Chemistry of Heterocyclic Compounds, Vol. 29, No. 12, 1993

SYNTHESIS OF DERIVATIVES OF PYRIDO[2,3-d]PYRIMIDINES CONDENSED WITH TETRAHYDROPYRAN AND TETRAHYDROTHIOPYRAN

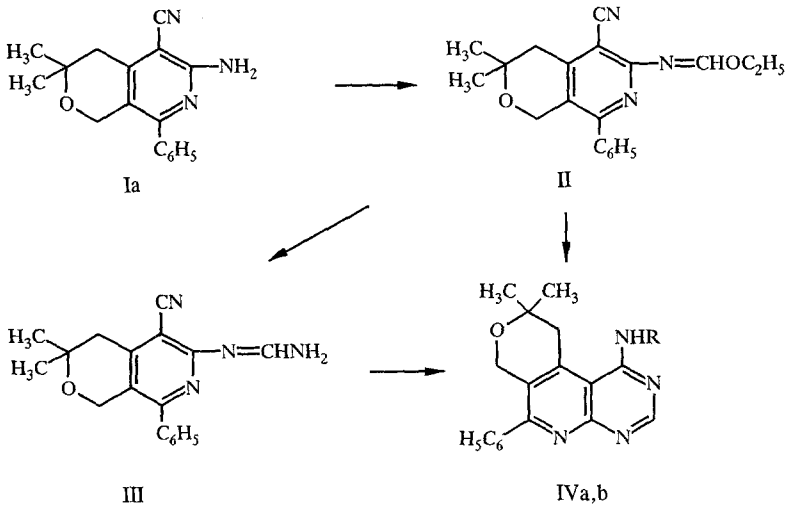
E. G. Paronikyan, S. N. Sirakanyan, and A. S. Noravyan

Methods have been developed for obtaining derivatives of 10-amino(oxo)-, 8,10-dioxo-, and 10-amino-8-oxo(thio)pyrano(thiopyrano)[4',3':4,5]pyrido[2,3-d]pyrimidine on the basis of 3-amino(benzylamino)-4-cyano(carbamoyl)pyrano(thiopyrano)[3,4-c]-pyridines.

In a series of derivatives of pyrido[2,3-d]pyrimidine, compounds having a broad spectrum of biological properties have been found [1-3]. This has stimulated our interest in searching for methods to synthesize new heterocyclic systems – pyrido[2,3-d]pyrimidines condensed with tetrahydropyran and tetrahydrothiopyran.

The synthesis was accomplished by closing a pyrimidine ring in position c of the pyrano(thiopyrano)[3,4-c]pyridine ring, by various methods.

The first method is based on the interaction of the aminonitrile Ia [4] with triethyl orthoformate. Under the action of an ethanol solution of ammonia, the 3-ethoxymethyleneamino derivative II that is formed in the first stage is converted to the 3-aminomethyleneamino derivative III, which is then cyclized by treatment with sodium ethylate to form the 10-aminopyrido[2,3-d]pyrimidine IVa. Interaction of compound II with hydrazine hydrate leads to the formation of the 10-hydrazino derivative IVb. In this case, there is no formation of a noncyclic intermediate product.

