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59. Yasuo Yura : Studies on Acetylenic Compounds. XXI.¹⁾
 Ring Closure. (3). New Synthetic Method for Thiazoles.

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There are many reports concerning a synthesis of heterocyclic compounds from derivatives of acetylene. According to them, most of these heterocyclic compounds were obtained by the addition of hetero compound to a triple bond. However, rather small cases have been reported in which the carbon atom adjacent to the triple bond takes part in a ring closure and forms a member of the ring. Moreover, in this type of a ring closure, only a few ring compounds containing sulfur atom have been obtained.

(1) Schlubach²⁾ synthesized thiophene derivative from ethynyl epoxide and hydrogen sulfide.

(2) Batty³⁾ intended to prepare dithiocarbamate from carbon disulfide and 3-isopropylamino-1-butyne. He could not obtain the expected compound but only thiazole derivatives.

(3) Ruhemann, *et al.*⁴⁾ obtained benzalthiohydantion by condensation of phenylacetylenic acid with thiourea.

Examinations have been made in this laboratory on the chemical activity of the halogen atom substituted in the carbon adjacent to the triple bond ($-\text{C}-\text{C}\equiv\text{C}-$) and a new synthetic method was found for thiazole derivatives.

When 3-bromo-1-propyne was refluxed with thiourea in ethanol for 2 hours, a basic substance of m.p. 43.5° was obtained after distillation of yellow oily product (b.p.₁₈ 130~135°). It showed ultraviolet absorption maximum at 255 mμ (log ε 3.754). Infrared absorption spectrum of this substance did not show any absorption of a triple bond (2100~2200 cm⁻¹) or of an endo-methylen group (870~910 cm⁻¹). It is therefore considered to be a ring compound. In that case two possible compounds, (III) and (IV), would be expected.

*¹ Nishi-Shinagawa, Shinagawa-Ku, Tokyo (由良靖雄).

1) Part XX : This Bulletin, 10, 81 (1961).

2) H. H. Schlubach, K. Repenning : *Ann.*, **614**, 37 (1958).

3) J. W. Batty, B. C. L. Weedon : *J. Chem. Soc.*, **1949**, 786.

4) S. Fuhemann, H. E. Stapleton : *Ibid.*, **77**, 239 (1900).

By the first step, a S-propynylisothioureahydrobromide (I) would be formed. If the amino group of (I) bonded to C-3, a six-membered ring (IV) would be produced and if it combined with C-2, a five-membered ring (III) would be produced via (II). However, infrared and ultraviolet absorption spectra of the product were superimposable on those of 2-amino-4-methylthiazole prepared from monochloroacetone and thiourea by the method of Byers, *et al.*⁵⁾ Moreover, a picrate of this compound showed no depression of melting point on admixture with the authentic sample. Thus, the substance obtained by this reaction was confirmed as (III).

When the reaction-time was shortened to 30 minutes, the product showed the infrared absorption at 900 cm^{-1} ($\text{C}=\text{CH}_2$). It means that (II) is the intermediate in this reaction and also supports the fact that the ring-closure does occur to the direction giving a five-membered ring (thiazole). The relationship between the yield of thiazole and refluxing time is summarized in Table I. As shown in the table, the yield of thiazole increased greatly when two moles of thiourea was used.

TABLE I.

Time (hr.)	Yield (g.)	Time (hr.)	Yield (g.)
1	1.3	5	0.78
2	1.2	6	0.96
2	2.8 ^{a)}	6.5	0.70
3	1.2	8	0.89

a) Using of 2 moles of thiourea.

In the place of 3-bromo-1-propyne, 3-bromo-1-phenyl-1-propyne, 1-(*p*-chlorophenyl)-3-bromo-1-propyne, and 1-bromo-2-hexyne were reacted with 2 moles of thiourea under the same condition. These acetylenic compounds also gave the corresponding thiazole derivatives (Table II).

TABLE II.

Starting material	Thiazole derivative	Yield (%)	UV _{max} ^{EtOH} mμ (log ε)
3-Bromo-1-propyne	2-Amino-4-methylthiazole	50	256.0 (3.75)
3-Bromo-1-phenyl-1-propyne	2-Amino-4-benzylthiazole	45	256.0 (3.79)
3-Bromo-1-(<i>p</i> -chlorophenyl)-1-propyne	2-Amino-4-(<i>p</i> -chlorobenzyl)thiazole	35	255.5 (3.89)
1-Bromo-2-hexyne	2-Amino-4-butylthiazole	poor	255.0 (3.77)

When the hydrogen atom of the ethynyl group is substituted with an alkyl group, the yield of thiazole compound is very poor. It would be due to the electron-releasing effect of alkyl group weakening the electron-deficiency at C-2 of (I), because the reaction mechanism is considered to be as shown in Chart 1.

