A Convenient Synthesis of Novel Pyridazino[3,4-*b*]quinoxalines

Yoshihisa Kurasawa*, Harumi Arai, Kiyoko Arai, Atsushi Satoh,
Satoyuki Ninomiya, Yoshihisa Okamoto and Atsushi Takada

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

Received February 4, 1987

Novel 4-chlorophenylhydrazono-3-oxo-1,2,3,4-tetrahydropyridazino[3,4-*b*]quinoxalines **10a-c** were synthesized by the cyclization of the α-hydrazonohydrazides **8a-c**. The chlorination of **10a** with phosphoryl chloride afforded 3-chloro-4-[2-(*o*-chlorophenyl)hydrazino]pyridazino[3,4-*b*]quinoxaline **12**.

J. Heterocyclic Chem., **24**, 1219 (1987).

There were a few papers concerning the synthesis of several pyridazino[3,4-*b*]quinoxalines **1-3** [1-3] (Chart 1) until 1973. Thereafter, we reported the synthesis of the pyridazino[3,4-*b*]quinoxalines **4,5** *via* a ring transformation of a furo[2,3-*b*]quinoxaline [4,5]. Thus, the pyridazino-[3,4-*b*]quinoxaline derivatives known so far are few. In the present investigation, we undertook a development of an additional route to new pyridazino[3,4-*b*]quinoxalines.

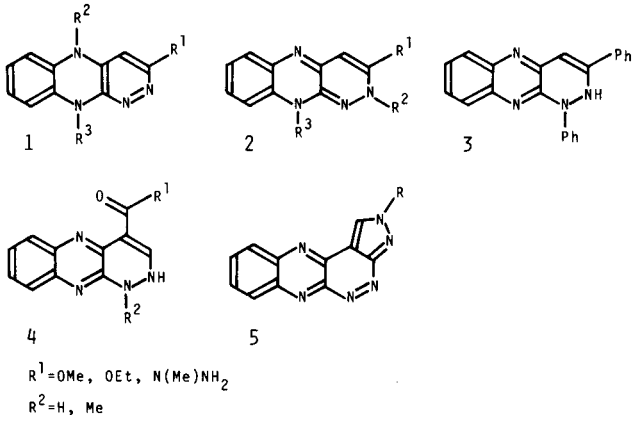


Chart 1

In a previous paper [6], we reported the diazotization of the ester **6** to the α-hydrazonoesters **7a-c**, which were converted into the 1-aryl-3-quinoxalinyl-1,2,4-triazoles **9a-c**

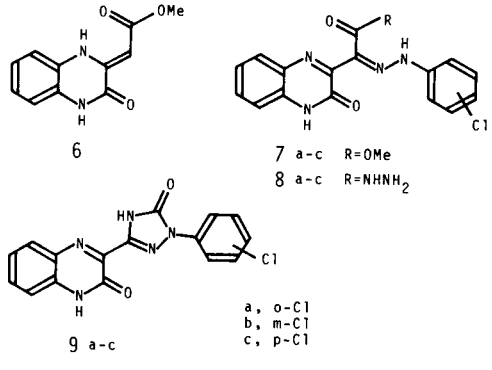


Chart 2

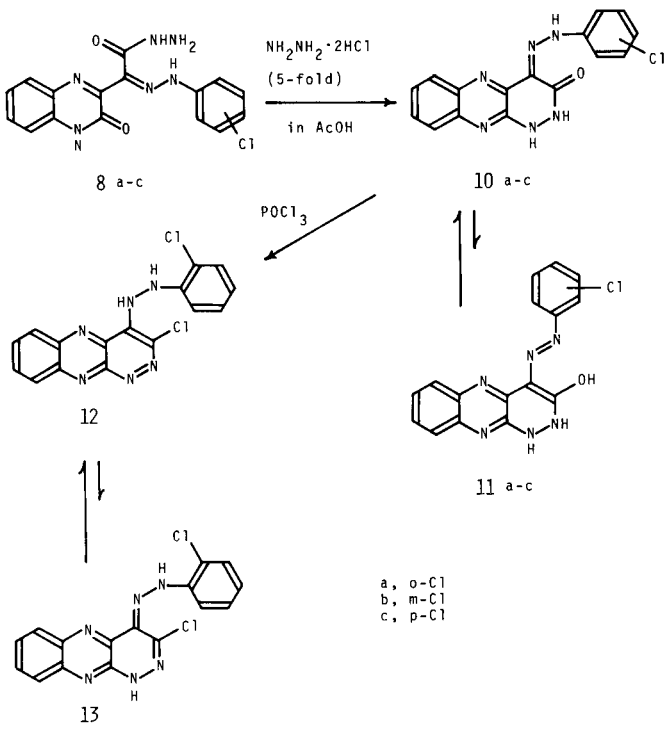
via the α-hydrazonohydrazides **8a-c** (Chart 2). Since a new route to construct the pyridazino[3,4-*b*]quinoxaline ring was considered to be on the extension of the above process, conditions were examined to cyclize **8a-c** into the pyridazino[3,4-*b*]quinoxalines. As the result, a simple method was found to accomplish the cyclization.

