TABLE. I.

Exp. No.	Addition	Concentration (M)	Radioactivity c.p.m./mmole	Radioactivity Ratio
1.	None		8,870	100.0
	4-Methoxycinnamic acid	0.015	3,017	34.1
	4-Methoxycinnamyl alcohol	0.015	2,359	26.6
	Cinnamyl alcohol	0.015	7,896	89.0
2.	None		14,805	100.0
	4-Methoxycinnamic acid	0.015	4,250	28.6
	4-Methoxycinnamyl alcohol	0.015	3,892	26.6

The incubation mixture contained 10 μc of 4-hydroxycinnamic acid-[1-^{14}C]. The assay conditions were described in the previous paper.[3] In Exp. 1, each incubation tube contained 135 mg. of protein and in Exp. 2, each tube contained 182 mg. of protein. Both tubes were incubated at 30° for 6 hr.

Scheme II was not examined under an identical condition but it may be concluded that Scheme I will furnish an important route of anethole biosynthesis in *Foeniculum* plant.

Sincere gratitude is expressed to Prof. H. Mitsuhashi of Hokkaido University for his kind encouragement. A part of the expenses of the present work was defrayed by the Grant-in-Aid for Institutional Research of Education and Rockefeller Foundation Grant which are gratefully acknowledged.

Summary

The anethole biosynthesis, using the cell-free enzyme system of *Foeniculum* plant was established as follows: 4-Hydroxycinnamic acid→4-methoxycinnamic acid→4-methoxycinnamyl alcohol→anethole.

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177. Yasuo Yura: Studies on Acetylenic Compounds. XXV.*2 Ring Closure. (5). New Synthetic Method of Heterocyclic Compounds from α-Amino- and α-N-substitued Aminoacetylenic Compounds.

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In the previous paper[1,2] the author reported that 2-aminothiazole, 2-thiazolethiol, and 2-aminoimidazole derivatives were easily synthesized by refluxing alcoholic solution of α-haloacetylenic compounds with thiourea, ammonium dithiocarbamate, and guanidine, respectively. As a general application of this reaction to another new ring closure, α-haloacetylenic compounds were allowed to with urea, amide, thioamide, or S-benzylisothiourea to obtain derivatives of imidazole, oxazole, or thiazole, respectively. In these

*1 Nishi-shinagawa, Shinagawa-ku, Tokyo (由良靖雄).
*2 Part XXIV. I. Iwai, T. Konotsune: Yakugaku Zasshi, **82**, 601 (1962).
1) Part XXI. Y. Yura: This Bulletin, **10**, 372 (1962).
2) Part XXII. *Idem*: *Ibid.*, **10**, 376 (1962).

cases, however, no expected heterocyclic compounds were obtained. This must be due to the fact that urea, amide, and thioamide are less reactive to the halogen atom adjacent to a triple bond than thiourea. The author intended to investigate more extensively the ring closure of α-substituted acetylenic compounds which are considered to be intermediates of the reaction.

In the present paper, new synthetic methods of heterocyclic compounds from α-amino- and α-N-substituted amino-acetylenic compounds are reported. The starting material, 3-amino-1-butyne (I) was prepared from 3-chloro-1-butyne and sodium amide according to Hennion's method.[3]

2-Thiazolethiols——Generally, a mercapto radical easily reacts with a triple bond. For example, mercaptan and thiol carboxylic acid easily add to a triple bond to give vinylthioethers. Batty *et al.*[4] reported that a thiazole derivative was obtained from 3-isopropylamino-1-butyne and carbon disulfide by heating the alcoholic solution of these compounds. Schulte *et al.*[5] also synthesized 2-thiazolidinethione in good yield from 2-heptynylamine and carbon disulfide by a similar way. 3-Amino-1-butyne (I) was heated with carbon disulfid to give (II) as white needles, m.p. 93°. The elementary analysis of (II) agreed well with an empirical formula $C_5H_7NS_2$. The infrared and ultraviolet spectra showed absorptions at 878 cm^{-1} ($C{=}CH_2$) and at 297.5 mμ, respectively. On the other hand, 4,5-dimethyl-2-thiazolethiol (III), which was synthesized from 3-bromo-2-butanone and ammonium dithiocarbamate, melted at 163°[6] and showed an absorption at 323.5 mμ in the ultraviolet spectrum. 4-Methylene-5-methyl-2-thiazoline-2-thiol, prepared from 3-bromo-1-butyne and ammonium dithiocarbamate,[2] showed an absorption at 878 cm^{-1} in the infrared spectrum. (Fig. 1). However, it melted at 153° and showed

