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N-Quaternary Compounds. Part LV.* Synthetic Studies of the 2,3-Dihydrothiazolo[3,2-*c*]pyrimidinium-8-olate System

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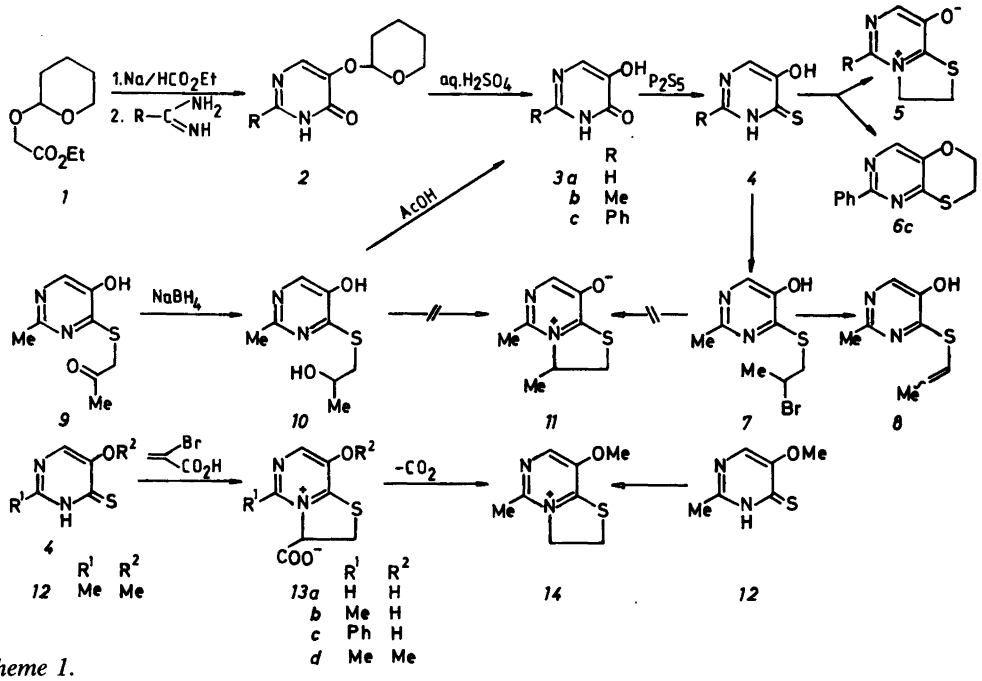
5-Hydroxy-4-pyrimidinethiones form the novel 2,3-dihydrothiazolo[3,2-*c*]pyrimidinium-8-olate system on reaction with vicinal dibromides or with 2-bromopropenoic acid. Steric or electronic effects may change the reaction path towards the formation of a 2,3-dihydro[1,4]oxathiino[5,6-*d*]-pyrimidine or may lead to *S*-vinylation.

For further comparisons of chemical and physical properties of the novel dihydrothiazolo[3,2-*a*]-pyridinium-8-olate system[2] with the aza-analogous dihydrothiazolo[3,2-*c*]pyrimidinium-8-olate system,[3] we herein report synthetic work leading to the latter system (Scheme 1).

The protected glycolic acid ester *1* is formylated on the methylene carbon and condensed with an amidine to yield the pyrimidine *2* with the desired 2-substituent. The latter can be isolated, or may advantageously have the protecting group removed *in situ* by aqueous acid. Phosphorus pentasulfide is used for the thiation. The reactivity depends on the 2-substituent; thus the 2-

* Part LIV, see Ref. 1.



Scheme 1.

0302-4369/83 $2.50

unsubstituted lactam *3a* requires heating in refluxing pyridine for 1 d whereas the reaction for the 2-phenyl derivative is complete after 7 d. *4a* reacts with 1,2-dibromoethane in the same manner as reported for *4b*.[3] The 2-phenyl derivative *4c* gives the same type of product *5c* in methanolic sodium methoxide; with sodium carbonate in DMF several products are formed, a major one being the bicyclic oxathiin *6c*. In the pyridine series the latter type of cyclization occurs only under strongly acid conditions.[2] The formation of *6c* is attributed to the steric effects of the vicinal phenyl substituent as well as to the low nucleophilicity of the pyrimidine nitrogen.

