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 mμ (log ε 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 admixure 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.

The author wishes to express his deep gratitude to Prof. K. Tsuda of the Institute of Applied Microbiology, University of Tokyo, to Mr. M. Matsui, Director of this Laboratory, and to Dr. I. Iwai for their kind guidance and encouragement throughout the course of this investigation, and to Mr. J. Ide of this Laboratory for his technical assistance. The measurement of I.R. and U.V. spectra were carried out by Messrs. O. Amakasu, H. Higuchi, N. Higosaki, and Miss. N. Sawamoto and micro-analyses were made by Messrs. T. Onoe and H. Nagashima, Misses. C. Furukawa, and H. Ohtsuka.

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 fromed 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.

(Received March 25, 1961)

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

UDC 547.583.2.07

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

(*Takamine Laboratory, Sankyo Co., Ltd.*[*1])

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-naphtyl)-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-

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

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

phenylthiazole (IId), respectively. The structure of these 2-aminothiazole homologs was confirmed by comparison with authentic samples prepared by the known methods. Namely, these haloacetylene compounds react with thiourea in just same way as in a primary haloacetylene compound.[1]

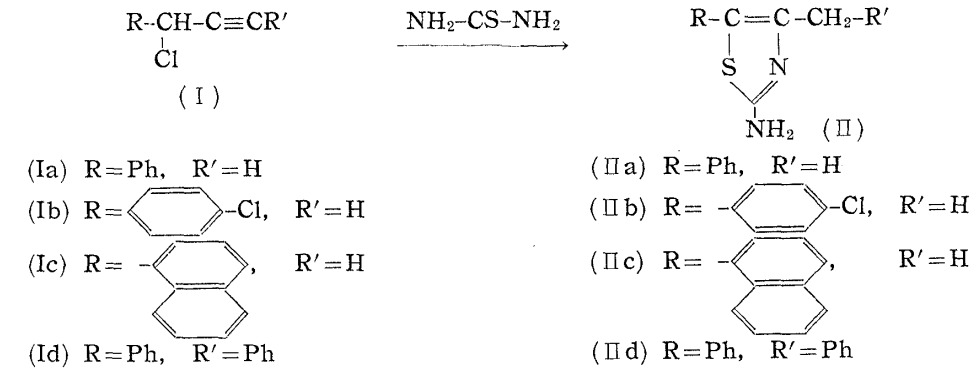


Table I. Physical Properties of 2-Aminothiazoles

2-Aminothiazole derivatives	m.p. (°C)	UV λ_{max}^{EtOH} mμ (log ε)
(IIa)	163	295 (4.09)
(IIb)	188.5~189	340 (4.17)
(IIc)	160 ~161	224.6 (4.55), 260.0 (3.94), 316.6 (4.02)
(IId)	137.5~138.5	293.6 (4.058)

On the other hand, secondary haloacetylene compounds substituted with alkyl group react with thiourea in a different way. For example, when 3-bromo-1-butyne (III) was refluxed with 2 moles of thiourea in ethanol, two kinds of thiazole compounds were isolated as their picrates. Elemental analysis of a mixture of basic oily products obtained by this reaction was in agreement with the calculated value for $C_5H_8N_2S$. The infrared spectrum of the oily product showed absorption at 878 cm^{-1} due to *end*-methylene group and its ultraviolet spectrum showed absorption at 255 mμ, which was recognized in 4-ethylthiazole.

From these results oily, the product was assumed to be a mixture of two kinds of thiazoles (IV and VI), in which (IV) would be expected to isomerise to (V) with mineral acid as reported in previous paper.[1] After the oily product was treated with sulfuric acid it was converted into its picrate. By repeated recrystallization of the picrate from ethanol, yellow prisms of m.p. 248° were obtained and the other picrate of m.p. 213~215° was obtained from its mother liquor. Infrared and ultraviolet spectra of the former coincided with those of the authentic picrate of 2-amino-4,5-dimethylthiazole (V) prepared from bromomethyl ethyl ketone and thiourea. Mixed melting point of the two picrates showed no depression.