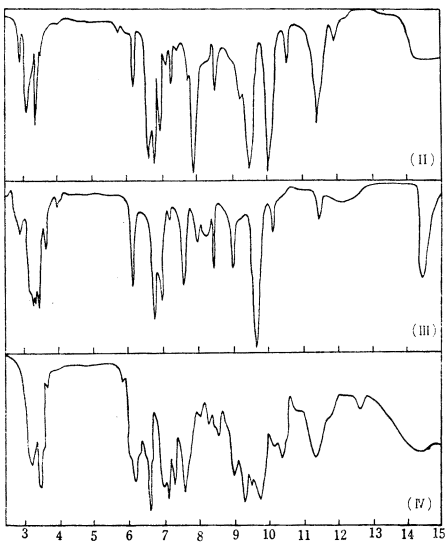

Fig. 1. Infrared Spectra of 4-Methyl-5-methylene-2-thiazoline-2-thiol (II : in $CHCl_3$), 4,5-Dimethyl-2-thiazolethiol (III : in $CHCl_3$) and 2-Methylthio-4-methylene-5-methyl-2-thiazoline (IV : liquid).

a depression in m.p. on admixture with (II). Moreover, (II) was transformed to (III) by treatment with sulfuric acid. Considering the reaction mechanism it is concluded that (II) is 4-methyl-5-methylene-2-thiazoline-2-thiol.

2-Alkylimidazoles——Primary amines afford amidines when heated with thioamide.

3) G.H. Hennion, J.M. Campbell: J. Org. Chem., **21**, 791 (1956).
4) J.W. Batty, B.C.L. Weedon: J. Chem. Soc., **1949**, 786.
5) K.E. Schlte, M. Goes: Arch. Pharm., **290**, 118 (1957).
6) E.R. Buchman, A.O. Reims, H. Sargent: J. Org. Chem., **6**, 767 (1941).

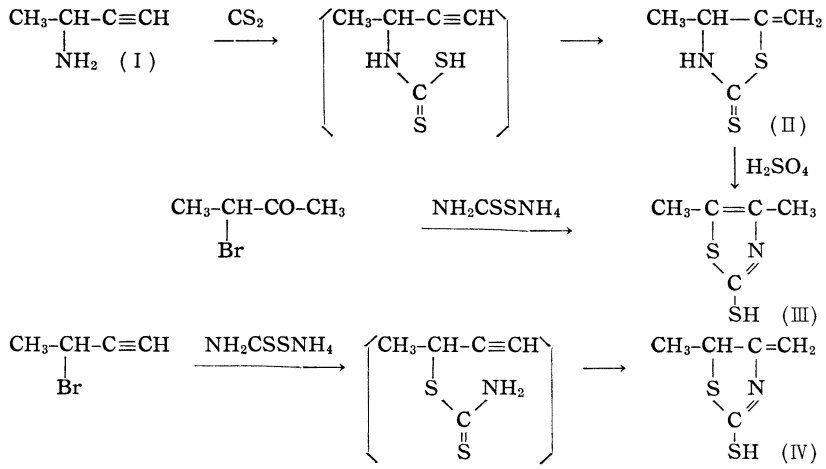

Chart 1.

Forssel[7] synthesized 2-phenyl-2-imidazoline from ethylene diamine and thiobenzamide. Heating of 3-amino-1-butyne with thioacetamide furnished no expected amidine compound, but 2,4,5-trimethylimidazole (VI) (m.p. 128~130°) was produced. (VI) did not show a depression in m.p. on admixture with the authentic sample (m.p. 128~130°) which was prepared from diacetyl and ammonia according to von Pechmann's method.[8] Infrared and ultraviolet spectra of both compounds were superimposable with each other. (Fig. 2). It was concluded, therefore, that the active intermediate amidine internally closed its ring to afford imidazole derivative (VI). The reaction mechanism is illustrated in Chart 2.

