[Chem. Pharm. Bull. 31(11)3897—3901(1983)]

Synthesis and Reactions of 3-(1,3,4-Oxadiazol-2-yl)methylene-2-oxo-1,2,3,4-tetrahydroquinoxalines[1)]

YOSHIHISA KURASAWA,* YUJIRO MORITAKI, TERUMI EBUKURO, and ATSUSHI TAKADA

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

(Received March 16, 1983)

Various 3-(1,3,4-oxadiazol-2-yl)methylene-2-oxo-1,2,3,4-tetrahydroquinoxalines (**4a**, **4b**, **5a**, **5b**, and **6**) were prepared from 3-methoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (**1**) *via* 3-hydrazinocarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (**2**) and 3-(substituted hydrazino)carbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxalines (**3a** and **3b**). Compound **3a** was also cyclized to 1,2-dihydro-2-oxo-3-(5-oxo-3-pyrazolin-4-yl)quinoxaline (**7**).

Keywords——hydrazine hydrate; triethyl orthoformate; triethyl orthoacetate; 1,8-diazabicyclo[5,4,0]-7-undecene; *m*-chloroperbenzoic acid; *N*-bromosuccinimide; tautomerism; furo[2,3-*b*]quinoxaline-3-carboxylic acid; 3-(*N,N*-dimethylcarbamoyl)furo[2,3-*b*]quinoxaline

Various 1,3,4-oxadiazole derivatives have been synthesized by several methods,[2)] and have been evaluated as fungicidal,[3)] herbicidal,[4)] and bactericidal[5)] agents. However, very few papers have been presented so far on the synthesis of 1,3,4-oxadiazoles possessing a quinoxaline moiety in the 2- or 5-position. In this paper, we undertook the synthesis of these novel 1,3,4-oxadiazoles using 3-methoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (**1**) as a starting material in order to search for new agents having some of the above activities.

Whereas **1** hardly reacted with most amines or with an equimolar to 5-fold molar amount of hydrazines,[6)] it was found to be converted easily to 3-hydrazinocarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (**2**) by reaction with a 10-fold molar amount of hydrazine hydrate. The reactions of **2** with triethyl orthoformate and triethyl orthoacetate in ethanol gave exclusively 3-(*N'*-ethoxymethylene)hydrazinocarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (**3a**) and 3-(*N'*-(1-ethoxyethylene))hydrazinocarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (**3b**), respectively. Refluxing of **3a** and **3b** with 1,8-diazabicyclo[5,4,0]-7-undecene (DBU) in pyridine afforded 3-(1,3,4-oxadiazol-2-yl)methylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (**4a**) and 3-(5-methyl-1,3,4-oxadiazol-2-yl)methylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (**4b**), respectively. In addition, refluxing of **3a** and **3b** with DBU in butanol provided **4a** and **4b**, respectively, in improved yields, as noted in Table I. The reactions of **4a** and **4b** with *N*-bromosuccinimide (NBS) effected N_4-bromination[7)] to produce 4-bromo-3-(1,3,4-oxadiazol-2-yl)methylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (**5a**) and 4-bromo-3-(5-methyl-1,3,4-oxadiazol-2-yl)methylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (**5b**), respectively. Moreover, the reaction of **4a** with *m*-chloroperbenzoic acid (MCPBA) induced methylenic C-hydroxylation[8)] to result in the formation of 3-[1-hydroxy-1-(1,3,4-oxadiazol-2-yl)]methylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (**6**). These results are formulated in Chart 1.