The 3,5-dimethyl derivative *11* could not be obtained by simple cycloalkylation reactions which we attribute to steric interaction between these substituents. The corresponding pyridine, however, can be formed in such reactions although there is a notable steric retardation.[2]

In the alkylation of *4b* by means of 1,2-dibromopropane, the *S*-vinyl derivative *8* was obtained as a 1:1 *cis–trans* mixture (^{1}H NMR). Formation of *8* by an elimination reaction from the desired bicyclic compound *11* present as an intermediate can be excluded since ring opening reactions of *11* would lead to a mixture of *N*- and *S*-vinyl derivatives by analogy to the behaviour of pyridine analogues.[2] Instead the formation of *8* corresponds to selective substitution at C–1 of the alkylating agent with subsequent HBr elimination; the pyridine corresponding to *7*, however, undergoes cycloalkylation to form the pyridine analogue of *11*.[2] The different reaction paths for the two azine systems we attribute to differences in the nucleophilicities of the heterocyclic nitrogens.

Assignment of structure *8* to the vinyl product is based on its UV absorption bands at 314 and 234 nm; isomeric *N*-vinyl 4-pyrimidinethiones absorb at 350–360 and *ca.* 280 nm.[4]

In an alternative approach to the preparation of *11*, the thiolactam *4b* was *S*-alkylated (*9*) by bromoacetone and the oxo function reduced by sodium borohydride to the alcohol *10*. Attempts to effect acid catalyzed cyclization as for the pyridine analogues, however, met with little success due to the ease of nucleophilic displacement of the 4-thioether group which results in the formation of the lactam *3b*.

The thiolactam *4b* will add in a Michael fashion over the sulfur to 2-bromopropenoic acid with subsequent cyclization to form the bicyclic pyrimidinium salt *13b*.[3] The thiolactam *4a* reacts in the same manner. The rate of this reaction is sensitive to the nucleophilicity of the Michael addend; the reaction time for the lactam *4a*, which is without a 2-substituent, is considerably increased over that for the 2-methyl derivative *4b* whereas the 2-phenyl thiolactam *4c* failed to react. The 5-methoxythiolactam *12* reacts with 2-bromopropenoic acid to form *13d*; the latter is very readily decarboxylated due to the activation from the quaternary nitrogen. The methoxy group does not counteract the electron deficiency of the pyrimidine ring to the same extent as does the hydroxy group, and hence the tendency for decarboxylation is greater in *13d* than in *13a* and *13b*. The product isolated from the reaction of *12* was therefore the decarboxylated product *14*; the latter is also available by the direct alkylation of *12* by 1,2-dibromoethane.

The mass spectra of the betaines *5* all have a molecular ion with mass number corresponding to the mass of the betaine. By analogy to our previous structure analyses of gaseous species from betaines in the gas phase in the mass spectrometer using appearance potentials,[5] the compounds *5* will go into the gas phase without any structure rearrangement. This is supported by the different fragmentation pattern of the phenyl isomers *5c* and *6c* and the different fragmentation of *5a* and *13a*. The latter is decarboxylated in the mass spectrometer to give a molecular ion of the same mass as for *5a*. The fragmentation pattern, however, is different because of ring-opening and formation of the corresponding *N*-vinyl isomer.

EXPERIMENTAL

The mass spectra are presented as MS[70 eV; *m/z* (% rel. int.)].

2-Phenyl-5-(tetrahydro-2-pyranyloxy)-4-pyrimidinone 2c. Ethyl (tetrahydro-2-pyranyloxy) acetate[6] (18.8 g, 0.1 mol) was added dropwise to a well-stirred mixture from sodium (2.3 g, 0.1 mol) and ethyl formate (7.4 g, 0.1 mol) in dry ether (100 ml) at 0 °C. The mixture was stirred at room temperature for 4 h before benzamidine (0.1 mol) in ethanol (100 ml) was added. The mixture was heated under reflux for 16 h, the solvent evaporated, water (300 ml) added, the pH adjusted to *ca.* 5 with acetic acid, the mixture

extracted with chloroform (3 × 90 ml), the chloroform solution washed with water and the dried ($MgSO_4$) solution evaporated; yield 14.3 g (53 %), m.p. 174 °C (EtOH). Anal. $C_{15}H_{16}N_2O_3$: C, H. ^{1}H NMR ($CDCl_3$): δ 1.8, 3.8, 5.65 (pyranyl), 7.8 (Ph, H–6) MS: (M, O), 188 (100), 116 (22), 104 (37), 85 (60), 84 (14), 77 (20), 57 (22).

