UDC 547.786.07

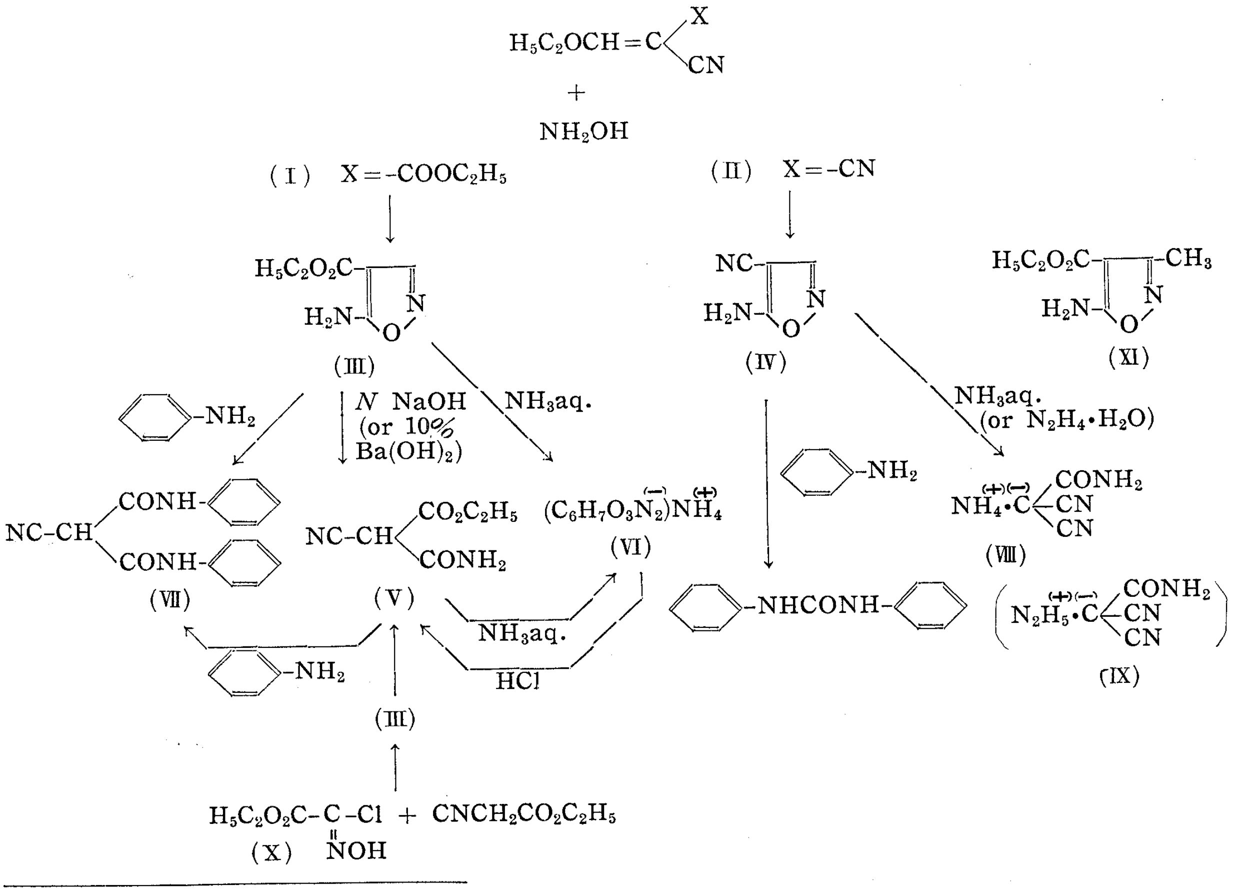
Hideo Kanō, Yasuo Makisumi, and Kazuko Ogata : Studies on Isoxazole Derivatives. XI.[1] Synthesis of 4-Ethoxycarbonyl- and 4-Cyano-5-aminoisoxazoles and Their Ring Cleavage.

(*Research Laboratory, Shionogi & Co., Ltd.**)

In the previous paper[2] of this series, the authors described an investigation on the ring cleavage of 5-aminoisoxazoles by catalytic hydrogenation, which occurred at the nitrogen-oxygen bond in the ring.

The present investigation was undertaken to prepare 4-ethoxycarbonyl-5-aminoisoxazole (Ⅲ) and 4-cyano-5-aminoisoxazole (Ⅳ), and to see if the ring cleavage of these 5-aminoisoxazoles would occur.