The nuclear magnetic resonance (NMR) spectrum of **1** in dimethylsulfoxide-d_6 (DMSO-d_6) or *N,N*-dimethylformamide (DMF) is known to exhibit signals due to vinyl and methylene

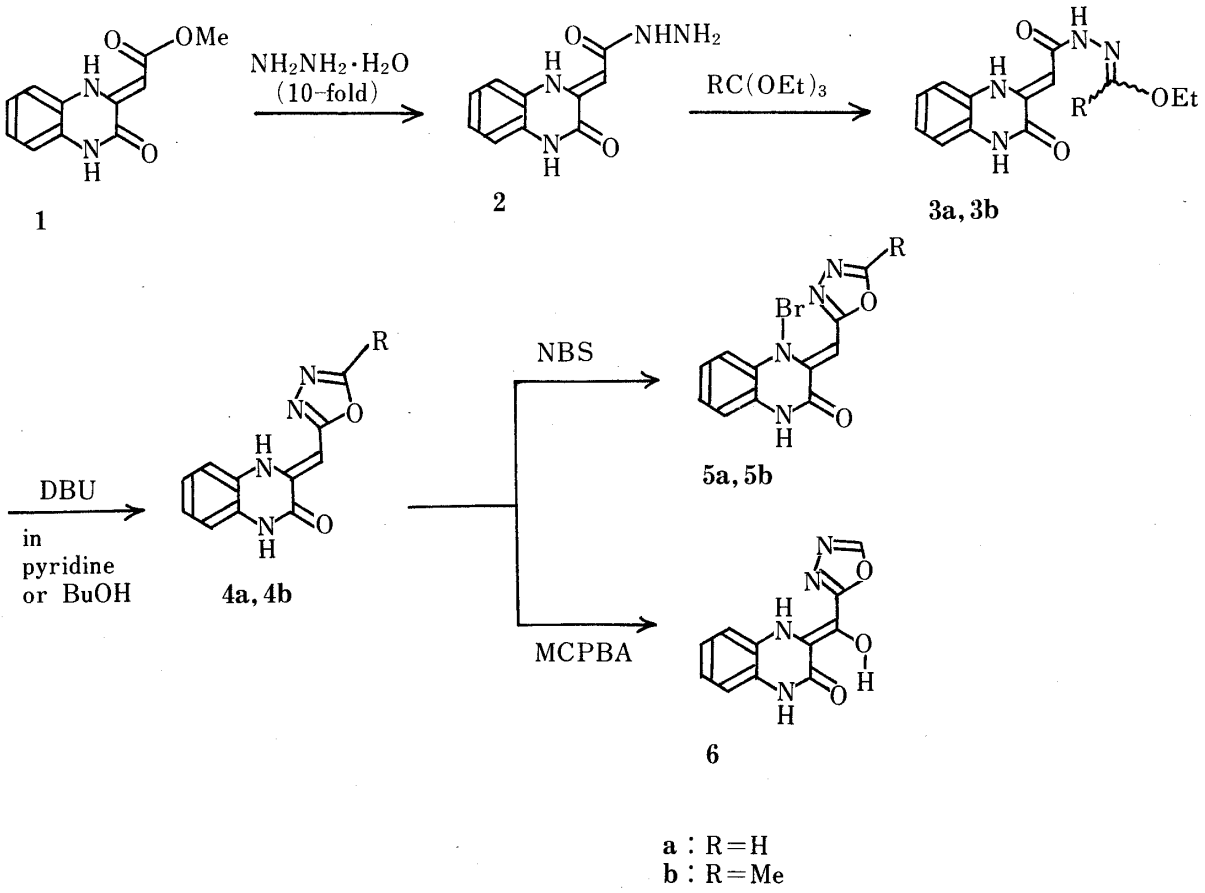

Chart 1

TABLE I. Yields of **4a** and **4b**

Solvent	Product (%)
Pyridine	**4a** (82)
	4b (40)
BuOH	**4a** (91)
	4b (91)

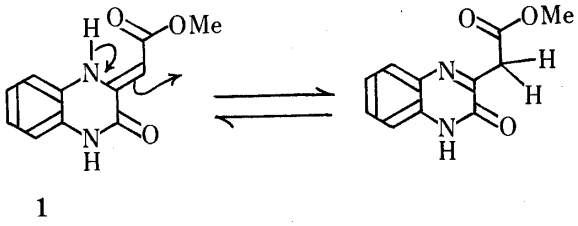

Chart 2

protons derived from the two tautomers shown in Chart 2.[9] The NMR spectra of **4a** and **4b** in DMSO-d_6 also showed the signals due to vinyl and methylene protons, while the spectra of **5a** and **5b** in DMSO-d_6 exhibited the vinyl proton signal, lacking the signals due to the N_4-proton and methylene protons. The spectrum of **6** showed no vinyl proton signal. These NMR spectral data provide good evidence for the assigned structures of **4**, **5**, and **6**.

