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

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The pyridazino[3,4-*b*]quinoxaline **12** was synthesized by the cyclization of the α-arylhydrazonoacylhydrazide **11**. The reaction of compound **12** with phosphoryl chloride gave pyridazino[3,4-*b*]quinoxaline **13**, whose reactions with sodium azide or cyclic secondary amines provided pyridazino[3,4-*b*]quinoxalines **14**, **17** and **18**, respectively. The acylhydrazide **15** was also cyclized to pyridazino[3,4-*b*]quinoxaline **16**.

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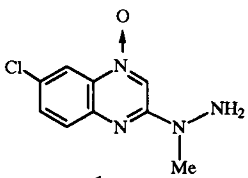
In the past decade, we have synthesized various pyridazinoquinoxalines from the interest in the biological activity [2]. For example, the 1,3-dipolar cycloaddition reaction of 6-chloro-2-(1-methylhydrazino)quinoxaline 4-oxide **1** with acetylenedicarboxylates gave pyridazino[3,4-*b*]quinoxalines **2** (Chart 1) [3,4]; the reaction of compound **1** with ethyl 2-ethoxymethylene-2-cyanoacetate gave 6-chloro-2-[2-(2-cyano-2-ethoxycarbonylvinyl)-1-methylhydrazino]quinoxaline 4-oxide **3**, whose reaction with 1,8-diazabicyclo[5.4.0]undec-7-ene in *N,N*-dimethylformamide afforded the pyridazino[3,4-*b*]quinoxaline **4** [5]; the reaction of compound **1** with β-ketoesters or β-diketones provided the pyridazino[3,4-*b*]quinoxalines **5** [6]; the oxidative ring transformation of the 1,2-diazepino[3,4-*b*]quinoxalines **6** with *N*-bromosuccinimide/water conveniently produced the pyridazino[3,4-*b*]quinoxalines **7** (Chart 2) [7]. In continuation of the above works, we further studied the synthesis

Chart 1



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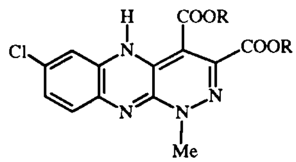

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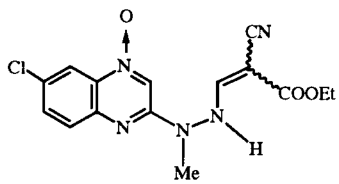
R = Me, Et



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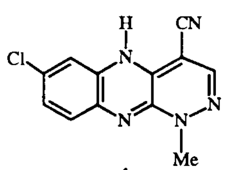

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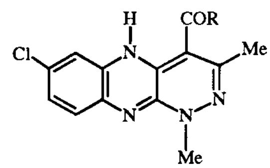

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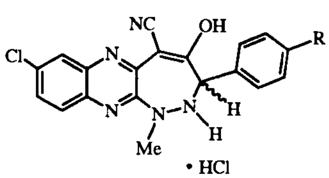
R = Me, Ph, OMe, OEt

Chart 2



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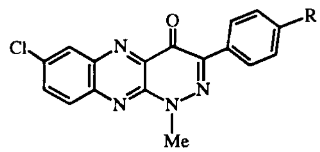
R = Cl, Br



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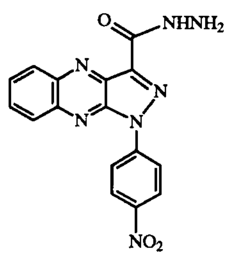
R = Cl, Br



