N-Quaternary Compounds. Part LIX [1]. Facile Synthesis of 3-Vinyl-4(3*H*)-pyrimidinethiones

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3-Vinyl derivatives of 4(3*H*)-pyrimidinethiones have been prepared from 2,3-dihydrothiazolo[3,2-*c*]pyrimidinium derivatives through ring-opening by a strong base such as potassium *t*-butoxide in DMF. The pyrimidinium derivative is initially prepared from 4(3*H*)-pyrimidinethiones. 3-Vinyl-4(3*H*)-pyrimidinethiones are also formed by the ready decarboxylation of 2,3-dihydrothiazolo[3,2-*c*]pyrimidinium-3-carboxylates. In the mass spectrometer the nature of the volatile species was elucidated by means of appearance potentials and fragmentation patterns.

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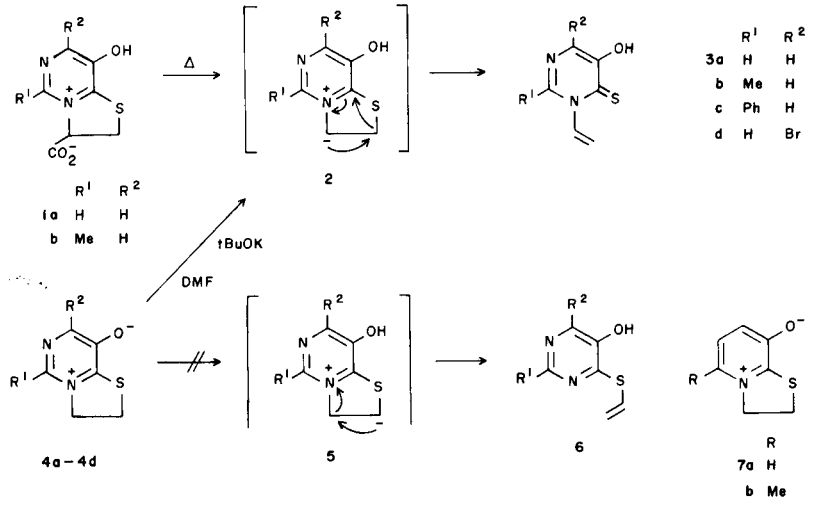
N-vinylpyrimidines from hydroxy- and amino-substituted pyrimidines can be prepared by a vinyl interchange reaction with vinyl acetate involving mercuric acetate catalysis in acid solution [2]. Dehydrohalogenation of *N*-(2-haloethyl)pyrimidinone precursors using a strong base is an alternative method [2b,3]. The vinyl group can also be attached to an acyclic-nitrogen intermediate such as in *N*-vinylisocyanate, which has been used in a cyclo-condensation reaction to form *N*-vinyluracil [4]. We were interested in developing a method for *N*-vinylation of pyrimidinethiones. Selective *N*-alkylation or *N*-alkenylation of the latter is difficult to achieve because of preferential reactivity of the sulfur with electrophilic carbon; *S*-vinyl derivatives are thus formed. *S, N*-Disubstitution proceeds readily, however, as in the formation of the novel 2,3-dihydrothiazolo-[3,2-*c*]pyrimidinium-8-olates **1** and **4** from 5-hydroxy-4(1*H*)-pyrimidinethiones [5]. The methylene protons of the dihydrothiazolo ring are activated. Hence proton abstraction and Hofmann type elimination will lead to a ring opening reaction and formation of *N*- or *S*- vinylpyrimidine derivatives. Generation of an anion at C-3 leads to *N*-vinylation (**3**), whereas an anion at C-2 leads to *S*-vinylation (**6**). Nonambiguous formation of the anion at C-3 is achieved by a different route, *viz.* by decarboxylation of the 3-carboxy derivatives **1**. The decarboxylation is facilitated by the adjacent pyrimidinium nitrogen atom, and the intermediate [2] in protic solvent will be protonated at C-3, whereas under aprotic conditions the desired ring opening will take place. The latter pathway is realized by heating a mixture of the 3-carboxy derivative **1** in quartz sand at reduced pressure when the *n*-vinyl derivative which is formed, is successively sublimed from the reaction mixture. Cosublimation of the betaine **4**, which is an alternative product which could arise by a prototropic shift, was not observed.

