Synthesis of some sulfur-containing pyrido[1,2-*a*]pyrimidines

K. L. Cherkasova,[a] V. S. Bogdanov,[a] V. A. Dorokhov,[a] O. V. Shishkin,[b] and Yu. T. Struchkov[b†]*

[a]N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 117913 Moscow, Russian Federation. Fax: +7 (095) 135 5328

[b]A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 ul. Vavilova, 117813 Moscow, Russian Federation. Fax: +7 (095) 135 5085

4-Methylthiopyrido[1,2-*a*]pyrimidin-2-one and 2-hydroxypyrido[1,2-*a*]pyrimidine-4-thione derivatives were synthesized by the addition of *N*-(4-R-pyrid-2-yl)acetoacetamides (R = H, Me) to CS_2 under phase-transfer conditions followed by the alkylation of the reaction products with MeI. The molecular structure of 3-acetyl-4-methylthiopyrido[1,2-*a*]pyrimidin-2-one is established by X-ray analysis.

Key words: 2-hydroxypyrido[1,2-*a*]pyrimidine-4-thione, 4-methylthiopyrido[1,2-*a*]pyrimidin-2-one, ketene thioacetals; phase-transfer catalysis.

The derivatives of pyrido[1,2-*a*]pyrimidine (PP) are characterized by diverse biological activity and, hence, are of interest for intensive studies (for example, see review in Ref. 1). *N*-(Pyrid-2-yl)-β-oxocarboxamides, which cyclize on heating in the presence of mineral acids into the corresponding substituted 4-oxo-PP (Refs. 1—3). (usually, these amides are obtained *in situ* from β-oxocarboxylates and 2-aminopyridine[1]), are often used to build this bicyclic system. Recently,[4] we suggested a method of synthesis of 4-anilinopyrido[1,2-*a*]pyrimidin-2-one based on the transformation of *N*-(pyrid-2-yl)acetoacetamide (**1a**) upon the action of phenyl isothiocyanate and MeI into the corresponding ketene aminal-thioacetal and the intramolecular cyclization of the latter with the elimination of MeSH under mild conditions.

In this paper, a similar approach was used for the synthesis of sulfur-containing derivatives of PP from **1a** and its methyl homolog **1b** *via* ketene thioacetals obtained from these reagents (Scheme 1).

It was found that the addition of CS_2 to **1a** in the presence of K_2CO_3 under phase-transfer conditions followed by alkylation with two equivalents of MeI afforded 3-acetyl-4-methylthiopyrido[1,2-*a*]pyrimidin-2-one (**3**).

Evidently, dimethyldithioacetal **2** formed as an intermediate easily cyclizes into **3** with the elimination of MeSH.

The molecular structure of **3** was established by X-ray analysis (Fig. 1, Tables 1 and 2).* All of the atoms of the bicyclic system are coplanar within 0.03 Å. The bonds of the pyridine ring as well as of the pyrimidone fragment are delocalized substantially. The acetyl group at the C(7) atom is not in fact involved in the conjugation (the C(8)—C(7)—C(9)—O(2) torsion angle is 72.6(3)°). The methyl group at the S(1) atom is rotated in relation to the plane of the bicyclic system by 74.0(2)° (N(2)—C(8)—S(1)—C(11) torsion angle).

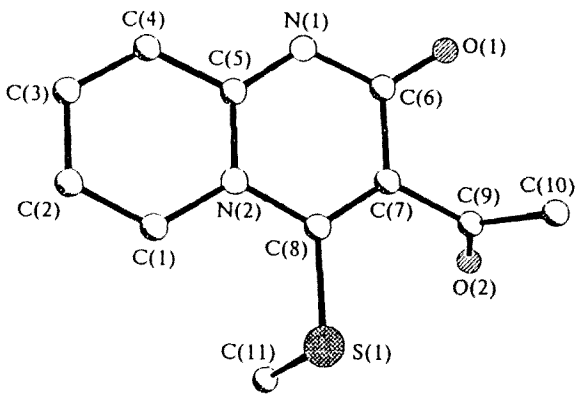

Fig. 1. The molecular structure of **3**.

