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Halogenations of 3-Methoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline

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The reactions of 3-methoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (**1**) with *N*-bromosuccinimide, *N*-chlorosuccinimide, Br_2–H_2O, and Cl_2–H_2O gave 4-halogeno-3-methoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxalines (**3a** and **3b**), while the reactions of **1** with H_2O_2–HBr and H_2O_2–HCl afforded 4-halogeno-3-(1-halogeno-1-methoxycarbonyl)-methylene-2-oxo-1,2,3,4-tetrahydroquinoxalines (**4a** and **4b**). Mechanisms are proposed for these halogenations.

Keywords——*N*-bromosuccinimide; *N*-chlorosuccinimide; hydrogen peroxide; bromine–water; chlorine–water; 4-halogeno-3-methoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxalines; 4-halogeno-3-(1-halogeno-1-methoxycarbonyl)methylene-2-oxo-1,2,3,4-tetrahydroquinoxalines; tautomeric behavior; zinc iodide

The tautomeric behavior of 3-methoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (**1**)[1] has been studied spectroscopically,[2] and its equilibrium is shown in Chart 1. In acidic media, N_4-H of **1** migrates to the methylenic carbon.[2] Based on its equilibrium, the reactions of **1** with various electrophilic reagents have been undertaken, that is, the reactions of **1** with isopentyl nitrite in acetic acid and trichloroacetic acid,[3] the Vilsmeier reagent,[4] and *m*-chloroperbenzoic acid in chloroform[5] gave methyl 2-(3,4-dihydro-3-oxo-2-quinoxalinyl)-2-hydroxyiminoacetate, 3-(*N*,*N*-dimethylaminocarbonyl)furo[2,3-*b*]quinoxaline, and 3-(1-hydroxy-1-methoxycarbonyl)methylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (**2**), respectively.

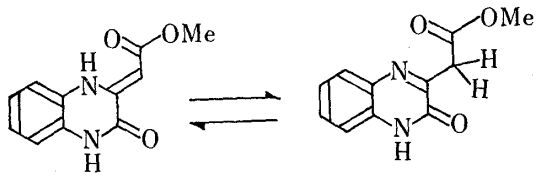

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Chart 1

Thus, the methylenic carbon of **1** has been functionalized with various electrophiles. However, no halogenated compounds at the methylenic carbon have been obtained to date. Such halogenated compounds would react with Grignard reagents to form the C–C bond[6] and a further condensed ring, as shown in Chart 2, which might provide a route to the synthesis of the novel quinoxaline derivatives. Therefore, conditions for methylenic *C*-halogenation of **1** were examined using various reagents, such as *N*-bromosuccinimide (NBS), *N*-chlorosuccinimide (NCS), bromine–water (Br_2–H_2O), chlorine–water (Cl_2–H_2O), hydrogen peroxide and hydrogen bromide (H_2O_2–HBr), and hydrogen peroxide and hydrochloric acid (H_2O_2–HCl).[7]

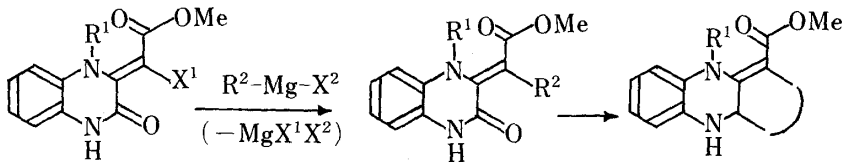

Chart 2

The reactions of **1** with NBS and NCS in carbon tetrachloride effected N_4-halogenation to precipitate 4-bromo-3-methoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (**3a**) and 4-chloro-3-methoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (**3b**), respectively. Since the media of Br_2–H_2O and Cl_2–H_2O are acidic, the methylenic carbon of **1** is expected to be halogenated. However, the reactions of **1** with Br_2–H_2O and Cl_2–H_2O also induced N_4- halogenation, but not *C*-halogenation, to precipitate **3a** and **3b**, respectively. On the other hand, the system of H_2O_2–HX (X=Br, Cl) may supply reactive species such as X_2, HOX (X^+), X^-, and $HO\text{–}\overset{+}{O}H_2$, and in fact, the application of H_2O_2–HX resulted in the *C*-halogenation of **1**, as well as the N_4-halogenation. The reactions of **1** with H_2O_2–HBr and H_2O_2–HCl caused both N_4- and methylenic *C*-halogenations to provide 4-bromo-3-(1-bromo-1-methoxycarbonyl)methylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (**4a**) and 4-chloro-3-(1-chloro-1-methoxycarbonyl)methylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (**4b**), respectively. Moreover, dehalogenation of **4a** and **4b** was examined with iodide anion, which is known to eliminate halogens from halide derivatives.[8] Treatment of **4a** with zinc iodide brought about elimination of the N_4-halogen to give 3-(1-bromo-1-methoxycarbonyl)-methylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (**5a**), while similar treatment of **4b** led to elimination of the N_4- and *C*-halogens to afford **1**, instead of 3-(1-chloro-1-methoxycarbonyl)methylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (**5b**).

