Synthesis of Quinoxaline Derivatives through Condensation of 1,2-Diaminobenzenes with β-Keto Sulfoxides

Shinzo Kano, Shiroshi Shibuya, and Yoko Yuasa*

Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan

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The reaction of *o*-phenylenediamine with α-methylsulfinylcyclohexanone and α-methylsulfinylcyclopentanone in the presence of acetic acid afforded 1,2,3,4-tetrahydrophenazine and 2,3-dihydro-1*H*-cyclopenta[*b*]-quinoxaline, respectively. 3,4-Diaminotoluene and 3,4-diaminochlorobenzene were reacted with α-methylsulfinylacetophenone to give a mixture of the corresponding 6- and 7-substituted 2-phenylquinoxaline. Condensation of 3,4-diaminomethoxybenzene with α-methylsulfinylacetophenone gave 7-methoxy-2-phenylacetophenone, whereas, the same reaction between 3,4-diaminonitrobenzene and α-methylsulfinylacetophenone yielded 6-nitro-2-phenylquinoxaline.

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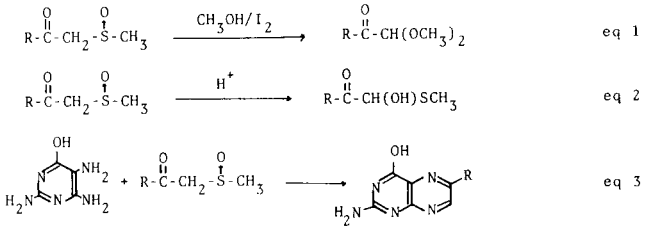
β-Keto sulfoxides may be viewed as 1,2-diketone equivalents, since they are easily converted to α,α-dimethoxy ketones by the reaction with methanol and iodine (1) (equation 1) and α-methylthio-α-hydroxy ketones on treatment with hydrochloric acid and DMSO (2) (equation 2). Furthermore, β-keto sulfoxides behave as 1,2-diketones upon treatment with 1,2-diamino compounds as illustrated by the synthesis of pteridine derivatives from β-keto sulfoxides with 2,4,5-triamino-6-hydroxypyrimidine (3) (equation 3). We have investigated a facile and general synthesis of quinoxaline derivatives through condensation of 1,2-diaminobenzenes with β-keto sulfoxide derivatives. The results of our studies were described in this paper.



eq 1

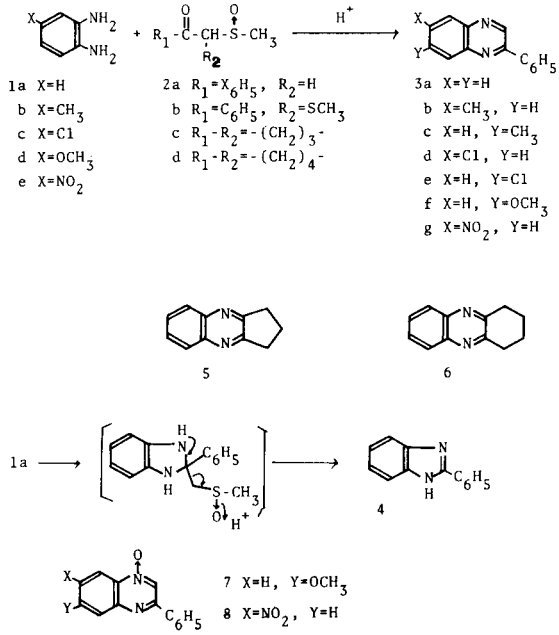
eq 2

eq 3

Condensation of *o*-phenylenediamine (**1a**) with α-methylsulfinylacetophene (**2a**) (4) in benzene under reflux in the presence of acetic acid gave 2-phenylquinoxaline (**3a**) (5) in 35% yield and 2-phenylbenzimidazole (**4**) in 30% yield. The reaction of **1a** with α-methylsulfinyl-α-methylthioacetophenone (**2b**) (7) under the same conditions afforded **3a** in 60% yield without formation of **4**. The formation of **4** can be accounted for elimination of the sulfoxide moiety through the dihydrobenzimidazole.