The latter picrate of m.p. 213~215° was identified as that of 2-amino-4-ethylthiazole by infrared and ultraviolet spectra, and by mixed melting point.

In the place of (III), 3-bromo-1-hexyne (VII) was employed as the starting material. In this case, the reaction also progressed in the same way and finally picrates of 2-amino-4-methyl-5-propylthiazole (IX) and 2-amino-4-butylthiazole (X) were obtained.

The most probable reaction mechanism for the formation of (VI) and (X) could be considered as shown in Chart 1.

In the case of 2-bromo-3-octyne (XVI), in which the hydrogen of ethynyl group was replaced by an alkyl group, thiazole compound was not obtained under the same condition. This fact also supports the foregoing reaction mechanism because the substituent alkyl group is considered to weaken the electron-deficiency at C-1 in (XIII).

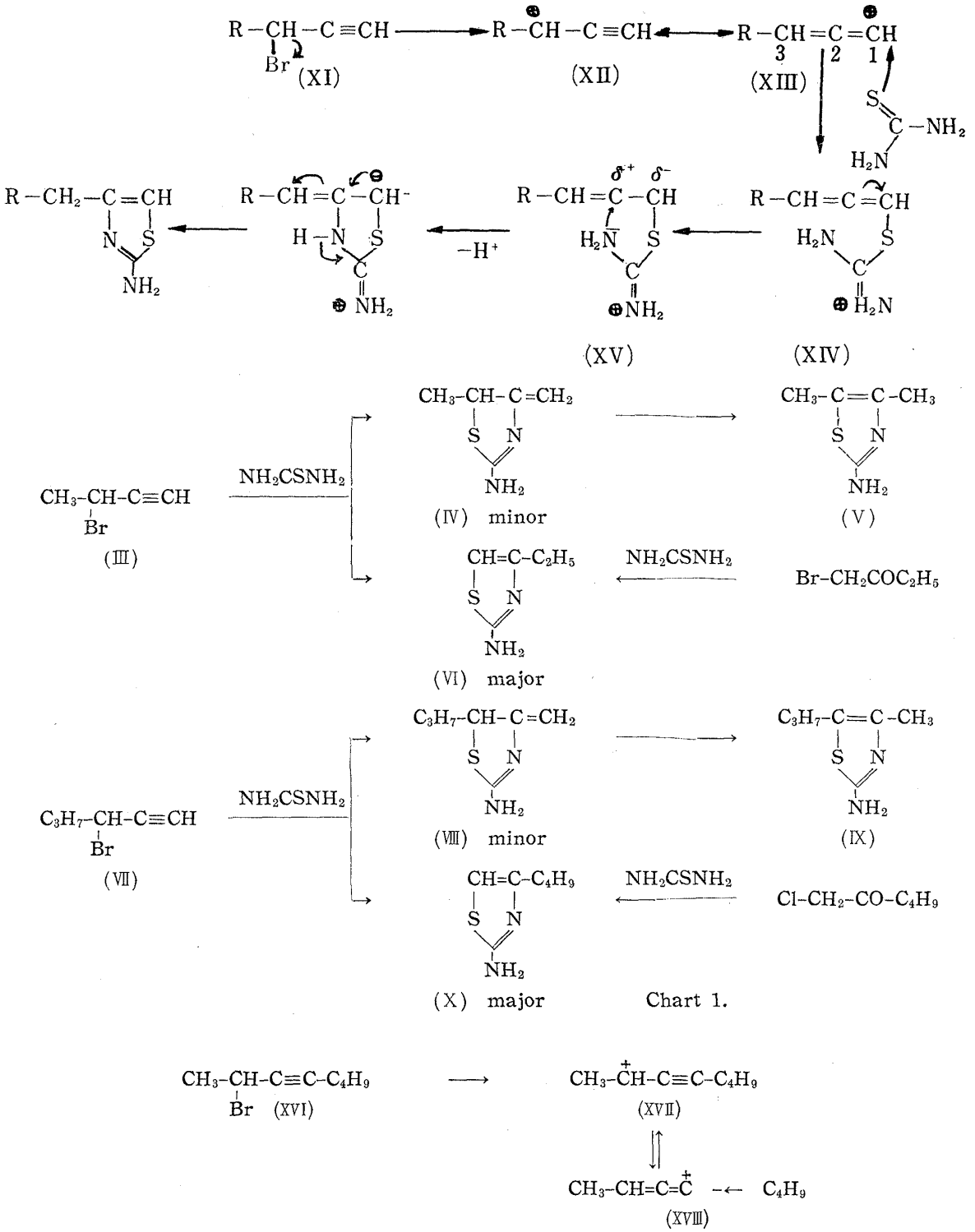


Chart 1.

Instead of thiourea, ammonium dithiocarbamate was reacted with 3-bromo-1-propyne and 3-bromo-1-phenyl-1-propyne (XXII) to gave 2-mercapto-4-methylthiazole (XX) and 2-mercapto-4-benzylthiazole (XXIII). These two thiazoles were converted into methylthio derivatives which were confirmed by comparing with authentic samples.

When guanidine was reacted with 3-bromo-1-propyne, 2-amino-4-methylimidazole (XXV) was obtained under the same reaction conditions. This compound is not obtained from bromoacetone and guanidine. It is very interesting that the imidazole ring can be synthesized by this ring closure reaction.

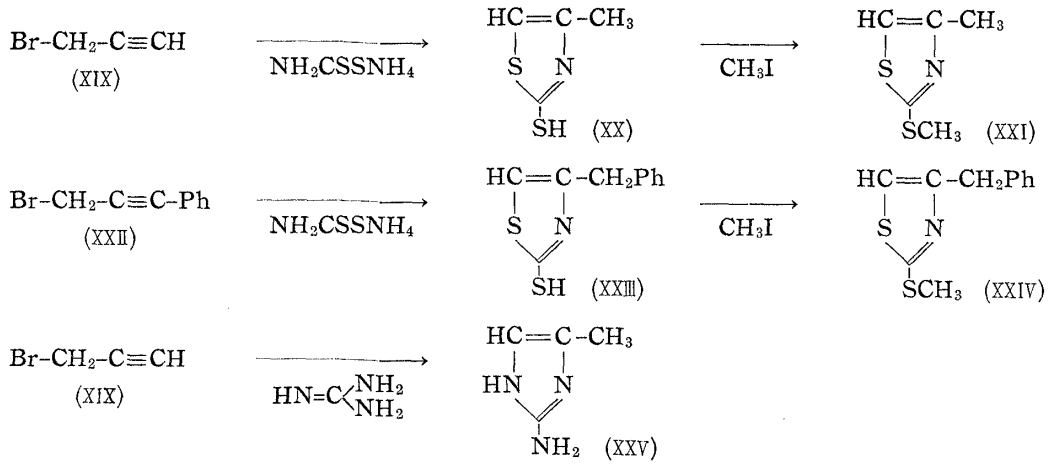
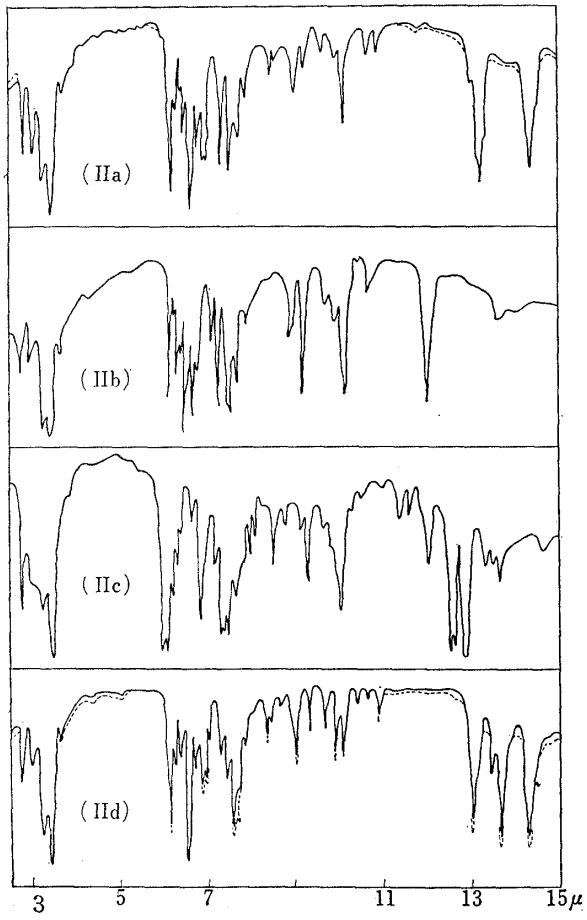
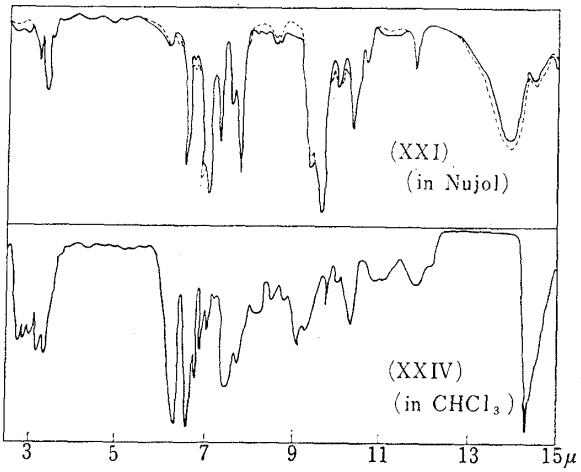


