[Chem. Pharm. Bull. 28(12)3537—3541(1980)]

Synthesis of 4-Substituted 1,2-Dihydropyridazino[3,4-*b*]quinoxalines from 3-(N,N-Dimethylaminocarbonyl)furo[2,3-*b*]quinoxaline[1]

Yoshihisa Kurasawa and Atsushi Takada

School of Pharmaceutical Sciences, Kitasato University[2]

(Received June 20, 1980)

4-Substituted 1,2-dihydropyridazino[3,4-*b*]quinoxalines (VII, VIIIa, and VIIIb) were synthesized from 3-(N,N-dimethylaminocarbonyl)furo[2,3-*b*]quinoxaline hydrochloride (I) *via* 3-oxo-2-(2′H-pyrido[1′,2′-*a*]pyrimidin-2′-on-3′-yl)-3,4-dihydroquinoxaline (III) and 3-chloro-2-(2′H-pyrido[1′,2′-*a*]pyrimidin-2′-on-3′-yl)quinoxaline (V).

Keywords——2-aminopyridine; hydrazine hydrate; methylhydrazine; hydrogen peroxide; chlorination; alcoholysis; hydrazinoazines

In a previous paper,[3] we reported that 3-(N,N-dimethylaminocarbonyl)furo[2,3-*b*]-quinoxaline hydrochloride (I) was easily synthesized from 3-ethoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (II), and that the reaction of I with hydrazines gave 4-(3′-ox-3′,4′-dihydroquinoxalin-2′-yl)pyrazolones (Chart 1). Since there are few reports concerning syntheses of 4-substituted 1,2-dihydropyriadzino[3,4-*b*]quinoxalines, we undertook to develop a route for the synthesis of them from I.

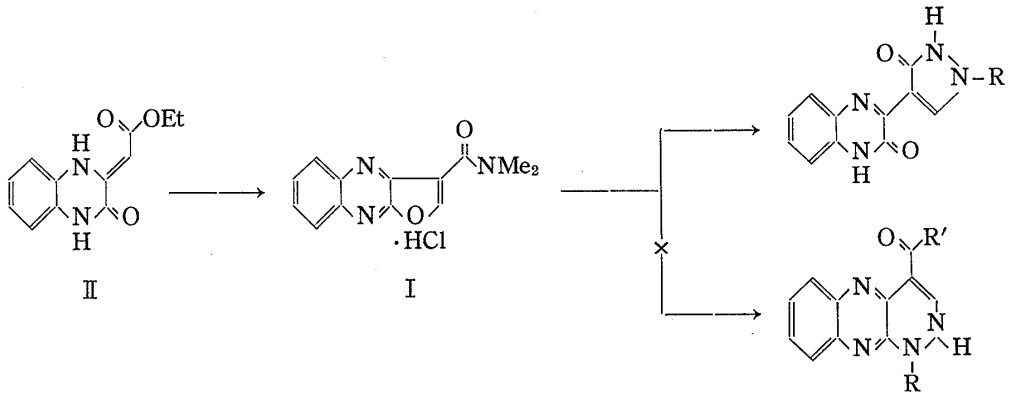


Chart 1

The reaction of I with 2-aminopyridine afforded a yellow compound, whose structure was assigned as 3-oxo-2-(2′H-pyrido[1′,2′-*a*]pyrimidin-2′-on-3′-yl)-3,4-dihydroquinoxaline(III) on the basis of the analytical and spectral data. Since the reaction of 2-aminopyridine with a carboxylic ester is known to give a 2-acylaminopyridine,[4,5] III may be formed *via* an intermediate (IV). Chlorination of III with phosphorus oxychloride provided 3-chloro-2-(2′H-pyrido[1′,2′-*a*]pyrimidin-2′-on-3′-yl)quinoxaline (V).

