Syntheses of 3,4-Dihydro-2H-pyridazino[4,5-b]-1,4-thiazin-8(7H)-one and -5(6H)-one

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Two novel fused ring systems made up of 1,4-thiazine and 3(2H)-pyridazinone were synthesized. 3,4-Dihydro-7-methyl-2H-pyridazino[4,5-b]-1,4-thiazin-8(7H)-one was obtained from the intramolecular cyclization of 4-chloro-5-(2-chloroethylamino)-2-methyl-3(2H)-pyridazinone with sodium sulfide. An isomer, 3,4-dihydro-6-methyl-2H-pyridazino[4,5-b]-1,4-thiazin-5(6H)-one, was directly afforded by the condensation of 4,5-dichloro-2-methyl-3(2H)-pyridazinone with sodium 2-aminoanthranilate.

Keywords—3,4-dihydro-2H-pyridazino[4,5-b]-1,4-thiazin-8(7H)-one; 3,4-dihydro-2H-pyridazino[4,5-b]-1,4-thiazin-5(6H)-one; 3(2H)-pyridazinone; intramolecular cyclization; analgesic activity.

It was previously reported that 4-chloro-5-(2-hydroxyethylamino)-3(2H)-pyridazinones were cyclized to give 3,4-dihydro-2H-pyridazino[4,5-b]-1,4-oxazin-8(7H)-ones by an intramolecular nucleophilic substitution reaction and that some of these compounds had potent analgesic activity.1) We supposed from the nature of this synthetic route that other new fused ring systems might be obtained by the conversion of the hydroxyethylamino moiety into other bifunctional groups. Thus we tried to construct a 2H-pyridazino[4,5-b]-1,4-thiazine structure; no chemical and pharmacological investigations have ever been reported on such compounds.

As shown in Chart 1, the reaction of 4,5-dichloro-2-methyl-3(2H)-pyridazinone (I) with ethanolamine gave the 5-hydroxyethylamino compound (IIa) as colorless plates in 66% yield. Heating IIa with excess thionyl chloride afforded the chloroethylamino derivative (IIa) in 84% yield. Similarly, the methyl analog of IIa (IIb) was converted to the corresponding chloride (IIIB). Compound IIIa was treated with sodium sulfide in ethanol, giving a product with a novel fused ring system, 3,4-dihydro-7-methyl-2H-pyridazino[4,5-b]-1,4-thiazin-8(7H)-one (IVa), as pale yellow crystals in 20% yield. The nuclear magnetic resonance (NMR) spectrum of the product suggested the presence of two methylenes (δ 2.79 t, J=6.3 Hz and δ 3.59 broad), a methyl (δ 3.61 s), a secondary amino group [δ 6.62 (disappeared on adding D₂O)], and a methine proton (δ 7.87 s). The analytical data were consistent with the molecular formula C₇H₇N₂O₂S and the infrared (IR) spectrum showed a lactam carbonyl absorption at 1620 cm⁻¹ as well as an absorption at 3320 cm⁻¹ attributable to a secondary amino group. These data unequivocally supported the structure IVa indicated in Chart 1. Compound IIIB was cyclized by the same procedure to provide the corresponding fused heterocycle (IVb) as pale yellow fine crystals in a yield of 27%. The structure was also confirmed by the elemental analysis and mass, IR, and NMR data.

The reaction of I with 2-mercaptopethylamine hydrochloride in the presence of three molar equivalents of sodium hydroxide in ethanol afforded fine crystals in 10% yield. The product was identified as an isomer of IVa, 3,4-dihydro-6-methyl-2H-pyridazino[4,5-b]-1,4-thiazin-5(6H)-one, on the basis of its elemental analysis and mass, IR, and NMR spectra: the experimental formula was C₇H₇N₂O₂S. IR cm⁻¹: 3290 (NH), 1620 (lactam CO), NMR (DMSO-d₆) δ: 2.97 (2H, t, J=4.8 Hz, 2-CH₂), 3.60 (3H, s, CH₃), 3.64 (2H, m, 3-CH₂), 7.04 (1H, b s, NH), 7.40 (1H, s, CH). This reaction may be explained as follows. The 2-mercaptop-
ethylamine hydrochloride was converted to sodium 2-aminoethanethiolate in the presence of excess sodium hydroxide, than the thiolate preferentially attacked the 5-position with lower electron density to afford the hypothetical intermediate (V), which might be converted to the product VI by the action of the base.

The analgesic activity of these compounds was evaluated by Haffner's method with a slight modification and by the acetic acid-stretching method. None of them showed stronger activity than aminopyrine, used as a positive control in both methods.

**Experimental**

All melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. NMR spectra were recorded on a JEOL JNM-PS-100 spectrometer with tetramethylsilane as an internal standard. IR spectra were taken on a JASCO DS-701G spectrometer and mass spectra were obtained with a JEOL JMS-01SG spectrometer.

