**Synthesis of 1,2-Diazepino[3,4-b]quinoxalines by 1,3-Dipolar Cycloaddition Reaction and Their Ring Transformation to Pyridazino[3,4-b]quinoxalines**

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Fused heterocyclic systems containing a quinoxaline ring were largely investigated because they were effective in pharmacological and agrochemical areas.1,2 In previous papers,3-8 we reported the synthesis of the 1,2-diazepino[3,4-b]quinoxaline-5-carbonitriles 3a-e from the quinoxaline N-oxide 1 via the hydrazones 2a-e and then the oxidative ring transformation of 3a-c with N-bromosuccinimide/water or selenium dioxide conveniently produced the pyridazino[3,4-b]quinoxalines 4a-c, respectively. From the data of the screening test, it was found that compound 3d showed a weak antibacterial activity against *Xanthomonas oryzae*, but compound 3e did not show antibacterial activity.8 Compound 4c exhibited antibacterial activity against *Bacillus subtilis*.6

In this note, we undertook the synthesis of 1,2-diazepino[3,4-b]quinoxalines 6 possessing the α,β-unsaturated moieties at the 3-position from compounds 5 and the synthesis of pyridazino[3,4-b]quinoxalines 7 by the oxidative ring transformation of compounds 6 (Scheme 1). We, also, tested *in vitro* antibacterial activity of these compounds.

The reaction of 6-chloro-2-(1-methylhydrazino)quinoxaline 4-oxide 1 with α,β-unsaturated aldehydes such as acrolein, crotonaldehyde, trans-cinnamaldehyde and 3-(2-furyl)acrolein gave 6-chloro-2-[1-methyl-2-(vinylmethylene)hydrazino]-quinoxaline 4-oxide 5a, 6-chloro-2-[1-methyl-2-(vinylvinyl-}

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**Scheme 1**

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pino[3,4-b]quinoxaline-5-carbonitrile 6d, respectively, presumably via intermediates A-D.\textsuperscript{3,4,6}

The reaction of the 1,2-diazepino[3,4-b]quinoxalines 6 with selenium dioxide in acetic acid/water resulted in oxidative ring transformation to provide 7-chloro-1-methyl-3-(methylvinyl)-4-oxo-1,4-dihydropyridazino[3,4-b]quinoxaline 7a, 7-chloro-1-methyl-3-(phenylvinyl)-1-methyl-4-oxo-1,4-dihydropyridazino[3,4-b]quinoxaline 7b and 7-chloro-3-(2-furylvinyl)-1-methyl-4-oxo-1,4-dihydropyridazino[3,4-b]quinoxaline 7c, respectively, presumably via intermediates E-H.\textsuperscript{5,6}

We transformed compound 1 into the hydrazone 8 so as to synthesize new condensed quinoxaline 10 by 1,3-dipolar cycloaddition reaction and an intramolecular alcoholysis.\textsuperscript{7,9,10}

The structure of new compounds 6 and 7 was supported by the spectral and analytical data. The 2,3-dihydro-4-hydroxy form of compounds 6 have already been clarified by the measurement of the NOE between the N2-H and C3-H protons in previous papers.\textsuperscript{3,4}

All the compounds (6 and 7) were tested for their antibacterial activity following paper disc method\textsuperscript{13} against Listera monocytogenes ATCC 19111, Staphylococcus aureus ATCC 29373, Bacillus cereus ATCC 21366, Escherichia coli ATCC 11775, Salmonella typhimurium ATCC 29373 and Pseudomonas fluorescens ATCC 21541. Paper disc were placed on the Tryptic soy agar spreaded with each bacteria. The plates were incubated at 37 °C for 24 hrs. The activity was recorded by measuring the diameter of inhibition zones in mm\textsuperscript{14,15} and results obtained are shown in Table 1. All the compounds showed inhibitory effect against tested bacteria.

