SYNTHESIS OF 2-MERCAPTO- AND 2-METHYLTHIO- DIHYDROPYRIMIDINE DERIVATIVES BY BIGUINELLI TYPE REACTION

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Abstract - The preparation of 6-(2,2-dimethyl-1,3-dioxolan-4-yl)-4-methyl-5-methoxycarbonyl-2-thio-1,2,3,6-tetrahydropyrimidine (1) and 6-(2,2-dimethyl-1,3-dioxolan-4-yl)-4-methyl-2-methylthio-5-methoxycarbonyl-1,6-dihydropyrimidine (6) by Biguinelli type reaction is described. The products resulting from the acidic hydrolysis are studied.

Previous papers report the synthesis of tetrahydropyrimidines with a sugar moiety in position 6, by the Biguinelli type reaction, starting from the sugar derivative, with urea and ethyl or methyl acetoacetate[1]. In this work the previous reaction is employed but with thiourea or S-methylthiourea in place of urea.

When the 2,3-O-isopropylidene-D-glyceraldehyde was made to react with methyl acetoacetate and thiourea, or S-methylthiourea, the following pyrimidine derivatives were obtained: 6-(2,2-dimethyl-1,3-dioxolan-4-yl)-4-methyl-5-methoxycarbonyl-2-thio-1,2,3,6-tetrahydropyrimidine (1); and 6-(2,2-dimethyl-1,3-dioxolan-4-yl)-4-methyl-2-methylthio-5-methoxycarbonyl-1,6-dihydropyrimidine (6).

The compounds resulting from acidic hydrolysis of the derivatives 1 and 6 are also studied (Fig. 1).

The reaction of 2,3-O-isopropylidene-D-glyceraldehyde with thiourea and methyl acetoacetate in equimolecular ratio, under our experimental conditions, resulted in the formation of only one pyrimidine derivative 1 (36.5%). At C-6 the R configuration was assigned after studying the acid hydrolysis of this compound 1. The acid hydrolysis did not yield the expected pyrimidine derivative 5, but traces were detected by ^{1}H-nmr in some experiments.

When 1 is refluxed in the presence of acetic acid:water (1:1), as described for 6-(2,2-dimethyl-1,3-dioxolan-4-yl)-4-methyl-5-methoxycarbonyl-2-oxo-1,2,3,6-tetrahydropyrimidine[1b] (8), compounds 2 and 3 were obtained and separated as described in Experimental. These compounds may result from a Michael type addition of C-5 hydroxyl to the double bond C-4,C-5 of the tetrahydropyrimidine ring, and further lactonization of compound 2.

Compounds 2 and 3 were characterized by their analytical and spectroscopic data. The ir spectrum of 2 shows 1780 cm^{-1} (C=O) corresponding to the γ-lactone ring. The ^{1}H-nmr data present a complex

signal for H-8 at 4.71 ppm, but the next coupling constants were measured, $J_{8,1}$ 6, $J_{8,7a\ trans}$ 2.4, $J_{8.7b\ cis}$ 1 Hz with a long-range coupling $J_{8,9}$ 1 Hz (suggesting W-geometry). Chemical shifts for geminal protons H-7 were at 3.80 and 3.72 ppm (J 12 Hz), both of them as a double doublet. The signal at 3.80 ppm was assigned for H-7a (cis for lactone ring). The proton H-1 appears at 4.44 ppm. Long-range coupling (W) of H-7 with H-1 is not seen in this compound because the ring force tension, C-7 must adopt a certain conformation.

The C-1 and C-9 configurations are R because C-8 is S (corresponding to D-glyceraldehyde) and C-1 consequently is R, because on cycling, the -COOR and -OH groups must lie on the same face of the plane to facilitate their later lactonization (fig. 2).