5) J.R. Byers, J.B. Dickey: *Org. Syntheses, Coll. Vol. 2*, 31 (1957).

Chart 1.

Experimental

1-(p-Chlorophenyl)-1-propyne-3-ol—To 200 cc. of liquid NH_3 , small pieces of 8.2 g. of metallic Na were added at such a rate that the blue color just disappeared before the next piece of Na was added under stirring and bubbling of acetylene. A solution of 50 g. of *p*-chlorobenzaldehyde in 100 cc. of dehyd. Et_2O was poured into the liquid NH_3 during 30 min. under gentle passage of acetylene, and the cooled reaction mixture was stirred for 10 hr. After the addition of 20 g. of NH_4Cl , NH_3 was allowed to evaporate. The product was extracted with Et_2O and the extract was washed successively with H_2O , saturated NaHSO_3 , NaHCO_3 , dil. H_2SO_4 , and H_2O . After it was dried over Na_2SO_4 , the solvent was evaporated. The residue was distilled *in vacuo*. b.p._{0.3} 75~76°. Yield, 36.4 g. (61.4%). *Anal.* Calcd. for $\text{C}_9\text{H}_7\text{OCl}$: C, 64.86; H, 4.20. Found: C, 64.50; H, 4.29. IR $\lambda_{\text{max}}^{\text{liquid}}$ μ : 2.9 (OH), 2.99 ($-\text{C}\equiv\text{CH}$), 4.7 ($-\text{C}\equiv\text{C}-$).

1-(p-Chlorophenyl)-1-propyne-3-ol—To the solution of EtMgBr (from Mg 2.43 g., EtBr 10.1 g., and tetrahydrofuran 100 cc.), a solution of 13.8 g. of *p*-chlorophenylacetylene in 25 cc. of tetrahydrofuran was added during 30 min. The mixture was heated at 40~50° for about 2 hr. After the evolution of C_2H_6 stopped, a stream of formaldehyde (from dried trioxymethylene, 4 g.) carried by N_2 was bubbled through the solution under mechanical stirring. The mixture was maintained at 55~60° for further 3 hr. and the cooled reaction mixture was decomposed by the addition of saturated NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with Et_2O . The organic layer was combined with the Et_2O extract, washed with saturated NaCl solution, dried over Na_2SO_4 , and evaporated. The viscous residue (18.8 g.) immediately solidified. The solid was recrystallized from hexane to colorless needles, m.p. 76.5~77.0° was obtained. Yield, 10.5 g.

Fig. 1. Infrared Spectra

— Authentic sample.
 - - - New synthesized compound.

- (1) 2-Amino-4-methylthiazole. (CCl_4)
 (2) 2-Amino-4-benzylthiazole. (Nujol)
 (3) 2-Amino-4-(*p*-chlorobenzyl)thiazole. (Nujol)
 (4) 2-Amino-4-butylthiazole picrate. (Nujol)

(62.5%). *Anal.* Calcd. for $\text{C}_9\text{H}_7\text{OCl}$: C, 64.86; H, 4.20. Found: C, 64.50; H, 4.29. IR: $\lambda_{\text{max}}^{\text{CCl}_4}$ μ : 2.92, 4.46.

3-Bromo-1-(*p*-chlorophenyl)-1-propyne—To a mixture of 4.5 g. of 1-(*p*-chlorophenyl)-1-propyne-3-ol, 4 cc. of pyridine, and 5 cc. of dry Et_2O , 2.35 g. of PBr_3 was added dropwise at such a rate that Et_2O keeps gentle boiling. After the addition of PBr_3 , the stirring and heating was continued for further 2 hr. and the reaction mixture was poured into ice-water. The separated Et_2O layer was washed with NaHCO_3 and H_2O , dried over Na_2SO_4 and evaporated. The viscous residue (5.7 g.) crystallised to needles, m.p. 43° . *Anal.* Calcd. for $\text{C}_9\text{H}_6\text{BrCl}$: C, 47.25; H, 2.62. Found: C, 47.17; H, 2.88. IR $\lambda_{\text{max}}^{\text{CCl}_4}$ μ : 4.38, 4.48.

2-Amino-4-methylthiazole from 3-Bromo-1-propyne—A mixture of 5 g. of 3-bromo-1-propyne, 6.4 g. of thiourea, and 10 cc. of 99% EtOH was heated on a water bath for 2 hr. EtOH was removed in vacuum, the residue was dissolved in H_2O , and the water-insoluble substance was removed by Et_2O extraction. After the aqueous solution was made alkaline with NaOH , it was extracted with Et_2O . The Et_2O extract was dried over NaOH and Et_2O was evaporated. The yellow oily residue distilled at $130\sim 135^\circ/18\text{ mm}$. On standing, the distillate solidified (m.p. 43.5°) at room temperature. It gave a monpicrate of m.p. 228° (decomp.) which was recrystallized from EtOH , and admixture of the picrate and the authentic sample⁵⁾ melted at 228° . *Anal.* Calcd. for $\text{C}_4\text{H}_6\text{NS}\cdot\text{C}_6\text{H}_5\text{O}_7\text{N}_3$: C, 35.00; H, 2.62; N, 20.41. Found: C, 34.97; H, 2.88; N, 20.38. UV: $\lambda_{\text{max}}^{\text{EtOH}}$ μ : 256 m μ ($\log \epsilon$ 3.75).