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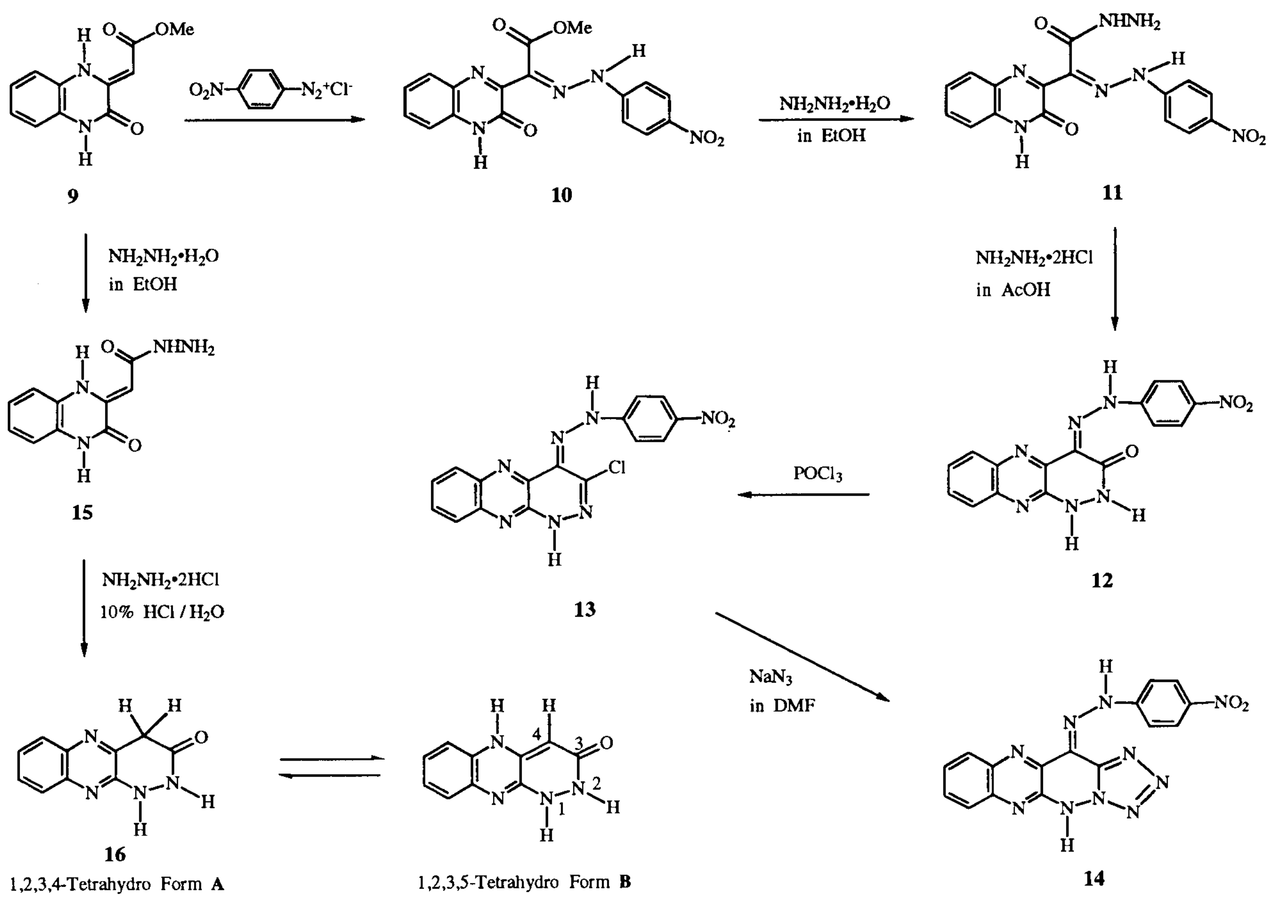
and biological activity of novel pyridazino[3,4-*b*]quinoxalines **12**, **13**, **14**, **16** (Scheme 1) and **17a,b**, **18** (Scheme 2) in the present investigation.

