A Convenient Synthesis of Novel Pyrazolo[1,5-*a*]quinoxalines

Yoshihisa KURASAWA*, Mitsugu ICHIKAWA, Atsuko SAKAKURA, Atsushi TAKADA

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

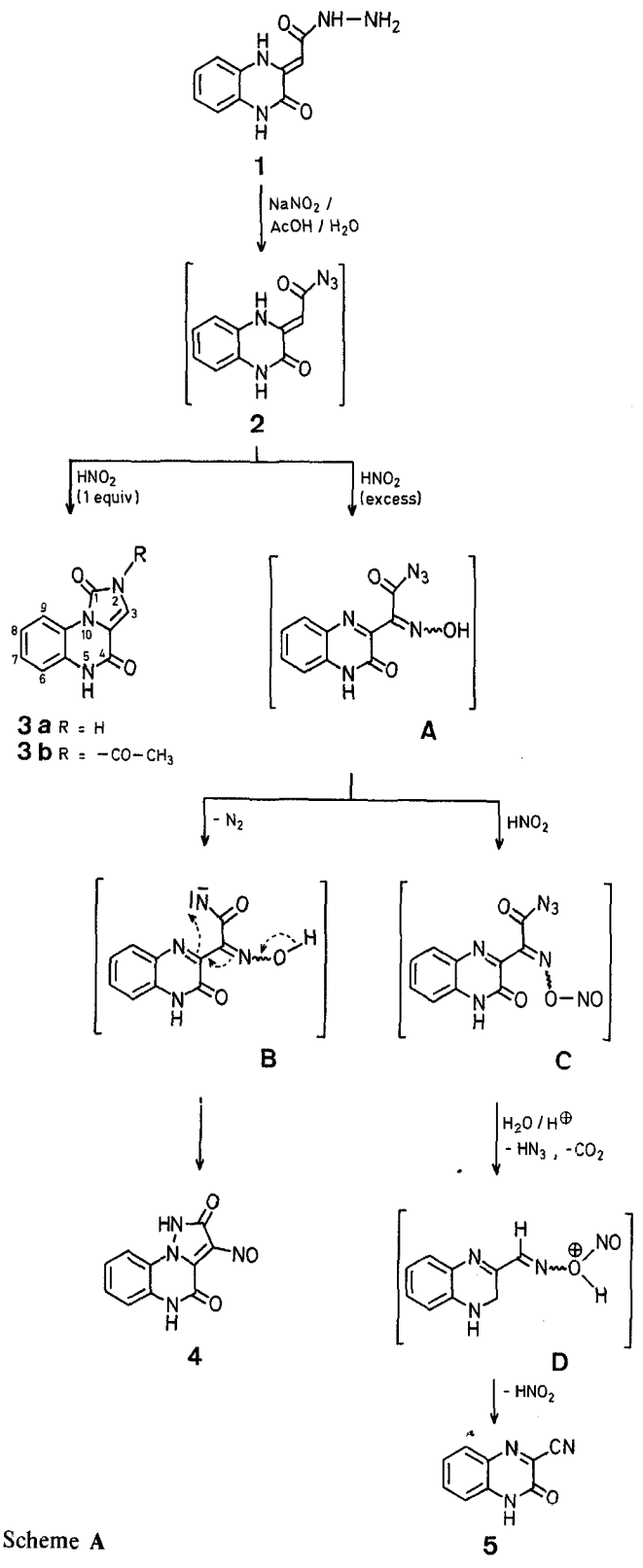
In connection with a previous study[1] on the synthesis of imidazo[1,5-*a*]quinoxalines, we reported that the reaction of 3-hydrazinocarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline **(1)** with an equimolar amount of nitrous acid gave 3-azidocarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline **(2)**, which was converted to imidazo[1,5-*a*]quinoxalines **(3)** via the Curtius rearrangement (Scheme A)[2]. In continuation of this study, we have now found that the reaction of **1** with an excess of nitrous acid afforded 2,4-dioxo-3-nitroso-1,2,4,5-tetrahydropyrazolo[1,5-*a*]quinoxaline **(4)** and 3-cyano-2-oxo-1,2-dihydroquinoxaline **(5)**[3,4], but no products resulting from the Curtius rearrangement of **2**.