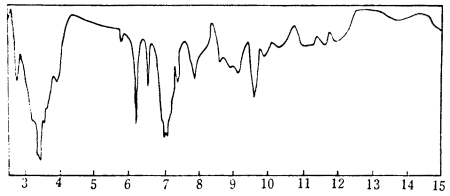

Fig. 2. Infrared Spectrum of 2,4,5-Trimethylimidazole ($CHCl_3$)

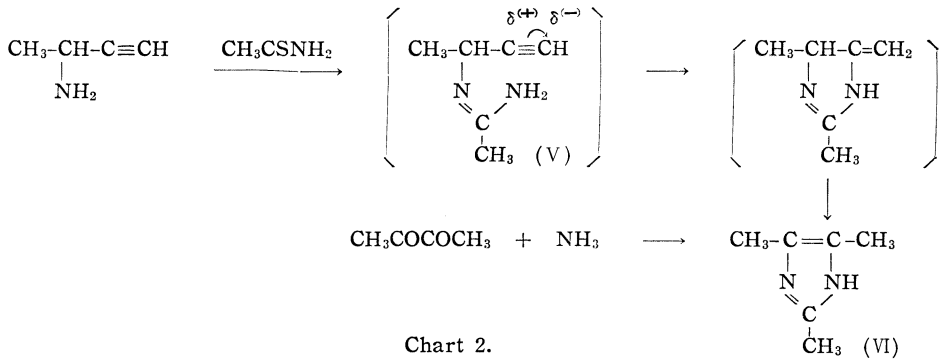

Chart 2.

2-Imidazolone Derivative——Hennion *et al.*[3] reported that cyanic acid reacted with acetylenic amines to give N-substituted ureas. By a similar way 1-(1-methyl-2-propynyl)-urea (VII) was synthesized from 3-amino-1-butyne hydrochloride and potassium cyanate. (VII) did not afford an imidazole compound only by heating.

7) G. Forssel: Ber., **25**, 2132 (1892).
8) von Pechmann: Ber., **21**, 1411 (1888).

Usually, sulfuric acid is employed as a catalyst for the hydration of the ethynyl group, the reaction mechanism is considered as shown in the following equation.

$$-C\equiv CH \xrightarrow{H\oplus} -\overset{\oplus}{C}=CH_2 \xrightarrow{H_2O} -\overset{H_2O\oplus}{\underset{|}{C}}=CH_2 \xrightarrow{\text{Rearrange}} -\overset{O}{\overset{\|}{C}}-CH_3 + H\oplus$$

With the expectation of bond formation between the carbonium ion and the nucleophilic center in (Ⅵ), (Ⅶ) was attempted to cyclize in sulfuric acid at 0~5° and the solution was allowed to stand over-night at room temperature, whereby white prisms which did not melt below 300° were obtained. The elemental analysis gave values corresponding to a formula $C_5H_8N_2O$. The infrared spectrum of this compound did not show any absorption caused by a triple bond but a strong absorption due to -NH-CO-, (Fig. 3), which coincided with that of 4,5-dimethyl-2-imidazolone (X), prepared from 2-amino-3-butanone and cyanic acid.[9] The reaction mechanism is considered as shown in Cart 3,

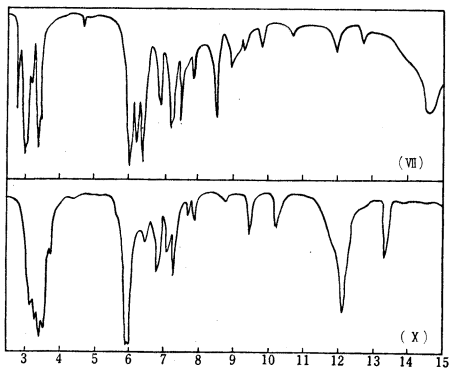

Fig. 3. Infrared Spectra of 1-(1-Methyl-2-propynyl) urea (Ⅶ) and 4,5-Dimethyl-2-imidazolone (X) (Nujol)

