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145. Haruo Saikachi*1 and Shoichiro Tagami*2 : Studies on Compounds related to Pyrazine. III.[1] Synthesis of 2-Substituted Thiazolo[*b*]quinoxaline.

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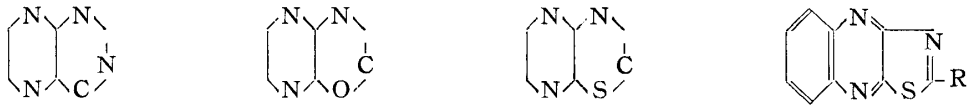
Oxazolo[*b*]quinoxaline had been synthesized, as reported in the preceding paper,[2] in order to examine growth inhibition of microörganisms by similarity in chemical structure, by synthesis of structural units (B) analogous to the structural unit (A) of isoalloxazine ring in folic acid, purine, and riboflavin, which are requisite substances in normal metabolic function of microörganisms. For the same purpose, thiazolo[*b*]quinoxaline (I) was prepared as a substance similar to structural unit (C).



(A) (B) (C) (I)

Condensation of *o*-phenylenediamine and oxalic acid or diethyl oxalate and heating of its product, 2,3-dihydroxyquinoxaline, with phosphorus pentachloride easily afforded the chlorinated product, 2,3-dichloroquinoxaline (II). Amination of (II) afforded, according to reaction conditions, 2-amino-3-chloroquinoxaline (III), 2,3-diaminoquinoxaline (IV), or their mixture.

Haworth[3] obtained (III) in a good yield by refluxing (II) with saturated alcoholic ammonia solution but this was found in the present case to result in recovery of the starting material. Consequently, various conditions were examined for this reaction and it was found that (III) is not obtained at all above 130°, the product being solely (IV), and that ethanol is better than water as a solvent. By heating (II) with ethanolic ammonia in an autoclave at 70~80° for 9 hours, (III) was obtained in 70% yield, and the result of these experiments is summarized in Table II.

2-Amino-3-chloroquinoxaline (III) so obtained was heated with excess of ethanolic potassium hydrogensulfide in an autoclave for 5 hours at 140~150° and 2-amino-3-mercaptoquinoxaline (VIII) was obtained. The isothiouronium salt[4] (VI) obtained by reaction of (III) and thiourea was boiled with 10% sodium hydroxide solution to obtain (VIII) but no reaction took place and decomposition occurred only when (VI) was boiled with 20% sodium hydroxide solution to give (VIII) in a good yield. (VIII) was also obtained by heating 2-amino-3-hydroxyquinoxaline (V), obtained by boiling 2,3-diaminoquinoxaline (IV) with hydro-