Scheme 1



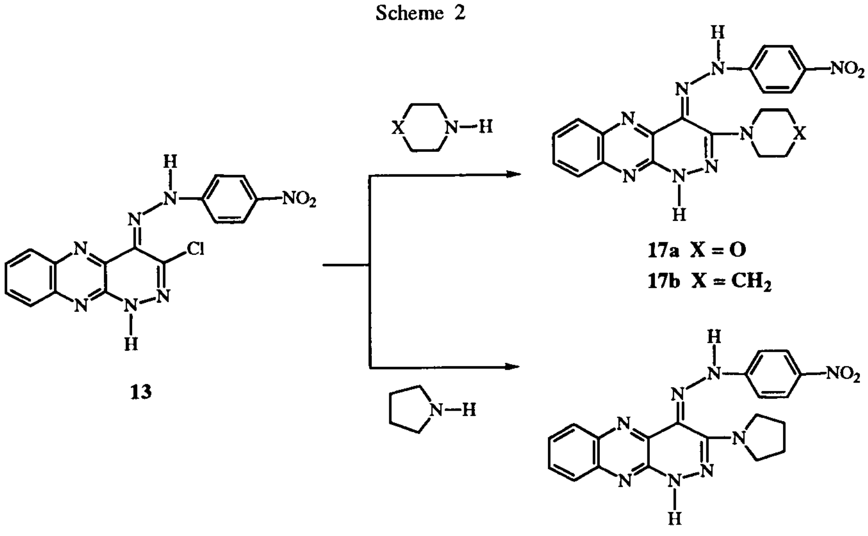
In a previous paper [8], we reported that the hydrazone **10** synthesized from compound **9** (Scheme 1) was transformed into the excellent antibacterial agent 1-(*p*-nitrophenyl)flavazole **8** (Chart 2), whose N_1-(*p*-nitrophenyl) moiety was found to contribute the biological activity. Based on these results, the *p*-nitrophenyl group was selected as the aryl substituent of the hydrazone moiety in the synthesis of the pyridazino[3,4-*b*]quinoxalines **12**, **13**, **14**, **17a,b**, and **18**, expecting the manifestation of a biological activity for these compounds.

The synthesis of compounds **10** [8], **11** [8], **15** [9] has already been reported in previous papers.

Refluxing of compound **11** and hydrazine dihydrochloride in acetic acid effected the cyclization to give 4-(*p*-nitrophenylhydrazono)-3-oxo-1,2,3,4-tetrahydropyridazino-[3,4-*b*]quinoxaline **12**. The reaction of compound **12** with phosphoryl chloride/pyridine afforded 3-chloro-4-(*p*-nitrophenylhydrazono)-1,4-dihydropyridazino[3,4-*b*]quinoxaline **13**, whose reaction with sodium azide furnished 4-(*p*-nitrophenylhydrazono)-4,11-dihydrotetrazolo[1',5':1,6]pyridazino[3,4-*b*]quinoxaline **14**. In order to prepare novel analogues, compound **13** was converted into compounds **17** and **18** (Scheme 2). The reaction of compound **13** with morpholine, piperidine and pyrrolidine gave 3-(morpholin-1-yl)-4-(*p*-nitrophenylhydrazono)-1,4-dihydropyridazino[3,4-*b*]-quinoxaline **17a**, 4-(*p*-nitrophenylhydrazono)-3-(piperidin-1-yl)-1,4-dihydropyridazino[3,4-*b*]quinoxaline **17b** and 4-(*p*-nitrophenylhydrazono)-3-(pyrrolidin-1-yl)-1,4-dihydropyridazino[3,4-*b*]quinoxaline **18**, respectively.

The reaction of 3-hydrazinocarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline **15** [9] with hydrazine dihydrochloride in 10% hydrochloric acid/water effected the cyclization to give 3-oxo-1,2,3,4-tetrahydropyridazino-[3,4-*b*]quinoxaline **16**. The pmr spectrum of compound **16** in deuteriodimethyl sulfoxide exhibited the tautomeric equilibria between the 1,2,3,4-tetrahydro **A** and 1,2,3,5-tetrahydro **B** forms (Scheme 1) [10]. Namely, the C_4-methylene and C_4-vinylic proton signals were observed at δ 2.41 (**A** form) and 6.49 (**B** form) ppm, respectively. From the integral curve of these proton signals, the ratio of **A** to **B** was determined as 75% *versus* 25%.

Scheme 2



Compounds **12**, **13**, **14**, **16**, **17**, and **18** were tested for their antibacterial activity *in vitro* against Gram-positive (*Bacillus licheniformis* KTCC 21415 and *Cellulomonas* sp) and Gram-negative (*Salmonella typhimurium* KCTC 1925 and *Flavobacterium devolans*) bacteria by the conventional serial two-fold agar dilution method. However, the above compounds did not exhibit the antibacterial activity against the above Gram-positive and Gram-negative bacteria.