In compound 3, proton H-8 appears at 3.95 ppm ($J_{8,1}$ 4, $J_{8,7a\ trans}$ 1 and $J_{8,7b\ cis}$ 2 Hz). Protons H-1 and H-7a (cis from hydroxyl in C-8) appear at 3.80 ($J_{1,8}$ 4, $J_{1,9}$ 2 and $J_{1,7a}$ 1 Hz) and 3.71 ppm respectively. The H-7a chemical shift is less than that of H-7b (3.54 ppm) and shows long-range coupling with H-1.

With the compound 3 traces of a new pyrimidine derivative were observed, their ^{1}H-nmr data seem to indicate the structure 6-((1S),2-dihydroxyethyl)-4-methyl-5-methoxycarbonyl-2-thio-1,2,3,6-tetrahydropyrimidine (5) but these data are insufficient to fully explain its formation.

To obtain compound 5 and complete the acidic hydrolysis study, we carried out several treatments with different reaction conditions.

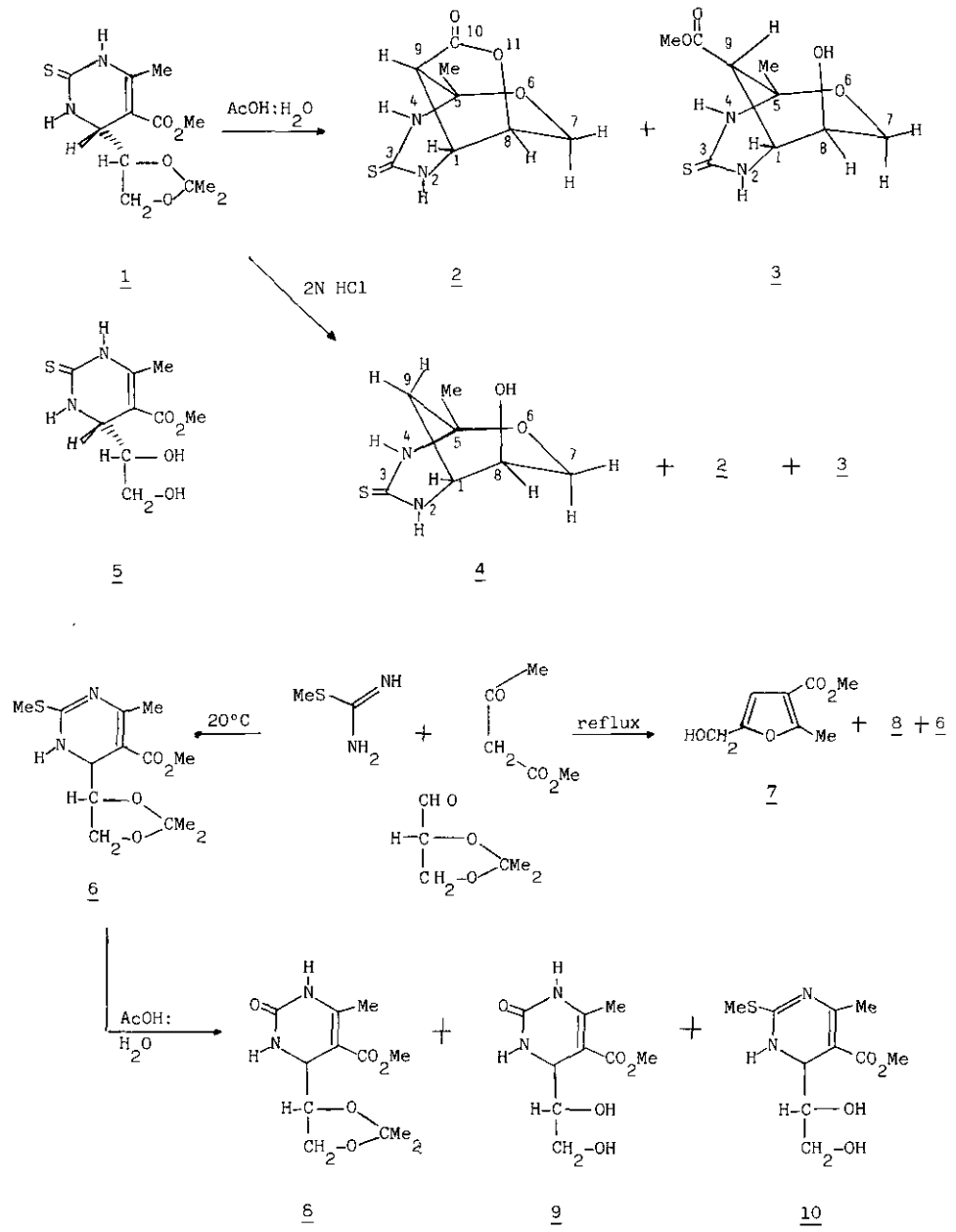
Derivative 5 was not observed in any experiment. The results of acetic acid:water (1:1) hydrolysis at room temperature were the same as those previously described. Methanolic hydrogen chloride hydrolysis gave only derivative 3, but 2N hydrochloric acid produced decomposition products and the derivatives 2 (15.5%), and 3 (12.8%), plus a new pyrimidine derivative characterized as follows: (1R),(8S)-hydroxy-(5R)-methyl-3-thio-2,4-diaza-6-oxabicyclo[3,3,1]nonane (4) (10.3%). There is no carbonyl group in the ir spectrum. The assigned structure was confirmed by ^{13}C-nmr and ^{1}H-nmr data. The C-9 diasterotopic hydrogens appear at 2.35 ppm ($J_{9a,9b}$ 13 and $J_{9a,1}$ 2.1 Hz) and 1.65 ppm ($J_{9a,9b}$ 13 and $J_{9b,1}$ 4 Hz).