The reaction of **1** with 5 equivalents of nitrous acid in acetic acid/water precipitated azide **2**, which gradually dissolved on prolonged stirring. On heating the solution, compound **4** was obtained as a solid product, while **5** remained in the mother liquor (Method A). The proportion of **4** to **5** was found to depend on the amount of water present in the system. The best yield of **4** was obtained with a 6 : 1 ratio of acetic acid to water. In addition, a similar reaction of **1** with two equivalents of nitrous acid provided **4** exclusively (Method B).

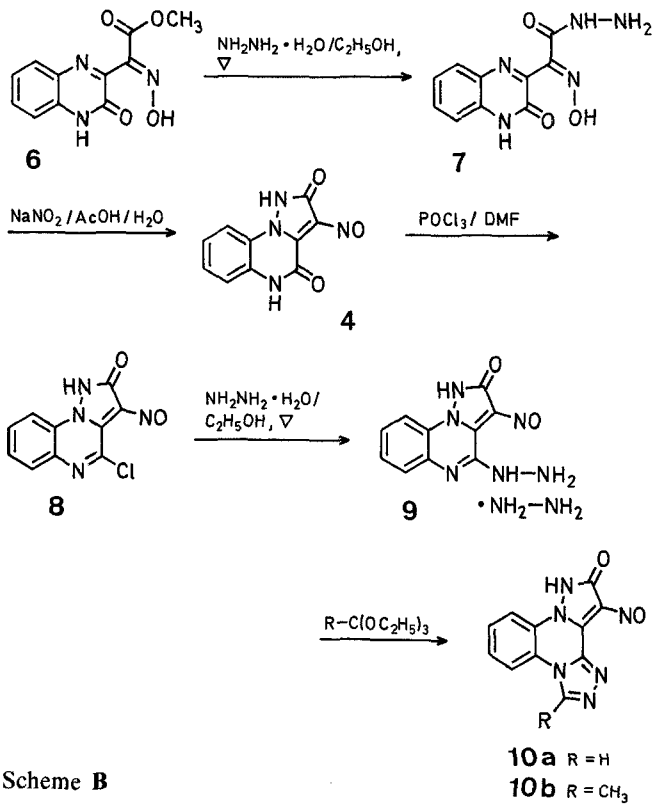
The above results are formulated in Scheme **A** together with a plausible mechanism, which involves the elimination of nitrogen from an intermediate **A** to form the nitrene **B** followed by its cyclization to give the pyrazolo[1,5-*a*]quinoxaline **4**. The 3-cyano-2-oxo-1,2-dihydroquinoxaline **5** is then probably formed by further nitrosation of the intermediate **A** with the excess nitrous acid present in the system to **C**, which is subsequently hydrolyzed and loses carbon dioxide to the intermediate **D**. The elimination of nitrous acid from **D** yields the product **5**. The route from **A** to **5** was supported by the fact that the increase in the amount of nitrous acid and water was advantageous to the formation of **5**.

Compound **4** was insoluble in most solvents and its ^{1}H-N.M.R. spectrum was not obtained. Therefore, its structure was established by an alternate synthesis and some of its transformation reactions, as illustrated in Scheme **B**.

For the synthesis of **4**, methyl 2-(3-oxo-3,4-dihydro-2-quinoxalinyl)-2-hydroxyiminoacetate **(6)**[3] was refluxed with hydra-