Chart 2.



← Fig. 1. Infrared spectra of Thiazoles (in Nujol)
—— New synthesized compounds.
····· Authentic samples.

↓ Fig. 2. Infrared spectra
—— New synthesized compounds.
····· Authentic samples.



Experimental

3-Chloro-1,3-diphenyl-1-propyne——This new compound was obtained by the method of Levy and Cope.[2] To the solution of 28 g. of 1,3-diphenyl-1-propyne-2-ol in a mixture of 2.5 g. of dehyd. pyridine and 30 cc. of dehyd. Et_2O, freshly distilled PCl_3 (6.13 g.) was gentlely added at 2° to −2°. After the ice-salt bath was removed, stirring was continued until the mixture warmed to the room temperature and allowed to stand at this temperature fro 6 hr. It was poured into ice-water and

2) H. Levy, A. Cope : J. Am. Chem. Soc., **66**, 1687 (1944).

the separated Et_2O layer was washed with H_2O, satd. $NaHCO_3$, and H_2O. The Et_2O solution was dried over Na_2SO_4 and evaporated in N_2 atmosphere and with a trace of hydroquinone. Distillation of the residue gave 1-chloro-1,3-diphenyl-2-propyne as a mobile pale yellow liquid, b.p. 90~100/8.5×10^{-4} mm. Yield, 25 g. (82%). *Anal.* Calcd. for $C_{15}H_{11}Cl$: C, 79.52; H, 4.85. Found: C, 78.91; H, 4.74. IR: λ_{max}^{liquid} 4.49 μ.

3-(*p*-Chlorophenyl)-1-propyne-3-ol——To 200 cc. of liquid NH_3 8.2 g. of metallic Na was added in small pieces 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 were was washed successively with H_2O, satd. aq. $NaHSO_3$, dil. H_2SO_4, and H_2O, and dried over Na_2SO_4. The solvent was evaporated. The residue was distilled in a reduced pressure. $b.p_{0.3}$ 75~76°. Yield, 36.4 g. (61.4%). *Anal.* Calcd. for C_9H_7OCl: C, 64.86: H, 4.20. Found: C, 64.50; H, 4.29. IR λ_{max}^{liquid} μ: 2.9 (-OH), 2.99 (-C≡CH), 4.7 (-C≡C-).