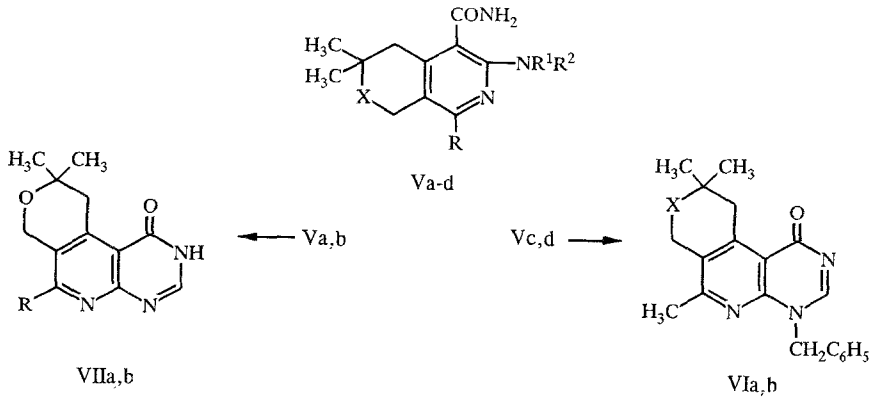


IVa) R = H; IVb) R = NH_2

The second method that we used for the synthesis of derivatives of condensed pyrido[2,3-d]pyrimidines includes cyclocondensation of the aminoamides Va-d [4, 5] with ethyl orthoformate.

A. L. Mndzhoyan Institute of Fine Organic Chemistry, National Academy of Sciences of the Republic of Armenia, Erevan 375014. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1683-1687, December, 1993. Original article submitted October 15, 1993.

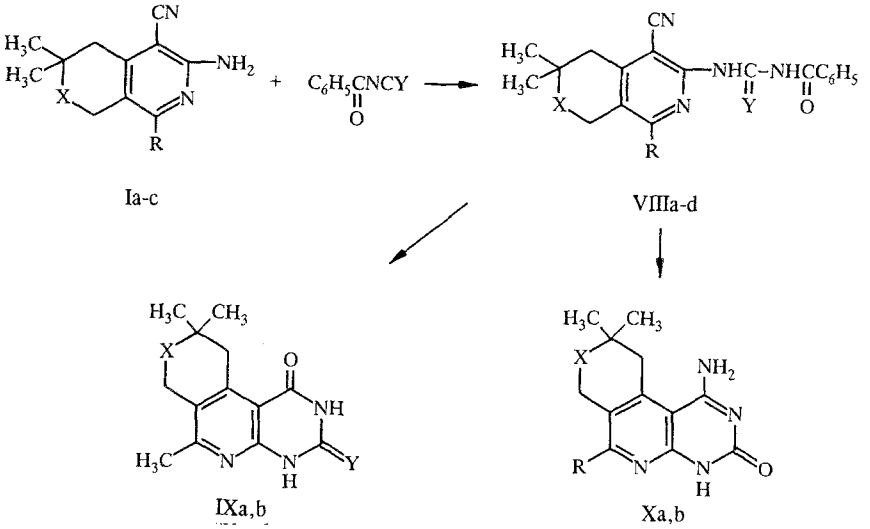
 0009-3122/93/2912-1454$12.50



Va) X = O, R = CH_3, $R^1 = R^2$ = H; Vb) X = O, R = C_6H_5, $R^1 = R^2$ = H; Vc) X = O, R = CH_3, R^1 = H, $R^2 = CH_2C_6H_5$; Vd) X = S, R = CH_3, R^1 = H, $R^2 = CH_2C_6H_5$; VIa) X = O; VIb) X = S; VIIa) R = CH_3; VIIb) R = C_6H_5.

As a result of the reaction, we obtained 10-oxopyrido[2,3-d]pyrimidines with a benzyl substituent in position 7 (compounds VIa,b) and analogous compounds without this substituent (compounds VIIa,b).

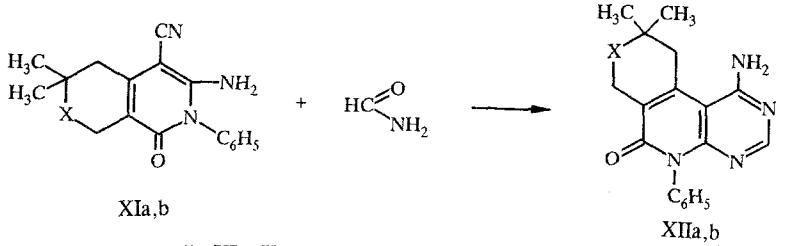
With the aim of synthesizing 8-oxo and 8-thio derivatives of condensed pyrido[2,3-d]pyrimidines, we developed a method consisting of interaction of the aminonitriles Ia-c [4, 5] with benzoyliso(thio)cyanates, followed by cyclization of the resulting N-benzoylureido(thioureido) derivatives VIIIa-d by the action of a base.



