Chemistry of Heterocyclic Compounds, Vol. 37, No. 6, 2001

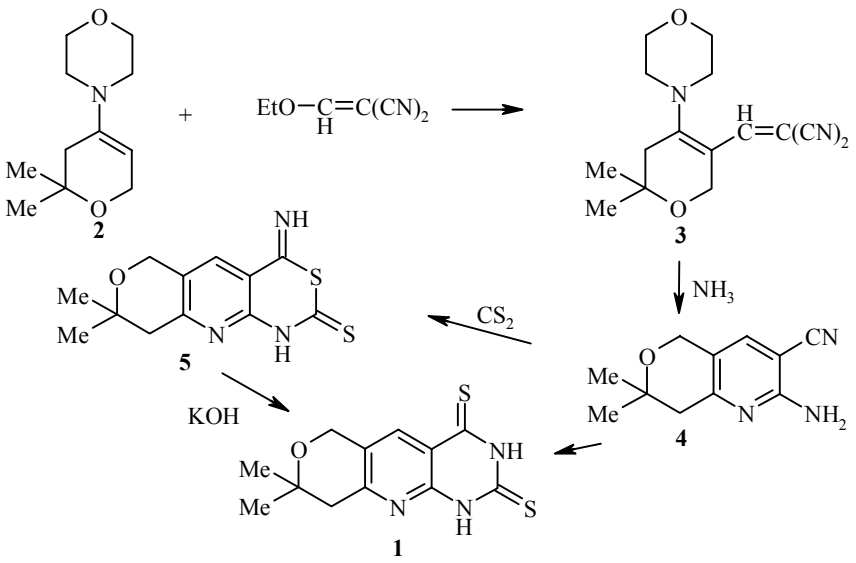
CONDENSED PYRIDOPYRIMIDINES.
2.* SYNTHESIS OF NEW DERIVATIVES
OF PYRANOPYRIDO[2,3-*d*]PYRIMIDINES

A. Sh. Oganisyan, A. S. Noravyan, and M. Zh. Grigoryan

New condensed derivatives of pyrido[2,3-d]pyrimidines were synthesized using the morpholine enamine of tetrahydro-4-pyranone.

Keywords: pyran, pyridine, pyrimidine, pyranopyridine, pyridopyrimidine, pyranopyridopyrimidine.

Condensed pyrimidine derivatives, which possess a broad spectrum of biological activity, occupy a special place in synthetic organic chemistry. Some such compounds have found use as drugs [2]. Pyrido[2,3-*d*]pyrimidines condensed with six-membered heterocycles have not been studied extensively [1]. In the present work, we synthesized 2,4-dithioxopyranopyrido[2,3-*d*]pyrimidine (**1**), which is convenient for subsequent transformations to give pyrido[2,3-*d*]pyrimidine derivatives.



* Communication 1, see ref. [1].

A. L. Mndzhoyan Institute of Fine Organic Chemistry, National Academy of Sciences of the Republic of Armenia, 375014 Yerevan, Armenia; e-mail: west@msrc.am. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 626-230, June, 2000. Original article submitted June 16, 1999.

0009-3122/01/3706-0763$25.00

The reaction of the morpholine enamine of 2,2-dimethyltetrahydro-4-pyranone (**2**) [3] with ethoxymethylenemalononitrile gave the 3-(dicyanoethenyl) derivative of this enamine **3**.

The action of 25% aqueous ammonia on dinitrile **3** led to its cyclization and formation of the corresponding 2-amino-3-cyanopyrano[4,3-*b*]pyridine (**4**). The reaction of **4** with carbon disulfide in pyridine at reflux gave tricyclic iminothiazinethione **5**.

Heating **5** in a solution of KOH in aqueous ethanol led to the Dimroth rearrangement and formation of tricyclic pyrimidinethione **1**, which may also be obtained without separation of intermediate **5** by heating pyranopyridine **4** with carbon disulfide in pyridine at reflux for 30 h.

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrometer for vaseline mulls. The ^{1}H NMR spectra were registered on a Varian T-60 spectrometer at 60 MHz for solutions in DMSO-d_6. Thin-layer chromatography was carried out on Silufol-254 plates with iodine vapor as the developer.

3-(2,2-Dicyanoethenyl)-6,6-dimethyl-4-morpholino-5,6-dihydro-2H-pyran (3). A solution of **2** (19.8 g, 0.1 mol) [4] in tetrahydrofuran (40 ml) was added with stirring in portions to a solution of ethoxymethylenemalononitrile (12.2 g, 0.1 mol) in tetrahydrofuran (60 ml) at room temperature and maintained for about 16 h. The solvent was then distilled off and cold absolute ethanol or ether (20 ml) was added to the viscous mass. The crystalline precipitate of **3** was filtered off, recrystallized from absolute ethanol, and dried to give 23.0 g (84%) **3**; mp 147°C (ethanol), R_f 0.58 (1:1:1 benzene–ether–methanol). IR spectrum (neat), ν, cm^{-1}: 2210 (C≡N), 1620 (C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.18 (1H, s, =CH); 4.58 (2H, s, –OCH_2–); 3.84 (4H, t, –CH_2–O–CH_2–); 3.74 (4H, t, –CH_2–N–CH_2–); 2.41 (2H, s, –CH_2–C=); 1.26 (6H, s, $(CH_3)_2$). Found, %: C 66.53; H 7.10; N 15.47. $C_{15}H_{19}N_3O_2$. Calculated, %: C 66.60; H 7.03; N 15.56.