Refluxing of **3a** and **3b** in DMF afforded 1,2-dihydro-2-oxo-3-(5-oxo-3-pyrazolin-4-yl)quinoxaline (**7**)[6,10] and **4b**, respectively, as shown in Chart 3. Thus, **3a** was found to be cyclized regioselectively in two solvent systems, DBU/butanol and DMF. Although DMF promotes the tautomerism shown in Chart 2, the pyrazolone ring is not formed in the reaction of **3b**, presumably due to steric hindrance by the methyl group.

The reactions of **4a** and **2** with the Vilsmeier reagent gave furo[2,3-*b*]quinoxaline-3-carboxylic acid (**8**)[6] and 3-(*N*,*N*-dimethylcarbamoyl)furo[2,3-*b*]quinoxaline hydrochloride (**9**),[6,10] respectively, as shown in Chart 4. The reaction mechanism for the formation of **9** has been reported in our previous papers,[6,10] and the furo[2,3-*b*]quinoxaline ring of **8** is assumed

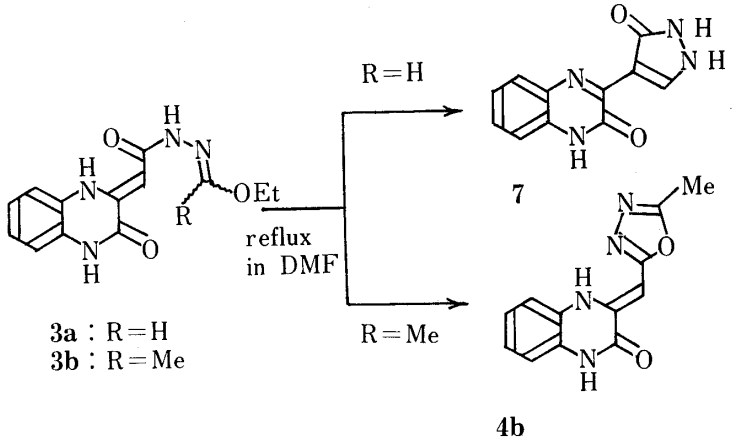

Chart 3

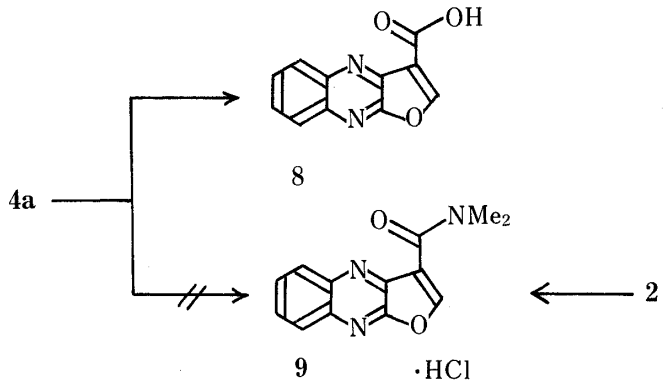

Chart 4

to be generated in a similar manner. The C_3-carboxyl group of **8** would be produced by hydrolysis of the 1,3,4-oxadiazole ring.

Experimental

All melting points are uncorrected. Infrared (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 standard. Mass spectra (MS) were determined with a JMS-01S spectrometer (Japan Electron Optics Laboratory Co., Ltd.).