3-Chloro-3-(*p*-chlorophenyl)-1-propyne (Ib)——A solution of 36.4 g. of 3-(*p*-chlorophenyl)-1-propyne-3-ol in a mixture of 4.5 g. of dehyd. pyridine and 50 cc. of dehyd. Et_2O was treated with PCl_3 (11 g.) as described above. 3-Chloro-3-(*p*-chlorophenyl)-1-propyne was purified by distillation. $b.p_{0.15}$ 55°. Yield, 20 g. (48%). *Anal.* Calcd. for $C_9H_6Cl_2$: C, 58.37; H, 3.24. Found: C, 58.03; H, 3.43. IR λ_{max}^{liquid} μ: 2.97, 4.67.

3-Chloro-3-(1-naphthyl)-1-propyne (Ic)——This compound was prepared from 30 g. of 3-(1-naphthyl)-1-propyne-3-ol, 3.67 g. of pyridine, and 8.94 g. of PCl_3 by the same procedure as above. $b.p_{0.1}$ 90°. Yield, 83.3%. *Anal.* Calcd. for $C_{13}H_9Cl$: C, 77.80; H, 4.48. Found: C, 77.45; H, 4.36. IR λ_{max}^{liquid} μ: 2.97, 4.65.

2-Amino-4-methyl-5-phenylthiazole (IIa) from 3-Chloro-3-phenyl-1-propyne (Ia)——To a mixture of 3 g. of thiourea and 10 cc. of EtOH (99%) 5 g. of 3-chloro-3-phenyl-1-propyne was added dropwise and the mixture was heated on a water bath for 2 hr. After EtOH was evaporated *in vacuo*, the residue was treated with H_2O and NaOH, and dissolved in Et_2O. Et_2O was evaporated and a product was obtained in a solid state. It was recrystallised from benzene to colorless needles, m.p. 163°, which showed no depression on admixture with the authentic sample of m.p. 162~162.5°, prepared by the method of Wilson and Woodger.[3] Yield, 4g. (63.2%). *Anal.* Calcd. for $C_{10}H_{10}N_2S$: C, 63.28; H, 5.23; N, 14.66. Found: C, 63.39; H, 5.11; N, 14.63. UV λ_{max}^{EtOH} 295 mμ (log ε 4.09).

2-Amino-4-methyl-5-(*p*-chlorophyl)thiazole (IIb) from 3-Chloro-3-(*p*-chlorophenyl)-1-propyne (Ib)——A mixture of 4.5 g. of 3-chloro-3-(*p*-chlorophenyl)-1-propyne 2.7 g. of thiourea, and 7 cc. of EtOH (99%) was heated for 2 hr. The residue partly solidified on standing at room temperature. The solid was separated by filtration and recrystallized from benzene to colorless needles, m.p. 188.5~189°. Yield, 1.5 g. (45.5%). *Anal.* Calcd. for $C_{10}H_9N_2SCl$: C, 53.45; H, 4.02; N, 12.50. Found: C, 53.51; H, 4.00; N, 12.21. UV λ_{max}^{EtOH} 340 mμ: (log ε 4.17).

2-Amino-4-methyl-5-(1-naphyl)thiazole (IIc) from 3-Chloro-3-(1-naphthyl)-1-propyne (Ic)——A mixture of 5 g. of 3-chloro-3-(1-naphthyl)-1-proypyne, 2.8 g. of thiourea, and 10 cc. of EtOH (99%) was reacted as mentioned to give 2-amino-4-methyl-5-(1-naphthyl)thiazole as colorless needles, m.p. 160~161°. Yield, 2.2g. *Anal.* Calcd. for $C_{14}H_{12}N_2S$: C, 70.00; H, 5.00; N, 11.66. Found: C, 70.45; H, 4.97; N, 11.87. UV λ_{max}^{EtOH} mμ (log ε): 224.6 (4.55), 260.0 (3.94), 316.0 (4.02).