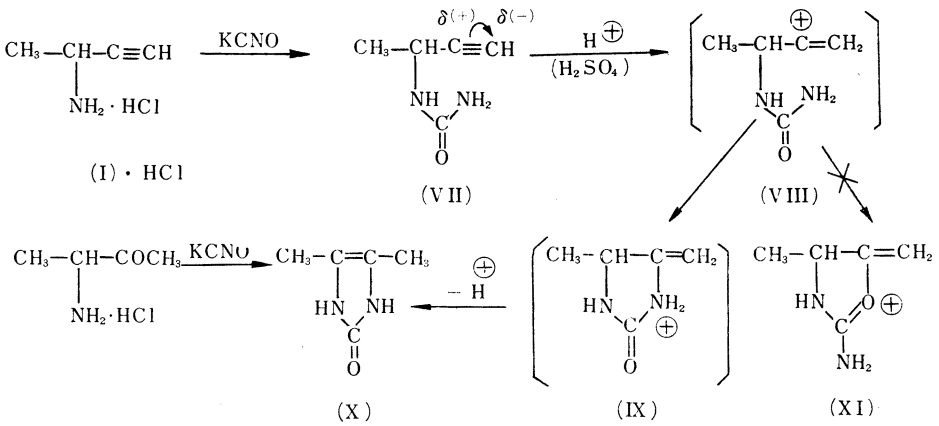

Chart 3.

It is apparent, therefore, that the carbonium ion which is produced by addition of a proton to a triple bond, attacks the NH_2-group to afford C-N bond. This reaction is expected to be applicable to other ring formations of acetylenic compounds having a electron releasing group -SH, -OH, etc. adjacent to a triple bond.

2-Imidadolethiol Derivative——1-(1-Methyl-2-propynyl)-2-thiourea (Ⅻ) was obtained from 3-amino-1-butyne hydrochloride and potassium thiocyanate. As (Ⅻ) can also have the structure (Ⅻ′), it is interesting to see how to close the ring to give imidazole or

9) E. Ochiai, S. Ikuma : Yakugaku Zasshi, **56**, 525 (1936).

thiazole. First, (XII) was tried to cyclize only by heating, but the starting material was recovered. Next, (XII) was treated with sulfuric acid, and in this case white needles of m.p. >300° were obtained. The structure of this compound was identified as 4,5-dimethyl-2-imidazolethiol by comparing the ultraviolet and infrared spectra with those of an authentic sample which was synthesized from 2-amino-2-butanone and thiocyanic acid by Ochiai's method.[9] (Fig. 4), (Chart 4).

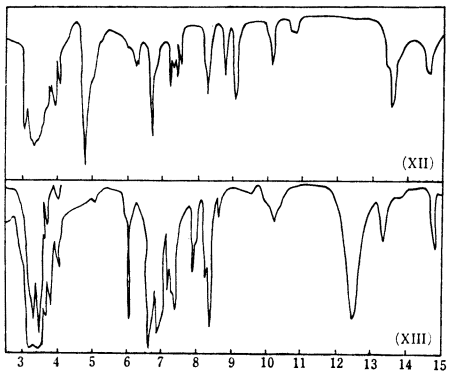

Fig. 4. Infrared Spectra of 1-(1-Methyl-2-propynyl)-2-propynyl)-2-urea (XII) and 4,5-Dimethyl-2-imidazolethiol (XIII) (Nujol)

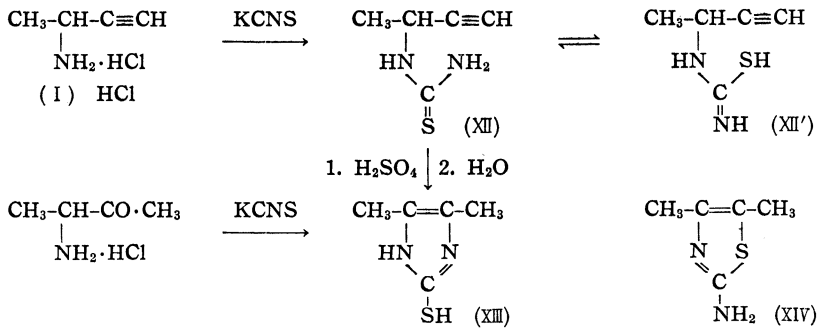

Chart 4.

