Synthesis of 3-(α-Chlorophenylhydrazono)heteroarylmethyl-2-oxo-1,2-dihydroquinoxalines with Antimicrobial Activity [1]

Yoshihisa Kurasawa*, Muneto Muramatsu, Kaoru Yamazaki,
Yoshihisa Okamoto and Atsushi Takada

School of Pharmaceutical Sciences, Kitasato University, Shirokane,
Minato-ku, Tokyo 108, Japan

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The reactions of 3-(α-chlorophenylhydrazono)hydrazinocarbonylmethyl-2-oxo-1,2-dihydroquinoxalines **4a,c** with triethyl orthoesters resulted in the intramolecular cyclization to give the 3-(α-chlorophenylhydrazono-1,3,4-oxadiazol-2-ylmethyl)-2-oxo-1,2-dihydroquinoxalines **5a-d**, but not the 1,2,4,5-tetrazepinylquinoxalines **6a-d**. The cyclization mode into the 1,3,4-oxadiazole ring was confirmed by the alternate syntheses of **5a,c** from the reactions of the 3-(1,3,4-oxadiazol-2-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxalines **7a,b** with *o*-chlorobenzenediazonium chloride. Moreover, the reactions of 3-(benzimidazol-2-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxaline hydrochloride **8** with *o*-, *m*- and *p*-chlorobenzenediazonium chlorides afforded the 3-(α-chlorophenylhydrazonobenzimidazol-2-ylmethyl)-2-oxo-1,2-dihydroquinoxaline hydrochlorides **9a-c**, respectively. Compounds **5a-d** and **9a-c** were found to exhibit antimicrobial activities.

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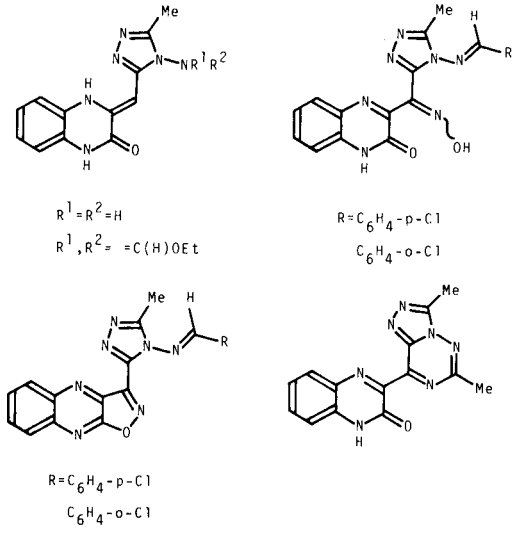
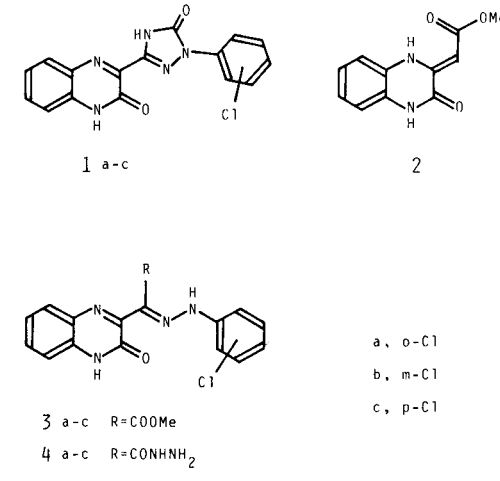
In previous papers, we reported the synthesis of various oxadiazoles [2-4] and triazoles [5-7] from the interest in their pharmacological activities as the bactericidal, fungicidal and herbicidal agents [3a,5a]. The azoles synthesized so far by us include the quinoxaline moiety in their molecules, and some of the representative compounds shown in Chart 1 have been found to exhibit the antifungal activity

