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Synthesis and Some Reactions of 6-(2-Hydroxyphenyl)-2-thiouracils

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6-(2-Hydroxyphenyl)-2-thiouracil (**2a**) and its 5-chloro and 5-bromo derivatives (**2b, c**) were synthesized by the reactions of 4-methoxycoumarin (**1a**) and 3-chloro- and 3-bromo-4-methoxycoumarins (**1b, c**), respectively, with thiourea in the presence of sodium ethoxide. In these reactions, compound **1c** gave not only the pyrimidine **2c**, but also the Perkin rearrangement product: *N*-(3-ethoxybenzofuran-2-carbonyl)thiourea (**3**). 2-Thiouracils **2a—c** were converted to the uracil derivatives (**6a, b**). Reactions of **2a—c** with some cyclic amines and the methylation of **2b, c** with methyl iodide were also examined.

Keywords——4-methoxycoumarin; 3-halo-4-methoxycoumarin; 6-(2-hydroxyphenyl)-2-thiouracil; benzofuran-2-carboxylic acid derivative; pyrimidine synthesis; Perkin rearrangement

Previously, we reported[1] that 4-ethoxycoumarin reacted with nucleophiles such as guanidine, amidines, thiourea and urea to give 2-substituted-6-(2-hydroxyphenyl)-4(3*H*)-pyrimidones, whereas 4-hydroxycoumarin did not react with the above nucleophiles except guanidine. We also showed[2] that 3-chloro- and 3-bromo-4-methoxycoumarins (**1b, c**) were more sensitive than 4-methoxycoumarin (**1a**) to nucleophilic attack of guanidine and amidines to give the pyrimidine derivatives. In these reactions, **1b, c** did not undergo the Perkin rearrangement.[3] As an extension of these studies, we examined the reaction of **1a—c** with thiourea to afford 6-(2-hydroxyphenyl)-2-thiouracils (**2**), which are of interest not only because of their biological activities,[4] but also because they are useful starting materials for the synthesis of a variety of pyrimidine derivatives. This paper deals with the synthesis of **2** and with some of their reactions.

Treatment of **1a** with an excess of thiourea in the presence of sodium ethoxide in boiling anhydrous ethanol gave 6-(2-hydroxyphenyl)-2-thiouracil (**2a**) in 64% yield; this product was identical with that obtained by the reaction of 4-ethoxycoumarin with thiourea.[1] Under the same conditions, **1b** afforded the 5-chloro derivative (**2b**) in 59% yield. However, when **1c** was treated with thiourea in the same manner, *N*-(3-ethoxybenzofuran-2-carbonyl)thiourea (**3**) was isolated as crystals in only 8% yield. In the above reaction, when the reaction temperature was fixed at 15—20 °C, the 5-bromo derivative (**2c**) and **3** were obtained in 60 and 11% yields, respectively (Chart 1).

The formation of **3** from **1c** may be explained in terms of the Perkin rearrangement. The transetherification of the methoxyl group with the ethoxide anion might occur during the reaction. In fact, treatment of **1c** with sodium ethoxide in anhydrous ethanol gave ethyl 3-ethoxybenzofuran-2-carboxylate (**4**)[5] which was converted to **3** by heating with thiourea in the presence of sodium ethoxide. Compound **3** was readily hydrolyzed to the corresponding acid (**5**). In the reaction of **1b** with thiourea, no formation of **3** was observed. Reduced mobility of the chlorine atom at the 3 position of **1b** might favor pyrimidine formation rather than the Perkin rearrangement.

Compound **2c** was debrominated to **2a** by treatment with zinc dust in aqueous ammonia (Chart 1), in contrast with **2b** which was not converted to **2a** under the same conditions, or by