Condensation of **1a** with α-methylsulfinylcyclopentanone (**2c**) gave 2,3-dihydro-1*H*-cyclopenta[*b*]quinoxaline (**5**) (8) in 17% yield. The reaction of **1a** with α-methylsulfinylcyclohexanone (**2d**) also gave the similar results and 1,2,3,4-tetrahydrophenazine (**6**) (9) was obtained in 16% yield.

Scheme 1



It was interest to examine whether 6-substituted 2-phenylquinoxaline or the corresponding 7-isomer would be obtained on treatment of 4-substituted 1,2-diaminobenzenes with the ketones **2a** and **2b**. 3,4-Diaminotoluene (**1b**) was treated with **2a** to give a mixture of 6-methyl-2-phenylquinoxaline (**3b**) (10,11) and 7-methyl-2-phenylquinoxaline (**3c**) (12) in a ratio of 1:2. The reaction of 3,4-diaminochlorobenzene (**1c**) with **2a** also gave a mixture of 6-chloro-2-phenylquinoxaline (**3d**) (11,12) and 7-chloro-2-phenylquinoxaline (**3e**) (11,12) in a ratio of 1:3. The reaction by the use of **2b** instead of **2a** also gave a mixture of **3b** and **3c** (and **3d** and **3e**) without any significant difference in the yields and ratio of the products. These mixtures were purified by column chromatography on silica gel and the structures and ratios of the products were determined by the method as Bannore reported (12). However, condensation of 3,4-diaminomethoxybenzene

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Table 1

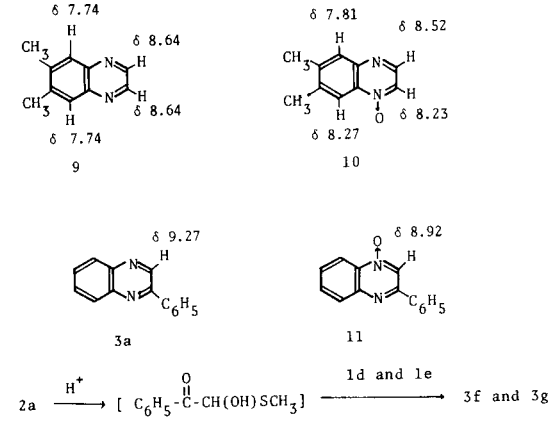
^{1}H Nmr Spectra (deuteriochloroform) of **3f**, **3g**, **7** and **8**

Compound No.	δ (ppm) H_3	H_5	H_6	H_7	H_8
3f	9.08 (s)	7.91 (d, J = 9 Hz)	7.40 (d, d, J = 1.5 and 9 Hz)		7.87 (d, J = 1.5 Hz)
3g	9.42 (s)	8.95 (d, J = 2 Hz)		8.50 (d, d, J = 2 and 10 Hz)	
	8.81 (s)	8.42 (d, J = 9 Hz)	7.44 (d, d, J = 1.5 and 9 Hz)		7.85 (d, J = 1.5 Hz)
8	8.90 (s)	9.38 (d, J = 9 Hz)		8.59 (d, d, J = 2 and 10 Hz)	8.23 (d, 10 Hz)