In a crystal, the molecules are arranged in chains due to intermolecular hydrogen bonds H(1)...O(2)′ (the H...O distance is 2.18(1) Å, the C—H...O′ angle is 138.5(7)°).

If the adducts of CS_2 to β-ketoamides **1a,b** are alkylated with one equivalent of MeI, the derivatives of 2-hydroxypyrido[1,2-*a*]pyrimidine-4-thione (**4a,b**) are formed following acidification (see Scheme 1).

The intense peaks of molecular ions are observed for the synthesized PP. The lowfield position of the H(6) signal is characteristic of the ^{1}H NMR spectra of com-

† Deceased in 1995.

* In the description of the molecular structure of **3**, atomic numbers are chosen arbitrarily and do not coincide with those accepted for the pyrido[1,2-*a*]pyrimidine system.

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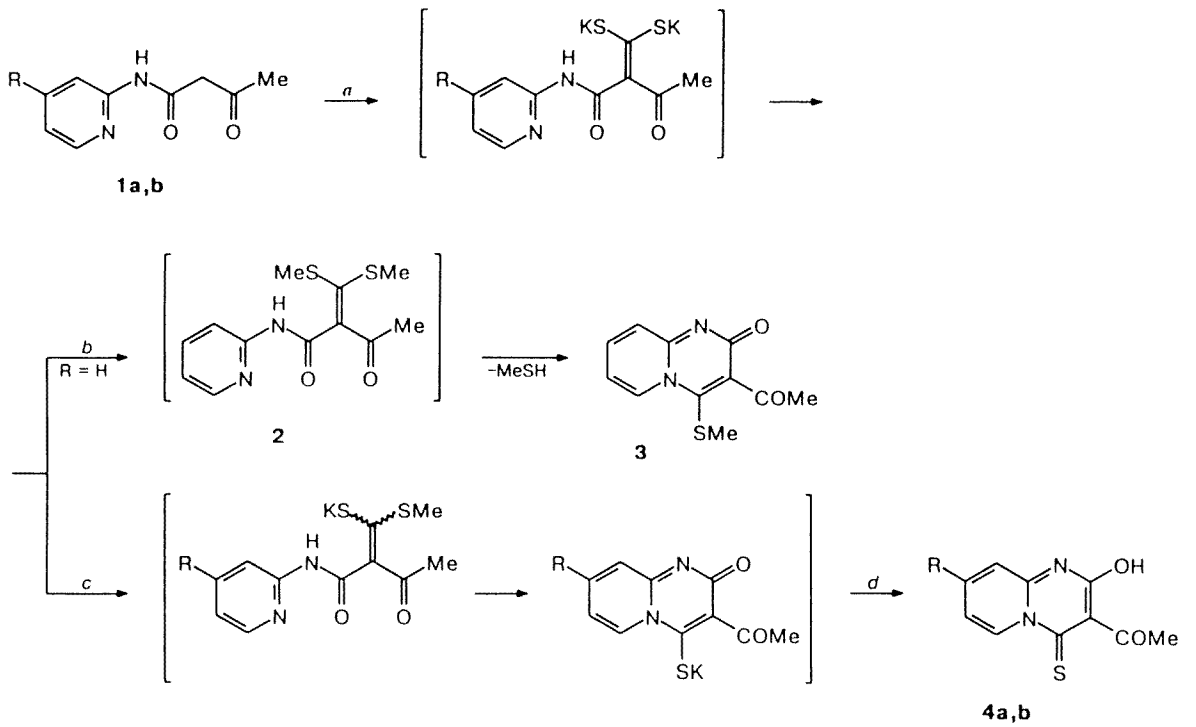
Scheme 1



R = H (**a**), Me (**b**)

Reagents and conditions: *a*. CS_2, K_2CO_3, DMF, BTEA—Cl,~20 °C; *b*. 2 equiv. MeI; *c*. 1 equiv. MeI; *d*, AcOH.