The reaction of V with methylhydrazine provided 3-(2′-methylhydrazino)-2-(2′H-pyrido-[1′,2′-*a*]pyrimidin-2′-on-3′-yl)quinoxaline (VI) (4.8%) and 1-methyl-4-(1′-methylhydrazino-

1) A part of this work was reported by Y. Kurasawa and A. Takada, in *Heterocycles*, **14**, 611 (1980).
2) Location: *Shirokane, Minato-ku, Tokyo 108, Japan.*
3) Y. Kurasawa and A. Takada, *Heterocycles*, **14**, 281 (1980).
4) M. Shur and S.S. Israelstam, *J. Org. Chem.*, **33**, 3015 (1968).
5) A.S. Tomcufcik and L.N. Starker, "Heterocyclic Compounds, Pyridine and Derivatives: Part III," ed. by E. Klingsberg, Interscience Publishers, New York, London, Sydney, 1962, p. 19.

carbonyl)-1,2-dihydropyridazino[3,4-*b*]quinoxaline (VII) (78%). The structures of these products were assumed from the spectral data. In the nuclear magnetic resonance (NMR) spectrum of VI in dimethylsulfoxide-d_6–trifluoroacetic acid (DMSO-d_6–TFA) (1 : 1), two signals for NH protons were observed at 12.01 and 4.33 ppm, indicating that the methyl group was attached to the terminal nitrogen atom of the 3-hydrazino group. Moreover, VI was not convertible into VII by the reaction of VI with methylhydrazine. The thin-layer chromatogram of the above reaction mixture showed two spots, neither of which corresponded to the spot of VII. These results suggested that the methyl group in the pyridazine ring of VII existed at the 1-position, not the 2-position.