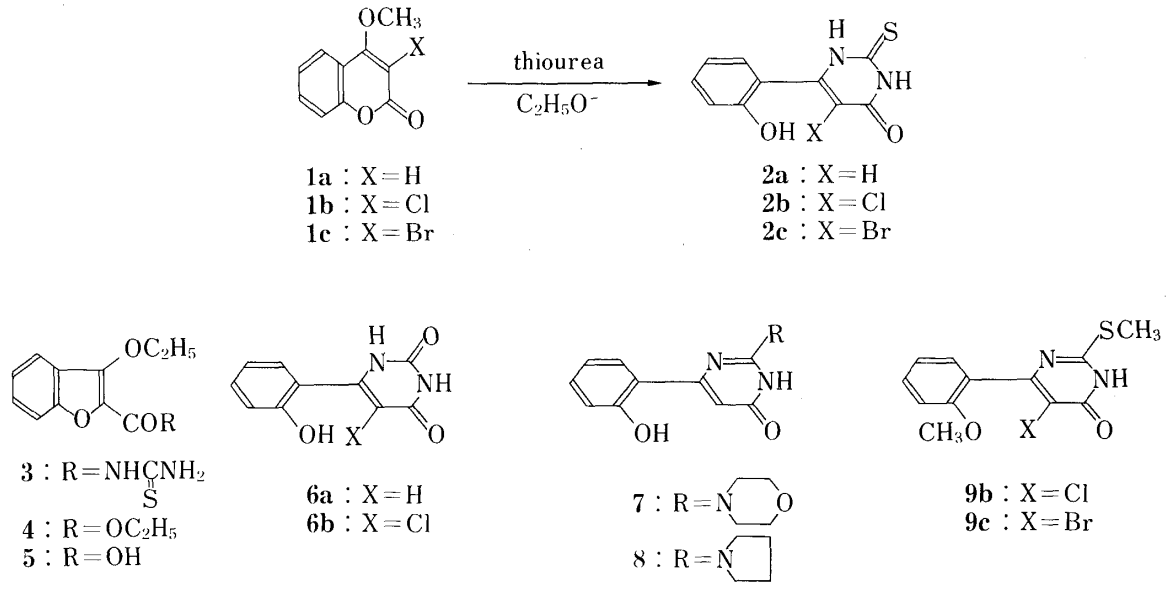

Chart 1

treatment with zinc dust in acetic acid. According to the method previously described for the transformation of **2a** to 6-(2-hydroxyphenyl)uracil (**6a**),[1] compound **2b** was converted to 5-chloro-6-(2-hydroxyphenyl)uracil (**6b**) in 31% yield on heating with monochloroacetic acid in boiling water, followed by acid hydrolysis. Upon application of this method to **2c**, compound **6a** was isolated in only 7% yield. Upon being heated with morpholine at 150 °C, **2a**—**c** afforded the same product, 6-(2-hydroxyphenyl)-2-morpholino-4-(3*H*)-pyrimidone (**7**), in 40, 18 and 20% yields, respectively (Chart 1). The dehalogenation at the 5 position of **2b, c** might be due to hydrogen sulfide which may be generated during the reactions. When heated with pyrrolidine under similar conditions, **2a** gave 6-(2-hydroxyphenyl)-2-pyrrolidino-4(3*H*)-pyrimidone (**8**) (Chart 1). Compounds **2b, c** were methylated with methyl iodide in the presence of an alkali, by the method employed for the methylation of **2a**,[1] to give the corresponding 6-(2-methoxyphenyl)-2-methylthio derivatives (**9b, c**) in 50 and 30% yields, respectively (Chart 1). The structural assignments of all the compounds obtained were based on the analytical and spectral data detailed in the experimental section.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were measured with JEOL KNM-C-60H spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were taken on a JEOL-01SG spectrometer. Ultraviolet (UV) and infrared (IR) spectra were recorded on Hitachi 320 and JASCO A-102 spectrophotometers, respectively.

6-(2-Hydroxyphenyl)-2-thiouracil (2a)——a) A mixture of thiourea (2.3 g, 30 mmol) and **1a** (1.8 g, 10 mmol) in ethanolic sodium ethoxide solution (0.7 g of Na in 50 ml of anhyd. ethanol) was heated under reflux for 10 h. The reaction mixture was treated according to the method[1] described for the preparation of **2a** from 4-ethoxycoumarin and thiourea. Recrystallization from water–ethanol gave 1.4 g (64%) of **2a**, mp 293—295 °C (lit.[1] mp 292—293 °C). NMR (δ in DMSO-d_6): 6.03 (1H, s, –CH=), 6.7—7.48 (4H, m, Ar-H), 11.65 (2H, br, 2NH), 12.01 (1H, br, OH).

b) A mixture of **2c** (0.3 g, 1 mmol) and zinc dust (1.5 g) in conc. NH_4OH (30 ml) was refluxed for 5 h with stirring. After cooling, the reaction mixture was alkalized with aq. 5% NaOH and filtered to eliminate zinc. The filtrate was acidified with AcOH and the precipitate was collected, washed with water and recrystallized from water–ethanol to give 0.11 g (50%) of **2a** mp 293—295 °C, which was identified by comparison of its IR spectrum with that of **2a** obtained previously.