5-Hydroxy-2-methyl-4-pyrimidinone 3b.[7] Ethyl (tetrahydro-2-pyranyloxy)acetate[6] (145.0 g, 0.77 mol) was added dropwise to a mixture from sodium (17.7 g, 0.77 mol) and ethyl formate (57.0 g, 0.77 mol) in dry ether (400 ml) at 0 °C. The mixture was stirred at room temperature for 4 h before acetamidine hydrochloride (72.8 g, 0.77 mol) in ethanol (500 ml) was added. The mixture was heated under reflux for 21 h, the solvent evaporated at reduced pressure, the residue dissolved in water (600 ml), sulfuric acid (20 ml) added, the mixture stirred for 2 h before addition of sodium carbonate to pH 5 and the precipitated product triturated with water (500 ml) to redissolve any inorganic salt; yield 41.4 g (43 %), m.p. 285 °C (H_2O).

5-Hydroxy-2-phenyl-4-pyrimidinone 3c.[8] 2-Phenyl-5-(tetrahydro-2-pyranyloxy)-4-pyrimidinone (20.0 g, 0.073 mol) was added to 1 M H_2SO_4 and the mixture stirred for 2 h before sodium carbonate was added to pH 5. The precipitate was recrystallized from water–ethanol (2:1); yield 11.4 g (83 %), m.p. 220–222 °C.

5-Hydroxy-4-pyrimidinethione 4a. A well-stirred mixture of 5-hydroxy-4-pyrimidinone[9] (10.0 g, 0.09 mol) and phosphorus pentasulfide (22.2 g, 0.1 mol) in dry pyridine (250 ml) was heated under reflux for 24 h. Water (150 ml) was added to the cold reaction mixture and the heating under reflux was resumed for 2 h to destroy excess phosphorus pentasulfide. Concentration of the solution to *ca.* 100 ml at reduced pressure precipitated the product which was recrystallized from water; yield 6.6 g (57 %), m.p. 212 °C (decomp.). Anal. $C_4H_4N_2OS$: C, H. ^{1}H NMR (TFA): δ 7.60 (H–6), 8.85 (H–2). MS: 128 (100, M), 100 (3), 95 (5), 84 (7), 73 (6), 68 (14).

5-Hydroxy-2-phenyl-4-pyrimidinethione 4c. 5-Hydroxy-2-phenyl-4-pyrimidinone (10.0 g, 0.053 mol) and phosphorus pentasulfide (15.6 g, 0.07 mol) were heated together with stirring in boiling pyridine (150 ml) for 7 d. Water (50 ml) was added to the cold mixture, the mixture refluxed for another 2 h, the solvents distilled off, the residue triturated with water and the solid recrystallized from H_2O–EtOH (3:1), yield 9.5 g (88 %), m.p. 195–196 °C. Anal. $C_{10}H_8N_2OS$: C, H. ^{1}H NMR (TFA): δ 7.8 (Ph and H–6). MS: 204 (100, M), 188 (55), 171 (15), 144 (40), 116 (57), 115 (11), 101 (13), 89 (26), 77 (34).

2,3-Dihydrothiazolo[3,2-c]pyrimidinium-8-olate 5a. 5-Hydroxy-4-pyrimidinethione (6.5 g, 0.05 mol), sodium carbonate (5.3 g, 0.05 mol) and 1,2-dibromoethane (9.4 g, 0.05 mol) in dry DMF (100 ml) were heated at 55 °C for 3 h. The mixture was evaporated, the residue dissolved in the minimum amount of boiling water, the pH brought to *ca.* 4, the precipitate was redissolved in water and passed through a DEAE-Sephadex A-25 column in the formate form and the title compound eluted with 0.01 M formic acid; yield 3.2 g (42 %), m.p. 213 °C. Anal. $C_6H_6N_2OS$: C, H. ^{1}H NMR (TFA): δ 4.02 (2H-2, t), 5.38 (2H-3, t), 8.57 (H-7), 9.13 (H-5), MS: 154 (100, M), 126 (21), 82 (22), 80 (22), 71 (41), 68 (17), 60 (36).