EXPERIMENTAL

All melting points were determined on a Haake Buchler melting point apparatus and are uncorrected. The ir spectra (potassium bromide) were recorded with a Mattson Polaris FT-IR spectrophotometer. The mass spectra (ms) were determined with a Shimadzu GC/MS QP-1000 spectrometer. The nmr spectra were measured in deuteriodimethyl sulfoxide with a Bruker AM-300 spectrometer. Chemical shifts are given in the δ scale. Elemental analyses were performed on a Perkin-Elmer 240B instrument.

4-(*p*-Nitrophenylhydrazono)-3-oxo-1,2,3,4-tetrahydropyridazino[3,4-*b*]quinoxaline **12**.

A suspension of compound **11** (2.5 g, 6.8 mmoles) and hydrazine dihydrochloride (3.57 g, 34 mmoles) in acetic acid (100 ml) was refluxed in an oil bath for 3 hours to give a clear solution. The solution was allowed to stand overnight at room temperature to precipitate brick red crystals **12**, which were collected by suction filtration and washed with water and then n-hexane. Recrystallization from *N,N*-dimethylformamide/ethanol afforded brick red needles (2.1 g, 88%), mp 339-340°; ir: ν cm^{-1} 3386, 1677, 1523, 1341, 852; ms: m/z 349 (M^+); pmr : 15.20 (brs, 1H, NH), 12.41 (brs, 1H, NH), 8.36-7.38 (m, 8H, aromatic).

Anal. Calcd. for $C_{16}H_{11}N_7O_3$: C, 55.02; H, 3.17; N, 28.07. Found: C, 55.15; H, 3.18; N, 27.96.

3-Chloro-4-(*p*-nitrophenylhydrazono)-1,4-dihydropyridazino[3,4-*b*]quinoxaline **13**.

A solution of compound **12** (2 g) in phosphoryl chloride (50 ml)/pyridine (5 ml) was refluxed in an oil bath for 2 hours. The solution was evaporated *in vacuo* to give red crystals, to which ethanol was added. The mixture was poured onto crushed ice to precipitate red crystals, which were collected by suction filtration (1.7 g, 77%). Recrystallization from *N,N*-dimethylformamide/ethanol gave red needles **13**, mp 299-300°; ir: ν cm^{-1} 1630, 1612, 1542, 1343, 860; ms: m/z 367 (M^+), 369 (M^+ +2); pmr: 8.45 (d, J = 9.0 Hz, 2H, aromatic), 8.16 (d, J = 9.0 Hz, 2H, aromatic), 7.80-7.32 (m, 4H, aromatic). The NH proton signals were unobservable.

Anal. Calcd. for $C_{16}H_{10}ClN_7O_2$: C, 52.26; H, 2.74; Cl, 9.64; N, 26.66. Found: C, 52.41; H, 2.76; Cl, 9.68; N, 26.75.

4-(*p*-Nitrophenylhydrazono)-4,11-dihydrotetrazolo[1',5':1,6]-pyridazino[3,4-*b*]quinoxaline **14**.

A solution of compound **13** (1 g, 2.72 mmoles) and sodium azide (0.35 g, 5.4 mmoles) in *N,N*-dimethylformamide (30 ml) was refluxed in an oil bath for 2 hours. The solvent was evaporated *in vacuo* to give brown crystals, which were collected by suction filtration and washed with water. Trituration with ethanol gave analytically pure sample of **14** (0.85 g, 84%), mp 275° dec; ir: ν cm^{-1} 3406, 1596, 1523, 1330, 1109, 857; ms: m/z 374 (M^+); pmr: 13.13 (br, 1H, NH), 8.49-7.25 (m, 8H, aromatic).

Anal. Calcd. for $C_{16}H_{10}N_{10}O_2$: C, 51.34; H, 2.69; N, 37.42. Found: C, 51.46; H, 2.71; N, 37.32.

3-Oxo-1,2,3,4-tetrahydropyridazino[3,4-*b*]quinoxaline **16**.