5-Chloro-6-(2-hydroxyphenyl)-2-thiouracil (2b)——A mixture of thiourea (2.3 g, 30 mmol) and **1b** (2.1 g, 10 mmol) in ethanolic sodium ethoxide solution (0.7 g of Na and 50 ml of anhyd. ethanol) was treated as described for the preparation of **2a** (method a). Recrystallization from ethanol gave 1.5 g (59%) of **2b**, mp 241—243 °C. IR ν_{max}^{KBr} cm^{-1}: 3380 (OH), 1660 (C=O). UV λ_{max}^{MeOH} nm (log ε): 215 (4.59), 280 (4.60), 310 inf. (4.28). NMR (δ in DMSO-

d_6): 6.67—7.50 (4H, m, Ar-H), 8.23 (3H, br, 2NH and OH). MS *m/e*: 256, 254 (M^+), 219 ($M^+ - Cl$), 202. *Anal.* Calcd for $C_{10}H_7ClN_2O_2S$: C, 47.19; H, 2.78; N, 11.01. Found: C, 46.87; H, 2.81; N, 10.73.

5-Bromo-6-(2-hydroxyphenyl)-2-thiouracil (2c) and *N*-(3-Ethoxybenzofuran-2-carbonyl)thiourea (3)——A mixture of thiourea (2.3 g, 30 mmol) and **1c** (2.6 g, 10 mmol) in ethanolic sodium ethoxide solution (0.7 g of Na and 60 ml of anhyd. ethanol) was stirred at 15—20 °C for 24 h. After removal of the solvent *in vacuo*, water was added to the residue and the mixture was treated as follows.

The insoluble product was collected by filtration, washed with water and recrystallized from ethanol to give 0.3 g (11%) of **3** as colorless needles, mp 180—182 °C. IR ν_{max}^{KBr} cm^{-1}: 3300 (NH), 1665 (CO amide). UV λ_{max}^{MeOH} nm (log ε): 220 (4.37), 233 (4.37), 311 (4.64) [similar to that of 2-acetylbenzofuran: 225 (3.96), 230 (3.92), 292 (4.41)]. NMR (δ in DMSO-d_6): 1.55 (3H, t, J=7 Hz, CH_3–), 4.76 (2H, q, J=7 Hz, –OCH_2–), 7.10—8.10 (4H, m, Ar-H), 9.57 (2H, br, –NH_2), 9.88 (1H, br, –NH–). MS *m/e*: 264 (M^+), 235. *Anal.* Calcd for $C_{12}H_{12}N_2O_3S$: C, 54.53; H, 4.58; N, 10.62. Found: C, 54.66; H, 4.55; N, 10.34.

The filtrate was acidified with aq. 10% HCl, with ice cooling, and the precipitate was collected, washed with water and recrystallized from water–ethanol to give 1.8 g (60%) of **2c** as colorless crystals, mp 221—223 °C. IR ν_{max}^{KBr} cm^{-1}: 3200 (OH), 1660 (C=O). UV λ_{max}^{MeOH} nm (log ε): 215 (4.44), 280 (4.46), 310 inf. (4.18). NMR (δ in DMSO-d_6): 6.67—7.50 (4H, m, Ar-H), 9.95 (1H, br, NH), 12.73 (2H, br, NH and OH). MS *m/e*: 300, 298 (M^+), 219 (M^+–Br), 202. *Anal.* Calcd for $C_{10}H_7BrN_2O_2S$: C, 40.15; H, 2.36; N, 9.36. Found: C, 40.36; H, 2.32; N, 9.36.

When the reaction was carried out under reflux, only compound **3** was isolated. Yield, 0.2 g (8%).

Preparation of 3——Compound **1c** (1.3 g, 5 mmol) was stirred in ethanolic sodium ethoxide solution (0.35 g of Na and 30 ml of anhyd. ethanol) at room temperature for 24 h. After removal of the solvent, water was added to the residue and the solution was extracted with chloroform. The extract was worked up to give ethyl 3-ethoxybenzofuran-2-carboxylate (**4**)[5] as a colorless oil [yield, 1.0 g; IR ν_{max} cm^{-1}: 1705 (CO ester)]. The ester was heated, without further purification, with thiourea (0.38 g, 5 mmol) in ethanolic sodium ethoxide solution (0.12 g of Na and 10 ml of anhyd. ethanol) for 3 h. After removal of the solvent, the residue was treated with water and the precipitate was collected and recrystallized from ethanol to give 0.7 g (53% from **1c**) of **3**, mp 180—183 °C, identical with **3** obtained previously.