### Experimental Section

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 nmr spectra were measured with a Vario Gemini-200 spectrometer. The chemical shifts are given in the δ scale. The mass spectra (ms) were determined with a shimadzu GC/MS QP-5050 spectrometer. Elemental analyses were performed on an Elementar Vario EL instrument.

General procedure for the preparation of the quinoxaline 4-oxides (5a-d)

To a stirred and ice cooled suspension of compound 1 (1 g, 4.45 mmol) and ethanol (30 mL)/water(10 mL) was added dropwise the appropriate α,β-unsaturated aldehydes (5.34 mmol, 1.2-fold molar amount) and concentrated sulfuric acid (4 mL). The reaction mixture was stirred at room temperature for 16 hours under nitrogen to precipitate yellow crystals, which were collected by suction filtration. Washing with ethanol and then n-hexane gave an analytically pure samples.

6-Chloro-2-[1-methyl-2-(vinylmethylene)hydrazino]-quinoxaline 4-Oxide (5a). Yield 60%, mp 154-156 °C; IR(KBr): 3086, 1577, 1536, 1491, 1386, 1221, 1096 cm\(^{-1}\); MS: m/z 262 (M\(^+\)), 264 (M\(^+2\)); \(^1\)H NMR (DMSO-d6): 8.75 (s, 1H, C3-H), 8.23 (s, 1H, C5-H), 7.80-7.74 (m, 3H, C7-H, C8-H and hydrazone CH), 6.75-6.52 (m, 1H, N=CH-CH=CH\(_2\)), 5.82-5.60 (m, 2H, N=CH-CH=CH\(_2\)), 3.59 (s, 3H, N-CH\(_3\)). Anal. calcd. for C\(_{12}\)H\(_{11}\)ClN\(_4\)O: C, 54.87; H, 4.22; N, 21.33. Found: C, 54.76; H, 4.23; N, 21.28.

6-Chloro-2-[1-methyl-2-(vinylmethylene)hydrazino]-quinoxaline 4-Oxide (5b). Yield 88%, mp 207-209; IR
6-Chloro-2-[1-methyl-2-(phenylvinyl)methylene]hydrazino]quinoxaline 4-Oxide (5c). Yield 86%, mp 132-134 °C; IR (KBr): 2227, 1598, 1557, 1526, 1486 cm⁻¹; MS: m/z 379 (M⁺), 381 (M⁺+2); 1 H NMR (CDCl₃): 8.35 (d, J = 1.8 Hz, 1H, C₇-H), 8.02 (d, J = 9.4 Hz, 1H, C₈-H), 7.83 (dd, J = 2.1, 9.0 Hz, 1H, C₉-H), 7.22-7.02 (m, 1H, CH=CH(CH₃)), 6.79 (d, J = 15.8 Hz, 1H, CH=CH(CH₃)), 4.26 (s, 3H, N-CH₃), 1.99 (s, J = 6.7 Hz, 3H, CH₃). Anal. calcd. for C₁₆H₁₁ClN₅O: C, 58.65; H, 3.87; N, 19.54. Found: C, 58.33; H, 3.87; N, 19.32.

General procedure for the preparation of the pyridazino[3,4-b]quinazolines (7a-c)

A solution of the appropriate compounds 6 (3.06 mmol) and selenium dioxide (6.12 mmol) in acetic acid (20 mL)/water (10 mL) was refluxed in an oil bath for 1 hour. The reaction mixture was filtered, and the filtrate was evaporated in vacuo to give brick red crystals, which were triturated with water and then collected by suction filtration. Recrystallization from N,N-dimethylformamide/ethanol/water afforded violet needles.