The protons at both C-2 and C-3 are activated by the positive charge carried by the adjacent heteroatoms; the lower field signals of the C-3 protons in ^{1}H nmr show that these are the more acidic, the signals for **4a** occurring at δ 4.02 and 5.38 (TFA) for C-2 and C-3, respectively. Accordingly treatment of **4** with potassium *t*-butoxide in DMF leads to proton abstraction at C-3 and exclusive formation

Scheme I

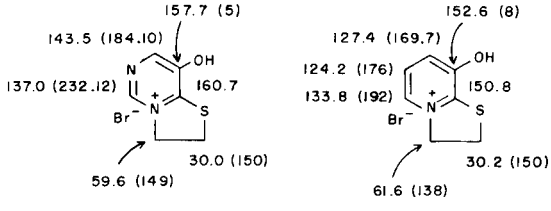


of the *N*-vinyl derivatives **3** (^{1}H nmr, glc). The assigned structure is further supported by uv absorption bands at *ca.* 355 and 280 nm, which compare closely with the absorption of 3-hydroxy-1-vinyl-2(1*H*)-pyridinethiones (370 and 280 nm) [6].

The absence of the *S*-vinyl isomer **6** is notable since both *N*- and *S*-vinylpyridines are formed in a closely related reaction developed from the dihydrothiazolo[3,2-*a*]pyridinium-8-olate system **7** [7]. Bulky substituents at C-5 in **7** promote the formation of the *S*-vinyl isomers; from the 5-phenylpyrimidine **4c**, however, only the *N*-vinyl isomer **3c** was seen. Nor does a bromine substituent at C-7 (**4d**) affect the selectivity in the elimination. The π-electron deficiency of the pyrimidinium ring is therefore more effeciently transmitted to C-3 than to C-2 than is the case in the corresponding pyridinium system. Relative chemical shifts in nmr, as an indicator for the relative acidities of the H-2 and H-3 protons in the two systems, hardly explain the high regioselectivity observed in the elimination reaction. Thus the differences in the chemical shifts between the H-2 and H-3 protons in the two series are similar, *viz.* 1.39 ppm for **4b** (δ 4.09, 5.48) and 1.22 ppm for **7b** (δ 3.88, 5.10) in TFA solution. In ^{13}C nmr the deshielding of the C-2 and C-3 carbons in the two series are almost the same, *viz.* δ 30.0 and 59.6 for **4a** and δ 30.2 and 61.6 for **7a** in water solution.

Table 1

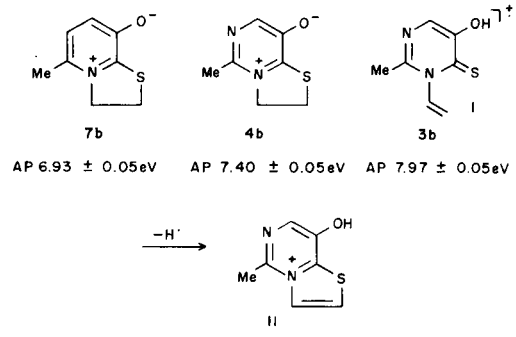
^{13}C Chemical Shifts in ppm Relative to TMS, C-H Coupling Constants in Hz (δ)



In the ^{13}C nmr spectrum of **4a** the signals from the substituted carbons C-8 and C-9 (δ 157.7 and 160.7) are distinguished from the signals belonging to the other pyrimidine cabons by the absence of the large one-bond carbon-proton couplings. The higher field signal is split by a two-bond carbon-proton coupling *ca.* 5 Hz, which is attributed to the coupling between C-8 and H-7; the magnitude of the coupling is in accordance with data for other pyrimidines [8-10]. The signals from C-5 and C-7 are split by the large one-bond carbon-hydrogen coupling. In pyrimidines it has been established that the order of $^1J_{CH}$ is C-2 > C-4 > C-5 [8,9], and that protonation increases the value of $^1J_{CH}$ with the largest effect on carbons adjacent to the protonation site; the coupling at C-2 is most strongly affected. Thus protonation of 4-methylpyrimidine and 4(1*H*)-pyrimidinone changes $^1J_{CH}$ at C-2 from 204.2 to 219.4 Hz, and from 209 to 222 Hz, respectively [8,10]. In the quaternary pyrimidinium salt **4a** the one-bond carbon-hydrogen coupling of the corresponding carbon at C-5 is even larger, *viz.* 232 Hz. The signals for the pyridinium analogue **7a** are assigned by similar multiplicity arguments. The C-5, which is adjacent to the nitrogen, has the largest one-bond carbon-hydrogen coupling, *viz.* 192 Hz, as has previously been found for related pyridinium salts [11]. The C-9, which is the other carbon adjacent to the nitrogen, gives rise to a broad signal due to its interaction with the latter. The assignment of the C-5 signals is also supported by the nuclear Overhauser effect; double irradiation at the field for C-3 absorption results in an increase in the intensity of the signal ascribed to C-5.