Ia, VIIIa, Xa) X = O, R = C_6H_5; Ib, VIIIb, Xb) X = O, R = CH_3; Ic, VIIIc,d, Xc) X = S, R = CH_3; VIIIa-c) Y = O; VIIId) Y = S; IXa) X = Y = O; IXb) X = Y = S.

When a 1.5% aqueous solution of potassium hydroxide is used as the base, 8,10-dioxo or 10-oxo-8-thio derivatives IXa,b are formed. With a 2.5% solution of potassium hydroxide in ethanol, the 10-amino-8-oxo derivatives Xa-c are obtained.

We were successful in obtaining the 5-oxo-6-phenylpyrido[2,3-d]pyrimidines XIIa,b from the corresponding aminonitriles XIa,b [6] through the action of formamide. Other methods proved to be unsuitable for the synthesis of derivatives of 5-oxo-6-phenylpyrido[2,3-d]pyrimidines.



1) XIa, XIIa) X = O; XIb, XIIb) X = S

TABLE 1. Characteristics of Compounds VI-XII

Compound	Empirical formula	mp, °C	R_f	Yield, %
VI a	$C_{20}H_{21}N_3O_2$	214...215	0,72	72
VIb	$C_{20}H_{21}N_3OS$	178...179	0,71	63
VII a	$C_{13}H_{15}N_3O_2$	351...352	0,52	86
VIIb	$C_{18}H_{17}N_3O_2$	246...247	0,66	65
VIII a	$C_{25}H_{22}N_4O_3$	227...228	0,58	88
VIIIb	$C_{20}H_{20}N_4O_3$	236...237	0,54	90
VIII c	$C_{20}H_{20}N_4O_2S$	193...194	0,62	86
VIII d	$C_{20}H_{20}N_4OS_2$	194...195	0,69	67
IX a	$C_{13}H_{15}N_3O_3$	275...276	0,78	71
IXb	$C_{13}H_{15}N_3OS_2$	253...254	0,81	73
X a	$C_{18}H_{18}N_4O_2$	273...274	0,59	67
Xb	$C_{13}H_{16}N_4O_2$	317...318	0,51	63
X c	$C_{13}H_{16}N_4OS$	265...266	0,74	83
XII a	$C_{18}H_{18}N_4O_2$	335...336	0,58	78
XIIb	$C_{18}H_{18}N_4OS$	258...259	0,62	58

The structures of the compounds that were obtained were confirmed by IR, PMR, and mass spectrometry.

EXPERIMENTAL

IR spectra were taken in a UR-20 instrument in white mineral oil. PMR spectra were recorded in a Varian T-60 instrument in $CDCl_3$ (II, VIa), DMSO-d_6 (III, IV, VIb, VIIb), or pyridine-d_5 (VIIIb,d, IXb, XIIa). Internal standard TMS. Mass spectra were obtained in an MKh-1303 mass spectrometer with direct introduction of the sample. The purity of the products was monitored by TLC on Silufol UV-254 plates, using the following systems: 1:2 ethanol–hexane (II, III, VIIIb,c, IXa,b); 4:2:5 butanol–acetic acid–water (IVa,b, VIa, VIIa,b, VIIId, Xa-c); 1:1 pyridine–ethanol (VIb, VIIIa, XIIa,b). Elemental analyses of the synthesized compounds for C, H, N, and S were consistent with the calculated contents.

The characteristics of compounds VI-XII are listed in Table 1.