Refluxing of **8a-c** [7] and an excess of hydrazine dihydrochloride in acetic acid conveniently effected the cyclization to give hydrochlorides of 4-chlorophenylhydrozono-3-oxo-1,2,3,4-tetrahydropyridazino[3,4-*b*]quinoxalines **10a-c**. Treatment of **10a-c** with 10% sodium hydroxide solution provided the free base **10a-c**. The reaction of **10a** with phosphoryl chloride resulted in the C_3-chlorination to afford 3-chloro-4-[2-(*o*-chlorophenyl)hydrazino]pyridazino-[3,4-*b*]quinoxaline **12**.

In our previous paper [4], compounds **4** were assigned as the 1,2-dihydro, but not the 2,10-dihydro, structure based on the pmr and uv spectral data. Moreover, the α-ketohydrazone form has been known to be more stable than the diazenyl enol form [8] (Chart 3). Accordingly, compounds **10a-c** in the present investigation may be assigned as the 1,2,3,4-tetrahydro form, but not the 1,2-dihydro form **11**.

Chart 3

On the other hand, compound **12** was assigned as the hydrazino, but not the hydrazone **13**, form based on the comparison of the NH proton signals of **10a-c** with those of **12**. Namely, the pmr spectra of **10a-c** in deuteriodimethylsulfoxide (DMSO-d_6) showed the NH proton signals in magnetic fields lower than δ 12 ppm, and the signal due to moisture appeared at δ 3.33 ppm, while the pmr spectrum of **12** in DMSO-d_6 exhibited the NH proton signal at δ 4.80 ppm together with the signal due to moisture.



Scheme

EXPERIMENTAL

All melting points were determined on a Ishii melting point apparatus and are uncorrected. The ir spectra (potassium bromide) were recorded with a JASCO IRA-1 spectrophotometer. The pmr spectra were measured in deuteriodimethylsulfoxide with an EM 390 spectrometer at 90 MHz using tetramethylsilane as an internal reference. Chemical shifts are given in the δ scale, relative to the internal reference. The mass spectra (ms) were determined with a JEOL JMS-01S spectrometer. Elemental analyses were performed on a Perkin-Elmer 240B instrument.

4-(*o*-Chlorophenylhydrazono)-3-oxo-1,2,3,4-tetrahydropyridazino[3,4-*b*]-quinoxaline **10a**.

A suspension of **8a** (10 g, 25.7 mmoles) and hydrazine dihydrochloride (13.1 g, 128.5 mmoles) in acetic acid (600 ml) was refluxed in an oil bath for 5 hours to give a clear solution. Evaporation of the solvent *in vacuo* afforded crystals as hydrochloride, which was collected by suction filtration. Treatment of the hydrochloride with a slight excess of 10% sodium hydroxide solution in ethanol/water gave a clear solution, which was filtered. Acetic acid was added so as to acidify the filtrate, and then an addition of water and a continuous heating on a boiling water bath provided yellow needles **10a** as monohydrate, which was collected by suction filtration (6.12 g, 70%).

Compounds **10b** and **10c** were obtained as monohydrates in a similar manner to the above [**10b**, 5.0 g (60%); **10c**, 5.44 g (62%)].

Compound **10a** had mp 283-284°; ir: ν cm^{-1} 3290, 1680; ms: m/z 338 (M^+), 340 ($M^+ + 2$) (M^+ of the free base due to thermal dissociation in the inlet system of the mass spectrometer); pmr: 15.07 (br, 1H, NH), 14.63 (br, 1H, NH), 12.27 (s, 1H, NH), 8.00-7.00 (m, 8H, aromatic), 3.33 (br, water).

