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Revised Structure for the Product from the Reaction of 3-Hydrazinocarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline with Nitrous Acid

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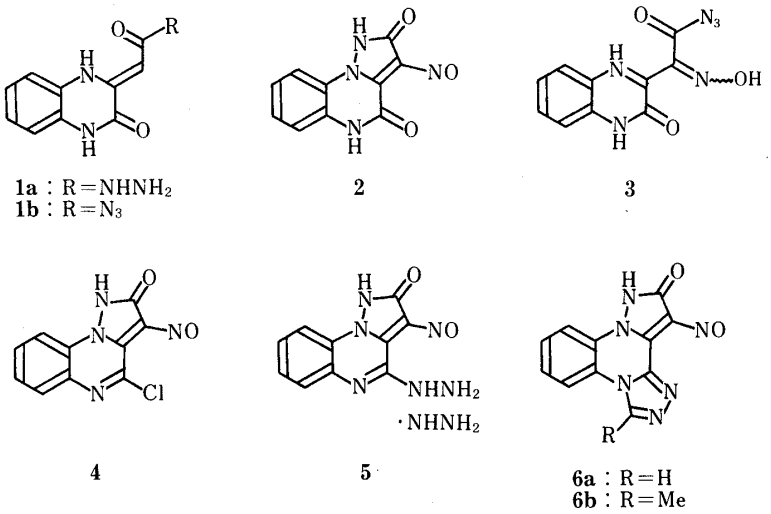
The structure of the compound **2**, 2,4-dioxo-3-nitroso-1,2,4,5-tetrahydropyrazolo[1,5-*a*]-quinoxaline, which was previously obtained from the reaction of 3-hydrazinocarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (**1a**) with an excess of nitrous acid, was revised to 3-(1,2,4-oxadiazolin-5-on-3-yl)-2-oxo-1,2-dihydroquinoxaline (**7**) on the basis of comparison with an authentic sample prepared from 3-cyano-2-oxo-1,2-dihydroquinoxaline (**8**) *via* an unambiguous route.

Keywords——3-hydrazinocarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline; 3-cyano-2-oxo-1,2-dihydroquinoxaline; triethylorthoformate; triethyl orthoacetate; hydrazine hydrate; phosphorus oxychloride; 2-oxo-1,2-dihydroquinoxaline-3-carboxamide oxime

In a previous paper,[1] we reported that the reaction of 3-hydrazinocarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (**1a**) with an excess of nitrous acid gave 2,4-dioxo-3-nitroso-1,2,4,5-tetrahydropyrazolo[1,5-*a*]quinoxaline (**2**) *via* an intermediate (**3**), but nuclear magnetic resonance (NMR) spectrum of **2** was not obtained because of the insolubility of **2**, and hence the structural assignment depended on the spectral and analytical data of the compounds (**4**, **5**, **6a**, **b**) derived from **2** (Chart 1). However, we encountered a discrepancy regarding the structure of **2** in the course of its further modification. Namely, no evidence was obtained to support the presence of the C_3-nitroso group, which should easily react with *p*-toluidine[2] and hydrazine.[2] Moreover, heating of **5** in acetic acid did not afford a product dehydrated between the nitroso and hydrazino groups.[2] These negative experimental results led us to correct the structure of **2**. It has been reported that various α-heteroaryl-α-hydroxyiminoacylazides (type **3** in Chart 1) cyclized to 3-(heteroaryl)-1,2,4-oxadiazolin-5-ones *via* the Curtius rearrangement.[3] Therefore, the structure of **2** should be revised to 3-(1,2,4-oxadiazolin-5-on-3-yl)-2-oxo-1,2-dihydroquinoxaline (**7**). This paper describes the unambiguous synthesis of **7** for the structural revision of **2**, leading to the further structural correction of **4**, **5**, and **6a**, **b**.