6,6-Dimethyl-1-phenyl-4-cyano-3-ethoxymethyleneamino-5,6-dihydro-8H-pyrano[3,4-c]pyridine (II, $C_{20}H_{21}N_3O_2$). A mixture of 2.8 g (0.01 mole) of compound Ia, 25 ml of triethyl orthoformate, and 1 ml of acetic anhydride was refluxed for 10 h. The excess ester was driven off, petroleum ether was added, and the resulting crystals were filtered off: mp 94-95°C (ethanol), R_f 0.71. IR spectrum, cm^{-1}: 1590 (C=C_{ar}), 1630 (C=N), 2230 (CN). PMR spectrum, ppm: 8.43 (1H, s, CH); 7.35 (5H, s, C_6H_5); 4.61 (2H, t, CH_2O); 4.36 (2H, t, J = 7 Hz, $\underline{CH_2}CH_3$); 2.88 (2H, t, CH_2); 1.23-1.43 (9H, m, $3CH_3$). Yield 2.3 g (68.5%).

3-Aminomethyleneamino-6,6-dimethyl-1-phenyl-4-cyano-5,6-dihydro-8H-pyrano[3,4-c]pyridine (III, $C_{18}H_{18}N_4O$). A mixture of 3.35 g (0.01 mole) of compound II and 60 ml of a 25% solution of ammonia in ethanol was held for 48 h at 20-22°C. The ethanol was driven off, 30 ml of water was added, and the resulting crystals were filtered off, washed with water, and dried: mp 152-153°C (ethanol), R_f 0.73. IR spectrum, cm^{-1}: 1580 (C=C_{ar}), 1670 (C=N), 2230 (CN), 2230 (CN), 3330, 3460 (NH_2). PMR spectrum, ppm: 8.43 (1H, s, CH); 8.01 (2H, br.s, NH_2); 7.43 (5H, s, C_6H_5); 4.55 (2H, t, CH_2O); 2.83 (2H, t, CH_2); 1.31 mp (6H, s, $2CH_3$). Yield 2.95 g (96.2%).

10-Amino-2,2-dimethyl-5-phenyl-1,2-dihydro-4,8H-pyrano[4′,3′:4,5]pyrido[2,3-d]pyrimidine (IVa, $C_{18}H_{18}N_4O$). To a solution of sodium ethylate, prepared from 0.69 g (0.03 mole) of sodium and 60 ml of ethanol, 3.06 g (0.01 mole) of compound III was added. The mixture was refluxed for 2 h. After cooling, the precipitated crystals were filtered off, washed with water, and dried: mp 283-284°C (DMSO), R_f 0.64. IR spectrum, cm^{-1}: 1580 (C=C_{ap}), 1650 (NH_2 def), 3290, 3430, (NH_2). PMR spectrum, ppm: 8.73 (1H, s, CH); 7.53-7.91 (7H, m, $NH_2C_6H_5$); 4.71 (2H, t, CH_2O); 3.36 (2H, t, CH_2); 1.23

Mass spectrum, m/z (and I, %): M^+ 306 (78), 291 (100), 262 (31), 236 (34). Yield 2.95 g (96.3%).

10-Hydrazino-2,2-dimethyl-5-phenyl-1,2-dihydro-4,8H-pyrano[4′,3′:4,5]pyrido[2,3-d]pyrimidine (IVb, $C_{18}H_{19}N_5O$). A mixture of 3.35 g (0.01 mole) of compound II, 8 ml of hydrazine hydrate, and 25 ml of ethanol was refluxed for 3.5 h. After cooling, the precipitated crystals were filtered off, washed with water, and dried: mp 327-328°C (DMSO), R_f 0.72. IR spectrum, cm^{-1}: 1590 (C=C_{ar}), 1650 (NH_2 def.); 3210-3440 (NH, NH_2). Mass spectrum, m/z (and I, %): M^+ 321 (75), 305 (50), 263 (67), 248 (100). Yield 2.25 g (70.2%).