Chart 1



against *Pathium debaryanum, Pyriclaria oryzae* and *Rhizoctonia solani* in 11-39%, 17-61% and 40-74% growth inhibition, respectively, at a concentration of 100 ppm [8]. In continuation of the above works, we synthesized 1-aryl-3-quinoxalinyl-1,2,4-triazoles **1a-c** from the ester **2** *via* the α-hydrazonoesters **3a-c** and α-hydrazonoacylhydrazides **4a-c** [9] (Chart 2) to carry out the screening test. As the

Chart 2

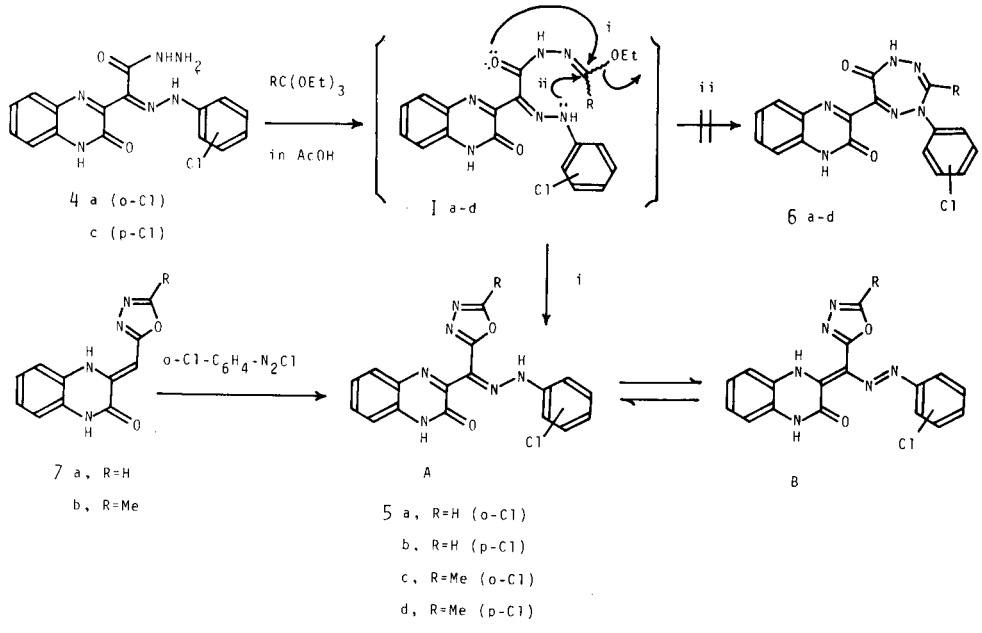


result, the 1-aryl-3-quinoxalinyl-1,2,4-triazoles **1a-c** did not show any growth inhibition activity against the above three kinds of fungi, but, unexpectedly, the α-hydrazonoesters **3a-c** were found to represent the 60-100% growth inhibition activity against *Pythium debaryanum* at a concentration of 100 ppm. These results suggested that the analogue of the α-hydrazono compounds **3a-c** would also have the antifungal activity. Accordingly, we undertook the conversion of the ester group of **3** into the heterocyclic moiety in order to search for the other fungicidal agents. This paper describes the synthesis of 3-(α-chlorophenylhydrazono)heteroarylmethyl-2-oxo-1,2-dihydroquinoxalines **5a-d** and **9a-c** and their antimicrobial activities.

Synthesis of 3-(α-Chlorophenylhydrazono-1,3,4-oxadiazol-2-ylmethyl)-2-oxo-1,2-dihydroquinoxalines **5a-d**.

The α-hydrazonoacylhydrazides **4a,c** are selected as

Scheme 1

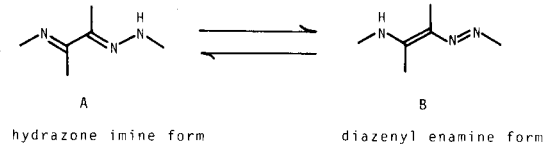


starting materials for the purpose of the construction of an additional heterocyclic ring in the molecule, since the acyl hydrazide moiety has been easily converted into the oxadiazole ring [3,10,11].