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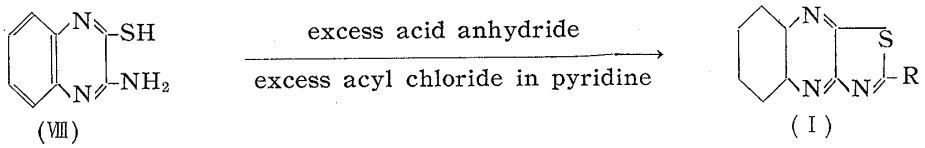
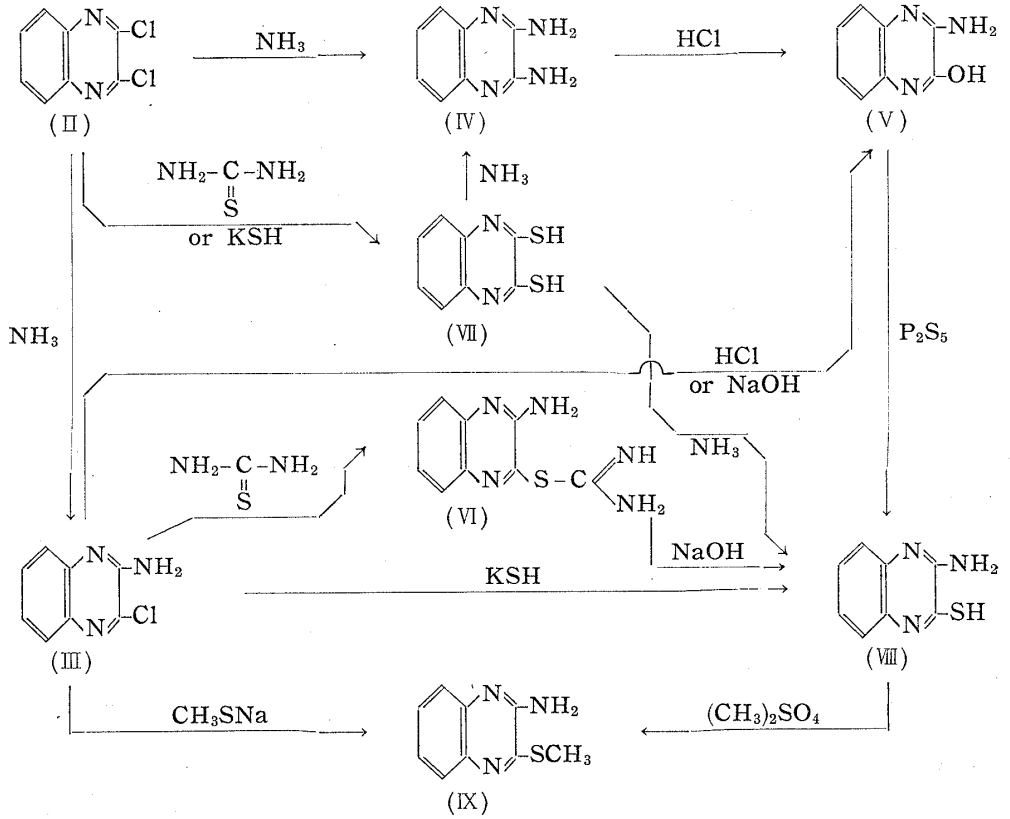
1) Part II. D. Shiho, S. Tagami : J. Am. Chem. Soc., **82**, 4044 (1960).
2) Part I. *Idem* : This Bulletin, **6**, 45 (1957).
3) R. D. Haworth, S. Robinson : J. Chem. Soc., **1948**, 777.
4) F. J. Wolf, R. M. Wilson, M. Tischler : J. Am. Chem. Soc., **76**, 4483 (1954).

chloric acid or (III) with hydrochloric acid or sodium hydroxide, with phosphorus pentasulfide in xylene. It was also obtained by reaction of (II) with potassium hydrogensulfide or thiourea and heating its product, 2,3-dimercaptoquinoxaline[5] (VII), with alcoholic ammonia solution. In this case, the reaction was carried out as in amination of (II) but majority of the starting material was recovered when heated at 70~80° and (VIII) was obtained in 64% yield when heated at 100~120°. (VIII) obtained by any of these reactions had a high melting point and easily underwent decomposition. Therefore, it was methylated with dimethyl sulfate and was identified with 2-amino-3-methylthioquinoxaline (IX) by admixture. (IX) was also obtained by the reaction of (III) and sodium methanethioxide. On boiling (IX) with 10% hydrochloric acid, only the methylthio group underwent hydrolysis to form (V).



(VIII) (I)

To obtain (I) from (VIII), its boiling with formic anhydride, organic acids, or ortho esters for a long period was carried out but all ended in recovery of the starting material. By boiling with acid anhydride, the desired 2-substituted thiazoloquinoxaline was finally prepared. (I) was also obtained by heating (VIII) with acid chloride alone or boiling with it in pyridine. In this case, the product became resinous when the substituent R was an aliphatic group, or when heated with *p*-chlorobenzoyl, 2,3-dimethoxybenzoyl, or cinnamoyl chloride. Ultraviolet absorption curves of thiazolo[*b*]quinoxaline was very similar to that of oxazolo[*b*]quinoxaline reported in the preceding paper.[2]

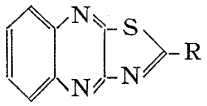


(II) (IV) (V) (VII) (VI) (III) (VIII) (IX)

Chart 1.

5) K. Asano: Yakugaku Zasshi, **78**, 729 (1958).

Table I.