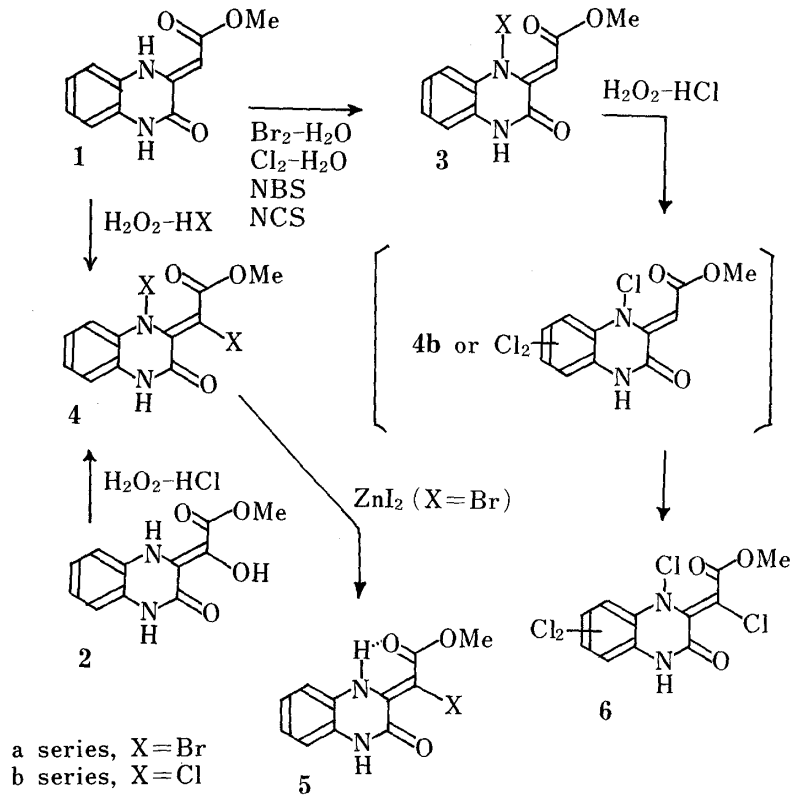

Chart 3

From the above results, the reaction mechanism for the formation of **3** from **1** was postulated to be as shown in Chart 4 (A), although **3** was not converted to **4** in the reactions with NBS, NCS, Br_2–H_2O, and Cl_2–H_2O. Mechanism (B) is plausible for the formation of **4** from **1**, in view of the result that the reaction of **2** with H_2O_2–HCl provided **4b**. In addition, the reaction of **3b** with H_2O_2–HCl effected chlorination at the methylenic carbon and dichlorination in the aromatic ring to produce the tetrachloride (**6**). The nuclear magnetic resonance (NMR) spectrum of **6** exhibited signals due to methyl, N_1-H, and two aromatic protons (two doublets, $J=8.8$ Hz), but the chlorinated positions in the aromatic ring could not be determined. The structure will be reported in detail elsewhere.