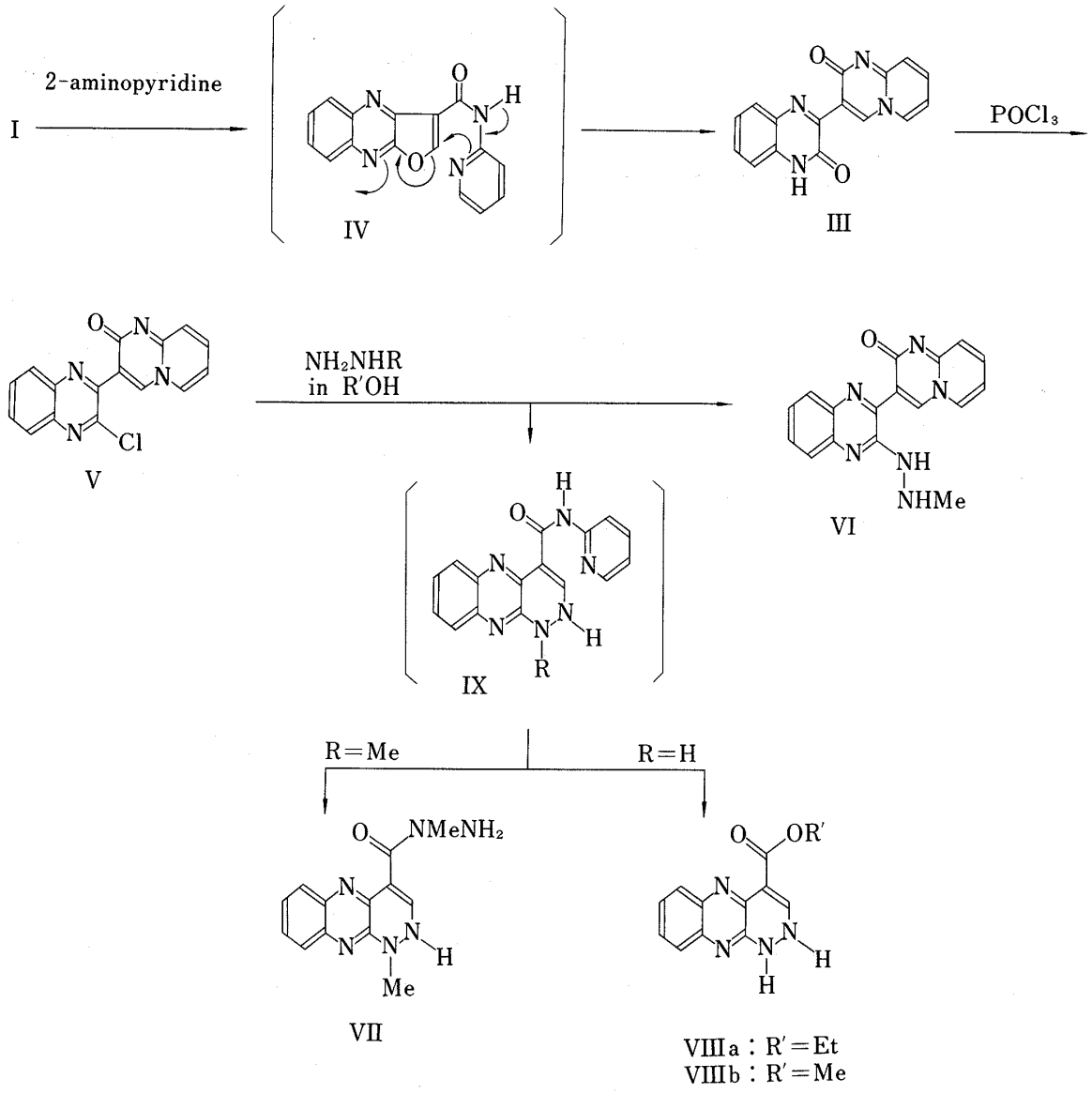


Chart 2

On the other hand, the reaction of V with hydrazine hydrate in ethanol-chloroform produced 4-ethoxycarbonyl-1,2-dihydropyridazino[3,4-*b*]quinoxaline (VIIIa). When methanol-chloroform was employed as the solvent system, 4-methoxycarbonyl-1,2-dihydropyridazino-[3,4-*b*]quinoxaline (VIIIb) was obtained.

The conversion of V to VII, VIIIa, and VIIIb was formulated as shown in Chart 2. The 2-aminopyridinyl group of an intermediate (IX) could be replaced with methylhydrazine to

provide VII. However, this replacement did not occur with hydrazine because of its low nucleophilicity as compared with methylhydrazine, so that alcoholysis took place to afford VIIIa and VIIIb.

Compounds III and V were oxidized with hydrogen peroxide in acetic acid to afford 2,3-dioxo-1,2,3,4-tetrahydroquinoxaline (X). Compound V was not hydrolyzed to III in water-acetic acid, and hence hydrogen peroxide was found to attack the 3-carbon atom of V. A reaction mechanism *via* the intermediates (XI and XII) was assumed, as shown in Chart 3.[6,7]

