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11. Den-itsu Shiho and Shoichiro Tagami : Studies on Compounds related to Pyrazine. I. Synthesis of 2-Substituted Oxazolo[*b*]quinoxaline.

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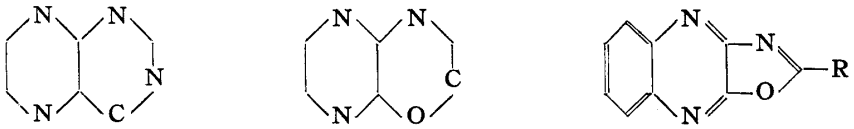
In recent years, numerous examples of growth inhibition of microörganisms by chemicals analogous to their essential nutrient have been reported. Structural unit (A) is found in the isoalloxazine ring of riboflavin, in the pterin structure of folic acid, and in purines, which are indispensable for normal metabolic functions. In the anticipation that antagonism of normal metabolism of microörganisms may appear in compounds with a structural unit (B), which is not found in nature, similar to (A), attempt was made for its synthesis.



(A) (B) (I)

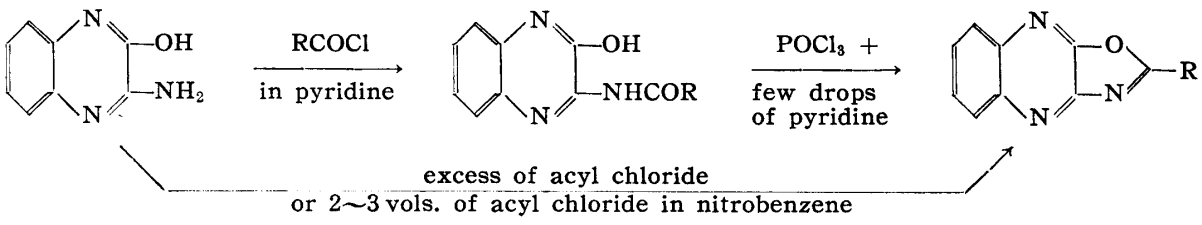
One of the ring systems selected for this study is oxazolo[*b*]quinoxaline (I) whose preparation is described below.

The starting material, 2-amino-3-quinoxalinol, was prepared by the method of Stevens,[1] by boiling 2,3-diaminoquinoxaline with dilute hydrochloric acid. 2,3-Diaminoquinoxaline was synthesized by Hinsberg's method,[2] by saturating cold dicyan in methanol solution of *o*-phenylenediamine. However, this method proved impractical, the yield being no more than 40% of a dark brown substance. By carrying out the reaction with addition of a small amount of sodium methoxide in methanol pale yellow brown crystals of comparatively high purity were obtained in about 80% yield. The polymerisation of dicyan during its bonding with *o*-phenylenediamine to brown black paracyan seems to be prevented in dilute methanol solution of sodium methoxide and the addition reaction occurs smoothly.

Monoacyl derivatives of 2-amino-3-quinoxalinol could not be obtained by boiling with acetic anhydride. They were obtained by heating on a water bath with acyl chloride in pyridine. 2-Substituted oxazolo[*b*]quinoxaline is prepared from 2-acylamino-3-quinoxalinol which, on heating with phosphoryl chloride at 100°, cyclized to oxazolo[*b*]quinoxaline ring through the free hydroxyl group.

Attempts to prepare 2-methyloxazolo[*b*]quinoxaline failed either by heating aminoquinoxalinol with glacial acetic acid in the presence of sodium acetate, with acetic anhydride with a few drops of concentrated sulfric acid under reflux, or by heating a monoacetyl derivative with phosphoryl chloride.

Attempts to prepare several kinds of oxazoles by the action of acyl chloride on the aminoquinoxalinol were successful, either by heating at 180~210° with excess of acyl



* Okuda, Toyama (志甫伝逸, 田上昇一郎).

1) L. R. Stevens : J. Am. Chem. Soc., **68**, 1035(1946).
2) Hinsberg : Ber., **36**, 4039(1903).

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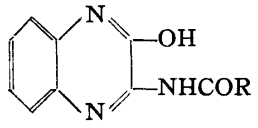
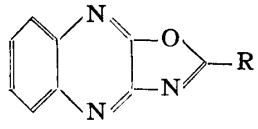
TABLE I.