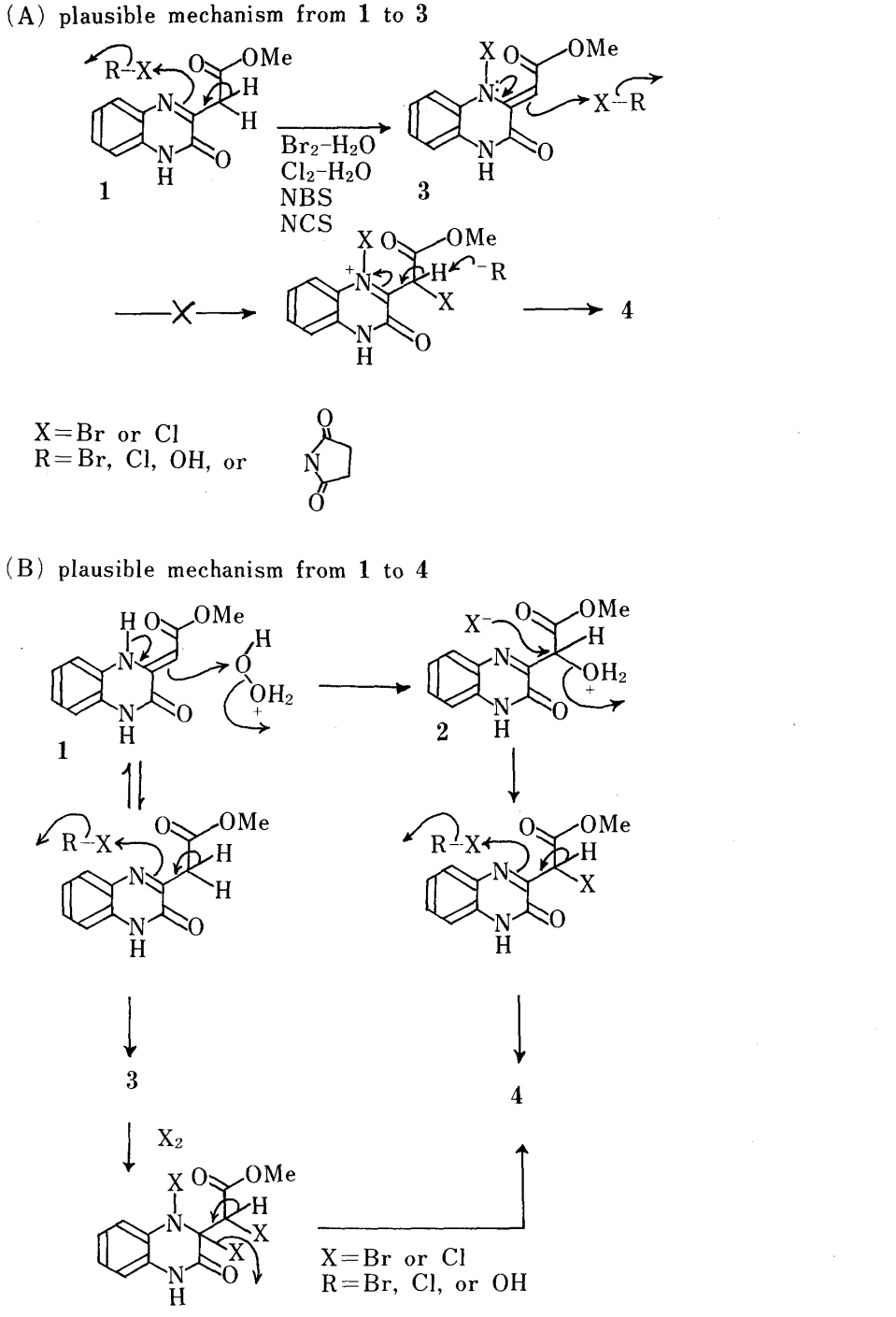

Chart 4

TABLE I. UV, IR, and NMR Data for **3**, **4**, **5**, and **6**

Compound No.	X	UV λ_{max} nm (log ε)	IR $\nu_{(C=O)}$ (cm^{-1})
3a	Br	230.0 (4.35), 286.0 (3.86), 350.0 (3.81)	1750, 1660
3b	Cl	230.0 (4.37), 285.5 (3.86), 350.0 (3.83)	1750, 1660
4a	Br	234.5 (4.33), 292.5 (3.88), 349.0 (3.92)	1760, 1665
4b	Cl	233.0 (4.34), 290.0 (3.88), 355.0 (3.89)	1770, 1660
5a	Br	—	1700, 1650
6			1770, 1660

No.	NMR δ (DMSO-d_6)			
	N_1–H	Aromatic	Vinyl	Me
3a	12.83 (s)	7.90—7.40 (m, 4H)	6.07 (s)	3.72 (s)
3b	12.79 (s)	8.00—7.30 (m, 4H)	6.07 (s)	3.73 (s)
4a				
4b	13.07 (s)	8.03—7.33 (m, 4H)	—	3.80 (s)
5a				
6	—[a]	7.88 (d, 1H)[b]	—	3.78 (s)
		7.62 (d, 1H)		

a) The signal due to the N_1–H proton was observed at δ 3.33 ppm as a broad singlet together with the signal due to H_2O.
b) J=8.8 Hz.