2-Phenyloxazole Derivative——1-(2-Propynyl)-urea and 1-(2-propynyl)-thiourea did not give 2-aminooxazole (XI) and 2-aminothiazole (XIV), respectively. These facts showed that the carbonium ion of a triple bond reacted with the terminal amino-group but not with >C=O and >C=S. Now in the case of N-(1-methyl-2-propynyl)-benzamide in which terminal amino group of (XII) is replaced by a phenyl group, attitude of a carbonyl function against the carbonium ion was examined. When (XV) was dissolved in concentrated sulfuric acid at 0~5°, and kept at room temperature over-night, a yellow oil ($b.p_{0.5}$ 65°) was obtained in good yield. The structure of this oil was confirmed by the elemental analysis and by comparing its ultraviolet and infrared (Fig. 5) spectra with those of an authentic sample of 2-phenyl-4,5-dimethyloxazole[10] which was synthesized from 3-bromo-2-butanone and benzamide. (Chart 5).

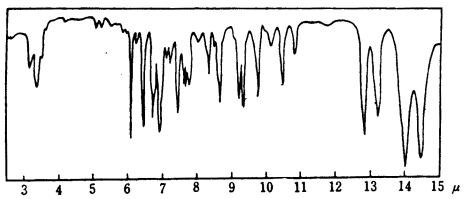

Fig. 5. Infrared Spectrum of 2-Phenyl-4,5-dimethyloxazole (liquid film)

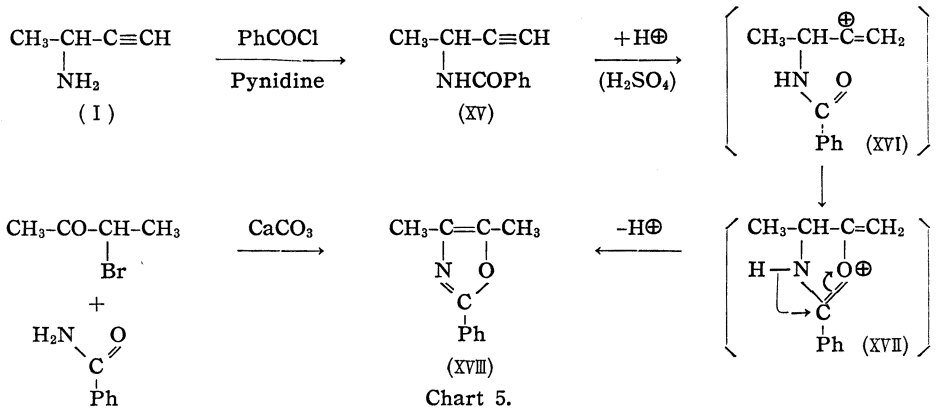

Chart 5.

Experimental

4-Methyl-5-methylene-2-thiazoline-2-thiole (II)——To a solution of 1.7 g. of CS_2 in abs. EtOH was slowly added 1 g. of 3-amino-1-butyne (I) with shaking. A vigorous reaction took place. Then the reaction mixture was refluxed on a water bath for 4 hr. After removal of EtOH under reduced pressure, the residue was crystallized from AcOEt to give white needles of m.p. 92~93°. Yield, 1.75 g. (82.7%). *Anal.* Calcd. for $C_5H_7NS_2$: C, 41.37; H, 4.82; N, 9.65. Found: C, 41.28; H, 4.89; N, 9.70. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480 (-SH), 878 (>C=CH_2). UV: λ_{max}^{EtOH} 297.5 mμ (log ε 4.35).

4,5-Dimethyl-2-thiazolethiol (III)——One gram of 4-methyl-5-methylene-2-thiazoline-2-thiol (II) was dissolved in 4 cc. of conc. H_2SO_4 with cooling in an ice-bath. After standing overnight at room temperature, the solution was poured on crushed ice and was neutralized with aq. NaOH. The resulting precipitate was extracted with Et_2O. After washing with H_2O and drying over Na_2SO_4 the extracts were evaporated to leave a solid residue. On crystallization from AcOEt the residue gave 0.9 g. of white needles, m.p. 161~163°. No depression in m.p. was observed on admixture with the authentic sample of m.p. 163° prepared from 3-bromo-2-butanone and ammonium dithiocarbamate by the method of Buchman *et al.*[6] *Anal.* Calcd. for $C_5H_7NS_2$: C, 41.37; H, 4.82; N, 9.65. Found: C, 41.33; H, 4.80; N, 9.95. UV: λ_{max}^{EtOH} 323.2 mμ (log ε 4.26).