(**1d**) with **2a** gave 7-methoxy-2-phenylquinoxaline (**3f**) in 60% yield without formation of either the alternative isomer or 6-methoxy-2-phenylbenzimidazole. On the other hand, the reaction between 1,2-diamino-4-nitrobenzene (**1e**) and **2a** afforded 6-nitro-2-phenylquinoxaline (**3g**) in 65% yield and the 7-nitro isomer was not obtained. The position of the substituent in **3f** and **3g** was determined by comparison of their ^{1}H nmr spectra with those of the corresponding 4-oxides **7** and **8**, prepared by oxidation of **3f** and **3g** with *m*-chloroperoxybenzoic acid (*m*-CPBA), respectively (12). The observed shifts of the aromatic proton signals of 6,7-dimethylquinoxaline (**9**) (13) and 6,7-dimethylquinoxaline 1-oxide (**10**), **3a** and 2-phenylquinoxaline 4-oxide (**11**) (14) were examined, respectively, for the further confirmation of the Bannore's method. The H_2 singlet at δ 8.64 in the ^{1}H nmr spectrum of **9** shifted to δ 8.23 in the spectrum of **9**. On the other hand, H_8 singlet at δ 7.74 in the spectrum of 9 shifted to δ 8.27. Furthermore, the H_3 singlet at δ 9.27 in the spectrum of **3a** shifted to δ 8.92 in the spectrum of **10**. Thus, the signals for the proton adjacent to the *N*-oxide underwent an upfield shift relative to the parent quinoxaline, whereas the signals due to the proton at the peri-position to the *N*-oxide were displaced downfield (12). In accordance with these characteristic shifts of aromatic proton signals between quinoxalines and quinoxaline *N*-oxides, the position of the substituent in the unsymmetrical adducts **3f** and **3g** was determined. As indicated in Table 1, the spectrum of **3f** contained doublets at δ 7.91, which could be assigned to H-5. The high coupling constant (J = 9 Hz) indicated that the methoxy group was located at the 7-position. On the other hand, the low coupling constant (J = 2 Hz) of δ 8.95 doublet attributable to H-5 in **3g** indicated attachment of the nitro group at the 6-position.

This positionally selective synthesis of disubstituted quinoxaline derivatives most probably proceeds *via* preferential reaction of the α-carbon in the intermediate with the more basic amino group in **1d** and **1e**. Actually, after **2a** was heated in benzene containing acetic acid for 1 hour and then **1a** was added to the reaction mixture, only **3a** was obtained in 65% yield without formation of **4** (15).

Scheme 2



EXPERIMENTAL

All melting points are uncorrected. ^{1}H nmr spectra were recorded with a JEOL PS-100 spectrometer at 100 MHZ. Mass spectra were obtained with a Hitachi RMU-7L mass spectrometer.

Condensation of *o*-Phenylenediamine (**1a**) with **2a**.

A mixture of 2.16 g. (20 mmoles) of **1a**, 3.66 g. (20 mmoles) of **2a**, 50 ml. of benzene and 1 ml. of acetic acid was heated under reflux for 2 hours. The solvent was evaporated and the resulting residue was chromatographed on silica gel (15 g.). Elution with benzene afforded 1.44 g. (35%) of **3a**, m.p. 75° [lit. (5) m.p. 77°]. Elution with chloroform gave 1.16 g. (30%) of **4**, m.p. 283-285° [lit. (6) m.p. 286].

2,3-Dihydro-1*H*-cyclopenta[*b*]quinoxaline (**5**).

A mixture of 2.16 g. (20 mmoles) of **1a** and 2.6 g. (20 mmoles) of **2c** was heated in 50 ml. of benzene containing 1 ml. of acetic acid for 2 hours and the mixture was worked up as above. Elution with benzene (150 ml.) yielded 0.6 g. (17%) of **5**, m.p. 97-99° [lit. (8) m.p. 99.7°].

1,2,3,4-Tetrahydrophenazine (**6**).

The reaction of 2.16 g. (20 mmoles) of **1a** and 2.9 g. (20 mmoles) of **2d** was carried out as above to give 0.59 g. (16%) of **6**, m.p. 90-92° [lit. (9) m.p. 92°].

General Procedure for the Synthesis of 2-Phenylquinoxaline Derivatives.

Method a.

A mixture of 20 mmoles of 4-substituted 1,2-diaminobenzene and 3.66 g. (20 mmoles) of **2a** was heated in a mixture of 50 ml. of benzene and 1 ml. of acetic acid under reflux for 2 hours. After removal of the solvent, the remaining residue was extracted with chloroform. The extract was washed with water, dried over sodium sulfate and evaporated. The resulting residue was chromatographed on silica gel (10 g.) by the use of chloroform as an eluant. Removal of the solvent (200-250 ml.) afforded 2-phenylquinoxaline derivatives.

Method b.

The reaction of 20 mmoles of 4-substituted 1,2-diaminobenzene and 4.56 g. (20 mmoles) of **2b** was carried out and worked up as above.