4-Chloro-5-(2-hydroxyethylamino)-2-methyl-3(2H)-pyridazinone (IIa)—A mixture of I (54 g, 0.3 mol), ethanolamine (56 g, 0.9 mol), and water (500 ml) was heated under reflux for 1 h. The reaction mixture was concentrated to about 150 ml and cooled in an ice bath, and the resulting precipitates were recrystallized from EtOH-isopropyl ether to give 40 g (66%) of IIa as colorless plates, mp 133—134°C. Anal. Calcd for C_{16}H_{18}ClN_{2}O_{2}: C, 41.29; H, 4.95; N, 20.64. Found: C, 41.47; H, 4.75; N, 20.61. NMR (CD_{3}OD) δ: 3.32 (2H, m, NCH_{2}CH_{2}O), 3.52 (2H, t, J = 5.4 Hz, NCH_{2}CH_{2}O), 4.80 (3H, s, CH_{3}), 7.86 (1H, s, CH). IR cm⁻¹:
3210 (OH and NH), 1620 (CO). MS m/z: 187 (M^+)  

4-Chloro-5-(2-chloroethylamino)-2-methyl-3(2H)-pyridazinone (IIIa) — A solution of IIa (2.44 g, 12 mmol) in thionyl chloride (5 ml, excess) was heated at 60°C with stirring for 1 h. The excess reagent was removed by distillation and the residue was recrystallized from EtOH to give 1.87 g (84%) of IIIa, mp 190—191°C. Anal. Calcd for C₆H₄ClN₂O: C, 37.86; H, 4.09; N, 18.92. Found: C, 37.83; H, 4.22; N, 18.72. MS m/z: 221 (M^+).  

4-Chloro-5-(2-chloroethyl) methylamino)-2-methyl-3(2H)-pyridazinone (IIIb) — Following the procedure mentioned above, IIIb was obtained from the reaction of IIb with thionyl chloride as colorless fine needles. Yield 82%, mp 196—197°C (EtOH). Anal. Calcd for C₆H₅ClN₂O: C, 40.70; H, 4.70; N, 17.80. Found: C, 40.77; H, 4.79; N, 17.66. MS m/z: 235 (M^+).  

3,4-Dihydro-7-methyl-2H-pyridazino[4,5-b]-1,4-thiazin-8(7H)-one (IVA) — A mixture of IIIa (1.11 g, 5 mmol), Na₂S·9H₂O (2.40 g, 10 mmol), and EtOH (50 ml) was heated under reflux for 4 h. The resulting precipitates were filtered off, the filtrate was concentrated in vacuo, and the residue was extracted with CHCl₃. The extract was washed with water, dried over Na₂SO₄, and concentrated under reduced pressure. Recrystallization of the residue from EtOH gave 180 mg (20%) of IVa as pale yellow needles, mp 156—157°C. Anal. Calcd for C₆H₅N₂O·SO: C, 45.89; H, 4.95; N, 22.93. Found: C, 45.91; H, 4.81; N, 23.02. NMR (DMSO-d₆) δ: 2.79 (2H, t, J = 6.3 Hz, 2-CH₂), 3.50 (2H, br, 3-CH₂), 3.61 (3H, s, CH₃), 6.62 (1H, t, NH), 7.87 (1H, s, CH). IR cm⁻¹: 3320 (NH), 1620 (CO). MS m/z: 183 (M^+).  

3,4-Dihydro-4,7-dimethyl-2H-pyridazino[4,5-b]-1,4-thiazin-8(7H)-one (IVB) — A mixture of IIIb (2.36 g, 10 mmol), Na₂S·9H₂O (4.80 g, 20 mmol), and EtOH (500 ml) was heated at 60—70°C for 3 h and the resulting precipitates were removed by filtration. After removal of the solvent by evaporation, the residue was recrystallized from EtOH to give 550 mg (27%) of IVB as pale yellow needles, mp 158.5—159.5°C. Anal. Calcd for C₆H₅N₂O·SO: C, 48.71; H, 5.62; N, 21.30. Found: C, 48.71; H, 5.51; N, 21.20. NMR (CDCl₃) δ: 3.02 (2H, t, J = 6.2 Hz, 2-CH₂), 3.06 (3H, s, 4-CH₃), 3.58 (2H, t, J = 6.2 Hz, 3-CH₂), 3.68 (3H, s, 7-CH₃), 7.49 (1H, s, CH). IR cm⁻¹: 1615 (CO). MS m/z: 197 (M^+).  

3,4-Dihydro-6-methyl-2H-pyridazino[4,5-b]-1,4-thiazin-5(6H)-one (V) — A mixture of I (1.79 g, 10 mmol), 2-mercaptoethylamine HCl (1.13 g, 10 mmol), NaOH (1.20 g, 30 mmol), and EtOH (30 ml) was heated under reflux for 3 h. The resulting precipitates were removed by filtration and the filtrate was concentrated to dryness in vacuo. The residue was extracted with CHCl₃. The extract was washed with water and dried over Na₂SO₄. Thin layer chromatograms (silica gel; methyl ethyl ketone—ammonia water, 9: 1) of the extract indicated the presence of a main product and at least nine by-products in small quantities, as well as a large amount of the starting material. After removal of the solvent by evaporation, the main product (V) was isolated by recrystallization from the residue of MeOH. Yield 180 mg (10%), mp 159—161°C. Anal. Calcd for C₆H₅N₂O·SO: C, 45.89; H, 4.95; N, 22.93. Found: C, 45.75; H, 4.90; N, 23.09. NMR (DMSO-d₆) δ: 2.97 (2H, t, J = 4.8 Hz, 2-CH₂), 3.60 (3H, s, CH₃), 3.64 (2H, m, 3-CH₂), 7.04 (1H, br s, NH), 7.40 (1H, s, CH). IR cm⁻¹: 3290 (NH), 1620 (CO). MS m/z: 183 (M^+).  

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References and Notes