4-Methylene-5-methyl-2-thiazoline-2-thiole (IV)——To a mixture of 3 g. (26.1 mmole) of ammonium dithiocarbamate and 15 cc. of dehyd. EtOH was added dropwise 2.5 g. (18.8 mmole) of 2-bromo-1-butyne. The mixture was heated on a water-bath for 1 hr. After the solvent was evaporated *in vacuo*, the residue was treated with H_2O and dissolved in Et_2O. The Et_2O was evaporated, and there was obtained a solid product which was recrystallized from AcOEt to give 1.5 g. of brownish needles, m.p. 152~153°. *Anal.* Calcd. for $C_5H_7NS_2$: C, 41.37; H, 4.82; N, 9.65. Found: C, 41.41; H, 4.92; N, 9.60. UV: λ_{max}^{EtOH} 324 mμ (log ε 4.26).

2,4,5-Trimethylimidazole (VI)——A mixture of 1 g. (14.5 mmole) of 3-amino-1-butyne and 1.1 g. (14.6 mmole) of thioacetamide was heated on a water-bath for 5 hr., whereby a reddish oily substance was obtained under evolution of H_2S. The crude product was distilled at 120° (bath-temp.)/5 mm. On standing at room temperature, the distillate gradually solidified. Yield, 0.4 g. (25%). The obtained white crystals showed no depression on admixture with an authentic sample of m.p. 128~129°, prepared from diacetyl and NH_3 according to the method of von Pechmann.[8] *Anal.* Calcd. for $C_6H_{10}N_2$: C, 65.45; H, 9.09; N, 25.45. Found: C, 65.43; H, 9.27; N, 25.46.

1-(1-Methyl-2-propynyl)-urea (VII)——To a solution of 3-amino-1-butyne hydrochloride (1 g.: 9.47 mmole) dissolved in 3.2 cc. of H_2O was added in one portion 3.5 cc. of an aqueous solution containing 0.78 g. (9.64 mmole) of KOCN. The mixture was heated on the water-bath at 90° for 4 hr. On standing at room temperature, 0.8 g. of the product crystallized out: Yield, 75.3%. It was recrystallized from 99% EtOH to give colorless needles, m.p. 164~165°. *Anal.* Calcd. for $C_5H_8ON_2$: C, 53.57; H, 7.14; N, 25.00. Found: C, 53.72; H, 7.10; N, 25.12. IR ν_{max}^{Nujol} cm^{-1}: 3540 (NH), 3315 (≡CH) 1650 (>C=O).

10) B. S. Friedman, M. Sparks: J. Am. Chem, Soc., **59**, 2262 (1937).

4,5-Dimethyl-2-imidazolone (X)——1-(1-Methyl-2-propynyl)-urea (400 mg.) was dissolved in ice-cooled conc. H_2SO_4 (10 cc.) with stirring, and the solution was allowed to stand overnight at room temperature. Then the acid solution was poured into ice-water, and neutralized with aq. $Ba(OH)_2$. The precipitated $BaSO_4$ was filtered off and washed with hot H_2O. The combined aqueous solutions were evaporated *in vacuo*. The residue was crystallized from H_2O give colorless prisms, m.p. >300°. *Anal.* Calcd. for $C_5H_8ON_2$: C, 53.57; H, 7.14; N, 25.00. Found: C, 53.66; H, 7.08; N, 25.07. The IR spectrum of this substance showed no absorption due to a triple bond and coincided with that of 4,5-dimethyl-2-imidazolone, prepared from 3-amino-2-butanone and cyanic acid by the method of E. Ochiai and S. Ikuma.[9]