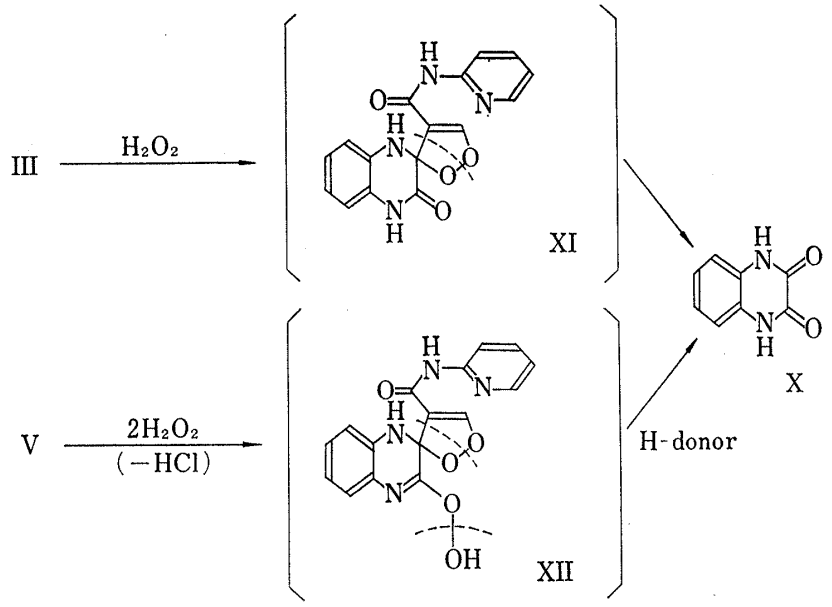


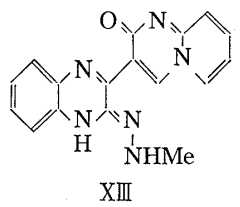
Chart 3

The NMR spectral data for III, V, and VI are shown in Table I. The 4′- and 6′-protons in the pyrido[1,2-*a*]pyrimidine rings are observed at lower magnetic field than the other aromatic protons in these compounds. The 6′-proton of V was observed at lower magnetic field than the 4′-proton in both solvent systems, DMSO-d_6 and DMSO-d_6–TFA (1: 1). The 6′-proton of III was also observed at lower magnetic field than the 4′-proton in DMSO-d_6. In contrast, the NMR spectrum of III in DMSO-d_6–TFA (1: 1) showed the 4′-proton at lower magnetic field than the 6′-proton. This solvent effect may be due to the 3-oxo-3,4-dihydroquinoxaline ring being attached to the 3-position of the pyrido[1,2-*a*]pyrimidine ring. The NMR spectrum of VI in DMSO-d_6–TFA (1: 1) also exhibited the 4′-proton at lower magnetic field than the 6′-proton, while its NMR spectrum in DMSO-d_6 was not obtained because of its insolubility. This observation suggests that the 3,4-dihydro form, such as the tautomer

Table I. NMR Spectral Data (δ-Value)

Compound	In DMSO-d_6		In DMSO-d_6-TFA (1: 1)	
	4′-H	6′-H	4′-H	6′-H
III	8.60	9.08	10.00	9.48
V	8.67	9.11	8.83	9.53
VI	—	—	9.93	7.73

6) Y. Kurasawa and A. Takada, *Heterocycles*, **14**, 333 (1980).
7) C.F. Cullis, A. Fish, and D.W. Turner, *Proc. Roy. Soc.* (London), **A 262**, 318 (1961); *idem*, *ibid.*, **A 267**, 433 (1962).



XIII

Chart 4

(XIII), may be the preferred structure of VI in DMSO-d_6–TFA (1: 1), although hydrazinoazines have been reported to exist predominantly in the hydrazino form.[8]

The ultraviolet (UV) spectral patterns of VII, VIIIa, and VIIIb were similar to each other, indicating that these compounds maintained the 1,2-dihydropyridazino[3,4-*b*]quinoxaline ring structure. This observation supported the view that VIIIa and VIIIb did not exist in the 2,10-dihydro form in solution, in agreement with the findings of Badger.[9]

Experimental

All melting points are uncorrected. IR spectra were recorded on a JASCO IRA-1 spectrophotometer from KBr discs. UV spectra were measured in EtOH on a Hitachi model 200-20 spectrophotometer. NMR spectra were obtained on a Varian T-60 spectrometer 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-01S spectrometer (Japan Electron Optics Laboratory Co., Ltd.). Pre-coated TLC plates, Silica Gel 60 F-254 (Merck), were used for the thin-layer chromatography.

3-Oxo-2-(2′H-pyrido[1′,2′-*a*]pyrimidin-2′-on-3′-yl)-3,4-dihydroquinoxaline (III)——A solution of I (5 g, 18.0 mmol) and 2-aminopyridine (9.7 g, 90 mmol) in BuOH (400 ml) was refluxed at 150—160° for 4 hr. The solution was concentrated *in vacuo* to a small volume to precipitate yellow crystals (III), which were collected by suction (3.2 g, 60%). Recrystallization from EtOH–AcOH followed by recrystallization from EtOH gave yellow needles, mp 306—309°. MS *m/e*: 290 (M^+). IR ν_{max}: 1720 (3-C=O), 1650 (2′-C=O). NMR (DMSO-d_6): 12.50 (1H, br.s, 4-NH), 9.08 (1H, d, J=6 Hz, 6′-H), 8.60 (1H, s, 4′-H), 8.33—7.00 (7H, m, aromatic); (DMSO-d_6–TFA) (1: 1): 10.00 (1H, s, 4′-H), 9.48 (1H, d, J=7 Hz, 6′-H), 8.83—7.00 (7H, m, aromatic). The 4-NH proton was not observed in DMSO-d_6–TFA (1: 1), presumably due to the presence of moisture in the solvent. UV λ_{max} nm (log ε): 214.0 (4.64), 297.0 (4.04), 380.0 (4.40). *Anal.* Calcd for $C_{16}H_{10}N_4O_2$: C, 66.20; H, 3.47; N, 19.30. Found: C, 66.25; H, 3.25; N, 19.49.