3-Hydrazinocarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (2)——A solution of **1** (10 g) with hydrazine hydrate (22.95 g) in EtOH (200 ml) was refluxed for 3 h on a boiling water bath to precipitate colorless needles **2**, which were collected by suction filtration (9.07 g). Evaporation of the filtrate gave additional product **2** (0.73 g). Total yield, 9.80 g (98%). An analytically pure sample was obtained by washing with hot EtOH several times, mp 264—265 °C. MS *m/e*: 218 (M^+). NMR (DMSO-d_6) δ: 11.67 (s, 1H, N_1–H), 11.40 (s, 1H, N_4–H), 9.13 (s, 1H, CONHNH$_2$), 7.83—6.70 (m, 4H, aromatic), 5.60 (s, 1H, vinyl), 4.33 (br s, 2H, CONHNH$_2$), 3.66 (s, CH_2).[9] IR ν_{max}: 3300, 1665, 1630 cm^{-1}. *Anal.* Calcd for $C_{10}H_{10}N_4O_2$: C, 55.04; H, 4.62; N, 25.68. Found: C, 54.79; H, 4.57; N, 25.38.

3-(*N'*-Ethoxymethylene)hydrazinocarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxalines (3)——A solution of **2** (5 g) with the appropriate orthoester (50 ml) in EtOH (700 ml) was refluxed for 3 h on a boiling water bath.

When triethyl orthoformate was used, the solvent was evaporated off to afford yellow needles **3a**, which were washed with hexane–EtOH and collected by suction filtration. Yield, 6.18 g (98%). An analytically pure sample was obtained by washing with hot EtOH several times, mp 213—214 °C. MS *m/e*: 274 (M^+). IR ν_{max}: 1690, 1630 cm^{-1}. *Anal.* Calcd for $C_{13}H_{14}N_4O_3$: C, 56.93; H, 5.15; N, 20.43. Found: C, 56.68; H, 5.16; N, 20.21.

When triethyl orthoacetate was employed, yellow needles **3b** precipitated during the reaction. The needles were collected by suction filtration (5.53 g), and the filtrate was evaporated to provide additional product **3b** (0.93 g). Total yield, 6.46 g (98%). An analytically pure sample was obtained by washing with hot EtOH several times, mp 248—

249 °C. MS *m/e*: 288 (M^+). IR ν_{max}: 1690, 1630 cm^{-1}. *Anal.* Calcd for $C_{14}H_{16}N_4O_3$: C, 58.32; H, 5.59; N, 19.44. Found: C, 58.23; H, 5.62; N, 19.44.

Compounds **3a** and **3b** were insoluble in most solvents, and heating of **3a** or **3b** in DMSO-d_6 gave a mixture of **3** and the cyclized compound **4**. Therefore, the NMR data were not obtained.

3-(1,3,4-Oxadiazol-2-yl)methylene-2-oxo-1,2,3,4-tetrahydroquinoxalines (4)——Method A: A solution of **3a** or **3b** (5 g) with DBU (5 ml) in pyridine or BuOH (500 ml) was refluxed for 20 h in an oil bath at 160—180 °C. The solvent was evaporated off to give an oily substance, which was dissolved in $CHCl_3$–EtOH (10 : 1) to precipitate a crystalline product, **4a** or **4b**. The product was collected by suction filtration, and the filtrate was passed through a silica gel column with $CHCl_3$–EtOH (10 : 1) as an eluent. The eluate was evaporated to afford additional product **4a** or **4b**. The yields of **4a** and **4b** are shown in Table I.

Method B: A solution of **3b** (3 g) in DMF (300 ml) was refluxed for 20 h in an oil bath at 170—190 °C. Evaporation of the solvent and column chromatography of the residue as described above gave **4b** (1.52 g, 60%).

Compound **4a**: Recrystallization from EtOH provided yellow needles, mp 290—292 °C. MS *m/e*: 228 (M^+). NMR (DMSO-d_6) δ: 11.67 (s, 1H, N_1–H), 10.57 (s, 1H, N_4–H), 9.13 (s, 1H, 5′-H), 7.80—6.87 (m, 4H, aromatic), 6.12 (s, 1H, vinyl), 4.47 (s, CH_2).[9] IR ν_{max}: 1695, 1640 cm^{-1}. *Anal.* Calcd for $C_{11}H_8N_4O_2$: C, 57.89; H, 3.53; N, 24.55. Found: C, 57.72; H, 3.56; N, 24.36.