The reaction of **1a** with a 5-fold molar excess of nitrous acid in acetic acid and water initially precipitated 3-azidocarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (**1b**), which was gradually dissolved to result in a clear solution. The resultant solution was heated on a boiling water bath to precipitate **7**, and 3-cyano-2-oxo-1,2-dihydroquinoxaline (**8**) was obtained from the mother liquor. In this reaction, the yield ratio of **7** to **8** was found to be affected by the ratio of acetic acid and water, as represented in Table I. A similar reaction of **1a** with a 2-fold molar excess of nitrous acid predominantly gave **7**. Compound **7** was also obtained from 3-(1-hydrazinocarbonyl-1-hydroxyimino)methylene-2-oxo-1,2-dihydroquinoxaline (**9**), which was derived from 3-(1-hydroxyimino-1-methoxycarbonyl)methylene-2-oxo-1,2-dihydroquinoxaline (**10**).[4] Furthermore, **7** was unambiguously synthesized



1a : R=$NHNH_2$
1b : R=N_3

2

3

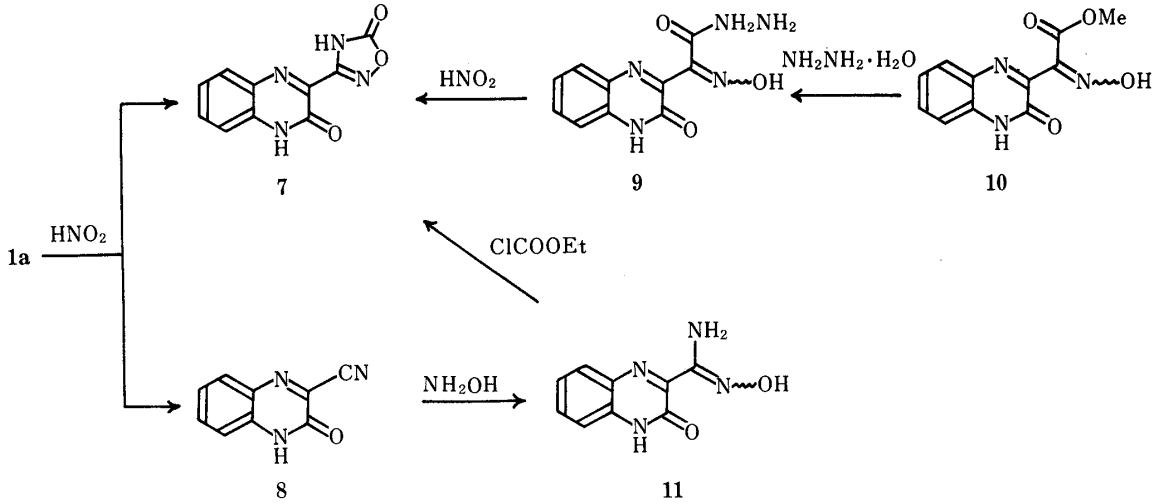
4

5

6a : R=H
6b : R=Me

Chart 1

from the nitrile **8** by the method of Iwao *et al.*[3] The reaction of **8** with hydroxylamine furnished 2-oxo-1,2-dihydroquinoxaline-3-carboxamide oxime (**11**), whose reaction with ethyl chlorocarbonate resulted in the formation of **7** (Chart 2). The infrared (IR) spectrum and melting point of **8** were identical with those of authentic samples,[4,5] and the conversion of **8** into **11** rationalized the structure of **8**.



7 **9** **10**

8 **11**

Chart 2

TABLE I. ' Yields of **7** and **8**

Molar ratio of **1a**:HNO_2	Ratio of AcOH:H_2O (ml)	Yield (%) **7**	**8**
1 5	300 50	60	27
	250 100	34	41
	200 150	28	52
1 2	300 50	90	—