Anal. Calcd. for $C_{16}H_{13}ClN_6O_2$: C, 53.87; H, 3.67; Cl, 9.94; N, 23.56. Found: C, 53.69; H, 3.65; Cl, 9.64; N, 23.39.

Compound **10b** had mp 283-284°; ir: ν cm^{-1} 3400, 1685; ms: m/z 338 (M^+), 340 ($M^+ + 2$) (M^+ of the free base due to thermal dissociation in the inlet system of the mass spectrometer); pmr: 15.05 (br, 1H, NH), 14.80 (br, 1H, NH), 12.25 (s, 1H, NH), 8.00-7.00 (m, 8H, aromatic), 3.33 (br, water).

Anal. Calcd. for $C_{16}H_{13}ClN_6O_2$: C, 53.87; H, 3.67; Cl, 9.94; N, 23.56. Found: C, 53.59; H, 3.49; Cl, 9.70; N, 23.50.

Compound **10c** had mp 307-308°; ir: ν cm^{-1} 3270, 1690; ms: m/z 338 (M^+), 340 ($M^+ + 2$) (M^+ of the free base due to thermal dissociation in the inlet system of the mass spectrometer); pmr: 15.00 (br, 2H, NH), 12.23 (s, 1H, NH), 7.90-7.00 (m, 8H, aromatic), 3.33 (br, water).

Anal. Calcd. for $C_{16}H_{13}ClN_6O_2$: C, 53.87; H, 3.67; Cl, 9.94; N, 23.56. Found: C, 54.11; H, 3.56; Cl, 9.71; N, 23.37.

3-Chloro-4-[2-(*o*-chlorophenyl)hydrazino]pyridazino[3,4-*b*]quinoxaline **12**.

A solution of **10a** (4.80 g) in phosphoryl chloride (50 ml) was refluxed in an oil bath for 2 hours. Removal of phosphoryl chloride *in vacuo* gave an oily residue, which was dissolved in dioxane (100 ml). The solution was poured onto crushed ice to precipitate yellow crystals **12**, which were collected by suction filtration (4.0 g, 83%). Recrystallization from *N,N*-dimethylformamide/ethanol afforded yellow needles, mp 294-295°; ir: ν cm^{-1} 1620, 1585, 1510, 1490, 1460, 1450, 1430, 1400, 1390; ms: m/z 356 (M^+), 358 ($M^+ + 2$); pmr: 8.00-7.20 (m, aromatic), 4.80 (br, NH and water).

Anal. Calcd. for $C_{16}H_{10}Cl_2N_6$: C, 53.80; H, 2.82; Cl, 19.85; N, 23.53. Found: C, 53.64; H, 2.83; Cl, 19.55; N, 23.48.

REFERENCES AND NOTES

[1] H. Dahn and J. P. Fumeaux, *Bull. Soc. Vandise Sci. Natur.*, **70**, 313 (1970); *Chem. Abstr.*, **75**, 140791g (1971).

[2] G. S. Predvoditeleva, T. V. Karteseva, T. N. Zykova, M. N. Shchukina and G. N. Persin, *Khim.-Pharm. Zh.*, **6**, 3 (1972); *Chem. Abstr.*, **78**, 4219m (1973).

[3] Yu. S. Andreichikov, G. D. Plakhina and R. F. Saraeva, *Khim. Khim. Tekhnol., Obl. Nauchno-Tekh. Konf.*, [Mater], 4th, **2**, 58 (1973); *Chem. Abstr.*, **82**, 140072t (1975).

[4] Y. Kurasawa and A. Takada, *Heterocycles*, **14**, 611 (1980); *Idem, Chem. Pharm. Bull.*, **28**, 3537 (1980).

[5] Y. Kurasawa and A. Takada, *Heterocycles*, **14**, 281 (1980); *Idem, Chem. Pharm. Bull.*, **29**, 2871 (1981).

[6] Y. Kurasawa, M. Muramatsu, K. Hotehama, Y. Okamoto and A. Takada, *J. Heterocyclic Chem.*, **22**, 1711 (1985).

[7] Compounds **8a** and **8b** were obtained as the hydrazinium salts, and compound **8c** as the free base.

[8] R. Jones, A. J. Ryan, S. Sternhell and S. E. Wright, *Tetrahedron*, **19**, 1497 (1963).