2-Amino-4-benzylthiazole from 1-Phenyl-3-bromo-1-propyne—A mixture of 10 g. of 3-bromo-1-phenyl-1-propyne, 8.6 g. of thiourea, and 40 cc. of EtOH (99%) was heated for 2 hr. The reaction proceeded smoothly and gave 2-amino-4-benzylthiazole as an oil, which solidified after standing for 2 days and was recrystallized from benzene to colorless needles, m.p. $92\sim 93^\circ$. It showed no depression on admixture with an authentic sample of m.p. 93° , prepared according to the method of Kaji, *et al.*⁶⁾ b.p._{0.05} $140\sim 145^\circ$ (bath. temp.). Yield, 45%. *Anal.* Calcd. for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{S}$: C, 63.15; H, 5.26; N, 14.73. Found: C, 63.28; H, 5.49; N, 14.56. UV: $\lambda_{\text{max}}^{\text{EtOH}}$ μ : 256 m μ ($\log \epsilon$ 3.79).

2-Amino-4-(*p*-chlorobenzyl)thiazole from 3-Bromo-1-(*p*-chlorophenyl)-1-propyne—The reaction was carried out in the same way as for 3-bromo-1-phenyl-1-propyne, by using 1-(*p*-chlorophenyl)-

6) K. Kaji, H. Nagashima, N. Ninou, T. Hanada: *Yakugaku Zasshi*, **77**, 438 (1955).

3-bromo-1-propyne (3 g.), thiourea (1.5 g.), and 99% EtOH (7 cc.). 2-Amino-4-(*p*-chlorophenyl)thiazole was obtained as colorless needles, m.p. 146° (from benzene). Yield, 1.5 g. or 35%. *Anal.* Calcd. for $C_{10}H_9N_2SCl$: C, 53.45; H, 4.02; N, 12.50. Found: C, 53.48; H, 4.21; N, 12.07. UV: λ_{max}^{EtOH} 255.5 m μ ($\log \epsilon$ 3.89).

2-Amino-4-butylthiazole from 1-Bromo-2-hexyne—A mixture of 10 g. of 1-bromo-2-hexyne, 6 g. of thiourea, and 30 cc. of EtOH was heated for 15 hr. The reaction mixture was treated as for 3-bromo-1-propyne. After evaporation of EtOH, the residual viscous oil (5.5 g.) was characterized as a picrate of yellow pillars, m.p. 180~182° (from EtOH). Only 15 mg. of the picrate was obtained in pure state, so the yield of 2-amino-4-butylthiazole was very poor. The picrate showed no depression of m.p. on admixture with the authentic sample of m.p. 180.5~182° prepared by the method of Cason.⁷⁾ The infrared spectra of the two compounds agreed well.

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Summary

It was found that the compounds containing primary halogen group adjacent to a triple bond, when reacted with thiourea, afforded heterocyclic compounds. In this case no six-membered ring compound was formed but a five-membered ring compound, thiazole derivative, was obtained. This is a new synthetic method for preparing thiazoles. The reaction mechanism of this ring closure was discussed.

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7) J. Cason: J. Am. Chem. Soc., 68, 2078 (1946).

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60. Yasuo Yura: Studies on Acetylenic Compounds. XXII.¹⁾ Ring Closure. (4). New Synthesis of Thiazoles and Imidazole.

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In the preceding paper,¹⁾ it was shown that primary haloacetylenic compounds reacted with thiourea to give thiazole derivatives. In the present series of work, examinations were made on this ring closure with secondary haloacetylenic compounds and it was found that two different types of ring closure occurred according to the kind of substituent present in the acetylenic compounds.

Secondary haloacetylenic compounds substituted with aryl group such as 3-chloro-3-phenyl-1-propyne (Ia), 3-(*p*-chlorophenyl)-3-chloro-1-propyne (Ib), 3-chloro-3-(1-naphthyl)-1-propyne (Ic), and 3-chloro-1,3-diphenyl-1-phenyl-1-propyne (Id) reacted with thiourea to form 2-amino-4-methyl-5-phenylthiazole (IIa), 2-amino-4-methyl-5-(*p*-chlorophenyl)thiazole (IIb), 2-amino-4-methyl-5-(1-naphthyl)thiazole (IIc), and 2-amino-4-benzyl-5-

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1) Part XXI: This Bulletin, 10, 372 (1962).