Thus, the structures of **4**, **5**, and **6a**, **b** are also revised to **12**, **13**, and **14a**, **b**, respectively, as described below. The reaction of **7** with phosphorus oxychloride afforded 3-(1,2,4-oxadiazolin-5-on-3-yl)-2-chloroquinoxaline (**12**), whose reaction with an excess of hydrazine

hydrate provided 3-(1,2,4-oxadiazolin-5-on-3-yl)-2-hydrazinoquinoxaline hydrazinium salt (**13**). The reaction of **13** with triethyl orthoformate and triethyl orthoacetate effected the cyclization to the *s*-triazole ring to produce 4-(1,2,4-oxadiazolin-5-on-3-yl)-*s*-triazolo[4,3-*a*]quinoxaline (**14a**) and 4-(1,2,4-oxadiazolin-5-on-3-yl)-1-methyl-*s*-triazolo[4,3-*a*]quinoxaline (**14b**), respectively (Chart 3). Such a cyclization has already been reported by many workers,[6] and the structural assignment of **14a** and **14b** is based on the NMR spectral data. The NMR spectra of **14a** and **14b** in trifluoroacetic acid (TFA) exhibited C_1–H and C_1–Me proton signals at δ 10.39 and 3.57 ppm, respectively, and the values were similar to those of the *s*-triazolo[4,3-*a*]quinoxalines **15a**[6] and **15b**[6] (Chart 4) [δ 10.50 and 3.55 (or 3.35) ppm, respectively].

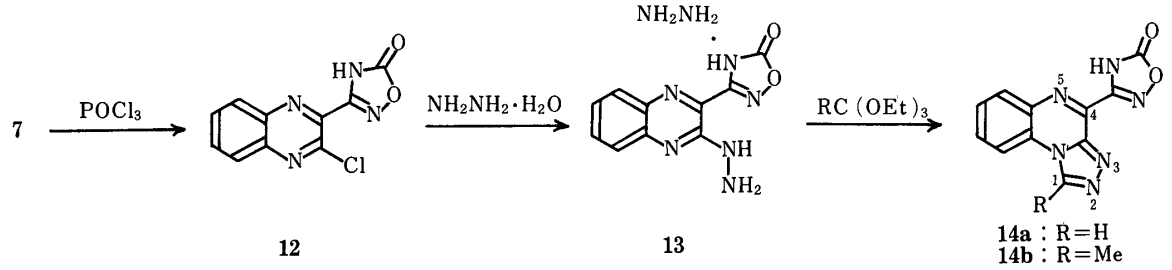


Chart 3

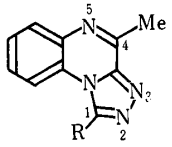


Chart 4

Experimental

All melting points are uncorrected. IR spectra were recorded from KBr discs on a JASCO IRA-1 spectrophotometer. NMR spectra were measured with an EM-390 spectrometer at 90 MHz using tetramethylsilane as an internal reference. Chemical shifts are given in the δ scale, relative to the internal reference. Mass spectra (MS) were determined with a JMS-D100 spectrometer. Microanalyses were carried out with Perkin-Elmer 240B microanalyzer.

3-(1,2,4-Oxadiazolin-5-on-3-yl)-2-oxo-1,2-dihydroquinoxaline (7) and 3-Cyano-2-oxo-1,2-dihydroquinoxaline (8)——General procedure. A solution of $NaNO_2$ (7.91 g, 5 eq for **1a**) in H_2O (20 ml) was added dropwise to a solution of **1a** (5 g, 22.9 mmol) in AcOH (300 ml) and H_2O (30 ml) with stirring in an ice-water bath to precipitate **1b**, which was dissolved by prolonged stirring. The resultant solution was heated on a boiling water bath for 2 h to precipitate **7**. The whole reaction mixture was cooled in an ice-water bath, and **7** was collected as yellow needles by suction filtration (3.17 g, 60%). An analytically pure sample was obtained by washing with hot EtOH several times, mp 263 °C. MS *m/z*: 230 (M^+). IR ν_{max}: 1785, 1660 cm^{-1}. *Anal.* Calcd for $C_{10}H_6N_4O_3$: C, 52.18; H, 2.63; N, 24.34. Found: C, 52.44; H, 2.60; N, 24.09.