No.	R	Yield (%)	m.p. (°C)	Appearance	Formula	Analyses (%) Calcd. C	Calcd. H	Found C	Found H
I	CH_3CO-	95	above 350	Colorless needles	$C_{10}H_9O_2N_3$	59.14	4.46	58.61	3.97
II	C_6H_5-	92	255	〃	$C_{15}H_{11}O_2N_3$	67.91	4.84	67.53	4.86
III	*m*-NO_2-C_6H_4-	89	272	Pale yellow needles	$C_{15}H_{10}O_4N_4$	58.05	3.17	58.31	2.95
IV	*p*-NO_2-C_6H_4-	88	288	〃	$C_{15}H_{10}O_4N_4$	58.05	3.17	58.20	3.09
V	*o*-Cl-C_6H_4-	85	230	Colorless needles	$C_{15}H_{10}O_2N_3Cl$	60.11	3.36	59.84	3.66
VI	*p*-Cl-C_6H_4-	80	281	〃	$C_{15}H_{10}O_2N_3Cl$	60.11	3.36	60.52	2.65

TABLE II.



No.	R	Preparative method	Yield (%)	m.p. (°C)	Appearance	Formula	Analyses (%) Calcd. C	Calcd. H	Found C	Found H
VII	C_6H_5-	A C	85 50	243	Colorless needles	$C_{15}H_9ON_3$	72.87	3.67	73.01	4.05
VIII	*m*-NO_2-C_6H_4-	A B	86 84	322	Pale yellow needles	$C_{15}H_8O_3N_4$	61.64	2.75	61.68	3.10
IX	*p*-NO_2-C_6H_4-	B	90	above 340	〃	$C_{15}H_8O_3N_4$	61.64	2.75	61.53	3.03
X	*o*-Cl-C_6H_4-	A	76	212	Colorless needles	$C_{15}H_8ON_3Cl$	63.95	2.86	63.94	2.89
XI	*p*-Cl-C_6H_4-	A	80	303	〃	$C_{15}H_8ON_3Cl$	63.95	2.86	64.03	3.16
XII	*p*-CH_3-C_6H_4-	B	75	254	〃	$C_{16}H_{11}ON_3$	73.55	4.24	73.27	5.54
XIII	2,3-$(CH_3O)_2$-C_6H_3-	B	82	262	Pale yellow needles	$C_{17}H_{13}O_3N_3$	66.44	4.26	66.35	4.50
XIV	C_6H_5CH=CH-	B	83	228	〃	$C_{18}H_{11}ON_3$	74.73	4.06	74.89	4.22

chloride or by boiling with 2～3 volumes of acyl chloride in nitrobenzene until no more hydrochloric acid evolved.

When R is aliphatic, e.g. methyl, ethyl, propyl, 2-R-oxazolo[*b*]quinoxaline was not obtained but were obtained when R is aromatic, e.g. phenyl, *m*-nitrophenyl, *p*-nitrophenyl, *o*-chlorophenyl, *p*-chlorophenyl, *p*-tolyl, and 2,3-dimethoxyphenyl.

To inquire into these circumstances we attempted to synthesize 2-benzyloxazolo[*b*]-quinoxaline, having an aliphatic methylene radical, and 2-styryloxazolo[*b*]quinoxaline, having an aliphatic vinylene radical. The former was not obtained, but the latter was and this problem is now under investigation.

Attempt to prepare the new heterocyclic rings by the condensation of 2-amino-3-quionoxalinol with thionyl chloride, potassium ethylxanthate, and urea was unsuccessful. Compounds containing oxadiazole ring was not obtained by the action of nitrous acid on 2-amino-3-quinoxalinol, but only 2,3-quinoxalinediol was obtained. Many of the compounds described in the present paper, though obtained in a pure state, resisted all attempts for crystallisation, evidently due to their high molecular complexity. In fact, many of them are scarcely soluble in any of organic solvents.

Finally, the ultraviolet absorption spectra of 2-benzamido-3- and 2-*o*-chlorobenzamido-3-quinoxalinol, reproduced in Fig. 1, exhibited the maximum absorption at 241 mμ. The spectra of 2-phenyl- and 2-*o*-chlorophenyl-oxazolo[*b*]quinoxaline, the cyclized products, exhibited the maximum at 272 aud 270 mμ, respectively.