The principal reaction product of 2,3-O-isopropylidene-D-glyceraldehyde, S-methylthiourea hydriodide and methyl acetoacetate in ethanol under reflux was a furanic derivative, 5-hydroxymethyl-2-methyl-3-methoxycarbonylfurane (7), with small amounts of the two pyrimidine derivatives, 6-(2,2-dimethyl-1,3-dioxolan-4-yl)-4-methyl-5-methoxicarbonyl-2-oxo-1,2,3,6-tetrahydropyrimidine (8) and 6-(2,2-dimethyl-1,3-dioxolan-4-yl)-4-methyl-2-methylthio-5-methoxycarbonyl-1,6-dihydropyrimidine (6). The furanic derivative results from the sugar aldehyde condensation to methyl acetoacetate and further cyclization, owed to the presence of free hydroxyl after acidic break down of the acetal group.

The tetrahydropyrimidine 8 is the same as that obtained by condensation of 2,3-O-isopropylidene-D-glyceraldehyde, urea and methyl acetoacetate [1b]. The ^{13}C-nmr and ^{1}H-nmr spectrum confirmed this structure, and the double resonance characterized the sugar ring hydrogens.

The reaction at room temperature gave the expected hydriodide of dihydropyrimidine 6 (25%). The absence of 7 is confirmed but under these conditions the reaction is slow (7-8 d) and the sugar decomposition causes a low yield.