Table 1. Bond lengths (*d*) and bond angles (ω) in molecule 3

Bond	*d*/Å	Angle	ω/deg
S(1)—C(8)	1.758(3)	C(8)—S(1)—C(11)	100.9(1)
N(1)—C(5)	1.321(4)	C(1)—N(2)—C(5)	121.4(2)
N(2)—C(1)	1.390(4)	C(5)—N(2)—C(8)	118.2(2)
N(2)—C(8)	1.415(3)	C(1)—C(2)—C(3)	119.7(3)
O(2)—C(9)	1.202(3)	C(3)—C(4)—C(5)	121.7(3)
C(2)—C(3)	1.392(5)	N(1)—C(5)—C(4)	119.4(3)
C(4)—C(5)	1.421(4)	N(1)—C(6)—O(1)	122.2(3)
C(7)—C(8)	1.333(4)	O(1)—C(6)—C(7)	120.0(2)
C(9)—C(10)	1.475(5)	C(6)—C(7)—C(9)	116.2(2)
S(1)—C(11)	1.803(4)	S(1)—C(8)—N(2)	119.4(2)
N(1)—C(6)	1.355(3)	N(2)—C(8)—C(7)	118.5(2)
N(2)—C(5)	1.380(4)	O(2)—C(9)—C(10)	122.2(2)
O(1)—C(6)	1.224(4)	C(5)—N(1)—C(6)	119.8(2)
C(1)—C(2)	1.346(4)	C(1)—N(2)—C(8)	120.4(2)
C(3)—C(4)	1.349(5)	N(2)—C(1)—C(2)	120.7(3)
C(6)—C(7)	1.472(4)	C(2)—C(3)—C(4)	120.2(3)
C(7)—C(9)	1.506(3)	N(1)—C(5)—N(2)	124.2(2)
		N(2)—C(5)—C(4)	116.4(3)
		N(1)—C(6)—C(7)	117.8(3)
		C(6)—C(7)—C(8)	121.2(2)
		C(8)—C(7)—C(9)	122.5(3)
		S(1)—C(8)—C(7)	121.9(2)
		O(2)—C(9)—C(7)	119.8(3)
		C(7)—C(9)—C(10)	118.0(2)

Table 2. Atomic coordinates ($\times 10^4$) in structure 3

Atom	*x*	*y*	*z*
S(1)	3061(1)	1646(1)	7752(1)
N(1)	−47(3)	2800(3)	4393(2)
N(2)	2698(3)	2449(2)	5076(2)
O(1)	−2444(3)	2249(3)	5988(2)
O(2)	−1924(3)	3155(3)	9257(2)
C(1)	4525(3)	2460(3)	4700(3)
C(2)	5328(4)	2875(3)	3385(3)
C(3)	4326(4)	3289(3)	2387(3)
C(4)	2569(4)	3251(3)	2731(3)
C(5)	1675(3)	2821(3)	4109(3)
C(6)	−902(3)	2374(3)	5700(3)
C(7)	55(3)	2112(3)	6806(2)
C(8)	1795(3)	2135(3)	6495(2)
C(9)	−1092(3)	1917(3)	8309(3)
C(10)	−1187(4)	201(4)	8552(3)
C(11)	2787(4)	3837(4)	8203(3)

pounds **4a,b** in DMSO-d_6 (δ 10.09 and 9.95, respectively) caused by the anisotropic effect of the C=S group.

The sulfur-containing PP are poorly studied,[5–9] and the data on the derivatives of pyrido[1,2-*a*]pyrimidine-

4-thione are absent in the literature. Thus, compounds **3**, **4a,b**, are apparently interesting for further chemical and biological studies.