2-Amino-3-cyano-7,7-dimethyl-7,8-dihydro-5H-pyrano[4,3-*b*]pyridine (4). A sample of 25% aqueous ammonia (10 ml) was added to a solution of **3** (2.7 g, 0.01 mol) in tetrahydrofuran (15 ml) and maintained in a sealed round-bottomed flask at 55-60°C for 6 h. Tetrahydrofuran was distilled off and crystalline **4** was filtered off, washed with water, and recrystallized from ethanol to give 1.8 g (90%) **4**, mp 216-217°C (ethanol), R_f 0.60 (1:3 chloroform–ether). IR spectrum (neat), ν, cm^{-1}: 3430, 3280, 3140 (NH_2), 2220 (C≡N), 1600 (arom). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.22 (1H, s, 4-H); 6.24 (2H, s, NH_2); 4.56 (2H, s, OCH_2); 2.60 (2H, s, CH_2); 1.24 (6H, s, $(CH_3)_2$). Found, %: C 65.07; H 6.35; N 20.58. $C_{11}H_{13}N_3O$. Calculated, %: C 65.02; H 6.40; N 20.69.

4-Imino-8,8-dimethyl-2-thio-8,9-dihydro-6H-pyrano[3',4':5,6]pyrido[2,3-*d*]-1,3-thiazine (5). A mixture of **4** (2 g, 0.01 mol), pyridine (10 ml), and carbon disulfide (7.6 g, 0.1 mol) was heated at reflux for 2 h. Pyridine was distilled off and ethanol or ether was added to the viscous residue. Crystalline **5** was filtered off, washed with ether, and dried to give 2.4 g (85%) **5**; mp 192-193°C (ethanol), R_f 0.57 (1:2 pyridine–ether). IR spectrum (neat), ν, cm^{-1}: 1430 (C=S), 1620 (C=N), 3120-3140 (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 13.20 (1H, s, NH); 7.40 (1H, s, 5-H); 6.42 (1H, s, =NH); 4.54 (2H, s, OCH_2); 2.60 (2H, s, CH_2); 1.24 (6H, s, $(CH_3)_2$). Found, %: C 51.67; H 4.46; N 15.13; S 22.87. $C_{12}H_{13}N_3OS_2$. Calculated, %: C 51.61; H 4.66; N 15.05; S 22.93.

8,8-Dimethyl-2,4-dithio-8,9-dihydro-6H-pyrano[3',4':5,6]pyrido[2,3-*d*]pyrimidine (1). A. A mixture of **5** (2.8 g, 0.01 mol) and KOH (1.12 g, 0.02 mol) in 50% aqueous ethanol (40 ml) was heated at reflux for 3 h. After cooling, the reaction mixture was filtered off and the filtrate was neutralized by adding 18% hydrochloric acid. The crystalline precipitate was filtered off, washed with water and ether, and recrystallized from ethanol to give 2.6 g (92%) **1**.

B. A mixture of **4** (2 g, 0.01 mol), pyridine (10 ml), and carbon disulfide (7.6 g, 0.01 mol) was heated at reflux for 30 h. Pyridine was distilled off and ethanol was added to the viscous residue. The crystalline precipitate was filtered off, washed with ether, and dried to give 2.5 g (90%) **1**; mp 276-278°C (ethanol), R_f 0.56

(1:1:2 pyridine–acetone–ether). IR spectrum (neat), ν, cm^{-1}: 1445 (C=S), 3135 (NH). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 12.80 and 12.26 (2H, two s, 2NH); 7.44 (1H, s, 5-H); 4.56 (2H, s, OCH_2); 2.58 (2H, s, CH_2); 1.26 (6H, s, $(CH_3)_2$). Found, %: C 51.65; H 4.51; N 15.03; S 22.79. $C_{12}H_{13}N_3S_2O$. Calculated, %: C 51.61; H 4.66; N 15.05; S 22.93.

REFERENCES

1. A. Sh. Oganisyan, A. S. Noravyan, M. Zh. Grigoryan, and A. Sh. Oganisyan, *Khim. Geterotsikl. Soedin.*, 1239 (1999).
2. M. Negwer, *Organisch-Chemische Arzneimittel und ihre Synonyma*, Vol. 1, Akad. Verlag, Berlin (1978), p. 454.
3. N. A. Arutyunyan, É. A. Abgaryan, S. A. Vartanyan, and L. A. Akopyan, *Arm. Khim. Zh.*, **40**, 570 (1987).