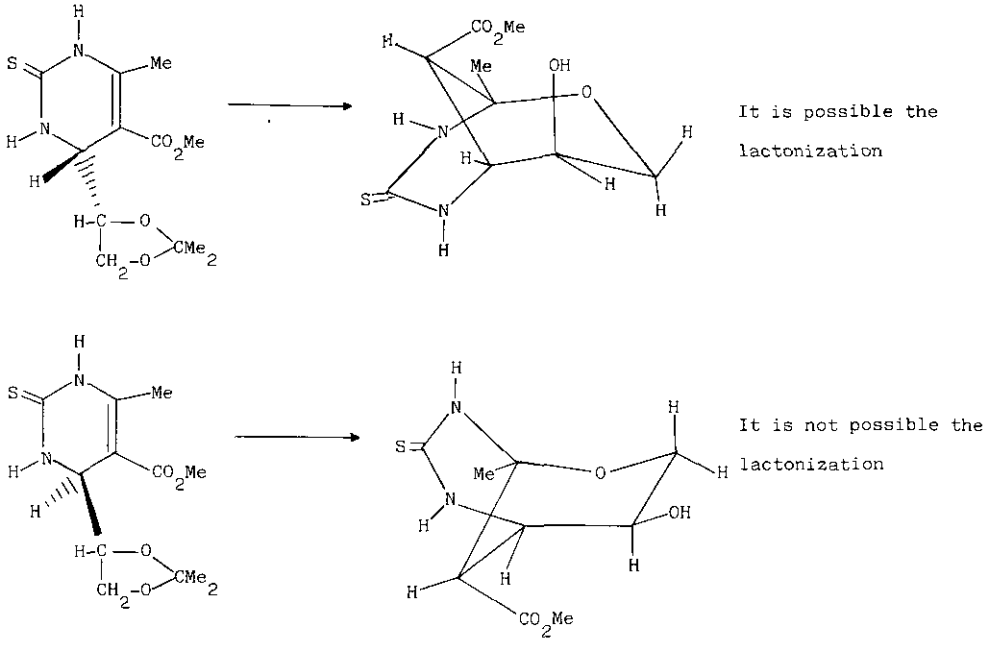
FIGURE I



Pyrimidine 6, and the hydriodide of 6, were characterized by their spectroscopic data. The acetic acid:water (1:1) hydrolysis of 6 at 60°C produced tetrahydropyrimidine 8 and 6-((1S),2-dihydroxyethyl)-4-methyl-5-methoxycarbonyl-2-oxo-1,2,3,6,-tetrahydropyrimidine [1b] (9). Traces of

a new pyrimidine derivative were detected in this reaction and the spectroscopic data indicated a structure 6-((1S),2-dihydroxyethyl)-4-methyl-2-methylthio-5-methoxycarbonyl-1,6-dihydropyrimidine (10).

FIGURE II



EXPERIMENTAL

Melting points were determined with a Gallemkamp instrument and are uncorrected. Optical rotations were measured with a Perkin-Elmer Optical 241 polarimeter (10-cm cell). Ir spectra (KBr disc) were recorded with a Beckman Aculab IV spectrophotometer. ^{1}H-nmr spectra were recorded for solutions in D_2O or $CDCl_3$ (internal DSS or Me_4Si) with a Perkin-Elmer Hitachi R-24B (60 MHz) or Bruker WP-200 SY (200 MHz) spectrometers. The ^{13}C-nmr spectrum was recorded with a Bruker WP-200 SY spectrometer. Chemical shifts are given on the δ scale, and coupling constants in Hz. Column chromatography was performed on silica gel 60 (0.063-0.200 or 0.040-0.063 mm) (Merck). Tlc was performed on silica gel GF_{254} (Merck) with detection by sulphuric acid charring or by uv absorption. Uv spectra in methanolic solutions were recorded with a Beckman DB-GT spectrometer.

6-(2,2-Dimethyl-1,3-dioxolan-4-yl)-4-methyl-5-methoxycarbonyl-2-thio-1,2,3,6-tetrahydropyrimidine (1)

To a solution of 2,3-O-isopropylidene-D-glyceraldehyde (15 g, 0.115 mol) and thiourea (9 g, 0.118 mol) in ethanol (75 ml) were added methyl acetoacetate (27 g, 0.232 mol). The mixture was boiled under reflux for 12 h and concentrated. Crystallization occurred slowly obtaining 1 (12 g, 36.5%), mp 203-205 °C (from ethanol), $[\alpha]_D^{20}$ -202 ° (c 1, water); R_F 0.77 (ethyl acetate-hexane, 2:1), λ_{max}^{MeOH} 305 nm (ε 15.600); ν_{max}^{KBr} 3340, 1675, 1565, 1380 and 1200 cm^{-1}. Nmr data: ^{1}H (200 MHz, $CDCl_3$): δ 8.35 (sb, 1H, NH-3), 7.80 (sb, 1H, NH-1), 4.37 (t, 1H, J 4 Hz, H-6), 4.15 (dt, 1H, J 4