3-Chloro-2-(2′H-pyrido[1′,2′-*a*]pyrimidin-2′-on-3′-yl)quinoxaline (V)——$POCl_3$ was added to a solution of III (500 mg, 1.72 mmol) in DMF (20 ml), and the solution was heated on a boiling water bath for 2 hr. The solution was concentrated *in vacuo* to leave a brown mixture, which was poured onto crushed ice. The reaction product was extracted with $CHCl_3$, and the extract was dried over Na_2SO_4 and evaporated to dryness *in vacuo* to give yellow crystals (V) (460 mg, 87%). Recrystallization from EtOH–AcOH followed by recrystallization from EtOH afforded pale yellow needles, mp 229—231°. MS *m/e*: 308 (M^+), 310 (M^++2). IR ν_{max}: 1690 (2′-C=O). NMR (DMSO-d_6): 9.11 (1H, d, J=6 Hz, 6′-H), 8.67 (1H, s, 4′-H), 8.30—7.03 (7H, m, aromatic); (DMSO-d_6–TFA) (1: 1): 9.53 (1H, d, J=7 Hz, 6′-H), 8.83 (1H, s, 4′-H), 8.80—7.67 (7H, m, aromatic). UV λ_{max} nm (log ε): 206.5 (4.65), 246.0 (4.53), 365.0 (4.32). *Anal.* Calcd for $C_{16}H_9ClN_4O$: C, 62.25; H, 2.94; N, 18.15. Found: C, 62.05; H, 2.81; N, 18.31.

3-(2′-Methylhydrazino)-2-(2′H-pyrido[1′,2′-*a*]pyrimidin-2′-on-3′-yl)quinoxaline (VI) and 1-Methyl-4-(1′-methylhydrazinocarbonyl)-1,2-dihydropyridazino[3,4-*b*]quinoxaline (VII)——A solution of V (500 mg, 1.62 mmol) and methylhydrazine (745 mg, 16.2 mmol) in EtOH (50 ml) and $CHCl_3$ (20 ml) was refluxed for 4 hr. Removal of the solvent by evaporation gave a mixture of VI and VII. Compound VII was taken up in a small amount of EtOH with heating, and insoluble VI was collected by suction while the solution was hot. Evaporation of the filtrate to dryness afforded VII.

Compound VI——Yield, 25 mg (4.8%). Recrystallization from EtOH–$CHCl_3$ provided red needles, mp 316—319°. MS *m/e*: 318 (M^+). IR ν_{max}: 1650 (2′-C=O). NMR (DMSO-d_6–TFA) (1: 1): 12.01 (1H, br.s, 3-N<u>H</u>NHMe), 9.93 (1H, s, 4′-H), 7.73 (1H, d, J=7 Hz, 6′-H), 7.47—6.67 (7H, m, aromatic), 4.33 (1H, br.s, 3-NHN<u>H</u>Me), 3.70 (3H, s, 3-NHNH<u>Me</u>). UV λ_{max} nm (log ε): 240.0 (4.70), 300.0 (4.24), 314.5 (4.25), 486.0 (4.20). *Anal.* Calcd for $C_{17}H_{14}N_6O$: C, 64.14; H, 4.43; N, 26.40. Found: C, 64.38; H, 4.20; N, 26.13.

Compound VII——Yield, 345 mg (78%). Recrystallization from EtOH–$CHCl_3$ gave yellow needles, mp 195—196°. MS *m/e*: 270 (M^+). IR ν_{max}: 3280, 3160 (NH), 1630, 1610 (C=O). NMR ($CDCl_3$): 10.24 (1H, br.s, 2-NH), 7.27 (1H, s, 3-H), 7.07—6.17 (4H, m, aromatic), 4.00 (2H, br.s, CONMeN<u>H</u>$_2$), 3.28 (3H, s, NMe), 3.23 (3H, s, NMe); (DMSO-d_6): 10.33 (1H, br.s, 2-NH), 7.23 (1H, s, 3-H), 7.00—6.47 (4H, m, aromatic), 4.83 (2H, br.s, CONMeN<u>H</u>$_2$), 3.13 (3H, s, NMe), 3.08 (3H, s, NMe); (DMSO-d_6–TFA) (1: 1): 10.47 (1H, br.s, 2-NH), 7.77 (1H, s, 3-H), 7.00—6.67 (4H, m, aromatic), 3.68 (3H, s, NMe), 3.33 (3H, s, NMe). Protons of

8) D.M. Brown, M.J.E. Hewlins, and P. Schell, *J. Chem. Soc.* (*C*), **1968**, 1925; J.A. Elvidge and A.P. Redman, *J. Chem. Soc.* (*Perkin I*), **1972**, 2820.