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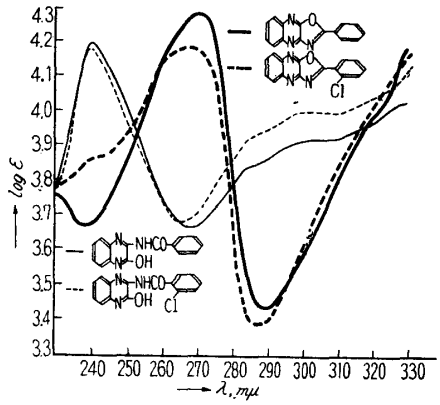

Fig. 1.

Ultraviolet Absorption Spectra
(in 95% EtOH)

The microanalyses were carried out by Miss T. Ishiguro of this faculty, to whom we are indebted.

Experimental

2,3-Diaminoquinoxaline—*o*-Phenylenediamine (10 g.) was added in MeOH solution of MeONa (0.5 g. Na in 100 cc. MeOH) and dicyan was added to the resulting solution under ice cooling until a saturated solution was obtained. The closed container was kept for 3 days while precipitation was formed. The mixture was filtered, the precipitate was washed with MeOH, and the separated solid was crystallised from pyridine to give 12 g. of 2,3-diaminoquinoxaline.

Acylation of 2-Amino-3-quinoxalinol—The following example illustrates a general method. BzCl (0.0065 mole) was added to cold pyridine (12 cc.), then 2-amino-3-quinoxalinol (0.005 mole) was added with stirring, and the mixture slowly heated on a steam bath. The reaction mixture was heated at 100° until most of the solid went into solution, the excess solvent was removed under a reduced pressure, and a small amount of water was added to the residue. The crude product obtained was recrystallized from hydrous EtOH.

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

(a) Well-powdered 2-amino-3-quinoxalinol (0.0025 mole) was boiled with BzCl (3 cc.) under reflux until a clear solution was obtained. The yellow precipitate was filtered, washed free from BzCl with ether, EtOH, and subsequently with 5% NaOH to remove any unchanged quinoxaline. The separated solid was crystallized from pyridine.

(b) 2-Amino-3-quinoxalinol (0.8 g., 0.005 mole) was boiled with *p*-nitrobenzoyl chloride (2.4 g., 0.013 mole) in nitrobenzene (20 cc.) until no more HCl evolved (for about 1 hr.). The precipitate was filtered, washed with EtOH, and 5% NaOH solution. The separated solid was crystallized from nitrobenzene.

(c) 2-Benzamido-3-quinoxalinol (0.005 mole) was heated gently with freshly distilled $POCl_3$ (7 cc.), with 7 drops of pyridine, in a dry atmosphere. The vigorous effervescence of HCl subsided after a few minutes, but heating was continued for about 1 hr. until red solution was obtained. Excess of $POCl_3$ was distilled off under a reduced pressure, the residue was cautiously decomposed with ice, and filtered. The crude product was washed with NH_3 aq. and crystallized from hydrous pyridine.

2,3-Quinoxalinediol from 2-Amino-3-quinoxalinol—2-Amino-3-quinoxalinol (0.4 g.) dissolved in 10% HCl (50 cc.) was treated with aq. $NaNO_2$ solution (0.3 g. in 2 cc.) at room temperature, and after 1 hr., the solution was heated at 90° with stirring. The precipitated solid was crystallized from 3% AcOH to colorles needles, m.p. above 350°, soluble in aq. alkali and ammonia.

Summary

2-Substituted oxazolo[*b*]quinoxaline with a new skeleton was synthesized by heating 2-amino-3-quinoxalinol with excess of acyl chlorides at 180~210°, by boiling with three volumes of acyl chlorides in nitrobenzene, or by heating 2-acylamino-3-quinoxalinol with phosphoryl chloride. When the 2-substituted radical of oxazolo[*b*]quinoxaline is aliphatic, 2-substituted oxazolo[*b*]quinoxaline was not obtained but the compounds formed when the substituents were aromatic radicals. This problem is now under investigation.

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