2-Amino-4-benzyl-5-phenylthiazole (IIb) from 3-Chloro-1,3-diphenyl-1-propyne (Id)——A mixture of 5 g. of 3-chloro-1,3-diphenyl-1-propyne, 2.5 g. of thiourea, and 20 cc. of EtOH (99%) was heated for 1.5 hr. and EtOH was evaporated in a reduced pressure. The residue was treated with H_2O and aq. NaOH, and extracted with Et_2O. By evaporation of Et_2O, a crude product was obtained in a solid state. The solid was treated with a mixture of benzene and hexane to give a crystalline of 2-amino-4-benzyl-5-phenylthiazole (5 g.), which was recrystallized from benzene to colorless needles, m.p. 137.5~139°, showing no depression on admixture with authentic sample of m.p. 137~138.5°, prepared from α-bromo-dibenzylketone and thiourea according to the method of Smith and Wilson.[4]. Yield, 5 g. (87%). *Anal.* Calcd. for $C_{16}H_{14}N_2S$: C, 72.18; H, 5.26; N, 10.52. Found: C, 72.46; H, 5.08; N, 10.64. UV: λ_{max}^{EtOH} 293.6 mμ (log ε 4.05).

2-Amino-4,5-dimethylthiazole (V) and 2-amino-4-ethylthiazole (VI) from 3-bromo-1-butyne (III)——A mixture of 5 g. 3-bromo-1-butyne, 4.3 g. of thiourea, and 15 cc. of EtOH was heated for 2 hr. and treated as for 2-amino-4-benzyl-5-phenylthiazole (IId). Distillation of the crude product gave a pale yellow oil, $b.p_{1.8\sim2.0}$ 85~90°. Yield, 37.4% *Anal.* Calcd. for $C_5H_8N_2S$: C, 46.87; H, 6.25; N, 21.85. Found: C, 47.15 H, 6.35; N, 21.09. UV: λ_{max}^{EtOH} 255 mμ (log ε 3.69).

3) W. Wilson, R. Woodger: J. Chem. Soc., **1955**, 2943.
4) A.C.B. Smith, W. Wilson: *Ibid.* **1955**, 1344.

The oil was dissolved in conc. H_2SO_4 under ice-cooling and regenerated by NaOH solution. It was converted into its picrate. Fractional crystallization of the picrate from EtOH gave yellow prisms, m.p. 248°, and an other picrate of m.p. 213~215°(from EtOH) was obtained from its mother liquor. The former showed no depression of m.p. on admixture with an authentic sample of 2-amino-4,5-dimethylthiazole, m.p. 248°, prepared from 1-bromoethyl methyl ketone and thiourea according to the method of Maeda,[5] and infrared spectra of the two picrates were identical. The latter picrate of m.p. 213~215° was identified by mixed m.p. as 2-amino-4-ethylthiazole of m.p. 214~215°, prepared from bromomethyl ethyl ketone and thiourea, and infrared spectra of these picrates were identical.

2-Amino-4-methyl-5-propylthiazole (IX) and 2-Amino-4-butylthiazole (X) from 3-Bromo-1-hexyne (VII)——3-Bromo-1-hexyne (6.3 g.) was heated with 5 g. of thiourea in 10 cc. of 99% EtOH for 2 hr. The reaction mixture was treated as above and the residue (2.4 g.) was distilled in a reduced pressure, $b.p_{0.06}$ 85~90°. Yield, 2.4 g. *Anal.* Calcd. for $C_7H_{12}N_2S$: C, 53.84; H, 7.69; N, 17.94. Found: C, 53.62; H, 7.99; N, 18.03. UV: λ_{max}^{EtOH} 255.3 mμ (log ε 3.658).

The distillate was divided into two parts, one part was added to EtOH solution of picric acid, and the precipitated picrate was recrystallized from EtOH to yellow plates, m.p. 180~182°, which showed no depression on admixture with an authentic sample of 2-amino-4-butylthiazole of m.p. 180~182°, prepared from 1-chloro-2-hexanone and thiourea, and IR spectra of the two picrates were identical.

The other part was dissolved in conc. H_2SO_4 and poured on crushed ice. The product was recrystallized from EtOH to yellow needles, m.p. 213~214°, which was not depressed when admixed with an authentic sample of 2-amino-4- methyl-5-propylthiazole, m.p. 214~215°, prepared from 3-bromo-2-hexaone and thiourea according to the method of Ganapathi *et al.*,[6] and infrared spectra of both picrates coincided with each other.