Experimental

The IR spectra were recorded with Perkin-Elmer 577 and UR-20 spectrophotometers, the ^{1}H NMR spectra were recorded with a Bruker WM-250 spectrometer, and the ^{13}C NMR spectra were recorded with a Bruker AM-300 spectrometer. The mass spectra were recorded with a Varian MAT-311A spectrometer (EI, 70 eV).

Compounds **1a,b** were prepared by the procedure described in Ref. 10.

3-Acetyl-4-methylthiopyrido[1,2-*a*]pyrimidin-2-one (3). Amide **1a** (1.85 g, 10.4 mmol) and a solution of CS_2 (0.80 g, 10.5 mmol) in DMF (10 mL) were added to a vigorously stirred mixture of a suspension of K_2CO_3 (2.9 g, 21 mmol) and a catalytic amount of benzyltriethylammonium chloride (0.23 g, 1 mmol) in DMF (25 mL) at 20 °C. After 40 min, K_2CO_3 (2.9 g, 21 mmol) and a solution of MeI (2.96 g, 20.8 mmol) in DMF (10 mL) were added and the mixture was stirred for 2 h. The mixture was left overnight, then the solvent was removed at *ca.* 60 °C (1 Torr). The residue was purified by passing its solution in $CHCl_3$ through a layer of SiO_2. Compound **3** (1.89 g, 78 %) was obtained, m.p. 146—147 °C (from benzene). Found (%): C, 56.63; H, 4.28; N, 12.01; S, 13.40. $C_{11}H_{10}N_2O_2S$. Calculated (%): C, 56.40; H, 4.30; N, 11.96; S, 13.68. IR (KBr), ν/cm^{-1}: 1704 (C=O), 1640 sh, 1618 v.s, (C=O, C=N). ^{1}H NMR ($CDCl_3$), δ: 2.48 (s, 3 H, $CO\underline{CH_3}$); 2.60 (s, 3 H, SCH_3); 6.97 (m, 1 H, H(7)); 7.39 (m, 1 H, H(9)); 7.62 (m, 1 H, H(8)); 8.89 (m, 1 H, H(6)). ^{13}C NMR (DMSO-d_6), δ: 17.87 (q, MeS, ^1J = 143 Hz); 30.30 (q, $\underline{CH_3}CO$, ^1J = 129 Hz); 114.05 (d, C(7), ^1J = 173 Hz); 123.96 (d, C(9), ^1J = 172 Hz); 131.14 (d, C(6), ^1J = 188 Hz); 136.14 (s, C(3)); 137.79 (d, C(8), ^1J = 167 Hz); 140.07 (q, C(4), ^3J = 4.5 Hz); 152.40 (C(10)); 199.12 (q, CO, ^2J = 6 Hz). MS, *m/z* (I_{rel} (%)): 234 $[M]^+$ (64), 219 $[M-Me]^+$ (96), 191 $[M-MeCO]^+$ (100), 187 $[M-SMe]^+$ (28).