Scheme **A**



Scheme **B**

Table. Preparation of Quinoxaline Derivatives

Product No.	Yield [%]	m.p. [°C][a]	Molecular formula[b]	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. (solvent) δ [ppm]
4	90[c]	262–263°	$C_{10}H_6N_4O_3$ (230.2)	1785, 1660	—[d]
7	93	260–261°	$C_{10}H_9N_5O_3$ (247.2)	3350, 3280, 1675	(DMSO-d_6): 7.8–7.1 (m, 4H)[e]
8	92	295–296°	$C_{10}H_5ClN_4O_2$ (248.6)	1790	(DMSO-d_6): 8.3–7.8 (m, 4H)[f]
9	98	220–221°	$C_{10}H_{12}N_8O_2$ (276.2)	3280, 1760	(DMSO-d_6): 8.0–7.2 (m, 4H); 7.0–5.0 (br. s, 7H)[f,g]
10a	98	>320°	$C_{11}H_6N_6O_2$ (254.2)	1780	(CF_3COOH): 10.39 (s, 1H); 8.7–8.4 (m, 2H); 8.4–8.0 (m, 2H)[f]
10b	83	>320°	$C_{12}H_8N_6O_2$ (268.2)	1780	(CF_3COOH): 8.7–8.4 (m, 2H); 8.4–8.0 (m, 2H); 3.57 (s, 3H)[f]

[a] All melting points are uncorrected.
[b] Satisfactory mass spectral and microanalytical data were obtained: C, H, N, all within ±0.3%.
[c] By method B.
[d] Insoluble in most of the solvents.
[e] Oxime OH, lactam NH, and hydrazide NH were observed as broad signal at δ = 12.67–3.33 ppm.
[f] 1-NH proton was not observed.
[g] Signal for —$NHNH_2$ and NH_2NH_2 protons.

zine hydrate in ethanol to give 2-(3-oxo-3,4-dihydro-2-quinoxalinyl)-2-hydroxyiminoacetic acid hydrazide **(7)**. The reaction of **7** with 1 equivalent of nitrous acid resulted in the formation of **4**.

Compound **4** was then transformed to 4-chloro-3-nitroso-2-oxo-1,2-dihydropyrazolo[1,5-*a*]quinoxaline **(8)** by reaction with phosphoryl chloride. Compound **8** was refluxed with hydrazine hydrate in ethanol to form 4-hydrazino-3-nitroso-2-oxo-1,2-dihydropyrazolo[1,5-*a*]quinoxaline hydrazine adduct **(9)**. The reactions of **9** with triethyl orthoformate and triethyl orthoacetate in *n*-butanol afforded 3-nitroso-2-oxo-1,2-dihydro-7*H*,12*H*-pyrazolo[1′,5′ : 1,2]quinoxalino[3,4-*c*][1,2,4]triazole **(10a)** and 6-methyl-3-nitroso-2-oxo-1,2-dihydro-7*H*,12*H*-pyrazolo[1′,5′ : 1,2]quinoxalino[3,4-*c*][1,2,4]-triazole **(10b)**, respectively. These compounds were characterized by analytical and spectroscopical methods.

In the ^{1}H-N.M.R. spectrum of **3**, the 9-H signal was observed at a much lower magnetic field as compared with the signals of the three other aromatic protons, due to the anisotropy of the carbonyl group in position 1[1,2]. On the contrary, the signals of the four aromatic protons in **10a** and **10b** appeared as multiplets of the A_2B_2 type. Furthermore, the 9-H signals of **8** and **9** were observed together with the three other aromatic protons. Therefore, the carbonyl group should be in the 2-position in compounds **4**, **8**, **9**, **10a**, and **10b**.

2,4-Dioxo-3-nitroso-1,2,4,5-tetrahydropyrazolo[1,5-*a*]quinoxaline (4) and 3-Cyano-2-oxo-1,2-dihydroquinoxaline (5):

Method A: To a solution of **1** (5.0 g, 22.9 mmol) in acetic acid (300 ml) and water (30 ml) is added dropwise a solution of sodium nitrite (7.91 g, 115 mmol) in water (20 ml) with stirring and cooling in an ice/water bath to precipitate **2**, which is then dissolved by prolonged stirring. The resultant solution is heated on a boiling water bath for 2 h. The whole reaction mixture is cooled in an ice bath and the yellow needles of **4** formed are collected by suction; yield: 3.17 g (60%). Analytically pure sample is obtained by washing with hot ethanol.

The above filtrate is evaporated to dryness to give a yellow residue, which is triturated with water. The yellow crystals of **5** formed are filtered under suction. Recrystallization from ethanol provides yellow plates; yield: 1.06 g (27%); m.p. 289 °C (Ref.[3], m.p. 290 °C; Ref.[4], m.p. 288 °C).