The above filtrate was evaporated to dryness to give a yellow mixture, which was triturated with H_2O. The residual yellow crystals **8** were collected by filtration (1.06 g, 27%). Recrystallization from EtOH provided yellow plates, mp 289 °C (lit., 290 °C,[4] 288 °C[5]). The IR spectrum of this sample was identical with that of authentic samples.[4,5]

A similar treatment of **1a** (5 g) with $NaNO_2$ (3.17 g, 2 eq for **1a**) in AcOH (300 ml) and H_2O (50 ml) precipitated **7**, which was collected by suction filtration (3.87 g, 73.3%). Evaporation of the filtrate afforded additional product **7** (0.89 g, 16.7%). Total yield, 4.7 g (90%).

3-(1-Hydrazinocarbonyl-1-hydroxyimino)methylene-2-oxo-1,2-dihydroquinoxaline (9)——A solution of **10** (10 g, 40.5 mmol) with $NH_2NH_2 \cdot H_2O$ (3.04 g, 60.8 mmol) in EtOH (200 ml) was refluxed for 3 h to precipitate **9** as yellow needles, which were collected by suction (9.34 g, 93.4%). An analytically pure sample was obtained by washing with hot EtOH several times, mp 260—261 °C. MS *m/z*: 247 (M^+). IR ν_{max}: 3350, 3280, 1675 cm^{-1}. NMR (DMSO-d_6): 7.83—7.13 (m, 4H, aromatic). A broad signal due to oxime OH, lactam NH, and hydrazide NH protons was

observed at δ 9.50 ppm. *Anal.* Calcd for $C_{10}H_9N_5O_3$: C, 48.58; H, 3.65; N, 28.33. Found: C, 48.52; H, 3.44; N, 28.15.

2-Oxo-1,2-dihydroquinoxaline-3-carboxamide Oxime (11)——A suspension of **8** (1 g, 5.85 mmol) with $NH_2OH \cdot HCl$ (813 mg, 11.7 mmol) in pyridine (5 ml), 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) (0.1 ml), and EtOH (30 ml) was refluxed for 2 h to precipitate **11** as orange needles, which were collected by suction filtration (1.14 g, 95.8%). Trituration of the needles with hot EtOH afforded an analytically pure sample, mp 270—271 °C. MS *m/z*: 204 (M^+). IR ν_{max}: 3485, 3385, 1665, 1640, 1615 cm^{-1}. NMR (DMSO-d_6): 11.33 (br s, 1H, N_1–H), 8.00—7.17 (m, 4H, aromatic), 5.84 (s, 2H, NH_2). A signal due to oxime OH proton was not observed. *Anal.* Calcd for $C_9H_8N_4O_2$: C, 52.94; H, 3.95; N, 27.44. Found: C, 52.73; H, 3.73; N, 27.66.

Preparation of 7 from 9——A solution of $NaNO_2$ (1.67 g, 24.2 mmol) in H_2O (20 ml) was added dropwise to a suspension of **9** (5 g, 20.2 mmol) in AcOH (300 ml) and H_2O (30 ml) with stirring in an ice-water bath. Further stirring of the solution at room temperature provided a clear solution, which was heated on a boiling water bath for 2 h to precipitate **7** as yellow needles. After cooling of the reaction mixture, the product **7** was collected by suction (3.20 g, 68.8%).

Preparation of 7 from 11——Ethyl chlorocarbonate (797 mg, 7.35 mmol) was added dropwise to a solution of **11** (1 g, 4.90 mmol) in dry pyridine (5 ml) and dry 1,4-dioxane (50 ml) with stirring, and the whole mixture was refluxed in an oil bath for 2 h to give a clear solution. Cooling of the reaction mixture to room temperature precipitated **7** as yellow crystals, which were collected by suction filtration (600 mg). Evaporation of the mother liquor provided an oily mixture, to which EtOH and H_2O were added to precipitate additional product **7** (290 mg). Total yield, 890 mg (78.8%).