7-Benzyl-10-oxo-2,2,5-trimethyl-1,2-dihydro-4,8H-pyrano(thiopyrano)[4′,3′:4,5]pyrido[2,3-d]pyrimidines (VIa,b). A mixture of 0.01 mole of compound Vc,d, 15 ml of triethyl orthoformate, and 15 ml of acetic anhydride was refluxed for 2 h. The ether and the anhydride were driven off, 5 ml of a 10% aqueous solution of potassium hydroxide was added, and the precipitated crystals were filtered off and washed with water, then recrystallized from ethanol. IR spectrum, cm^{-1}: 1580 (C=C_{ar}), 1600-1610 (C=N), 1640-1650 (CO). PMR spectrum of VIa, ppm: 8.56 (1H, s, CH); 7.36 (5H, m, C_6H_5); 5.61 (2H, s, $\underline{CH_2}C_6H_5$); 4.81 (2H, t, CH_2O); 3.46 (2H, t, CH_2); 2.53 (3H, s, CH_3); 1.33 (6H, s, $2CH_3$). PMR spectrum of VIb, ppm: 8.33 (1H, s, CH); 7.36 (5H, m, C_6H_5); 5.46 (2H, s, $\underline{CH_2}C_6H_5$); 3.78 (2H, t, CH_2S); 3.53 (2H, t, CH_2); 2.55 (3H, s, CH_3); 1.25 (6H, s, $2CH_3$). Mass spectrum of VIa, m/z (and I, %): M^+ 335 (41), 320 (100), 276 (13), 228 (15). Mass spectrum of VIb: M^+ 351 (100), 336 (64), 323 (93), 318 (29), 308 (42).

2,2-Dimethyl-5-substituted-10-oxo-1,2-dihydro-4,8H-pyrano[4′,3′:4,5]pyrido[2,3-d]pyrimidines (VIIa,b). A mixture of 0.01 mole of compound Va,b, 5 ml of triethyl orthoformate, and 5 ml of acetic anhydride was refluxed for 7 h. After cooling, the precipitated crystals were filtered off, then washed with water and ethanol and recrystallized from acetic acid. IR spectrum, cm^{-1}: 1580-1600 (C=C_{ar}), 1620 (C=N), 1700 (CO), 3480 (NH). PMR spectrum of VIIb, ppm: 8.26 (1H, s, CH); 7.56 (5H, s, C_6H_5); 4.66 (2H, t, CH_2O); 1.95 (2H, t, CH_2); 1.28 (6H, s, $2CH_3$). Mass spectrum of VIIa, m/z (and I, %): M^+ 245 (54), 230 (35), 216 (34), 188 (73), 187 (100).

6,6-Dimethyl-3-N-benzoylureido(thioureido)-5-substituted-4-cyano-5,6-dihydro-8H-pyrano(thiopyrano)[3,4-c]pyridines (VIIIa-d). To a solution of 0.01 mole of compounds Ia-c in 40 ml of dry benzene, 0.015 mole of benzoyl iso(thio)cyanate was added dropwise. The mixture was refluxed for 4 h. After cooling, the precipitated crystals were filtered off, washed with ether, and recrystallized from benzene. IR spectrum, ppm: 1180 (C=S), 1580-1600 (C=C_{ar}), 1700-1740 (CO), 2220-2250 (CN), 3200-3400 (NH). PMR spectrum of VIIIb, ppm: 7.61-8.26 (5H, m, C_6H_5); 4.81 (2H, t, CH_2O); 2.95 (2H, t, CH_2); 2.21 (3H, s, CH_3); 1.23 (6H, s, $2CH_3$). PMR spectrum of VIIIc, ppm: 7.93-8.26 (2H, br.s, C_6H_5); 7.33-7.76 (3H, br.s, C_6H_5); 3.71 (2H, t, CH_2S); 3.15 (2H, t, CH_2); 2.41 (3H, s, CH_3); 1.32 (6H, s, $2CH_3$). PMR spectrum of VIIIb) 7.83-8.16 (2H, br.s, C_6H_5); 7.31-7.66 (3H, br.s, C_6H_5); 3.78 (2H, t, CH_2S); 3.18 (2H, t, CH_2); 2.45 (3H, s, CH_3); 1.3 (6H, s, $2CH_3$).