Ultraviolet (UV) spectral data for **3a**, **3b**, **4a**, and **4b** are listed in Table I; their spectral patterns are similar. In the infrared (IR) spectra of **3a**, **3b**, **4a**, **4b**, and **6**, ester C=O absorption bands appeared at 1750 cm^{-1} or above. These data indicated the absence of an intramolecular hydrogen bond between N_4-H and the ester C=O group.[1] In mass spectral (MS) fragmentations, **3a**, **3b**, and **5a** exhibited fragment ions corresponding to $M^+ - MeOH$, whereas **4a**, **4b**, and **6** did not, supporting the presence of N_4-H or a vinyl proton in **3a**, **3b**, and **5a**. While the NMR spectrum of **1** in dimethylsulfoxide-d_6 (DMSO-d_6) showed the signals of both vinyl and methylene protons as represented in Chart 1,[2] the NMR spectra of **3a** and **3b** exhibited vinyl protons, but no methylene protons. These data provide additional evidence for the presence of the N_4-halogen in **3a** and **3b**. On the other hand, the NMR spectra of **4a** and **5a** were measured in DMSO-d_6 or *N*,*N*-dimethylformamide-d_7 because of insolubility of the compounds in other solvents, but the *C*-bromo atoms of these compounds were replaced by hydrogen atoms originating from moisture in the above solvents, and hence the NMR spectra showed vinyl protons and did not correspond to the proposed structures. The structures of **4a** and **5a** were established on the basis of the microanalytical, MS, and IR spectral data as described above.

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 with tetramethylsilane as an internal standard. UV spectra were obtained in EtOH on a Hitachi model 200-20 spectrophotometer. MS were determined with a JMS-01S spectrometer (Japan Electron Optics Laboratory Co., Ltd.).

4-Halogeno-3-methoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxalines (3)——Method A: A suspension of **1** (10 g, 45.9 mmol) with NBS (9.79 g, 55.1 mmol) in CCl_4 (200 ml) was refluxed on a boiling water bath for 2 h. Colorless crystals of **3a** precipitated during the reaction. The crystals were collected by suction filtration and washed

with hot EtOH. Yield, 13.62 g (95%). Recrystallization from EtOH afforded colorless needles, mp 198—200 °C. MS *m/e*: 296 (M^+-1), 298 (M^++1). *Anal.* Calcd for $C_{11}H_9BrN_2O_3$: C, 44.47; H, 3.05; N, 9.43. Found: C, 44.46; H, 3.02; N, 9.30.

Compound **3b** was obtained in a similar manner to that described above. Yield, 10.98 g (95%). Recrystallization from EtOH provided colorless needles, mp 202—203 °C. MS *m/e*: 252 (M^+), 254 (M^++2). *Anal.* Calcd for $C_{11}H_9ClN_2O_3$: C, 52.29; H, 3.59; N, 11.09. Found: C, 52.23; H, 3.48; N, 11.04.

Method B: Br_2–water (100 ml) was added dropwise to a suspension of **1** (1 g) in EtOH (20 ml) with stirring under cooling in an ice-water bath. Stirring was continued for 2 h at room temperature to precipitate colorless crystals of **3a** which were collected by suction filtration (1.34 g, 99.2%).

Compound **3b** was obtained by a similar manner to that described above. Yield, 1.13 g (98%).