9) G.M. Badger and P.J. Neilson, *Aust. J. Chem.*, **16**, 455 (1963); *idem*, *J. Chem. Soc.*, **1962**, 3926.

CONMeN$\underline{H}_2$ were not observed in DMSO-d_6–TFA (1: 1), presumably due to the presence of moisture in the solvent. UV λ_{max} nm (log ε): 254.5 (4.64), 412.0 (4.06), 447.5 (4.06). *Anal.* Calcd for $C_{13}H_{14}N_6O$: C, 57.76; H, 5.22; N, 31.10. Found: C, 57.96; H, 5.21; N, 29.98.

4-Ethoxycarbonyl-1,2-dihydropyridazino[3,4-*b*]quinoxaline (VIIIa) and 4-Methoxycarbonyl-1,2-dihydropyridazino[3,4-*b*]quinoxaline (VIIIb)——Procedure. A solution of V (500 mg, 1.62 mmol) and hydrazine hydrate (810 mg, 16.2 mmol) in EtOH (or MeOH) (50 ml) and $CHCl_3$ (20 ml) was refluxed for 4 hr. Removal of the solvent by evaporation afforded a yellow product (VIIIa or VIIIb).

Compound VIIIa——Yield, 380 mg (92%). Recrystallization from EtOH–$CHCl_3$ provided yellow needles, mp 255—257°. MS *m/e*: 256 (M^+). IR ν_{max}: 1660, 1650 (C=O). NMR (DMSO-d_6–TFA) (1: 1): 10.33 (1H, br.s, 2-NH), 8.28 (1H, s, 3-H), 7.27—6.47 (4H, m, aromatic), 4.33, (2H q, J=7 Hz, CH_2), 1.35 (3H, t, J=7 Hz, Me). The 1-NH proton was not observed, presumably due to the presence of moisture in the solvent. UV λ_{max} nm (log ε): 244.5 (4.62), 418.0 (3.97), 444.0 (4.02), 469.0 s (3.87). *Anal.* Calcd for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72; N, 21.87. Found: C, 60.71; H, 4.72; N, 22.06.

Compound VIIIb——Yield, 320 mg (82%). Recrystallization from MeOH–$CHCl_3$ gave yellow needles, mp 252—254°. MS *m/e*: 242 (M^+). IR ν_{max}: 1665, 1650 (C=O). NMR (DMSO-d_6–TFA) (1: 1): 10.30 (1H, br.s, 2-NH), 8.28 (1H, s, 3-H), 7.23—6.43 (4H, m, aromatic), 3.87 (3H, s, Me). The 1-NH proton was not observed, presumably due to the presence of moisture in the solvent. UV λ_{max} nm (log ε): 245.5 (4.63), 416.0 (3.96), 441.0 (4.01), 473.0 s (3.85). *Anal.* Calcd for $C_{12}H_{10}N_4O_2$: C, 59.72; H, 4.16; N, 23.13. Found: C, 59.72; H, 4.15; N, 23.26.

Reaction of III with Hydrogen Peroxide——A solution of III (500 mg, 1.72 mmol) in AcOH (50 ml) was treated with 30% H_2O_2 (10 g, 88.2 mmol), and the mixture was heated on a boiling water bath for 3 hr. The solution was evaporated to dryness *in vacuo* to give 2,3-dioxo-1,2,3,4-tetrahydroquinoxaline (X) (220 mg, 79%).

Reaction of V with Hydrogen Peroxide——A solution of V (200 mg, 0.65 mmol) in AcOH (20 ml) was treated with 30% H_2O_2 (3.8 g, 33 mmol), and the solution was heated on a boiling water bath for 3 hr. The solution was evaporated to dryness *in vacuo* to afford X (70 mg, 63%).

Acknowledgement The authors are indebted to Mr. Jun Satoh and Miss Mie Ogura for their technical assistance and to Dr. Yoshihisa Okamoto for his valuable suggestions.