2-Methylmercapto-4-methylthiazole (XXI) from 3-Bromo-1-propyne (XIX) and Ammonium Dithiocarbamate——To a mixture of 10 g. of ammonium dithiocarbamate and 40 cc. of dehyd. EtOH 10 g. of 3-bromo-1-propyne was added dropwise with cooling. The mixture was heated under gentle boilng on a water bath for 1 hr. After cooling, NH_4Br was removed by filtration the precipitate was washed with dehyd. EtOH and the combined EtOH solution was evaporated. The residue (8 g.) was dissolved in EtOH (20 cc.) and after 8 g. of CH_3I was added, mixture was stirred for 5 hr. at room temperature. After EtOH was evaporated *in vacuo*, the residue was treated with NaOH solution and extracted with Et_2O to give a basic oily product which distilled at 68°/3 mm. Yield, 1.3 g. UV: λ_{max}^{EtOH} 276.3 mμ (log ε 3.847).

The picrate was recrystallized from AcOEt to a sample of m.p. 123~124°, undepressed on admixture with an authentic sample of m.p. 123~124°, prepared from monochloroacetone and ammonium dithiocarbamate according to the method of Buchman, *et al.*[7] *Anal.* Calcd. for $C_5H_7NS_2 \cdot C_6H_3O_7N_3$: C, 40.35; H, 3.03; N, 17.12. Found: C, 40.55; H, 3.23; N, 17.09.

2-Methylthio-4-benzylthiazole (XXIV) from 3-Bromo-1-phenyl-1-propyne(XXII)——To a mixture of 4 g. of ammonium dithiocarbamate and 20 cc. of dehyd. EtOH 7.1 g. of 2-bromo-1-propyne was dropwise and the mixture was heated on a water bath at 85° for 45 min. After NH_4Br was filtered off, the filtrate was treated with CH_3I 2.6 g for 48 hr. at room temperature. By the same procedure as for (XXI), pale yellow oil $b.p_{0.08}$ 120~125. UV λ_{max}^{EtOH} mμ (log ε): 257 (3.880), 368.5 (3.889).

The picrate was recrystallized from EtOH to yellow needles, m.p. 201°. *Anal.* Calcd. for $C_{11}H_{11}NS_2 \cdot C_6H_3O_7N_3$: C, 45.35; H, 3.11; N, 24.88. Found: C, 45.10; H, 3.03; N, 24.59.

2-Amino-4-methylimidazole (XXV) from 3-Bromo-1-propyne (XIX) and Guanidine——To a solution of 4 g. of guanidine in 10 cc. of dehyd. EtOH 5 g. of 3-bromo-1-propyne was added dropwise with cooling and the mixture was heated under gentle reflux for 15 hr. After EtOH was evaporation *in vacuo*, the residue was treated with 5% NaOH solution. Extraction with Et_2O and evaporation gave a viscous oil. The picrate of the oil was recrystallized from EtOH to yellow micro needles, m.p. 185~187°, undepressed on admixture with an authentic sample of m.p. 186~187°, prepared according to the method of Burtles and Pyman,[8] and infrared spectra of the two picrates were identical. *Anal.* Calcd. for $C_4H_7N_3 \cdot C_6H_3O_7N_3$: C, 36.80; H, 3.07; N, 34.35. Found: C, 36.84; H, 3.03; N, 34.72.

The auther wishes to express his appreciation for the kindness shown by Prof. Dr. K. Tsuda of Tokyo University and Mr. M. Matsui, Director of this Laboratory, and gratefully acknowledge kind guidance of Dr. I. Iwai and the technical cooperation of Mr. J. Ide. The author also wishes to thank Mrs. O. Amakasu and Mr. N. Higosaki for the mesurement of infrared and ultraviolet spectra.