Method B: To a solution of **1** (5.0 g, 22.9 mmol) in acetic acid (300 ml) and water (30 ml) is added dropwise a solution of sodium nitrite (3.16 g, 45.8 mmol) in water (20 ml) with stirring and cooling in an ice/water bath. The precipitated **2** is dissolved by prolonged stirring and the resultant solution is heated on a boiling water bath for 2 h. The yellow needles of **4** formed on cooling are filtered by suction. Evaporation of the filtrate afforded additional amount of **4**; yield: 4.7 g (90%).

2-(3-Oxo-3,4-dihydro-2-quinoxalinyl)-2-hydroxyiminoacetic Acid Hydrazide (7):

A solution of **6**[3] (10 g, 40.5 mmol) in hydrazine hydrate (3.04 g, 60.8 mmol) in ethanol (200 ml) is refluxed for 3 h and the precipitated yellow needles of **7** are collected by suction filtration. Evaporation of the filtrate gives additional product **7**. Analytically pure sample is obtained by washing with hot ethanol.

4-Chloro-3-nitroso-2-oxo-1,2-dihydropyrazolo[1,5-*a*]quinoxaline (8):

A solution of **4** (5 g, 21.7 mmol) and phosphoryl chloride (100 ml) in dimethylformamide (50 ml) is heated on a boiling water bath for 6 h. The solution is cooled, poured into crushed ice (500 g), filtered, and the precipitate recrystallized from ethanol to give colorless crystals of **8**.

4-Hydrazino-3-nitroso-2-oxo-1,2-dihydropyrazolo[1,5-*a*]quinoxaline Hydrazine Adduct (9):

A solution of **8** (5 g, 20 mmol) and hydrazine hydrate (5 g, 0.1 mol) in ethanol (300 ml) is refluxed for 1 h and the precipitated yellow needles of **9** are collected by suction. Analytically pure sample of **9** is obtained as yellow needles by recrystallization from ethanol.

3-Nitroso-2-oxo-1,2-dihydro-7*H*,12*H*-pyrazolo[1′,5′ : 1,2]quinoxalino[3,4-*c*][1,2,4]triazole (10a) and 6-Methyl-3-nitroso-2-oxo-1,2-dihydro-7*H*,12*H*-pyrazolo[1′,5′ : 1,2]quinoxalino[3,4-*c*][1,2,4]triazole (10b):

A solution of **9** (3 g, 10.9 mmol) and the appropriate orthoester (30 ml) in *n*-butanol (270 ml) is refluxed in an oil bath for 2 h. The solution is evaporated to afford colorless needles of **10**, which are collected by suction filtration. Analytically pure sample is obtained by washing with hot ethanol.

Preparation of 4 from 7:

To a suspension of **7** (5.0 g, 20.0 mmol) in acetic acid (300 ml) and water (30 ml) is added dropwise a solution of sodium nitrite (1.67 g, 24.2 mmol) in water (20 ml) with stirring in an ice/water bath. Further stirring of the solution at room temperature provides a clear solution, which is heated on a boiling water bath for 2 h to precipitate yellow needles of **4**. After cooling, the product **4** is collected by filtration; yield: 3.2 g (69%).

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* Address for correspondence.

[1] G. W. Danswan, P. W. Hairsine, D. A. Rowlands, J. B. Taylor, R. Westwood, *J. Chem. Soc. Perkin Trans. 1* **1982**, 1049.
[2] Y. Kurasawa, M. Ichikawa, A. Takada, *Heterocycles* **20**, 269 (1983).
[3] D. D. Chapman, *J. Org. Chem.* **37**, 2498 (1972).
[4] R. Fusco, S. Rossi, *Chim. Ind. (Milan)* **45**, 834 (1963).

F. Babudri, L. Di Nunno, S. Florio, *Synthesis* **1983** (3), 230–231:

The title compounds **5** and **7** should be named (*Z*)-2-alkylidene-4-methyl-3-oxo-2,3-dihydro-4*H*-1,4-benzothiazines; compound **10** as 11-methyl-3-(2-methylaminophenylthio)-2-oxo-4,5-diphenyl-2,5-dihydro-11*H*-oxepino[3,2-*b*][1,4]benzothiazine.