7-Chloro-1-methyl-3-(methylvinyl)-4-oxo-1,4-dihydropyridazino[3,4-b]quinazoline (7a). Yield 58%, mp 174-176 °C; IR (KBr): 1645, 1537, 1467 cm⁻¹; MS: m/z 348 (M⁺), 350 (M⁺+2); 1 H NMR (CDCl₃): 8.38 (d, J = 1.5 Hz, 1H, C₇-H), 8.02 (d, J = 9.4 Hz, 1H, C₈-H), 7.83 (dd, J = 2.1, 9.0 Hz, 1H, C₉-H), 7.22-7.02 (m, 1H, CH=CH(CH₃)), 6.67 (d, J = 15.8 Hz, 1H, CH=CH(CH₃)), 4.26 (s, 3H, N-CH₃), 1.99 (s, J = 6.7 Hz, 3H, CH₃). Anal. calcd. for C₁₆H₁₁ClN₅O: C, 58.65; H, 3.87; N, 19.54. Found: C, 58.33; H, 3.72; N, 19.32.

Chloro-3-(2-furylvinyl)-1-methyl-4-oxo-1,4-dihydropyridazino[3,4-b]quinazoline (7b). Yield 56%, mp 273-275 °C; IR (KBr): 1632, 1536, 1461 cm⁻¹; MS: m/z 348 (M⁺), 350 (M⁺+2); 1 H NMR (CDCl₃): 8.37 (d, J = 2.2 Hz, 1H, C₇-H), 8.06-7.28 (m, 9H C₈-H, C₉-H, aromatic and vinylic H), 4.33 (s, 3H, N-CH₃). Anal. calcd. for C₁₇H₁₁ClN₅O: C, 65.43; H, 3.76; N, 16.06. Found: C, 65.57; H, 3.62; N, 15.87.

Chloro-3-(2-furylvinyl)-1-methyl-4-oxo-1,4-dihydropyridazino[3,4-b]quinazoline (7c). Yield 71%, mp 257-259 °C; IR (KBr): 1644, 1535, 1462 cm⁻¹; MS: m/z 338 (M⁺), 340 (M⁺+2); 1 H NMR (CDCl₃): 8.33 (d, J = 2.1 Hz, 1H, C₇-H), 8.02 (d, J = 9.1 Hz, 1H, C₈-H), 7.92-7.72 (m, 2H, C₈-H and furan C₉-H), 7.51-7.22 (m, 2H, CH=CH(Furan)), 6.52 (d, J = 3.3 Hz, 1H, furan C₉-H), 6.45 (dd, J = 1.5, 3.2 Hz, 1H, furan C₉-H), 4.31 (s, 3H, N-CH₃). Anal. calcd. for C₁₇H₁₀ClN₅O: C, 60.28; H, 3.27; N, 16.54. Found: C, 60.12; H, 3.38; N, 16.37.

Chloro-2-[1-methyl-2-[4-(2,2-dimethyl-1,3-dioxolanyl-methylene)]hydrazino]quinoxaline 4-Oxide (8). A suspension of compound 1 (10 g, 44.5 mmol) and 2,3-O-isopropylidene-D-glyceraldehyde (8.7 g, 66.9 mmol) in dry
benzene (300 mL) was refluxed on a boiling water bath for 4 hours to give a clear solution. Evaporation of the solvent in vacuo gave yellow crystals, which were collected by suction filtration and washed with ethanol and then n-hexane to give an analytically pure sample (8.12 g). Evaporation of the solvent in vacuo afforded yellow crystals of compound 8, which were collected by suction filtration and washed with ethanol (5.51 g), total yield, 13.63 g (91%).

Compound 8 had mp 153-155 °C; IR (KBr) 3073, 2922, 1575, 1540, 1486, 1402, 1227, 1069 cm⁻¹; MS: m/z 336 (M⁺), 338 (M⁺+2); ¹H NMR (DMSO-d₆): 8.76 (s, 1H, C₃-H), 8.26 (s, 1H, C₅-H), 7.80 (s, 2H, C₇-H and C₈-H), 7.22 (d, J = 6.1 Hz, 1H, hydrazone CH), 4.79 (q, J = 6.3 Hz, dioxolane C₄-H), 4.26-3.92 (m, 2H, dioxolane C₅-H), 3.56 (s, 3H, N-CH₃), 1.42 (s, 3H, dioxolane C₂-CH₃), 1.36 (s, 3H, dioxolane C₂-CH₃).

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References