Compound **4b**: Recrystallization from EtOH afforded yellow needles, mp 255—256 °C. MS *m/e*: 242 (M^+). NMR (DMSO-d_6) δ: 11.67 (s, 1H, N_1–H), 10.43 (s, 1H, N_4–H), 7.77—6.83 (m, 4H, aromatic), 6.02 (s, 1H, vinyl), 4.37 (s, CH_2),[9] 2.50 (s, 3H, Me). IR ν_{max}: 1695, 1640 cm^{-1}. *Anal.* Calcd for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.13. Found: C, 59.38; H, 4.16; N, 23.19.

4-Bromo-3-(1,3,4-oxadiazol-2-yl)methylene-2-oxo-1,2,3,4-tetrahydroquinoxalines (5)——A suspension of **4a** or **4b** (1 g) with NBS (1.2 eq for **4**) in CCl_4 (100 ml) was refluxed for 4 h on a boiling water bath to precipitate colorless crystals of **5a** or **5b**, which were collected by suction filtration. The crystals were taken up in EtOH by heating, and the solution was immediately filtered. Evaporation of the filtrate gave an analytically pure colorless powder, **5a** or **5b**.

Compound **5a**: Yield, 1 g (74%), mp 223—224 °C. MS *m/e*: 306 ($M^+ - 1$), 308 ($M^+ + 1$). NMR δ (DMSO-d_6): 12.83 (s, 1H, N_1–H), 9.40 (s, 1H, 5′-H), 7.90—7.10 (m, 4H, aromatic), 6.90 (s, 1H, vinyl). IR ν_{max}: 1670 cm^{-1}. *Anal.* Calcd for $C_{11}H_7BrN_4O_2$: C, 43.02; H, 2.30; N, 18.24. Found: C, 43.13; H, 2.37; N, 18.20.

Compound **5b**: Yield, 1 g (80%), mp 214—216 °C. MS *m/e*: 320 ($M^+ - 1$), 322 ($M^+ + 1$). NMR (DMSO-d_6) δ: 12.82 (s, 1H, N_1–H), 7.90—7.20 (m, 4H, aromatic), 6.83 (s, 1H, vinyl), 2.55 (s, 3H, Me). IR ν_{max}: 1670 cm^{-1}. *Anal.* Calcd for $C_{12}H_9BrN_4O_2$: C, 44.88; H, 2.82; N, 17.45. Found: C, 44.81; H, 2.72; N, 17.46.

3-[1-Hydroxy-1-(1,3,4-oxadiazol-2-yl)]methylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (6)——A solution of **4a** (1 g, 4.39 mmol) with MCPBA (1.2 eq for **4a**) in EtOH (100 ml) was refluxed for 1 h to precipitated **6** as yellow needles, which were collected by suction filtration (230 mg, 21.5%). Recrystallization from EtOH provided analytically pure yellow needles, mp 256—258 °C. MS *m/e*: 244 (M^+). NMR (DMSO-d_6) δ: 11.50 (s, 1H, N_1–H), 11.40 (s, 1H, N_4–H), 9.34 (s, 1H, 5′-H), 9.23 (s, 1H, OH), 7.90—6.50 (m, 4H, aromatic). IR ν_{max}: 3150, 1660, 1610 cm^{-1}. *Anal.* Calcd for $C_{11}H_8N_4O_3$: C, 54.10; H, 3.30; N, 22.94. Found: C, 54.11; H, 3.31; N, 22.68.