The reactions of **4a,c** with triethyl orthoesters (R = H, Me) would afford intermediates **Ia-d** [3] (Scheme 1), whose subsequent cyclizations provided a sole product. The pmr spectral data of these cyclization products in deuteriodimethylsulfoxide supported the structures of the 3-(α-chlorophenylhydrazono-1,3,4-oxadiazol-2-ylmethyl)-2-oxo-1,2-dihydroquinoxalines **5a-d**, but not the 1,2,4,5-tetrazepinylquinoxalines **6a-d**. Namely, the spectra of **5a-d** exhibited the tautomeric equilibria between the hydrazone imine form **A** and the diazenyl enamine form **B** (Scheme 2) [12]. The hydrazone NH (due to the **A** form) and N_4-H (due to the **B** form) proton signals were observed in the spectra of **5a-d** [12]. In addition, the two C_5-H proton signals due to the **A** and **B** forms were observed in the respective spectra of **5a,b**, while the two C_5-Me carbon signals due to the **A** and **B** forms were observed in the ^{13}C-nmr spectra of **5c** (δ 10.67, 10.48 ppm) and **5d** (δ 10.71, 10.51 ppm) [12].

The above cyclization mode of **4a,c** into the oxadiazole ring were ascertained by the following alternate syntheses. The reactions of 3-(1,3,4-oxadiazol-2-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxalines **7a,b** (R = H, Me) [3] with *o*-chlorobenzenediazonium chloride resulted in the diazotization at the methylenic carbon [9] to furnish **5a,c**.

Thus, the above spectral data and alternate syntheses enabled us to deny the cyclization manner of **Ia-d** into the 1,2,4,5-tetrazepinylquinoxalines **6a-d**.



SCHEME 2

Synthesis of 3-(α-Chlorophenylhydrazonobenzimidazol-2-ylmethyl)-2-oxo-1,2-dihydroquinoxaline Hydrochlorides **9a-c**.

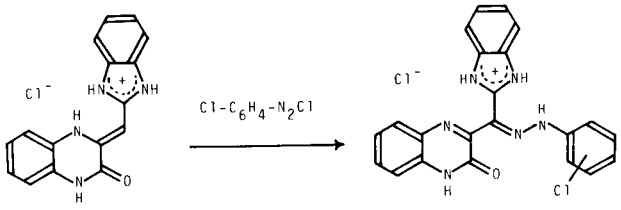
Since the above alternate syntheses of **5a,c** from **7a,b** supplied a convenient method for the syntheses of the 3-(α-chlorophenylhydrazono)heteroarylmethyl-2-oxo-1,2-dihydroquinoxalines, this method was utilized as follows.

The reactions of 3-(benzimidazol-2-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxaline hydrochloride **8** [13] with *o*-, *m*- and *p*-chlorobenzenediazonium chlorides effected the diazotization at the methylenic carbon to give the 3-(α-chlorophenylhydrazonobenzimidazol-2-ylmethyl)-2-oxo-1,2-dihydroquinoxaline hydrochlorides **9a-c**, respectively. The pmr spectra of **9a-c** were measured in trifluoroacetic acid because of their insolubility in most of the solvents, and hence the tautomeric equilibria between the **A** and **B** forms (Scheme 2) could not be examined in **9a-c**.

Antifungal and Antibacterial Activities.

Compounds **5a-d** exhibited the weak antifungal activity

Scheme 3



8

9 a, o-Cl
b, m-Cl
c, p-Cl

(11-33% growth inhibition) against *Pathium debaryanum*, *Pyriclaria oryzae* and *Rhizoctonia solani* at the concentrations of 10 and 100 ppm, while **5b,d** (*p*-chloro series) showed the antibacterial activity (100% growth inhibition) against *Xanthomonas oryzae* at 100 ppm. On the other hand, **9a-c** represented the antifungal activity (68-88% growth inhibition) against *Pathium debaryanum* at 100 ppm, whereas the weak antifungal activity (6-36% growth inhibition) was shown against *Pyriclaria oryzae* and *Rhizoctonia solani* at 50 and 100 ppm.