R	Preparative method	Yield[a] (%)	m.p.[b] (°C)	Appearance	Formula	Analysis (%) Calcd. C	Calcd. H	Found C	Found H
CH_3	A	85	141	Orange needles	$C_{10}H_7N_3S$	59.68	3.51	60.02	3.80
C_2H_5	A	55.6	157	Pale yellow needles	$C_{11}H_9N_3S$	61.38	4.21	61.09	4.27
C_3H_7	A	47.6	66	〃	$C_{12}H_{11}N_3S$	62.85	4.84	62.76	4.83
C_6H_5	B	50	189	Yellow needles	$C_{15}H_9N_3S$	68.35	3.44	68.90	3.75
(*m*)-NO_2-C_6H_4	B	40	321	Pale yellow needles	$C_{15}H_8O_2N_4S$	58.43	2.62	58.22	2.62
(*p*)-NO_2-C_6H_4	B	58.4	234	〃	$C_{15}H_8O_2N_4S$	58.43	2.62	58.56	2.67

a) Yield calculated as crude product.
b) All melting points are uncorrected.

Experimental

2-Amino-3-chloroquinoxaline (III)——A mixture of 2,3-dichloroquinoxaline (2 g.) and EtOH (10 cc.), saturated with NH_3 at 0°, was heated in an autoclave at 70~80° for 9 hr. Most of EtOH was evaporated, the residue was diluted with H_2O, the precipitate was collected, dried, and extracted with Et_2O in a Soxhlet apparatus. The extract was saturated with HCl and the precipitated hydrochloride was collected, dissolved in H_2O, and basified. 2-Amino-3-chloroquinoxaline (1.27 g.) crystallized from hydr. EtOH in colorless needles, m.p. 139°.

These experimental examples are illustrated in Table II.

Table II. Reaction of 2,3-Dichloroquinoxaline with NH_3

2,3-Dichloroquinoxaline (g.)	Solvent[a] (cc.)	Temp. (°C)	Time of heating (hr.)	Yield[b] of 2-amino-3-chloroquinoxaline (%)
5.8	H_2O(25)	130	9	0[c]
5.8	H_2O(25)	100	9	trace[c]
5	EtOH(25)	120	5	33
2	EtOH(8)	reflux	20	0[d]
2	EtOH(10)	90~100	9	35.3
2	EtOH(10)	80~ 90	9	60.6
2	EtOH(10)	70~ 80	9	70.0

a) All solvents were saturated with NH_3 at 0°.
b) Yield calculated as a crude product.
c) Main product was 2,3-diaminoquinoxaline.
d) Unchanged 2,3-dichloroquinoxaline was recovered.

2-Amino-3-hydroxyquinoxaline (V)——a) From 2-Amino-3-chloroquinoxaline: The chloroamine (0.5 g.) in EtOH (7 cc.) was treated with 20% KOH (5 cc.) and the mixture was refluxed for 5 hr. The mixture was cooled and acidified to litmus with dil. HCl. The precipitated solid was collected (dry weight, 0.35 g.) and identified as 2-amino-3-hydroxyquinoxaline by conversion into 2-amino-3-methoxyquinoxaline which separated as white micro-crystals (from pyridine), m.p. 270°, alone or when mixed with an authentic specimen.

b) From 2-Amino-3-methylthioquinoxaline: A mixture of the methylthio-amine (0.33 g.) and 10% HCl (10 cc.) was heated on a water bath for 2 hr., cooled, filtered, and neutralized with 10% Na_2CO_3. The precipitated solid (dry weight, 0.3 g.) was identified as 2-amino-3-hydroxyquinoxaline by conversion into 2-amino-3-methoxyquinoxaline.