3-Ethoxybenzofuran-2-carboxylic Acid (5)——Compound **3** (0.26 g, 1 mmol) was refluxed in 5% ethanolic KOH (40 ml) for 5 h to give **5**. Recrystallization from ethanol afforded 0.13 g (63%) of pure sample, mp 181—182 °C. IR ν_{max}^{KBr} cm^{-1}: 1670 (CO acid). MS *m/e*: 206 (M^+). *Anal.* Calcd for $C_{11}H_{10}O_4$: C, 64.08; H, 4.89; Found: C, 64.21; H, 4.91.

6-(2-Hydroxyphenyl)uracils (6a, b)——A mixture of **2b** (0.5 g, 2 mmol), monochloroacetic acid (0.4 g, 4.2 mmol) and dimethylformamide (0.4 ml) in water (8 ml) was refluxed for 5 h, then allowed to stand overnight at room temperature. The precipitate was collected and heated under reflux in a mixture of conc. HCl (5 ml) and dioxane (1.5 ml) for 8 h. The resulting solution was concentrated *in vacuo* to give crystals, which were recrystallized from water–ethanol to give 0.16 g (31%) of **6b**, mp 263—265 °C. IR ν_{max}^{KBr} cm^{-1}: 3200 (OH), 1700 (C=O). MS *m/e*: 240, 238 (M^+), 203 ($M^+ - Cl$). *Anal.* Calcd for $C_{10}H_7ClN_2O_3$: C, 50.32; H, 2.96; N, 11.74. Found: C, 50.02; H, 3.01; N, 11.35.

In a similar manner, **2c** (0.6 g, 2 mmol) gave 0.03 g (7.4%) of **6a**, mp >300 °C, identical with **6a** obtained from **2a** (lit.[1] mp 306—307 °C).

2-Substituted Amino-6-(2-hydroxyphenyl)-4-(3*H*)-pyrimidones (7, 8)—— A mixture of a thiouracil (**2a**, **b** or **c**, 2 mmol) and morpholine (7 ml) was heated at 140—150 °C in a sealed tube for 7 h. The reaction mixture was poured into water and the resulting solution was acidified with AcOH. The precipitate was collected, washed with water and recrystallized from ethanol to afford **7**, mp 257—259 °C. Yield, 0.22 g (40%) from **2a**, 0.1 g (18%) from **2b** and 0.1 g (20%) from **2c**. IR ν_{max}^{KBr} cm^{-1}: 1640 (C=O). MS *m/e*: 273 (M^+). *Anal.* Calcd for $C_{14}H_{15}N_3O_3$: C, 61.54; H, 5.49; N, 15.38. Found: C, 61.28; H, 5.47; N, 15.14.

Similarly, treatment of **2a** with pyrrolidine in the place of morpholine gave 0.15 g (29%) of **8**, mp 280—283 °C. IR ν_{max}^{KBr} cm^{-1}: 1640 (C=O). MS *m/e*: 257 (M^+). *Anal.* Calcd for $C_{14}H_{15}N_3O_2$: C, 65.43; H, 5.88; N, 16.35. Found: C, 65.13; H, 5.81; N, 16.45.

5-Halo-6-(2-methoxyphenyl)-2-methylthio-4-(3*H*)-pyrimidones (9b, c)—— A mixture of a thiouracil (**2b** or **c**, 5 mmol), methyl iodide (2.1 g, 15 mmol) and KOH (0.56 g, 10 mmol) in methanol (40 ml) was heated in a sealed tube at 80—90 °C for 2 h. After removal of the solvent, the residue was treated with water and the resulting resinous product was triturated in a small amount of ethanol. The solid thus obtained was recrystallized from ethanol to give **9b** or **c** as colorless needles. **9b**, mp 163—164 °C, yield, 0.7 g (50%). IR ν_{max}^{KBr} cm^{-1}: 1663 (C=O). MS *m/e*: 284, 282 (M^+), 247 ($M^+ - Cl$). *Anal.* Calcd for $C_{12}H_{11}ClN_2O_2S$: C, 50.98; H, 3.92; N, 9.91. Found: C, 51.14; H, 3.87; N, 10.06. **9c**, mp 159—161 °C, yield, 0.5 g (30%). IR ν_{max}^{KBr} cm^{-1}: 1663 (C=O). MS *m/e*: 328, 326 (M^+), 247 ($M^+ - Br$). *Anal.* Calcd for $C_{12}H_{11}BrN_2O_2S$: C, 44.05; H, 3.39; N, 8.57. Found: C, 44.29; H, 3.39; N, 8.60.

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