and 6 Hz, H-4'), 4.00 (dd, 1H, J 4 and 9 Hz, H-5'), 3.92 (dd, 1H, J 4 and 9 Hz, H-5''), 3.75 (s, 3H, OMe), 2.34 (s, 3H, MeC=), 1.47 and 1.31 (2s, 6H, Me_2C); ^{13}C ($CDCl_3$): δ 176.4 (C=S), 165.8 (C=O), 146.2 (C-4), 110.0 ($\underline{C}Me_2$), 98.7 (C-5), 77.6 (C-4'), 65.4 (C-5'), 54.1 (C-6), 51.5 (OMe), 26.4 and 24.9 (Me_2C) and 18.6 (CMe). Anal. Calcd. for $C_{12}H_{18}O_4N_2S$: C, 50.33; H, 6.33; N, 9.78. Found: C, 50.32; H, 6.50; N, 9.74.

Acid hydrolysis of 6-(2,2-dimethyl-1,3-dioxolan-4-yl)-4-methyl-5-methoxycarbonyl-2-thio-1,2,3,6-tetrahydropyrimidine (1)

A) With acetic acid-water. A solution of 1 (3 g, 0.0104 mol) in acetic acid:water (1:1) (30 ml) was boiled under reflux for 2 h and then concentrated. The residue was washed with water and ethanol. The dried syrup was purified by column chromatography (ethyl acetate-hexane, 2:1) to obtain (1R,9R,5R)-methyl-10-oxo-3-thio-2,4-diaza-6,11-dioxatricyclo|3,3,1,2 ^{9,8}|undecane (2)(0.26 g, 11.6%) and (1R),(8S)-hydroxy-(5R)-methyl-(9S)-methoxycarbonyl-3-thio-2,4-diaza-6-oxabicyclo |3,3,1|nonane (3), (2.15 g, 83%). Compound 2 had mp 183-185 °C (from ethanol), $|\alpha|_D^{20}$ -9 ° (c 1, methanol); R_F 0.5 (ethyl acetate-hexane, 3:1); λ_{max}^{MeOH} 252 nm (ε 5.210) and 302 nm (ε 3.850); ν_{max}^{KBr} 3200-3160, 3080, 1780, 1560, 1510, 1310, 1230 and 1170 cm^{-1}. Nmr data: ^1H (200 MHz, CD_3OD): δ 4.71 (dddd, 1H, J 1, 1, 2.4 and 6 Hz, H-8), 4.44 (dd, 1H, J 6 and 6 Hz, H-1), 3.80 (dd, 1H, J 2.4 and 12 Hz, H-7a), 3.72 (dd, 1H, J 1 and 12 Hz, H-7b), 2.68 (dd, 1H, J 1 and 6 Hz, H-9) and 1.51 (s, 3H, Me); ^{13}C (D_2O): δ 177.58 (C=S), 174.71 (C=O), 79.60 (C-5), 77.59 (C-8), 61.00 (C-7), 51.11 (C-9), 41.93 (C-1) and 23.48 (Me). Anal. Calcd. for $C_8H_{10}O_3N_2S$: C, 44.85; H, 4.71; N, 13.07. Found: C, 44.84; H, 4.67; N, 12.84.