Table 2

Appearance Potentials by the Semilog-plot Method



In the mass spectrometer the 3-carboxy derivatives **1** undergo decarboxylation thereby furnishing species with the same fragmentation pattern as for the *N*-vinyl derivatives **3a** and **3b**. The same mass number for the molecular ion is also seen for the betaine isomers **4a** and **4b**, but the fragmentation pattern is different. The betaines have the molecular ion as the base peak, whereas the vinyl derivatives **3** have [M-H] as the base peak. The ready loss of hydrogen from **3** is rationalized as an expulsion of a β-vinyl hydrogen after ionization to form the thiazolo[3,2-*c*]pyrimidinium ion (I → II, Table 2).

Previously we have developed a method for the analysis and identification of isomeric structures in the gas phase in the mass spectrometer by comparison of appearance potentials (AP) [12]. Application of this technique to the present case gave 7.97 and 7.40 eV, respectively, for the isobaric molecular ions from the *N*-vinyl derivative **3b** and its betaine isomer **4b**. This is a significant difference, and the low AP for **4b** is consistent with charge separation in the volatile species. Hence the mesoionic betaine is volatilized structurally unchanged in the same way as has been proven for pyridine analogues [12]. The pyridine analogue **7b** has AP 6.93 eV for its molecular ion as compared to 7.40 eV for **4b**. These findings agree with previous data which

show that an increase in the number of nitrogen atoms in a heteroaromatic system will lead to an increase in the AP for the molecular ions [12]. This also correlates with the relative size of the AP's for the *N*-vinyl derivative **3b** (7.97 eV) and its pyridine analogue (7.45 eV) [7].

EXPERIMENTAL

The mass spectra are presented as ms [70 eV, m/z (% relative intensity)]. The AP's (±0.05 eV) for **3b** and **4b** were determined by G. Hvistendahl using the semilog-plot method previously described [12]. The ^{1}H nmr spectra were recorded at 60 MHz. The ^{13}C nmr spectra were recorded in deuterium oxide solution at 25.05 MHz on a Jeol FX-100 instrument. Chemical shifts were measured with respect to internal dioxane. The chemical shift of dioxane with respect to TMS is 67.4 ppm in deuterium oxide solution. The glc analyses of the reaction products were run on 10% SP 2100 Chrom WAW DCMS 80/100 (2 mm i.d. × 2 m); flow rate 20 ml of nitrogen per minute, injector and detector temperature 250°. The samples were injected at 180°, the instrument being programmed for 16°/minute increase up to 250°.

5-Hydroxy-3-vinyl-4(3*H*)-pyrimidinethione (**3a**).

8-Hydroxydihydrothiazolo[3,2-*c*]pyrimidinium-3-carboxylate (**5a**) (0.20 g, 0.6 mmole) was ground well together with quartz sand (0.35 g), and the mixture heated in a sublimation apparatus at 150°/10 mm Hg. The decarboxylative vinylation requires 15-20 minutes for completion. The product was isolated as a sublimate, yield 0.06 g, (65%), mp 143°. The physical data are given under the alternative synthesis described below.

5-Hydroxy-2-methyl-3-vinyl-4(3*H*)-pyrimidinethione (**3b**).

This compound was prepared as above from 8-hydroxy-5-methyldihydrothiazolo[3,2-*c*]pyrimidinium-3-carboxylate (**5b**) (0.20 g, 0.94 mmole) and quartz sand (0.6 g) in 70% yield. mp 150-152°; ^{1}H nmr (TFA): δ 2.89 (2-Me), 5.72 (H-βJ_{trans} 16 Hz, J_{gem} 2 Hz), 6.06 (H-β, J_{cis} 8 Hz, J_{gem} 2 Hz), 6.79 (H-α, m), 7.48 (H-6); uv (ethanol): log ε 354 (4.01), 277 nm (3.62); ms: 168 (95, M), 167 (100), 126 (26), 82 (37), 59 (14).

Anal. Calcd. for $C_7H_8N_2OS$: C, 49.98; H, 5.01. Found; C, 50.08; H, 5.01.

N-Vinyl Formation by Base Treatment. 5-Hydroxy-3-vinyl-4(3*H*)-pyrimidinethione (**3a**).