8-Oxo(thio)-10-oxo-2,2,5-trimethyl-1,2-dihydro-4,7,9H-pyrano(thiopyrano)[4′,3′:4,5]pyrido[2,3-d]pyrimidines (IXa,b). A mixture of 0.01 mole of compounds VIIIb,d and 80 ml of a 1.5% aqueous solution of potassium hydroxide was refluxed for 10 h. After cooling, the solution was neutralized with an 18% hydrochloric acid solution, and the precipitated crystals were filtered off, washed with water, and recrystallized from DMF. IR spectrum, cm^{-1}: 1180 (C=S), 1580 (C=C_{ar}), 1660-1670 (CO), 1700 (CO), 3460-3590 (NH). PMR spectrum of IXb, ppm: 2.51 (2H, t, CH_2S); 2.22 (5H, m, CH_2, CH_3); 1.24 (6H, s, $2CH_3$). Mass spectrum of IXa, m/z (and I, %): M^+ 261 (44), 246 (54), 232 (22), 204 (75), 203 (100). IXb: M^+ 293 (97), 278 (17), 260 (13), 250 (100), 233 (10).

10-Amino-2,2-dimethyl-5-substituted-8-oxo-1,2-dihydro-4,7H-pyrano(thiopyrano)[4′,3′:4,5]pyrido[2,3-d]-pyrimidines (Xa-c). A mixture of 0.01 mole of compounds VIIIa-c and 55 ml of a 2.5% ethanol solution of potassium hydroxide was refluxed for 8 h. After cooling, the precipitated crystals were filtered off, washed with water, and recrystallized from nitromethane. IR spectrum, cm^{-1}: 1580-1600 (C=C_{ar}), 1660-1690 (CO), 3330-3450 (NH_2, NH). Mass spectrum of Xa, m/z (and I, %): M^+ 322 (100), 307 (87), 292 (38), 278 (20), 262 (82).

10-Amino-2,2-dimethyl-5-oxo-6-phenyl-1,2-dihydro-4,8H-pyrano(thiopyrano)[4′,3′:4,5]pyrido[2,3-d]pyrimidines (XIIa,b). A mixture of 0.01 mole of compounds XIa,b and 30 ml of formamide was refluxed for 4 h. After cooling, the precipitated crystals were filtered off, washed with ethanol, and recrystallized from DMF. IR spectrum, cm^{-1}: 1600-1630 (C=C, C=N), 1650-1670 (CO), 3310-3480 (NH_2). PMR spectrum of XIIa, ppm: 8.31 (1H, s, CH); 8.0 (2H, s, NH_2); 7.05-7.56 (5H, m, C_6H_5); 4.92 (2H, t, CH_2O); 3.24 (t, CH_2); 1.46 (6H, s, $2CH_3$).

REFERENCES

1. D. S. Duch, M. P. Edelstein, S. W. Bowers, and C. A. Nichol, Cancer Res., **42**, 3987 (1982).
2. M. I. Abu El-Haj, U.S. Pat. 3,950,160 [Chem. Abstr., **85**, 29577j (1976)].
3. L. R. Bennett, C. L. Blakley, and R. W. Fleming, J. Med. Chem., **24**, 382 (1981).
4. E. G. Paronikyan, S. N. Sirakanyan, A. S. Norovyan, and R. G. Paronikyan, Arm. Khim. Zh., **42**, 766 (1989).
5. E. G. Paronikyan, S. N. Sirakanyan, A. S. Norovyan, and Dzh. A. Melkonyan, Arm. Khim. Zh., **44**, 250 (1991).
6. E. G. Paronikyan, G. V. Mirzoyan, A. A. Noravyan, and S. A. Vartanyan, Khim. Geterotsikl. Soedin., No. 7, 989 (1987).