Y. Kurasawa, Y. Moritaki, A. Takada, *Synthesis* **1983** (3), 238–240:

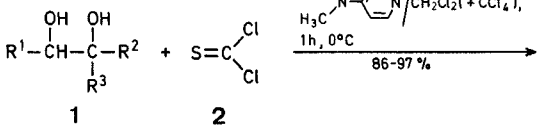
The title compounds **6** and **7** should be named 3-(1-ethoxyalkylidenehydrazinocarbonylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxalines and 3-(1,3,4-oxadiazol-2-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxalines, respectively.

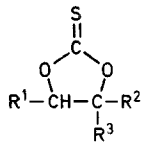
Abstract **6589**, *Synthesis* **1983** (3), 247:

The title should be *N*-(1-Aroyloxyalkyl)-pyridinium and *P*-(1-Aroyloxyalkyl)-phosphonium Salts.

Abstract **6593**, *Synthesis* **1983** (4), 335:

The formula scheme **1** + **2** ⟶ **3** should be:





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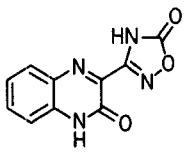
Y. Otsuji, S. Nakanishi, N. Ohmura, K. Mizuno, *Synthesis* **1983** (5), 390:

The substituents for compound **2g** (Table) should be R=H, X=H, n=1.

Y. Kurasawa, M. Ichikawa, A. Sakakura, A. Takada, *Synthesis* **1983** (5), 399–400:

The structures of products **4, 8, 9,** and **10** given have since been found to be erroneous, the corrected structures are given below. A revision will be published in *Chem. Pharm. Bull.* in 1984.



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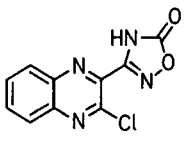

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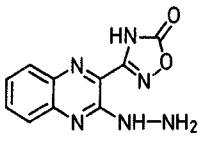

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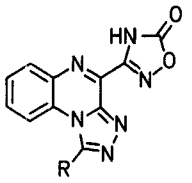
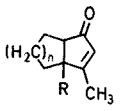


10a R = H
b R = CH_3

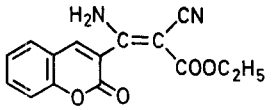
C. Santelli-Rouvier, M. Santelli, *Synthesis* **1983** (6), 429–442:

The structure of the third product in Table 4 (p. 435) should be:



S. M. Fahmy, R. M. Mohareb, *Synthesis* **1983** (6), 478–480:

The structure of product **5** should be:



L. Jacob, M. Julia, B. Pfeiffer, C. Rolando, *Synthesis* **1983** (6), 451–452:

The first three entries in Table 1 (p. 451) should be as follows:

Table 1. Demethylation of Mixed Alkyl Methyl Phosphates **(1, 3, 4)** and of Dimethyl Heptanephosphonate **(5)** using Dimethyl Sulfide (2.5 equiv) and Methanesulfonic Acid (10 equiv)

Substrate	Product	Reaction conditions		Yield[a] [%]	m.p. [°C][b] (solvent)	Molecular formula[c] or m.p. [°C] reported
		Scale [mmol]	Time [h]			
1a n-C_6H_{13}–O–P(O)(OCH$_3$)–OCH$_3$	**2a** · H_2N–C_6H_5	10	22	82 (93)	133–134° (ethanol)	$C_{12}H_{22}NO_4P$ (275.3)
1b n-C_8H_{17}–O–P(O)(OCH$_3$)–OCH$_3$	**2b** · H_2N–C_6H_5	5	7	(88)	135–137° (acetone)	129–130°[22] (ethanol)
		5	12	(93)		
		5	48	(98)		
		5	19	65		
		10	92	83		
		10	52[c]	83		
1c n-C_6H_{13}–CH(CH_3)–O–P(O)(OCH$_3$)–OCH$_3$	**2c** · H_2N–C_6H_5	5	19	68	154° (ethanol)	$C_{14}H_{26}NO_4P$ (303.3)
		10	92	79		