Potassium *t*-butoxide (3.0 g, 0.026 mole) in dry DMF (150 ml) was added dropwise over 15 minutes at room temperature to a solution of the hydrobromide salt of dihydrothiazolo[3,2-*c*]pyrimidinium-8-olate (**5a**) (3.1 g, 0.013 mole) in dry DMF (100 ml). The reaction mixture was stirred at room temperature for 90 minutes before acetic acid was used to adjust the *p*H to *ca.* 5, the solution evaporated at reduced pressure, water added to the residue and the mixture extracted with ethyl acetate (4 × 25 ml), the washed and dried (magnesium sulfate) organic solution evaporated and the residue recrystallized from ethanol, yield 1.2 g (60%), mp 143°; ^{1}H nmr (TFA): δ 5.8 (2H-β, m), 7.37 (H-α), 7.60 (H-6), 9.03 (H-2); uv (ethanol): log ε 359 (3.97), 281 (3.77), 259 nm (3.78); ms: 154 (74, M), 153 (100), 68 (20), 54 (14).

Anal. Calcd. for $C_6H_6N_2OS$: C, 46.74; H, 3.92. Found: C, 46.92; H, 3.85.

5-Hydroxy-2-methyl-3-vinyl-4(3*H*)-pyrimidinethione (**3b**).

This compound was prepared as above from 5-methyldihydrothiazolo-[3,2-*c*]pyrimidinium-8-olate (**5b**). The reaction mixture after acidification with acetic acid was poured into water, the resultant mixture extracted several times with ether, the washed and dried (magnesium sulfate) ether extracts evaporated and the residue recrystallized from ethanol, yield 0.6 g (59%), mp 150-152°. Physical data are given above.

5-Hydroxy-2-phenyl-3-vinyl-4(3*H*)-pyrimidinethione (**3c**).

This compound was prepared from the hydrobromide salt of 5-phenyldihydrothiazolo[3,2-*c*]pyrimidinium-8-olate (**5a**) (0.60 g, 1.9 mmoles) in dry DMF (25 ml) to which was added dropwise over 15 minutes, potassium *t*-butoxide (0.43 g, 3.8 mmoles) in dry DMF (25 ml). The mixture was stirred at room temperature for 90 minutes before the *p*H was adjusted to *ca.* 5 by the addition of acetic acid, the mixture evaporated, water added to the residue before extraction with ether (5 ×), the washed and dried (magnesium sulfate) ether extracts evaporated and the residue recrystallized from ethanol, yield 0.28 g (64%), mp 120-122°; ^{1}H nmr (deuteriochloroform): 4.90 (H-β, J_{trans} 16 Hz, J_{gem} 2 Hz), 5.33 (H-β, J_{cis} 8 Hz, J_{gem} 2 Hz), 6.90 (H-α, m), 7.37 (Ph, s), 7.77 (H-6); uv (ethanol): log ε 376 (4.68), 296 (4.75), 245 nm (sh); ms: 230 (95, M), 229 (100), 144 (28), 116 (44), 105 (37), 104 (24), 89 (23), 77 (39).

Anal. Calcd. for $C_{12}H_{10}N_2OS$: C, 62.59; H, 4.64. Found: C, 62.58; H, 4.64.

6-Bromo-5-hydroxy-3-vinyl-4(3*H*)-pyrimidinethione (**3d**).

This compound was prepared from the hydrobromide salt of 7-bromo-2,3-dihydrothiazolo[3,2-*c*]pyrimidinium-8-olate [1] (0.50 g, 1.6 mmoles) in dry DMF (30 ml) to which was added dropwise over 15 minutes a solution of potassium *t*-butoxide (0.36 g, 3.2 mmoles) in dry DMF (25 ml). The reaction mixture was stirred at room temperature for 2½ hours before the *p*H was brought to *ca.* 5 by the addition of acetic acid, the mixture evaporated, water added to the residue before extraction with ether (5 ×), the washed and dried (magnesium sulfate) ether solution evaporated and the residue recrystallized from ethanol, yield 0.26 g (70%), mp 118°; ^{1}H nmr (deuteriochloroform): δ 5.7 (2H-β, m), 7.6 (H-α, m), 8.15 (H-2); uv (ethanol): log ε 3.65 (3.96), 280 (3.75); ms: 234/232 (49/46, M), 233/231 (100/100), 59 (14), 54 (28), 45 (21).

Anal. Calcd. for $C_6H_5BrN_2OS$: C, 30.92; H, 2.16; N, 12.02. Found: C, 31.42; H, 2.34; N, 11.78.

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