1,2-Dihydro-2-oxo-3-(5-oxo-3-pyrazolin-4-yl)quinoxaline (7)——A solution of **3a** (3 g) in DMF (300 ml) was refluxed for 20 h in an oil bath at 170—190 °C. Evaporation of the solvent gave a crystalline product **7**, which was washed with hexane–EtOH to obtain a yellow powder (2.15 g, 86%). Recrystallization from AcOH and then from EtOH gave yellow needles, mp 304—305 °C. The IR spectrum and melting point of this sample coincided with those of an authentic sample.[6]

Furo[2,3-*b*]quinoxaline-3-carboxylic Acid (8)——A solution of **4a** (1 g) in DMF (50 ml) and $POCl_3$ (50 ml) was heated on a boiling water bath for 2 h, then cooled in an ice-water bath, and poured onto crushed ice. The reaction product was extracted with $CHCl_3$. The organic layer was washed with H_2O and then dried over Na_2SO_4, and evaporation of the solvent afforded yellow crystals, **8** (80 mg, 8.5%). Recrystallization from EtOH–AcOH gave yellow needles, mp 280—282 °C. The IR spectrum and melting point of this sample coincided with those of an authentic sample.[6]

3-(*N*,*N*-Dimethylcarbamoyl)furo[2,3-*b*]quinoxaline hydrochloride (9)——$POCl_3$ (10 ml) was added dropwise to a suspension of **2** (1 g) in DMF (10 ml) with stirring in an ice-water bath. The suspension was heated on a boiling water bath to afford a clear solution, which precipitated crystals **9**. The mixture was cooled in an ice-water bath and then poured onto crushed ice to precipitate yellow crystals **9**, which were collected by suction filtration (790 mg, 62.2%). The IR spectrum of this sample coincided with that of an authentic sample.[6]

References and Notes

1) A part of this work was reported by Y. Kurasawa, Y. Moritaki, and A. Takada, *Synthesis*, **1983**, 238.
2) *a*) C. Ainsworth, *J. Am. Chem. Soc.*, **77**, 1148 (1955); *b*) *Idem, ibid.*, **87**, 5800 (1965); R. Stolle and K. Fehrenbach, *J. Prakt. Chem.*, **122**, 289 (1929); R. N. Butler, T. M. Lambe, J. C. Tobin, and F. L. Scott, *J. Chem. Soc., Perkin Trans. 1*, **1973**, 1357; J.-F. Giudicelli, J. Menin, and H. Najer, *Bull. Soc. Chim. Fr.*, **1968**, 4568; *idem, ibid.*, **1969**, 870; M. M. Kochhar, *J. Heterocycl. Chem.*, **19**, 153 (1972); G. Werber, F. Buccheri, and F.

Maggio, *ibid.*, **19**, 107 (1972); K. Peseke, *Z. Chem.*, **17**, 262 (1977).
3) S. P. Suman and S. C. Baher, *Agric. Biol. Chem.*, **43**, 1339 (1979); Fr. Patent 2382445 [*Chem. Abstr.*, **91**, 74624*g* (1979)]; R. B. Pathak, B. Jahan, and S. C. Bahel, *Bokin Bobai*, **8**, 64 (1980).
4) Jpn. Tokkyo Koho, 80, 27042 [*Chem. Abstr.*, **93**, 232719*g* (1980)]; L. D. S. Yadav and R. K. Khare, *Indian J. Chem.*, **19B**, 417 (1980).
5) A. K. Sengupta and U. Chandra, *Indian J. Chem.*, **17B**, 655 (1979); U. S. Patent 4218458 [*Chem. Abstr.*, **94**, 30763*j* (1981)].
6) Y. Kurasawa and A. Takada, *Chem. Pharm. Bull.*, **29**, 2871 (1981).
7) Y. Kurasawa, Y. Moritaki, M. Ichikawa, M. Ogura, and A. Takada, *Chem. Pharm. Bull.*, **31**, 3009 (1983).
8) Y. Kurasawa, Y. Moritaki, and A. Takada, *Heterocycles*, **19**, 1619 (1982).
9) R. Mondelli and L. Merlini, *Tetrahedron*, **22**, 3253 (1966).
10) Y. Kurasawa and A. Takada, *Heterocycles*, **14**, 281 (1980).