonate, reactions of (I) with nitromethane, or nitroethane give 4-nitromethylquinazoline (IV), and 4-(1-nitroethyl)quinazoline (V), respectively.

The foregoing results showed that the 4-position of (I) was very reactive to anionoid reagents, as was already demonstrated in Parts I, II, and III of this series.

(Received September 30, 1961)

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*UDC 612.386[615.7]-84*

## 170. Hisashi Nogami and Tai Matsuzawa*[1] : Studies on Absorption and Excretion of Drugs. II.*[2] Kinetics of Penetration of Basic Drug, Aminopyrine, through the Intestinal Barrier *in vitro*.*[3]

(*Faculty of Pharmaceutical Sciences, University of Tokyo*[4])

In the previous paper,*[2] a penetration of drug through the rat small intestine was investigated from the physico-chemical standpoint and the theoretical equations were derived from the assumption that the absorption of foreign organic electrolytes was carried out by a simple diffusion process with each specific permeability coefficient for both undissociated and dissociated forms. A previous study on the penetration of salicylic acid demonstrated that its penetration rate was dependent on the degree of dissociation of salicylic acid and the penetration process was thoroughly explainable from the basis of the above assumption. The present report describes the intestinal penetration of aminopyrine (pKa : 5.00) as a representative of basic drugs. Generally, the amount of the drug, *C*, appeared in the outer solution from the inner solution at

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*2 Part I : H. Nogami and T. Matsuzawa : This Bulletin, **9**, 532 (1961).

*3 Presented before the Kanto Local Meeting of the Pharmaceutical Society of Japan, Tokyo, February, 1961.

*4 Hongo, Tokyo (野上 寿, 松沢 兌).