4-Bromo-3-(1-bromo-1-methoxycarbonyl)methylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (4a)——KBr (137 g, 1.15 mol), 40% H_2SO_4 (150 ml), and 35% H_2O_2 (50 ml) were added to a suspension of **1** (5 g, 22.9 mmol) in EtOH (300 ml) with stirring under cooling in an ice-water bath. After addition of H_2O_2, the whole was stirred for 2 h at room temperature; colorless crystals of **4a** precipitated. The crystals were collected by suction filtration and washed with H_2O. Yield, 3.66 g. The filtrate was shaken with several portions of $CHCl_3$, and the combined organic layer was washed with $Na_2S_2O_3$ solution, $NaHCO_3$ solution, and H_2O, then dried over Na_2SO_4. The solvent was evaporated off to leave colorless crystals of **4a** (3.50 g). Total yield, 7.16 g (87%). Recrystallization from EtOH gave colorless needles, mp 248—250 °C. MS *m/e*: 374 (M^+-2), 376 (M^+), 378 (M^++2). *Anal.* Calcd for $C_{11}H_8Br_2N_2O_3$: C, 35.14; H, 2.14; N, 7.45. Found: C, 35.38; H, 2.16; N, 7.63.

4-Chloro-3-(1-chloro-1-methoxycarbonyl)methylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (4b)——Conc. HCl (200 ml), KCl (8.55 g, 114.5 mmol), 40% H_2SO_4 (50 ml), and 35% H_2O_2 (50 ml) were added to a suspension of **1** (5 g, 22.9 mmol) in EtOH (300 ml) with stirring under cooling in an ice-water bath. After addition of H_2O_2, the whole was stirred for 24 h at room temperature. The product **4b** was obtained in a similar manner to that described above. Yield, 4.62 g (70%). Recrystallization from EtOH gave colorless needles, mp 208—210 °C. MS *m/e*: 286 (M^+), 288 (M^++2). *Anal.* Calcd for $C_{11}H_8Cl_2N_2O_3$: C, 46.02; H, 2.81; N, 9.76. Found: C, 46.14; H, 2.74; N, 9.63.

3-(1-Bromo-1-methoxycarbonyl)methylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (5a)——A solution of the dibromide **4a** (5 g, 13.30 mmol) with ZnI_2 (8.49 g, 26.60 mmol) in AcOH (300 ml) and CF_3COOH (10 ml) was heated on a boiling water bath for 6 h. Evaporation of the solvent afforded an oily residue, which was dissolved in $CHCl_3$. The organic layer was washed with $Na_2S_2O_3$ solution then H_2O, and dried over Na_2SO_4. Evaporation of the solvent gave yellow crystals. Recrystallization from EtOH provided yellow needles of **5a** (1.60 g, 41%), mp 238—240 °C. MS *m/e*: 296 (M^+-1), 298 (M^++1). *Anal.* Calcd for $C_{11}H_9BrN_2O_3$; C, 44.47; H, 3.05; N, 9.43. Found: C, 44.64; H, 3.06; N, 9.39.

Treatment of 4b with ZnI_2——A solution of **4b** (500 mg, 1.75 mmol) with ZnI_2 (1.11 g, 3.5 mmol) in AcOH (30 ml) and CF_3COOH (1 ml) was heated on a boiling water bath for 6 h. A similar procedure to that described above gave **1** (220 mg, 57.7%).

Preparation of 4b from 2——Conc. HCl (40 ml) and 35% H_2O_2 (4 ml) were added to a suspension of **2** (1 g) in MeOH (100 ml) with stirring under cooling in an ice-water bath. After 2 h stirring at room temperature, the product was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, saturated $Na_2S_2O_3$ solution, and H_2O, then dried over Na_2SO_4. Evaporation of the solvent afforded an oily residue, which was treated with hexane to provide pale yellow crystals (770 mg, 62.8%). Recrystallization from EtOH gave colorless needles (**4b**).

Preparation of Tetrachloride (6) from 3b——A suspension of **3b** (500 mg) in EtOH (50 ml) and conc. HCl (50 ml) was treated dropwise with 35% H_2O_2 (5 ml) with stirring under cooling in an ice-water bath. Stirring at room temperature afforded a clear solution, and further stirring for 3 h resulted in the precipitation of colorless crystals, which were collected by suction filtration (190 mg, 26.9%). Recrystallization from EtOH gave colorless needles, mp 258—261 °C. MS *m/e*: 354 (M^+-2), 356 (M^+), 358 (M^++2). *Anal.* Calcd for $C_{11}H_6Cl_4N_2O_3$: C, 37.11; H, 1.70; N, 7.87. Found: C, 37.04; H, 1.65; N, 7.85.

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