Compound 3 had mp 214-215 °C (from ethanol), $|\alpha|_D^{20}$ +43 ° (c 1, methanol); R_F 0.13 (ethyl acetate-hexane, 3:1); λ_{max}^{MeOH} 250.6 nm (ε 2.340); ν_{max}^{KBr} 3340-3300, 3260-3200, 1730-1710, 1540-1520, 1320 and 1060 cm^{-1}. Nmr data: ^1H (200 MHz, D_2O): δ 3.95 (ddd, 1H, J 1, 2 and 4 Hz, H-8), 3.80 (ddd, 1H, J 1, 2 and 4 Hz, H-1), 3.71 (ddd, 1H, J 1, 1 and 13.5 Hz, H-7a), 3.70 (s, 3H, OMe), 3.54 (dd, 1H, J 2 and 13.5 Hz, H-7b), 3.39 (d, 1H, J 2 Hz, H-9) and 1.55 (s, 3H, Me); ^{13}C (D_2O): δ 177.37 (C=S), 171.08 (C=O), 91.37 (C-5), 67.04 (C-8), 64.10 (C-7), 53.10 (OMe), 54.15 (C-9), 40.55 (C-1) and 23.63 (Me). Anal. Calcd. for $C_9H_{14}O_4N_2S$: C, 43.88; H, 5.73, N, 11.37. Found: C, 43.66; H, 5.69; N, 11.01.

At a slighly different R_F value compound 3 gave a new product. Its Nmr data could indicate the pyrimidine 5, ^1H (200 MHz, D_2O): δ 4.45 (d, 1H, J 2.6 Hz, H-6), 3.65-3.55 (m, 3H, H-1', 2' and 2''), 3.75 (s, 3H, OMe) and 2.31 (s, 3H, Me).

A solution of 1 (0.5 g, 0.00175 mol) in methanol (3 ml) and acetic acid-water (1:1) (5 ml) was stirred at room temperature for 48 h gave 2 (0.04 g, 10%) and 3 (0.346 g, 75%).

B) Hydrolysis with methanolic hydrogen chloride. To a methanol suspension (3 ml) of 1 (0.067 g, 0.0023 mol) hydrogen chloride saturated methanol (6 ml) was added. After stirring at room temperature for 2.30 h, this gave 3 (0.45 g, 80%). Compound 2 was not found.

C) Hydrolysis with 2N hydrochloric acid. A solution of 1 (1 g, 0.0035 mol) in methanol (2 ml) and

2N hydrochloric acid (9 ml) was boiled under reflux for 3 h. The product was purified by column chromatography (ethyl acetate-hexane, 1:1) to obtain 2 (0.116 g, 15.5%), 3 (0.107 g, 12.8%) and a new derivative (1R),(8S)-hydroxy-(5R)-methyl-3-thio-2,4-diaza-6-oxabicyclo[3,3,1]nonane (4) (0.068 g, 10.3%) had mp 210-212 °C, $|\alpha|_D^{20}$ +13 ° (c 1, methanol); R_F 0.28 (ethyl acetate); λ_{max}^{MeOH} 247 nm (ε 580); ν_{max}^{KBr} 3340-3280, 3240-3200, 1560, 1520, 1250 and 1180 cm^{-1}. Nmr data: ^1H (200 MHz, D_2O): δ 3.80-3.50 (m, 4H, H-1, 7a, 7b and 8), 2.35 (dd, 1H, J 2.1 and 13 Hz, H-9a), 1.65 (dd, 1H, J 4 and 13 Hz, H-9b) and 1.47 (s, 3H, Me); ^{13}C (D_2O): δ 176.8 (C=S), 80.8 (C-5), 66.3 (C-8), 64.6 (C-7), 49.2 (C-1), 27.9 (C-9) and 25.6 (Me). Anal. Calcd. for $C_7H_{12}O_2N_2S$: C, 44.67; H, 6.43; N, 14.88. Found: C, 44.74; H, 6.06; N, 14.09.