5-Phenyl-2,3-dihydrothiazolo[3,2-c]pyrimidinium-8-olate 5c. 1,2-Dibromoethane (6.0 g, 0.032 mol) in methanol (35 ml) was added to a solution from 5-hydroxy-2-phenyl-4-pyrimidinethione (6.6 g, 0.032 mol) in methanolic sodium methoxide (100 ml; 0.064 mol) and the mixture refluxed for 24 h. The solvent was then distilled off at reduced pressure, water added to the residue, the solution washed with chloroform (5×), the aqueous solution evaporated at reduced pressure, the dry residue extracted with 2-propanol, the alcohol evaporated and the residue recrystallized from water; yield 0.8 g (11 %), m.p. 237 °C. Anal. $C_{12}H_{10}N_2OS$: C, H. ^{1}H NMR (TFA): δ 3.92 (2H-2, t), 5.20 (2H-3, t), 7.63 (5-Ph, s), 8.70 (H-7). MS: 230 (100, M), 204 (79), 172 (30), 147 (63), 144 (30), 116 (35), 115 (24), 105 (24), 104 (49), 103 (81), 77 (40).

6-Phenyl-2,3-dihydro[1,4]oxathiino[5,6-d]pyrimidine 6c. 1,2-Dibromoethane (2.8 g, 0.015 mol) in dry DMF (15 ml) was added dropwise to a mixture of 5-hydroxy-2-phenyl-4-pyrimidinethione (3.0 g, 0.015 mol) and sodium carbonate (1.6 g, 0.015 mol) in dry DMF (100 ml) at room temperature. The mixture was stirred at 55 °C for 4 d, the DMF distilled off at reduced pressure, water added to the residue and the mixture extracted with chloroform (5×), the chloroform extracts washed with water, the dried ($MgSO_4$) solution concentrated and chromatographed on a silica gel column eluting with chloroform. The first fraction contained the title compound which was recrystallized from ethanol; yield 0,2 g (6 %), m.p. 109 °C. Anal. $C_{12}H_{10}N_2OS$: C, H. ^{1}H NMR ($CDCl_3$): δ 3.27 (2H-3, t), 4.39 (2H-2, t), 7.8 (Ph, H-8). MS: 230 (100, M), 170 (12), 149 (13), 147 (62), 115 (19), 103 (40), 77 (9).

cis/trans-*5-Hydroxy-2-methyl-4-propenylthiopyrimidine* 8. 1,2-Dibromopropane (1.4 g, 0.007 mol) in dry DMF (20 ml) was added dropwise to a mixture of 5-hydroxy-2-methyl-4-pyrimidinethione[3] (1.0 g, 0.007 mol) and sodium carbonate (0.74 g, 0.007 mol) in dry DMF (50 ml). The

mixture was stirred at 60 °C for 4 h, the solvent was distilled off at reduced pressure, water added to the residue and the mixture extracted with ether (5×), the ether washed and dried ($MgSO_4$) and the ether distilled off leaving the title compound as a 1:1 *cis–trans* mixture; yield 0.67 g (53 %). The product can be further purified by sublimation at 100 °C/0.05 mmHg. Anal. $C_8H_{10}N_2OS$: C, H. ^{1}H NMR ($CDCl_3$; 200 MHz): δ 1.85–1.95 (*cis/trans* β-Me, $J_{al.}$ 1.6 Hz, $J_{vic.}$ 7 and 10 Mz), 5.95–6.15 (H–β), 6.82 (H_α, J_{trans} 16 Hz), 7.06 (H_α, J_{cis} 10 Hz), 7.63 and 7.67 (C–6; *cis/trans* isomers). UV (EtOH, log ε): 314 (4.08), 234 nm (3.65). MS: 182 (8, M), 167 (100), 126 (24), 109 (15), 82 (20), 54 (17).

1-(5-Hydroxy-2-methyl-4-pyrimidinylthio)-2-propanone 9. Bromoacetone (3.4 g, 0.025 mol) in methanol (15 ml) was added dropwise to a solution from 5-hydroxy-2-methyl-4-pyrimidinethione [3] (2.9 g, 0.02 mol) in 0.4 M methanolic sodium methoxide (50 ml). The reaction mixture was stirred at room temperature for 4 h, the solvent distilled off, water added to the residue and the mixture extracted with chloroform (5 × 50 ml), the washed and dried ($MgSO_4$) chloroform solution evaporated and the residue recrystallized from ethanol–benzene 1:1; yield 3.0 g (76 %), m.p. 153 °C (decomp.). Anal. $C_8H_{10}N_2O_2S$: C, H. ^{1}H NMR (TFA): δ 2.58 (MeCO), 2.80 (2-Me), 4.37 (CH_2), 7.97 (H-6). MS: 198 (12, M), 157 (11), 156 (89), 155 (100), 123 (36), 109 (29), 82 (26), 78 (30).