3-(1,2,4-Oxadiazolin-5-on-3-yl)-2-chloroquinoxaline (12)——A solution of **7** (5 g) with $POCl_3$ (100 ml) in DMF (50 ml) was heated on a boiling water bath for 6 h. The solution was cooled and poured onto crushed ice to precipitate **12** as colorless crystals, which were collected by filtration (5.0 g, 92.3%). Recrystallization from EtOH afforded colorless needles, mp 295—296 °C. MS *m/z*: 248 (M^+), 250 ($M^+ + 2$). IR ν_{max}: 1790 cm^{-1}. NMR (DMSO-d_6): 8.27—7.83 (m, 4H, aromatic). A signal due to N_2–H proton was not observed. *Anal.* Calcd for $C_{10}H_5ClN_4O_2$: C, 48.30; H, 2.03; N, 22.53. Found: C, 48.40; H, 1.99; N, 22.77.

3-(1,2,4-Oxadiazolin-5-on-3-yl)-2-hydrazinoquinoxaline Hydrazinium Salt (13)——A solution of **12** (5 g, 20.0 mmol) with $NH_2NH_2 \cdot H_2O$ (5 g, 100 mmol) in EtOH (300 ml) was refluxed for 1 h to precipitate **13** as yellow needles, which were collected by suction filtration (5.50 g, 99.46%). Recrystallization from EtOH gave analytically pure yellow needles, mp 220—221 °C. MS *m/z*: 244 (M^+). IR ν_{max}: 3280, 1670 cm^{-1}. NMR (DMSO-d_6): 8.00—7.20 (m, 4H, aromatic), 7.00—5.00 (br s, 7H, –$NHNH_2$ and NH_2NH_2). *Anal.* Calcd for $C_{10}H_8N_6O_2 \cdot NH_2NH_2$: C, 43.47; H, 4.38; N, 40.56. Found: C, 43.47; H, 4.44; N, 40.44.

4-(1,2,4-Oxadiazolin-5-on-3-yl)-*s*-triazolo[4,3-*a*]quinoxaline (14a) and 4-(1,2,4-Oxadiazolin-5-on-3-yl)-1-methyl-*s*-triazolo[4,3-*a*]quinoxaline (14b)——A solution of **13** (3 g) with the appropriate orthoester (30 ml) in BuOH (270 ml) was refluxed in an oil bath for 2 h. The solution was evaporated to afford the product, **14a** or **14b**, which was collected by suction filtration. An analytically pure sample was obtained by trituration with hot EtOH several times.

Compound 14a——Yield, 2.70 g (97.8%). Colorless needles, mp above 320 °C. MS *m/z*: 254 (M^+). IR ν_{max}: 1780 cm^{-1}. NMR (CF_3COOH): 10.39 (s, 1H, C_1–H), 8.70—8.40 (m, 2H, aromatic), 8.40—8.00 (m, 2H, aromatic). A signal due to N_2–H proton was not observed. *Anal.* Calcd for $C_{11}H_6N_6O_2$: C, 51.97; H, 2.38; N, 33.06. Found: C, 51.86; H, 2.36; N, 33.12.

Compound 14b——Yield, 2.40 g (82.5%). Colorless needles, mp above 320 °C. MS *m/z*: 268 (M^+). IR ν_{max}: 1780 cm^{-1}. NMR (CF_3COOH): 8.67—8.37 (m, 2H, aromatic), 8.37—8.00 (m, 2H, aromatic), 3.57 (s, 3H, C_1–Me). A signal due to N_2–H proton was not observed. *Anal.* Calcd for $C_{12}H_8N_6O_2$: C, 53.73; H, 3.01; N, 31.33. Found: C, 53.57; H, 3.05; N, 31.42.

NMR Spectral Data for 15a and 15b in TFA——**15a**: 10.50 (s, 1H, C_1–H), 8.70—8.33 (m, 2H, aromatic), 8.33—7.90 (m, 2H, aromatic), 3.47 (s, 3H, C_4–Me). **15b**: 8.70—8.30 (m, 2H, aromatic), 8.30—7.90 (m, 2H, aromatic), 3.55 (s, 3H, Me), 3.35 (s, 3H, Me).

References and Notes

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