The two new 5-aminoisoxazoles, (Ⅲ), m.p. 73~74.5°, and (Ⅳ), m.p. 146~147°, were prepared by the reaction of hydroxylamine with ethyl α-ethoxymethylenecyanoacetate (Ⅰ) or α-ethoxymethylenemalononitrile (Ⅱ), respectively. Formation of the isoxazole ring was confirmed by their infrared spectra, which indicated the presence of an amino group in that of (Ⅲ) and (Ⅳ), and the absence of a cyano group in that of (Ⅲ). These 5-aminoisoxazoles were very unstable in basic solution and their ring cleavage occurred readily. By reaction with a cold *N* sodium hydroxide solution or a hot 10% barium hydroxide solution, (Ⅲ) was readily converted into its isomer of m.p. 162~163°.



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[1] Part Ⅹ : Ann. Rept. Shionogi Research Lab., **7**, (1), 1(1957).

[2] Part Ⅷ : This Bulletin, **3**, 270(1955).

This was found to be identical with α-ethoxycarbonylcyanoacetamide (V),[3,4] which was also obtained from the oxime of ethyl α-chloroglyoxalate (X) and ethyl cyanoacetate by Musante,[4] though he failed to isolate the probable intermediate (III). (III) was also converted by conc. ammonia water or by aniline into its ammonium salt[5] (VI), m.p. 191~191.5°, or cyanomalonic acid dianilide (VII),[6] m.p. 195~196°. A similar cleavage of the isoxazole ring occurred with (IV). Treatment with warm conc. ammonia water or cold hydrazine hydrate caused a cleavage of the ring in (IV), giving the salts of its isomer, which were assumed to be carbamoyl-malononitrile salts (VIII), m.p. 208~209°, and (IX), m.p. 133~135°, but the free amide could not be isolated.

Contrary to these two 5-aminoisoxazoles with the 3-position vacant, 3-methyl-4-ethoxycarbonyl-5-aminoisoxazole (XI) is comparatively stable toward bases. In *N* sodium hydroxide solution, hydrolysis and subsequent decarboxylation of (XI) at the 4-position was observed by Shaw and Sugowdz.[6] There is a considerable difference in the ease with which the ring is opened, depending on the substituents on the ring of isoxazole. As Burns[7] described, isoxazoles having a free 3-position are less stable toward bases than those having a substituent in the 3-position.

The authors are grateful to Dr. K. Takeda, Director of this Laboratory, for his helpful advice and encouragement. Their thanks are also due to Mr. M. Narisada for the infrared spectral measurements and to the members of the analysis room of this Laboratory for elemental analyses.

Experimental

4-Ethoxycarbonyl-5-aminoisoxazole (III)—To a stirred solution of $NH_2OH \cdot HCl$ (7 g.) dissolved in 10% NaOH (40 cc.), (I) (17 g.) was added gradually at a rate that did not cause the temperature to exceed 50°. After cool, the resulting precipitate was filtered and recrystallized from 50% EtOH to colorless needles (12 g.), m.p. 73~74.5°. *Anal.* Calcd. for $C_6H_8O_3N_2$: C, 46.15; H, 5.06; N, 17.95. Found: C, 46.25; H, 5.54; N, 17.84. I.R. $\lambda_{\max}^{\mathrm{CHCl_3}}$: 2.90, 3.02. 6.09 μ ($NH_2$).

4-Cyano-5-aminoisoxazole (IV)—To a stirred solution of $NH_2OH \cdot HCl$ (3.5 g.) dissolved in 10% NaOH (20 cc.), (II) was added under the same conditions as for (III) and colorless needles (3.3 g.), m.p. 146~147°(from H_2O), were obtained. *Anal.* Calcd. for $C_4H_3ON_3$: C, 44.07; H, 2.77; N, 36.52. Found: C, 43.77; H, 3.03; N, 36.52. I.R. $\lambda_{\max}^{\mathrm{CHCl_3}}$: 2.99, 3.15, 6.02 μ ($NH_2$), 4.48 μ (CN).

Ring Cleavage of 4-Ethoxycarbonyl-5-aminoisoxazole—(a) (III) (1 g.) was dissolved in *N* NaOH solution with stirring. After standing for 20 mins., the solution was acidified with HCl to deposit colorless needles, m.p. 162~163°(decomp.). This was found to be identical with the authentic specimen of α-ethoxycarbonyl-cyanoacetamide (V). *Anal.* Calcd. for $C_6H_8O_3N_2$: C, 46.15; H, 5.06; N, 18.95. Found: C, 45.95; H, 5.34; N, 17.70.

By the same procedure, (III) was converted to (V) in a hot 10% $Ba(OH)_2$ solution.

(b) A mixture of (III) (3 g.) and conc. NH_3 aq. (10 cc.) was warmed on a water bath 15~20 mins. After cool, the separated crystals were collected and recrystallized from EtOH-ether to colorless plates (2.2 g.), m.p. 191~191.5°, found identical with the authentic specimen of the ammonium salt of (V). This was converted to (V) with HCl, and (V) back to its ammonium salt with NH_3 aq.