1-(5-Hydroxy-2-methyl-4-pyrimidinylthio)-2-propanol 10. Sodium borohydride (0.8 g, 0.021 mol) was added to a solution of 1-(5-hydroxy-2-methyl-4-pyrimidinylthio)-2-propanone (3.2 g, 0.016 mol) in 2-propanol (150 ml) and the mixture stirred at room temperature for 2 h. The solvent was then removed at reduced pressure, water added to the residue, the pH brought to *ca.* 6 with HCl, the mixture extracted with ethyl acetate (10 × 75 ml), the washed and dried ($MgSO_4$) extracts evaporated and a chloroform solution of the residue filtered through a silica gel column; yield 2.3 g (72 %) of oily material. Anal. $C_8H_{12}N_2O_2S$: C, H: ^{1}NMR (TFA): δ 1.52 (β-Me), 2.82 (2-Me), 3.63 (CH_2), 4.4 (CH), 7.82 (H-6). MS: 200 (0.8, M), 167 (16), 156 (52), 143 (17), 142 (100), 126 (13), 123 (49), 109 (34).

5-Hydroxy-2-methyl-4-pyrimidinone 3b *from* 10. A solution of 1-(5-hydroxy-2-methyl-4-pyrimidinylthio)-2-propanol (0.005 mol) in acetic acid (20 ml) was heated under reflux for 24 h before the acetic acid was removed by distillation. The residue was heated in 6 M hydrochloric acid for 1 h to hydrolyze any acetate. Evaporation and trituration with sodium carbonate solution left the lactam *3b* in 70 % yield.

8-Hydroxy-2,3-dihydrothiazolo[3,2-c]pyrimidinium-3-carboxylate 13a. A solution of 5-hydroxy-4-pyrimidinethione (1.0 g, 0.008 mol) and 2-bromopropenoic acid (1.5 g, 0.01 mol) in aqueous (1:1) methanol (50 ml) was stirred at room temperature for 14 d. During this period additional 2-bromopropenoic acid (4 × 0.9 g) was added. Evaporation of the reaction mixture and trituration with ethyl acetate left the hydrobromide of the title compound. The zwitterion was obtained from this salt using a DEAE-Sephadex A-25 column in the formate form and 2 % formic acid; yield 0.55 g (35 %), m.p. 150 °C (decomp.); (EtOH). Anal. $C_7H_6N_2O_3S$: C, H. ^{1}H NMR (TFA): δ 4.44 (2H-2), 6.53 (H-3), 8.67 (H-7), 9.34 (H-5). MS: (M, O), 154 (47), 153 (61), 128 (20), 68 (14), 44 (100).

8-Methoxy-5-methyl-2,3-dihydrothiazolo[3,2-c]pyrimidinium bromide 14. Method A: 5-Methoxy-2-methyl-4-pyrimidinethione [10] (6.0 g, 0.038 mol), sodium carbonate (2.0 g, 0.038 mol) and 1,2-dibromoethane (7.1 g, 0.038 mol) in dry DMF (100 ml) were heated together at 70 °C for 4 h. The mixture was then concentrated to *ca.* 50 ml, the precipitate collected and triturated with a little water to dissolve inorganic material; yield 4.9 g (49 %), m.p. 220–222 °C (MeOH). Anal. $C_8H_{11}BrN_2OS$: C, H. ^{1}H NMR (TFA): δ 3.03 (5–Me), 4.10 (2H–2), 4.23 (OMe), 5.38 (2H–3), 8.48 (H–7), MS: 183 (39, M), 182 (87), 181 (100), 168 (33), 167 (25), 156 (13), 123 (23), 96 (35), 94 (37).

Method B: 5-Methoxy-2-methyl-4-pyrimidinethione (3.0 g, 0.019 mol) and 2-bromopropenoic acid (4.4 g, 0.029 mol) were heated together at 60 °C in methanol (140 ml) for 5 d. Trituration of the precipitates with water left the title compound; yield 1,3 g (26 %).

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