EXPERIMENTAL

All melting points were determined on an Ishii melting point apparatus and are uncorrected. Infrared (ir) spectra were recorded from potassium bromide discs on a JASCO IRA-1 spectrophotometer (JEOL). The pmr spectra were measured with an EM 390 spectrometer at 90 MHz, using tetramethylsilane as an internal standard. Chemical shifts are given in a δ scale relative to the internal standard. The mass spectra (ms) were determined with a JEOL JMS-01S spectrometer.

3-(α-Chlorophenylhydrazono-1,3,4-oxadiazol-2-ylmethyl)-2-oxo-1,2-dihydroquinoxalines **5a,b**.

A solution of **4a** or **4c** (10 g) and triethyl orthoformate (100 ml) in acetic acid (500 ml) was refluxed in an oil bath for 5 hours to precipitate crystals, which were excluded by suction filtration. Evaporation of the filtrate *in vacuo* afforded yellow crystals **5** [**a**, 5.17 g (55%), **b**, 5.94 g (63%)]. Recrystallization from *N,N*-dimethylformamide/ethanol provided yellow needles, mp 281-282° (**5a**), 270-271° (**5b**); ms: m/z 366 (M^+), 368 (M^++2) (**5a,b**); ir: ν cm^{-1} 1660, 1607, 1590, 1570 (**5a**), 1670, 1605, 1590 (**5b**); pmr (deuteriodimethylsulfoxide): 14.35 (s, 2/3 H, =N-NH-) [12], 12.80 (s, 1H, N_1-H), 12.45 (s, 1/3 H, N_4-H) [12], 9.47 (s, 1/3 H, C_5-H [12], 9.30 (s, 2/3 H, C_5-H) [12], 8.03-6.80 (m, 8H, aromatic) (**5a**); 12.80 (s, 1H, N_1-H), 11.97 (s, 1/6 H, N_4-H) [12], 11.45 (s, 5/6 H, =N-NH-) [12], 9.42 (s, 1/6 H, C_5-H [12], 9.27 (s, 5/6 H, C_5-H) [12], 8.07-7.10 (m, 8H, aromatic), (**5b**).

Anal. Calcd. for $C_{17}H_{11}ClN_6O_2$: C, 55.67; H, 3.02; Cl, 9.67; N, 22.91. Found: C, 55.45; H, 3.06; Cl, 9.65; N, 23.06 (**5a**); C, 55.48; H, 3.11; Cl, 9.41; N, 22.67 (**5b**).

3-(α-Chlorophenylhydrazono-5-methyl-1,3,4-oxadiazol-2-ylmethyl)-2-oxo-1,2-dihydroquinoxalines **5c,d**.

A solution of **4a** or **4c** (10 g) and triethyl orthoacetate (100 ml) in acetic acid (500 ml) was refluxed in an oil bath for 5 hours. Evaporation of the solvent *in vacuo* furnished yellow crystals **5** [**c**, 7.10 g (73%), **d** 8.28 g (78%)]. Recrystallization from *N,N*-dimethylformamide/ethanol gave yellow needles, mp 276-277° (**5c**), 267-268° (**5d**); ms: m/z 380 (M^+), 382 (M^++2) (**5c,d**); ir: ν cm^{-1} 1670, 1607, 1590, 1570 (**5c**), 1660, 1605, 1590, 1565 (**5d**); pmr (deuteriodimethylsulfoxide): 14.22 (s, 1/2 H, =N-NH-) [12], 12.77 (s, 1H, N_1-H), 12.42 (s, 1/2 H, N_4-H) [12], 8.00-6.93 (m, 8H, aromatic), 2.57 (s, 3H, C_5-Me) (**5c**); 12.76 (s, 1H, N_1-H), 11.95 (s, 1/5 H, N_4-H) [12], 11.18 (s, 4/5 H, =N-NH-) [12], 8.07-7.17 (m, 8H, aromatic), 2.59 (s, 3H, Me) (**5d**).

Anal. Calcd. for $C_{18}H_{13}ClN_6O_2$: C, 56.78; H, 3.44; Cl, 9.31; N, 22.07. Found: C, 56.55; H, 3.44; Cl, 9.16; N, 22.28 (**5c**); C, 56.52; H, 3.50; Cl, 9.23; N, 22.14 (**5d**).