(c) A mixture of (III) (0.5 g.) and aniline (1 cc.) was warmed on a water bath for a few mins. After cool, the solution was acidified with HCl and separated crystals, m.p. 195~196°(from EtOH), undepressed on admixture with a sample of cyanomalonic acid anilide (VII).

Ring Cleavage of 4-Cyano-5-aminoisoxazole—(a) (III) (2 g.) in conc. NH_3 aq. (2 cc.) was warmed on a water bath for 10~15 mins. After cool, the resulting precipitate (1.8 g.) was collected and recrystallized from water to colorless needles, m.p. 208~209°. This compound in EtOH solution colored reddish brown with $FeCl_3$ solution. *Anal.* Calcd. for $C_4H_6ON_4$: C, 38.10; H, 4.80; N, 44.43. Found: C, 38,53; H, 5.02; N, 44.64.

(b) To $NH_2NH_2 \cdot H_2O$ (1 g.), (IV) (2 g.) was added gradualy with stirring. To the resulting solution, dehyd. EtOH (3 cc.) was added and colorless crystals, m.p. 133~135°(from EtOH), were obtained. *Anal.* Calcd. for $C_4H_7ON_5$: C, 34.04; H, 5.00; N, 49.64. Found: C, 34.20, H, 5.28; N, 49.89.

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3) Frerichs: Chem. Zentr., 2. **37**, 74(1913).
4) C. Musante: Gazz. chim. ital., **69**, 523(1939).
5) Frerichs, Hartwig: J. prakt. Chem., [2] **72**, 495(1904).
6) Pabst: Arch. Pharm., **267**, 332(1929).
7) "Heterocyclic Compounds," Wiley & Sons, N.Y., **V**, 464(1957).

(c) A mixture of (IV) (0.5 g.) and aniline (1 g.) was warmed on a water bath for a few mins. After cool, the solution was acidified with HCl and separated colorless needles, m.p. 235~236°, which was undepressed on admixture with diphenylurea. *Anal.* Calcd. for $C_{13}H_{12}ON_2$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.33; H, 6.06; N, 13.28.

Summary

4-Ethoxycarbonyl- (III) and 4-cyano-5-aminoisoxazole (IV) were prepared by reacting hydroxylamine and ethyl α-ethoxymethylenecyanoacetate (I) or α-ethoxymethylenemalononitrile (II), respectively. These 5-aminoisoxazoles were very unstable toward bases compared with a compound (XI) substituted in 3-position and the ring cleavage occurred at the nitrogen-oxygen bond with subsequent isomerisation to their corresponding nitriles, (V) and (VIII).

(Received October 31, 1957)

UDC 547.94 : 582.675.1

Eiichi Fujita and Toshiaki Tomimatsu: Studies on the Alkaloids of *Thalictrum Thunbergii* DC. II.[1] A Quaternary Base in the Stem and Leaves.

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In the preceding paper,[1] it was shown that the quaternary base isolated from the root of *Thalictrum Thunbergii* DC. was only magnoflorine. The present paper deals with the evidence for the presence of magnoflorine in the stem and leaves of the same plant.

The stems and leaves of plant, which grew wild in Otani district of Tokushima City were collected and the presence of a quaternary base was examined by the method described below.

Crystals of m.p. 252° (decomp.) were isolated as the iodide, and the base was established as magnoflorine iodide by the comparison of general chemical properties and infrared spectra with the authentic specimen.

Furthermore, it was proved that no other quaternary bases are contained, and therefore that this plant, in its stem and leaves, as well as in its root, contains magnoflorine alone as the quaternary base. The stem and leaves, however, contain only 0.004% of magnoflorine, whereas the base is obtained in 0.08% yield from the root.

Recently, magnoflorine has been found in a fairy wide range of plant families, including Magnoliaceae, Menispermaceae, Berberidaceae, Rutaceae, Aristolochiaceae, and Ranunculaceae. The presence of magnoflorine in the plant of Ranunculaceae family was hitherto known only in one example[2] (*Coptis japonica* MAKINO), and this is the second case.

Examination of tertiary bases in *Thalictrum Thunbergii* DC. is now being continued by the authors.

The infrared spectra were measured by Mr. M. Narisada of the Research Laboratory, Shionogi & Co. Ltd., through the good offices of Prof. Dr. M. Tomita, University of Kyoto. The authors acknowledge their indebtedness to them. Their thanks are due to Mr. A. Takamatsu for the microanalyses.

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[1] Part I. E. Fujita, T. Tomimatsu: This Bulletin, **4**, 489(1956).

[2] M. Tomita, S. Kura: Yakugaku Zasshi, **76**, 1425(1956).