6-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2-methylthio-4-methyl-5-methoxycarbonyl-1,6-dihydropyrimidine (6). To a solution of 2,3-O-isopropylidene-D-glyceraldehyde (6.78 g, 0.052 mol) and S-methylthiourea hydriodide (11.53 g, 0.052 mol) in ethanol (34 ml), methyl acetoacetate (12.2 g, 0.104 mol) was added. After stirring at room temperature for 8 d, aldehyde disappeared (tlc, ethyl acetate-hexane, 1:1). The mixture was then extracted with ethyl acetate (3 x 5 ml) to give a residue whose principal product gave R_F 0.44 (ethyl acetate-hexane, 1:1). Several recrystallizations from methanol gave the hydriodide of 6 (5.42 g, 25%). This compound was positive for iodide and had mp 193-194 °C, $|\alpha|_D^{20}$ -2.8 ° (c 1, methanol); λ_{max}^{MeOH} 307 nm (ε 5.200) and 220 nm (ε 13.700); ν_{max}^{KBr} 3280-3240, 3180, 1690-1670, 1605, 1530-1510, 1380, 1370 and 1230-1210 cm^{-1}. Nmr data: ^1H (200 MHz, D_2O): δ 4.73 (s, 1H, H-6), 4.50-4.38 (m, 1H), 4.30-4.10 (m, 2H), 3.73 (s, 3H, OMe), 2.67 (s, 3H, SMe), 2.30 (s, 3H, MeC=), 1.40 and 1.30 (2s, 6H, Me_2C); ^1H ($CDCl_3$): δ 4.81 (sb, 1H, H-6), 4.51 (dd, 1H, J 4 and 10 Hz, H-5'), 4.20 (m, 1H, H-4'), 4.00 (dd, 1H, J 6 and 10 Hz, H-5''), 3.76 (s, 3H, OMe), 2.96 (s, 3H, SMe), 2.50 (s, 3H, MeC=), 1.32 and 1.25 (2s, 6H, Me_2C); ^{13}C (D_2O): 167.9 (C=O), 166.5 (C-2), 147.9 (C-4), 111.1 ($\underline{C}Me_2$), 102.0 (C-5), 78.5 (C-4'), 65.2 (C-5'), 54.2 (C-6), 52.8 (OMe), 25.1 and 24.2 (Me_2C), 18.1 (CMe) and 14.1 (SMe). Anal. Calcd. for $C_{13}H_{20}O_4N_2S.HI$: C, 36.45; H, 4.94; N, 6.54. Found: C, 36.07; H, 4.99; N, 6.49.

This compound was dissolved in water and neutralized with 2N sodium hydroxide and evaporated to dryness. The residue was extracted with chloroform and recrystallized from ethanol to give 6, mp 164-165 °C, $|\alpha|_D^{20}$ -151 ° (c 1, methanol); λ_{max}^{MeOH} 310 nm (ε 6.000); ν_{max}^{KBr} 3310-3280, 3100, 1660, 1640, 1490, 1450, 1380 and 1370 cm^{-1}. Nmr data: ^1H (200 MHz, $CDCl_3$): δ 6.16 (sb, 1H, NH), 4.59 (d, 1H, J 2 Hz, H-6), 4.23 (ddd, 1H, J 2, 6 and 6 Hz, H-4'), 4.17 (dd, 1H, J 6 and 6 Hz, H-5'), 3.93 (dd, 1H, J 6 and 6 Hz, H-5''), 3.66 (s, 3H, OMe), 2.41 (s, 3H, SMe), 2.22 (s, 3H, MeC=), 1.28 and 1.26 (2s, 6H, Me_2C). Anal. Calcd. for $C_{13}H_{20}O_4N_2S$: C, 51.96; H, 6.71; N, 9.32. Found: C, 52.01; H, 6.67; N, 9.25.