Alternate Syntheses of **5a,c**.

A solution of sodium nitrite (0.364 g, 5.27 mmoles) in water (10 ml) was added dropwise to a suspension of *o*-chloroaniline hydrochloride (0.864 g, 5.27 mmoles) in acetic acid (20 ml) with stirring in an ice-water bath to give a clear solution, which was added to a suspension of **7a** (1 g, 4.93 mmoles) in acetic acid (30 ml) and water (10 ml) with stirring in an ice-water bath. After stirring was continued for 30 minutes, the reaction mixture was heated on a boiling water bath for 1 hour with an initial stirring to afford a clear solution and then to precipitate yellow crystals **5a**, which were collected by suction filtration (0.64 g). Evaporation of the filtrate *in vacuo* afforded yellow crystals **5a** (0.50 g). Total yield, 1.14 g (71%).

Compound **5c** was obtained by a similar manner to the above (73%).

3-(α-Chlorophenylhydrazonobenzimidazol-2-ylmethyl)-2-oxo-1,2-dihydroquinoxalines **9a-c**.

A solution of sodium nitrite (0.53 g, 7.68 mmoles) in water (20 ml) was added dropwise to a suspension of the appropriate chloroaniline hydrochloride (1.26 g, 7.68 mmoles) in 5% hydrochloric acid (20 ml) with stirring in an ice-water bath to give a clear solution, which was added to a suspension of **8** (2.0 g, 6.40 mmoles) in acetic acid (30 ml) and water (30 ml) with stirring in an ice-water bath. After stirring was continued for 10 minutes, the reaction mixture was heated on a boiling water bath for 1 hour with an initial stirring to give yellow needles **9**, which were collected by suction filtration [**a**, 2.60 g (98%), **b**, 2.65 g (100%), **c**, 2.66 g (100%)]. Trituration with hot *N,N*-dimethylformamide afforded analytically pure yellow needles, mp, 301-302° (**9a**), 299-300° (**9b**), 291-292° (**9c**); ms: m/z 414 (M^+), 416 (M^++2) (**9a-c**); ir: ν cm^{-1} 1680 (**9a**), 1665 (**9b**), 1665 (**9c**); pmr (trifluoroacetic acid): 8.33-6.90 (m, aromatic) (**9a**), 8.33-6.90 (m, aromatic) (**9b**), 8.33-6.90 (m, aromatic) (**9c**). The NH proton signals were unobservable.

Anal. Calcd. for $C_{22}H_{16}Cl_2N_6O$: C, 58.55; H, 3.57; Cl, 15.71; N, 18.62. Found: C, 58.78; H, 3.59; Cl, 15.58; N, 18.44 (**9a**); C, 58.58; H, 3.46; Cl, 15.44; N, 18.52 (**9b**); C, 58.72; H, 3.50; Cl, 15.45; N, 18.41 (**9c**).

Table

Antifungal and Antibacterial Activities of Compounds **5a-d** and **9a-c**

Compound	Concentration (ppm)	Activity [a] P.d.	P.o.	R.s.	X.o. [b]
5a	100	14	29	27	
	10	12	12	14	
5b	100	21	2	24	100
	10	14	2	10	
5c	100	30	62	27	
	10	11	0	13	
5d	100	19	28	33	100
	10	11	9	27	
9a	100	68	22	67	
	50	46	21	6	
9b	100	78	24	27	
	50	50	23	16	
9c	100	88	35	36	
	50	49	29	10	

[a] Growth inhibition (%). [b] P.d.: *Pythium debaryanum;* P.o.: *Pyriclaria oryzae;* R.s.: *Rhizoctonia solani;* X.o.: *Xanthomonas oryzae.*

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The tautomer ratios of the **A** form versus the **B** form are as follows; 2:1 (**5a**), 5:1 (**5b**), 1:1 (**5c**), 4:1 (**5d**).

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[8] These screening data have not been reported previously.