1-(1-Methyl-2-propynyl)-2-thiourea (XII)——To a solution of 1 g. of 3-amino-1-butyne dissolved in 7.25 cc. of 2*N* HCl was added a saturated aqueous solution of KCNS (1.41 g.). After heating on a water-bath for 5 hr. the reaction mixture was evaporated to dryness *in vacuo*. The residue was extracted twice with hot EtOH. After evaporating the soluvent, the residue was distilled at 100~108°/4 mm. On standing at room temperature, the distillate solidified. m.p. 65°. Yield, 1.59 g. (85.6%). *Anal.* Calcd. for $C_5H_8N_2S$: C, 46.87; H, 6.25; N, 21.87. Found: C, 46.95; H, 6.11; N, 21.66. IR ν_{max}^{Nujol} cm^{-1}: 3290 (C≡CH), 2190 (-C≡C-).

4,5-Dimethyl-2-imidazolethiol (XIII)——One gram of 1-(1-methyl-2-propynyl)-2-thiourea was dissolved in 10 cc. of conc. H_2SO_4 with cooling in an ice-bath, and the solution was allowed to stand overnight at room temperature. The acid solution was then poured into ice-H_2O and neutralized with $Ba(OH)_2$. The precipitated $BaSO_4$ was filtered off and washed with hot H_2O. The combined aqueous solutions were evaporated *in vacuo*. The residue was crystallized from H_2O to give pale yellow needles, m.p. >300°. *Anal.* Calcd. for $C_5H_8N_2S$: C, 46.87; H, 6.25; N, 21.87. Found: C, 46.87; H, 6.10; N, 21.97. UV: λ_{max}^{EtOH} 266.5 mμ (log ε 4.27).

2-Phenyl-4,5-dimethyloxazole (XVIII)——To an ice-cooled solution of 2 g. of 3-amino-1-butyne (I) dissolved in 15 cc. of dry pyridine, was dropwise added 4.48 g. of benzoyl chloride. After 8 hr. at room temperature, the reaction mixture was poured into H_2O. The precipitated solid was extracted with Et_2O. The ethereal extract was washed with dil. H_2SO_4, aq. $NaHCO_3$ and then saturated aq. NaCl solution. After evaporation of Et_2O, the solid residue was recrystallized from benzene to give white needles, m.p. 115°. Yield, 4.5 g. (89.7%). *Anal.* Calcd. for $C_{11}H_{11}ON$: C, 76.30; H, 6.35; N, 8.09. Found: C, 76.41; H, 6.43; N, 8.09. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3560 (NH), 3340 (≡CH), 1665 (>C=O).

Then N-(1-methyl-2-propynyl)-benzamide (XV) (1 g.) was dissolved in ice-cooled conc. H_2SO_4 (10 cc.), and the solution was allowed to stand for 3 hr. at 5~10° and then at room temperature overnight. After pouring onto crushed ice, the reaction mixture was made alkaline with K_2CO_3. The resulting precipitated oil was extracted with Et_2O. The ethereal extract was dried over Na_2SO_4. After removal of Et_2O, a yellow oily residue was distilled at 65°/0.5 mm. Yield, 500 mg. (50%). *Anal.* Calcd. for $C_{11}H_{11}ON$: C, 76.30; H, 6.35; N, 8.09. Found: C, 76.31; H, 6.57; N, 8.01. UV: λ_{max}^{EtOH} 280 mμ (log ε 4.23).

The author would like to thank Prof. K. Tsuda of Tokyo University and Mr. M. Matsui, Director of this Laboratory for their encouragements during this work. Grateful thanks are also due to Dr. I. Iwai of this Laboratory for his kind guidance and valuable suggestions throughout this work. The author also wishes to express his gratitude to Mr. T. Onoe for microanalysis and to Mr. O. Amakasu and Mr. N. Higosaki for the mesurement of infrared spectra.

Summary

A new ring closure of α-amino- and α-N-substituted aminoacetylenic compounds has been studied. 2-Methylimidazole and 2-thiazolethiol derivatives were easily synthesized by heating α-aminoacethylenic compound with thioacetamide and carbon disulfide, respectively. By treating 1-(2-propynyl)-urea, 1-(2-propynyl)-thiourea and 1-(2-propynyl)-benzamide with concentrated sulfuric acid, there were obtained 2-imidazolone, 2-imidazolethiole and 2-phenyloxazole derivatives, respectively.

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