6-Methyl- and 7-Methyl-2-phenylquinoxaline (**3b** and **3c**).

This synthesis was accomplished as indicated, yield, by Method a, 2.7 g. (61%), by Method b, 2.8 g. (64%), m.p. 127-134° (petroleum ether); ms: m/e 220 (M^+). The ^1H nmr (deuteriochloroform) spectrum of the mixture of *N*-oxides indicated that this was a 1:2 mixture of **3b** and **3c** (14).

6-Chloro- and 7-Chloro-2-phenylquinoxalaine (**3d** and **3e**).

This synthesis was accomplished as indicated, yield, by Method a, 2.4 g. (50%), by Method b, 2.53 g. (53%), m.p. 123-125°. The ^1H nmr (deuteriochloroform) spectrum of the corresponding *N*-oxide indicated that this was a mixture of **3d** and **3e** in a ratio of 1:3 (14).

7-Methoxy-2-phenylquinoxaline (**3f**).

This synthesis was accomplished as indicated, yield, by Method a, 2.9 g. (62%), by Method b, 2.9 g. (62%), m.p. 86-88° (methanol-ether); ms: m/e 236 (M^+).

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.33; H, 5.08; N, 11.92.

6-Nitro-2-phenylquinoxaline (**3g**).

This synthesis was accomplished as indicated, yield, by Method a, 3.26 g. (63%), by Method b, 3.26 g. (62%), m.p. 209-210° (methanol-ether); ms: m/e 251 (M^+).

Anal. Calcd. for $C_{14}H_9N_3O_2$: C, 66.92; H, 3.61; N, 16.73. Found: C, 67.05; H, 3.41; N, 16.93.

General Procedure for the Oxidation of Quinoxalines.

A mixture of quinoxaline (10 mmoles), *m*-CPBA (1.72 g., 10 mmoles) and methylene chloride (40 ml.) was stirred at room temperature for 14 hours. The mixture was washed with 5% sodium bicarbonate and water, and dried over sodium sulfate. Evaporation of the solvent gave a mixture of the mono *N*-oxide and the starting material. The mixture was chromatographed on silica gel (15 g.) by the use of the methylene chloride was an eluant. Removal of the solvent (100-120 ml.) yielded the pure mono *N*-oxide.

6,7-Dimethylquinoxaline 1-Oxide (**10**).

This compound was synthesized in 65% yield (1.05 g.), m.p. 108-110° (methanol); ms: m/e 150 (M^+), 134 (M^+-16).

Anal. Calcd. for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 10.65. Found: C, 63.73; H, 6.58; N, 10.81.

2-Phenylquinoxaline 4-Oxide (**11**).

This compound was synthesized in 60% yield (1.33 g.), m.p. 135-138° (methanol) [lit. (13) m.p. 138°]; ms: m/e 222 (M^+), 208 (M^+-16).

Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.65; H, 4.54; N, 12.61. Found: C, 75.38; H, 4.58; N, 12.77.

7-Methoxy-2-phenylquinoxaline 4-Oxide (**7**).

This compound was synthesized in 63% yield (1.58 g.), m.p. 160-161°; ms: m/e 252 (M^+), 236 (M^+-16).

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.80; N, 11.11. Found: C, 71.28; H, 4.70; N, 11.15.

6-Nitro-2-phenylquinoxaline 4-Oxide (**8**).

This compound was obtained in 60% yield (1.6 g.), m.p. 214-216° (methanol); ms: m/e 267 (M^+), 251 (M^+-16).

Anal. Calcd. for $C_{14}H_9N_3O_3$: C, 62.92; H, 3.39; N, 15.73. Found: C, 63.05; H, 3.48; N, 15.95.

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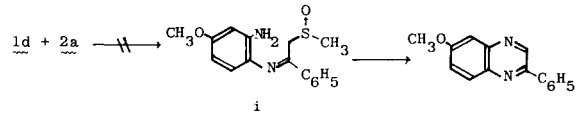
(15) Although formation of shiff base *i* was also examined to get 6-substituted 2-phenylquinoxalines through cyclization of *i* with an acid as Rosowsky reported, *i* was not formed under the usual conditions.



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