N-Quaternary Compounds. Part LVIII.* Substitution Reactions in the 2,3-Dihydrothiazolo-[3,2-*c*]pyrimidinium-8-olate Ring System

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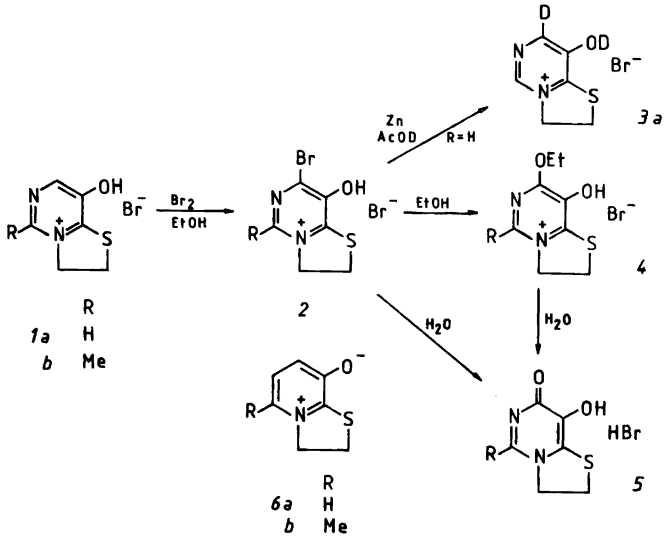
In our continuing work on elucidating the properties of novel mesoionic ring systems,[2] we recently reported synthetic studies of 2,3-dihydrothiazolo[3,2-*c*]pyrimidinium-8-olates.[3] This report describes substitution studies in this ring system and the results are compared with the previously reported findings for the 6-deaza analogue ring system *viz.* 2,3-dihydrothiazolo[3,2-*a*]pyridinium-8-olates.[4] The latter react readily with electrophiles under a variety of conditions. Both the azinium containing systems owe their reactivity towards electrophiles to the presence of the olate function. Hence substitution may occur in *o*- or *p*-position to this function. The introduction of a second nitrogen into the pyridine ring in *6*, as in the case of the pyrimidine *1*, has been found to markedly reduce the reactivity towards electrophiles and has the opposite effect on nucleophilic substitution.

The pyrimidine *1a* can be monobrominated by heating with bromine in ethanol. The substitution takes place at C-7. Substitution at the alternative 5-position was not seen (TLC, ^{1}H NMR). For comparison it is pointed out that the pyridine *6a* was brominated at both C-5 and C-7 at room temperature and that the 5-bromo compound was obtained from the reaction at −50 °C in methanol.[4] Also in the chlorination reaction using sulfuryl chloride the two compounds *6a* and *1a* differ. The former gave the 5-chloro derivative,[4] whereas several products were seen from the reaction with *1a* (TLC).

The identification of the monobrominated product as *2a* rests on ^{1}H NMR. H-5 and H-7 in *1a* resonate at δ 8.78 and 8.17, respectively (D_2O). This assignment is in accordance with the nuclear Overhauser effect by double irradiation of the protons at C-3 which led to a 10 % increase in the intensity of the signal at δ 8.78; double irradiation of the C-2 protons had no effect on the relative intensities of the pyrimidine protons. Reductive removal of the bromine in the brominated product by means of zinc in acetic acid-d_1 gave a product with retention of the pyrimidine signal at δ 8.70 (D_2O); hence this product must be the 7-deuterio derivative *3a*.

The 5-methyl derivative *1b* can also be brominated in the pyrimidine ring by heating with bromine in ethanol. Under the vigorous conditions of the experiment the reaction proceeds further to yield the lactam *5b* as the major product; the minor product is the 7-ethoxy derivative *4b*.

* See Ref. 1.



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Nucleophilic substitutions on *2a* under basic conditions were unsatisfactory because of decomposition. Under acidic conditions the betaine is protected as the acid salt; heating *2a* in water led to the 7-oxo derivative *5a*, and heating *2a* in ethanol yielded the 7-ethoxy derivative *4a*. The latter is converted to *5a* by heating in water. These reactions clearly demonstrate the ease of nucleophilic substitution at C-7 in this system.

Experimental. The MS spectra are presented as MS[70 eV; *m/z* (% rel. int,)] The ^{1}H NMR spectra were recorded at 60 MHz.

7-Bromo-8-hydroxy-2,3-dihydrothiazolo[3,2-c]-pyrimidinium bromide 2a. Bromine (0.32 ml, 6.4 mmol) was added gradually to a solution of 8-hydroxy-2,3-dihydrothiazolo[3,2-*c*]pyrimidinium bromide (1.50 g, 6.4 mmol) in ethanol (30 ml) and the mixture stirred at 55 °C for 90 min. More bromine (0.16 ml, 3.2 mmol) was then added and the stirring continued at the same temperature for 4 h. Filtration of the cold reaction mixture gave the title compound; yield 1.36 g (68 %) m.p. 275–277 °C (EtOH). Anal. $C_6H_6Br_2N_2OS$: C,H. ^{1}H NMR (TFA): δ 4.08 (2H-2), 5.39 (2H-3), 8.93 (H-5). MS: 234/232 (22/22, M for betaine), 226/224 (22/23), 207/205 (22/16), 82/80 (95/100), 81/79 (41/42).