5) R. Maeda: Yakugaku Zasshi, **78**, 91 (1958).
6) K. Ganapathi, M.V. Shirsat, C.V. Delimala: Proc. Indian. Acad. Sci., **14A**, 630 (1941). (C.A., **36**, 4102 (1942)).
7) E.R. Buchman, A.U. Reims, H. Sargent: J. Org. Chem., **6**, 764 (1941).
8) R. Burtles, F.L. Pyman: J. Chem. Soc., **127**, 2012 (1925).

Summary

It was found that the compounds having the general formula RCH(X)-C≡C-R′ gave thiazole derivatives by reaction with thiourea. The relationship between the structure of thiazoles and substituent groups was clarified as follows: (1) When R=R′=Ph, 2-amino-4-benzyl-5-phenylthiazole (IId) is obtained, (2) When R=alkyl, R′=H, two kinds of thiazoles are obtained; and (3) when R=R′=alkyl, thiazole derivative is not obtained.

Similarly, propargyl bromide and phenylpropargyl bromide, when reacted with ammonium dithiocarbamate, afforded 2-mercapto-4-methylthiazole (XX) and 2-mercapto-4-benzylthiazole (XXIII), respectively. Further, 2-amino-4-methylimidazole (XXV) was obtained from guanidine and propargyl bromide.

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UDC 547.92.07

61. Hiromu Mori: Studies on Steroidal Compounds. VI. Grignard Reaction of 19-Nor-4-en-3-oxo-steroids.[1]

(*Research Laboratory, Teikoku Hormone Mfg. Co., Ltd.*[*1])

In the Grignard reaction of cholest-4-en-3-one, 1,2-addition product, 3-methylcholest-4-en-3-ol (I) has been produced even in the presence of cuprous chloride, which is known as a reagent promoting 1,4-addition,[2] and not 1,4-addition product.[3] On the other hand, in the case of 4,6-dien-3-oxo steroids (II) and 16-en-20-oxo steroids (V), 1,6- (III and IV) and 1,4-addition products (VI) have been obtained respectively.[4,5] These differences are considered to depend upon stereochemical factors. The difference of the Grignard reaction between 4-en-3-oxo-steroids and 19-nor-4-en-3-oxo-steroids is described.

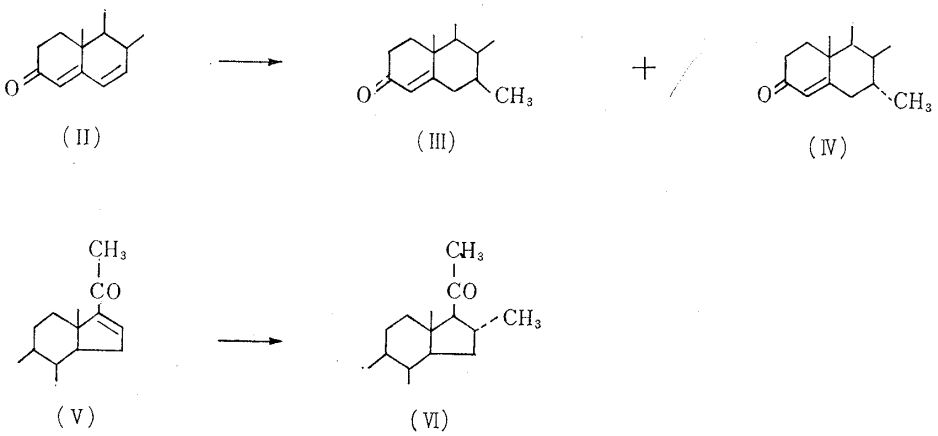

Chart 1.

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*1 1604, Shimosakunobe, Kawasaki-shi, Kanagawa-ken (森 弘).

1) Part V: Yakugaku Zasshi, in press.
2) M. S. Kharasch, O. Reinmuth: "Grignard Reactions," 219 (1954). Prentice-Hall, Inc., New York.
3) O. C. Musgrave: J. Chem. Soc., **1951**, 3121.
4) J. A. Campbell, J. C. Babcock: J. Am. Chem. Soc., **81**, 4069 (1959).
5) R. E. Marker, H. M. Crooks: *Ibid.*, **64**, 1280 (1942).