2-Amino-3-mercaptoquinoxaline (VIII)——a) A mixture of 2-amino-3-chloroquinoxaline (1.05 g.) and KSH (0.72 g.) in MeOH (5 cc.) was heated in an autoclave at 150° for 5 hr. Most of MeOH was evaporated, the precipitate was dissolved in 5% NaOH, and acidified with AcOH. The separated solid was crystallized from MeOH to yellow needles (0.1 g.). *Anal.* Calcd. for $C_8H_7N_3S$: C, 54.23; H, 3.98. Found: C, 53.85; H, 4.32.

b) A mixture of 2-amino-3-hydroxyquinoxaline (2 g.) and P_2S_5 (5 g.) in xylene was refluxed in an oil bath for 20 min. with stirring, cooled, and filtered. The filter cake was washed with a small amount of benzene, dried, dissolved in 5% NaOH, decolorized with charcoal, and neutralized with AcOH. The yellow precipitate was extracted with AcOEt. The extract was heated with charcoal, filtered,

and the filtrate was concentrated to dryness. The crude product was recrystallized from MeOH to pale yellow needles. Yield, 0.47 g.

c) A solution of 2-amino-3-chloroquinoxaline (0.54 g.) and thiourea (0.3 g.) in EtOH (4 cc.) was refluxed for 20 min. When cooled, crystalline crude isothiouronium hydrochloride separated; m.p. above 300°. Yield, 0.7 g.

A mixture of the crude isothiouronium hydrochloride (0.6 g.) and 20% NaOH (20 cc.) was refluxed for 40 min. The yellow solution was cooled, acidified with AcOH, and the product was separated. Yield, 0.34 g.

d) A mixture of 2,3-dimercaptoquinoxaline (2 g.) and EtOH (20 cc.), saturated with NH_3 at 20°, was heated in an autoclave at 100~120°. Most of EtOH was evaporated, the precipitate was collected, and extracted with 10% NaOH. The insoluble fraction (0.5 g.) recrystallized from pyridine was 2,3-diaminoquinoxaline. The extract was neutralized with AcOH and the precipitate was collected. Yield, 1.15 g.

2-Amino-3-methylthioquinoxaline (IX)——a) From 2-Amino-3-mercaptoquinoxaline: The mercapto-amine (0.5 g.), obtained as above, was dissolved in 5% NaOH (75 cc.), the solution was filtered, and cooled in ice. Me_2SO_4 (1 cc.) was added in small portions with occasional shaking during 30~40 min. A precipitate formed and, after standing for 1 hr. in an ice bath, the reaction mixture was filtered and the precipitate was washed with H_2O. The crude product was recrystallized from hydr. pyridine to pale yellow needles, m.p. 170°. *Anal.* Calcd. for $C_9H_9N_3S$: C, 56.51; H, 4.74. Found: C, 56.44; H, 5.10.

b) From 2-Amino-3-chloroquinoxaline: A mixture of 2-amino-3-chloroquinoxaline (0.64 g.) and MeSNa, prepared by saturating MeSH in a mixture of powdered Na (0.16 g.) and benzene (15 cc.), was heated at 60~80° for 10 hr. with stirring. Most of benzene was evaporated, the residue was triturated with H_2O, and the crude product was collected, dried, and recrystallized from hydr. pyridine to pale yellow needles, which melted at 170°, alone and on admixture with an authentic sample prepared as in (a).

Preparation of Thiazolo[*b*]quinoxaline——The following examples illustrate a general method.

a) Reaction of the Mercapto-amine with Acid Anhydride: 2-Amino-3-mercaptoquinoxaline (0.00226 mole) was refluxed for 4 hr. with Ac_2O (5 cc.). Most of Ac_2O was evaporated, the residue was diluted with H_2O, and the precipitate was collected, washed with 5% NaOH to remove any unchanged quinoxaline, and dried. The crude product was recrystallized from hydr. MeOH.

b) Reaction of the Mercapto-amine with Acyl Halide: 2-Amino-3-mercaptoquinoxaline (0.00226 mole) was boiled for 3 hr. with BzCl (0.017 mole) in pyridine (5 cc.). The precipitate was collected, washed with EtOH and 5% NaOH, and recrystallized from hydr. pyridine.

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Summary

2-Amino-3-mercaptoquinoxaline was prepared by the reaction of 2-amino-3-chloroquinoxaline with thiourea or potassium hydrogensulfide, 2-amino-3-hydroxyquinoxaline with phosphorus pentasulfide, or 2,3-dimercaptoquinoxaline with ammonia. 2-Substituted thiazolo[*b*]quinoxaline was prepared by boiling 2-amino-3-mercaptoquinoxaline with excess of acid anhydride or by heating with excess of acid chloride in pyridine.

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