7-Bromo-8-hydroxy-5-methyl-2,3-dihydrothiazolo[3,2-c]pyrimidinium bromide 2b has previously been described.[5] Heating *1b* under reflux with bromine in ethanol gave *5b*; see below.

7-Deuterio-8-deuterioxy-2,3-dihydrothiazolo-[3,2-c]pyrimidinium bromide 3a. 7-Bromo-8-hydroxy-2,3-dihydrothiazolo[3,2-*c*]pyrimidinium bromide (200 mg, 0.6 mmol) was dissolved in deuterium oxide (3 ml) and zinc dust (40 mg, 0.6 mmol) and acetic acid-d_1 (1 ml) added. The resulting mixture was stirred for 1 h at room temperature before the insoluble material was removed by filtration. Evaporation of the filtrate left the title compound (TLC as *1a*) admixed with some Zn-salts. ^{1}H NMR (D_2O): δ 3.9 (2H-2), 5.2 (2H-3), 8.70 (H-5).

7-Ethoxy-8-hydroxy-2,3-dihydrothiazolo[3,2-c]-pyrimidinium bromide 4a. A solution of 7-bromo-8-hydroxy-2,3-dihydrothiazolo[3,2-*c*]pyrimidinium bromide (0.30 g, 0.96 mmol) in ethanol (30 ml) was heated under reflux for 24 h before the solvent was removed by evaporation. Recrystallization of the residue from a small volume of ethanol yielded the title compound in 63 % yield (0.17 g), m.p. 183 °C. Anal. $C_8H_{11}BrN_2O_2S$: C, H. ^{1}H NMR (TFA): δ 1.53 and 4.77 (OEt), 3.87 (2H-2), 5.12 (2H-3), 8.67 (H-5). MS: 198 (5, M for betaine), 170 (74), 142 (21), 114 (17), 110 (96), 108 (100), 87 (21).

8-Hydroxy-2,3-dihydrothiazolo[3,2-c]pyrimidin-7-one HBr salt, 5a. (a) From 7-bromo-8-hydroxy-2,3-dihydrothiazolo[3,2-*c*]pyrimidinium bromide: a solution of the latter (0.40 g, 1.3 mmol) in water (20 ml) was heated under reflux for 18 h before evaporation of the water. Recrystallization of the residue from ethanol yielded the title compound in 58 % yield (0.19 g), m.p. 240 °C (decomp.). High resolution MS: M 170.0151. Calc. for $C_6H_6N_2O_2S$: 170.0150. ^{1}H NMR (TFA): δ 3.83 (2H-2), (5.10 (2H-3), 9.37 (H-5). IR (KBr): 1669 cm^{-1} (CO). MS: 170 (86, M for free base), 142 (25), 114 (14), 87 (23), 82/80 (94/100), 81/79 (39/41).

(b) From 7-ethoxy-8-hydroxy-2,3-dihydrothiazolo[3,2-*c*]pyrimidinium bromide: a solution of the latter (0.50 g, 1.8 mmol) in water (40 ml) was heated under reflux for 2 d before evaporation of the water. The residue was worked up as above; yield 0.22 g (49 %).

8-Hydroxy-5-methyl-2,3-dihydrothiazolo[3,2-c]-pyrimidin-7-one HBr salt 5b. Bromine (1.54 ml, 0.03 mol) was gradually added to a solution of 8-hydroxy-5-methyl-2,3-dihydrothiazolo[3,2-*c*]-pyrimidinium bromide (3.70 g, 0.015 mol) in ethanol (50 ml) and the solution heated under reflux for 4 h. Essentially pure title compound was filtered off from the cold reaction mixture; yield 2.10 g (53 %), m.p. 250 °C (decomp,; EtOH). The filtrate contained a mixture of *5b* and the 7-ethoxy (*4b*) derivatives (TLC, MS, ^{1}H NMR). The filtrate was therefore evaporated and the residue dissolved in water and this solution heated under reflux overnight before the water was evaporated. Recrystallization of the residue from ethanol furnished another crop of *5b*; yield 0.60 g (15 %). High resolution MS: M 184.0289. Calc. for $C_7H_8N_2O_2S$ 184.0307. ^{1}H NMR (TFA): δ 2.90 (5-Me), 4.02 (2H-2), 5.18 (2H-3). IR (KBr): 1690 cm^{-1} (CO). MS: 184 (16, M for free base), 87 (14), 82/80 (95/100), 81/79 (37/39).

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