Heating also produced this reaction but then the principal product was a furanic derivative, 5-hydroxymethyl-2-methyl-3-methoxycarbonylfuran [2] (7) with small amounts (in different proportions, according to temperature of heating and time of reaction) of 6 and 6-(2,2-dimethyl-1,3-dioxolan-4-yl)-4-methyl-5-methoxycarbonyl-2-oxo-1,2,3,6-tetrahydropyrimidine [1b] (8). This mixture was separated by flash chromatography (ethyl acetate-hexane, 1:1). Compound 8 had nmr data: ^1H (200 MHz, $CDCl_3$): δ 8.92 (sb, 1H, NH-3), 6.55 (sb, 1H, NH-1), 4.25 (dd, 1H, J 4 and 4 Hz, H-6), 4.10 (ddd, 1H, J 4,

6 and 6.5 Hz, H-4'), 3.92 (dd, 1H, J 6.5 and 8.5 Hz, H-5'), 3.80 (dd, 1H, J 6 and 8.5 Hz, H-5'') 3.67 (s, 3H, OMe), 2.23 (s, 3H, MeC=), 1.35 and 1.26 (2s, 6H, Me_2C); ^{13}C ($CDCl_3$): δ 166.2 (COOMe), 155.2 (NCO), 149.7 (C-4), 109.6 ($\underline{C}Me_2$), 97.2 (C-5), 77.9 (C-4'), 65.4 (C-5'), 53.5 (C-6), 51.2 (OMe), 26.2 and 25.1 (Me_2C) and 18.9 (CMe).

Acid hydrolysis of 6-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylthio-4-methyl-5-methoxycarbonyl-1,6-dihydropyrimidine (6)

A) With acetic acid-water at room temperature. A solution of 6 (0.182 g, 0.0006 mol) in methanol (2 ml) and acetic acid-water (1:1) (2 ml) was stirred at room temperature; after 17 h tlc (ethyl acetate-hexane, 2:1) showed the presence of 6 together with other new products of R_F 0.2 and 0.1. The mixture reaction was concentrated and washed with ethanol-water (1:1) to eliminate the acid excess. The dry residue was purified by preparative tlc on silica gel (ethyl acetate-ether, 1:3). Three fractions were removed. The first fraction was the unreacting initial pyrimidine 6 (0.130 g), R_F 0.53. The second fraction was 8 (0.020 g, 42% of the reacting pyrimidine). The remaining third fraction (0.020 g) was again chromatographed to give 6-((1S),2-dihydroxyethyl)-4-methyl-5-methoxycarbonyl-2-oxo-1,2,3,6-tetrahydropyrimidine [1b] (9) (0.012 g, 30% of the reacting pyrimidine) and 0.008 g of a product whose ^1H-nmr spectrum indicated 6-((1S),2-dihydroxyethyl)-2-methylthio-4-methyl-5-methoxycarbonyl-1,6-dihydropyrimidine (10) (10% of the reacting pyrimidine).

The compound 9 gave nmr data: ^1H (200 MHz, D_2O): δ 4.38 (d, 1H, J 2.2 Hz, H-6), 3.65-3.58 (m, 3H, H-1', 2' and 2''), 3.71 (s, 3H, OMe) and 2.25 (s, 3H, MeC=); ^{13}C (D_2O): δ 169.0 (COOMe), 156.3 (NCO), 151.7 (C-4), 97.7 (C-5), 74.9 (C-1'), 62.3 (C-2'), 53.1 (C-6), 52.3 (OMe) and 18.4 (CMe). Compound 10 gave λ_{max}^{MeOH} 307 nm (ε 3.000) and 226 nm (ε 6.100); ν_{max}^{KBr} 3480-3440, 3100, 1700, 1650, 1600, 1370, 1250 and 720 cm^{-1}. ^1H-nmr (60 MHz, D_2O): δ 4.4-3.7 (m, 4H, H-6, 1', 2' and 2''), 3.73 (s, 3H, OMe), 2.67 (s, 3H, SMe) and 2.33 (s, 3H, MeC=).

B) With acetic acid-water at 60 °C. To a solution of 6 (0.097 g, 0.00032 mol) in methanol (2 ml) acetic acid-water (1:1) (3 ml) was added. The mixture was stirred at 60 °C. The progress of the reaction was monitored by tlc. After 27 h the reaction was worked-up following the above procedure. The preparative tlc gave 8 (0.030 g, 34.7%), 9 (0.030 g, 47%) and 10 (0.010 g, 10.2%).

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