3-Acetyl-2-hydroxypyrido[1,2-*a*]pyrimidine-4-thione (4a). The reaction was carried out as described above. The mixture obtained from **1a** (1.57 g, 8.8 mmol), CS_2 (0.68 g, 8.8 mmol), K_2CO_3 (5.0 g, 36.4 mmol), benzyltriethylammonium chloride (0.12 g, 0.5 mmol), and MeI (1.27 g, 8.94 mmol) in DMF (50 mL) (the total amount) was concentrated at *ca.* 95 °C (1 Torr). The residue was washed with ether, dried at *ca.* 20 °C (1 Torr), and dissolved in H_2O (10 mL), and a 10 % solution of AcOH (5 mL) was added. The precipitate was filtered off, dried over P_2O_5 at *ca.* 20 °C (1 Torr), washed with $CHCl_3$ and ether, and dried at *ca.* 20 °C (1 Torr). Compound **4a** (1.3 g, 68 %) was obtained, m.p. 227 °C (decomp., from acetone). Found (%): C, 54.69; H, 3.88; N, 12.63; S, 14.35. $C_{10}H_8N_2O_2S$. Calculated (%): C, 54.53; H, 3.66; N, 12.72; S, 14.56. IR (KBr), ν/cm^{-1}: 3440 br, 2000—2800 br, (OH), 1708 (C=O), 1660 sh, 1630 v.s, (C=O, C=N). ^{1}H NMR (DMSO-d_6), δ: 2.42 (s, 3 H, CH_3CO); 7.49 (m, 1 H, H(9)); 7.56 (m, 1 H, H(7)); 8.25 (m, 1 H, H(8)); 10.09 (d, 1 H, H(6), J = 5 Hz); 13.20 (br.s, 1 H, OH). ^{13}C NMR (DMSO-d_6), δ: 29.62 (q, Me, ^1J = 128 Hz); 116.10 (d, C(9), ^1J = 173 Hz); 117.19 (d, C(7), ^1J = 174 Hz); 122.93 (s, C(3)); 133.28 (d, C(6), ^1J = 191 Hz); 142.78 (d, C(8), ^1J = 170 Hz); 147.21 (C(10)); 153.63 (s, C(2)); 166.13 (d, C(4), ^3J = 4 Hz); 199.07 (q, (CO), ^2J = 6 Hz). MS, *m/z* (I_{rel} (%)): 220 $[M]^+$ (100), 205 $[M-Me]^+$ (35), 177 $[M-MeCO]^+$ (30).

3-Acetyl-2-hydroxy-8-methylpyrido[1,2-*a*]pyrimidine-4-thione (4b). Similarly to **4a**, compound **4b** (1.44 g, 44 %) was obtained from **1b** (2.7 g, 14 mmol), m.p. 232—234 °C (from THF). Found (%): C, 55.97; H, 4.20; N, 12.69; S, 13.62. $C_{11}H_{10}N_2O_2S$. Calculated (%): C, 56.39; H, 4.30; N, 11.96; S, 13.68. IR (KBr), ν/cm^{-1}: 3400 br, 2000—2800 br (OH), 1715 (C=O), 1650 sh, 1630 v.s (C=O, C=N). ^{1}H NMR (DMSO-d_6), δ: 2.39 (s, 3 H, CH_3CO); 2.53 (s, 3 H, Me); 7.23 (s, 1 H, H(9)); 7.41 (m, 1 H, H(7)); 9.95 (d, 1 H, H(6), J = 7.3 Hz). MS, *m/z* (I_{rel} (%)): 234 $[M]^+$ (100), 219 $[M-Me]^+$ (21), 191 $[M-MeCO]^+$ (27).

X-ray analysis of compound 3. Crystals of **3** possess triclinic syngony. At 20 °C, a = 7.992(5) Å, b = 8.358(5) Å, c = 9.782(4) Å, α = 87.28(2)°, β = 71.11(2)°, g = 63.29°, V = 548.5(4) Å^3, d_{calc} = 1.418 g cm^{-3}, Z = 2, space group $P\bar{1}$. The parameters of the unit cell and intensities of 1277 reflections with $F > 6\sigma(F)$ were measured with an automatic, four-circle diffractometer Syntex $P2_1$ (λ(Mo-K), a graphite monochromator, $\theta/2\theta$-scan, $2\theta_{max}$ = 60°).

The structure was solved by the direct method using the SHELXTL PLUS batch program. The coordinates of hydrogen atoms were evaluated from the differential synthesis of the electron density. The refinement in the full-matrix, anisotropic approximation by the least-squares method (isotropic for hydrogen atoms) was performed to R = 0.040 (R_w = 0.044, S = 2.27). The atomic coordinates are presented in Table 2.

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