A solution of compound **15** (1 g, 4.6 mmoles) and hydrazine dihydrochloride (4.83 g, 46 mmoles) in 10% hydrochloric acid (5 ml)/water (50 ml) was refluxed on a boiling water bath for 3 hours. Evaporation of the solvent *in vacuo* afforded yellow crystals, which were collected by suction filtration and washed with water. Trituration with ethanol gave an analytically pure sample of **16** (0.43 g, 47%), mp 256-257°; ir: ν cm^{-1} 3425, 3266, 1666; ms: m/z 200 (M^+); pmr: 12.33 (brs, 1H, NH), 11.68 (brs, 1H, NH), 7.83-7.22 (m, 4H, aromatic), 6.49 (s, 0.5H, C_4-H of **B** form), 2.41 (s, 1.5H, C_4-H of **A** form). The N_5-H proton signal of **B** form was overlapped with other proton signals.

Anal. Calcd. for $C_{10}H_8N_4O$: C, 59.99; H, 4.03; N, 27.99. Found: C, 60.13; H, 4.05; N, 28.07.

3-(Morpholin-1-yl)-4-(*p*-nitrophenylhydrazono)-1,4-dihydropyridazino[3,4-*b*]quinoxaline **17a**, 4-(*p*-Nitrophenylhydrazono)-3-(piperidin-1-yl)-1,4-dihydropyridazino[3,4-*b*]quinoxaline **17b**, and 4-(*p*-Nitrophenylhydrazono)-3-(pyrrolidin-1-yl)-1,4-dihydropyridazino[3,4-*b*]quinoxaline **18**.

General Procedure.

A solution of compound **13** (1 g, 2.72 mmoles) and the cyclic secondary amines (10 ml) was refluxed in an oil bath for 2 hours. The solution was evaporated *in vacuo* to give brown crystals, which were collected by suction filtration and washed with ethanol. Recrystallization from *N,N*-dimethylformamide/ethanol provided brown needles.

Compound **17a** (757 mg, 67%) had mp 285-286°; ir: ν cm^{-1} 3445, 1590, 1515, 1332, 852; ms: m/z 418 (M^+); pmr: 8.37 (d, J = 9.0 Hz, 2H, aromatic), 7.94 (d, J = 9.0 Hz, 2H, aromatic), 7.76-7.71 (m, 2H, aromatic), 7.32-7.27 (m, 2H, aromatic), 3.82 (t, J = 4.5 Hz, 4H, CH_2-O-CH_2), 3.55 (t, J = 4.5 Hz, 4H, CH_2-N-CH_2).

Anal. Calcd. for $C_{20}H_{18}N_8O_3$: C, 57.41; H, 4.34; N, 26.78. Found: C, 57.54; H, 4.35; N, 26.69.

Compound **17b** (504 mg, 45%) had mp 263-264°; ir: ν cm^{-1} 3412, 1598, 1516, 1331, 850; ms: m/z 416 (M^+); pmr: 8.37 (d, J = 9.0 Hz, 2H, aromatic), 7.87 (d, J = 9.0 Hz, 2H, aromatic), 7.73-7.69 (m, 2H, aromatic), 7.30-7.25 (m, 2H, aromatic), 3.68-3.53 (m, 4H, CH_2-N-CH_2), 1.74-1.63 (m, 6H, CH_2-CH_2-CH_2).

Anal. Calcd. for $C_{21}H_{20}N_8O_2$: C, 60.57; H, 4.84; N, 26.91. Found: C, 60.41; H, 4.85; N, 26.99.

Compound **18** (553 mg, 51%) had mp 268-269°; ir: ν cm^{-1} 3382, 1596, 1516, 1330, 852; ms: m/z 402 (M^+); pmr: 8.39-7.22 (m, 8H, aromatic), 3.78-3.61 (m, 4H, CH_2-N-CH_2), 2.11-1.78 (m, 4H, CH_2-CH_2).

Anal. Calcd. for $C_{20}H_{18}N_8O_2$: C, 59.69; H, 4.51; N, 27.85. Found: C, 59.54; H, 4.53; N, 27.76.

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