Chemistry of Heterocyclic Compounds, Vol. 34, No. 10, 1998

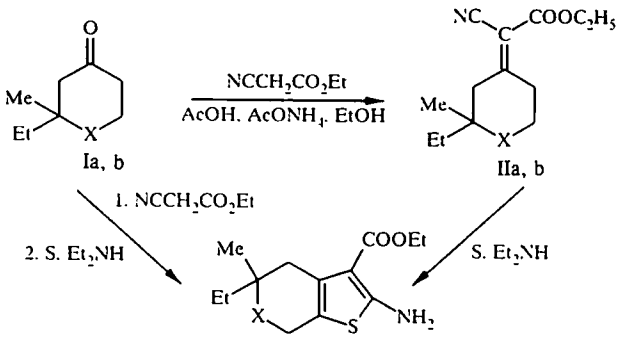
DERIVATIVES OF CONDENSED THIENOPYRIMIDINES 12.* SYNTHESIS OF SUBSTITUTED PYRANO(THIOPYRANO)-[4′,3′:4,5]THIENO[2,3-*d*]PYRIMIDINES

A. Sh. Oganisyan and A. S. Noravyan

A method for the synthesis of new condensed derivatives of 4-oxo-2-thioxo-5,6-dihydro-8H-pyrano(thiopyrano)[4′,3′:4.5]thieno[2,3-d]pyrimidines has been developed. It has been established that with increasing electron acceptor ability of the substituents on the nitrogen atom of the isothiocyanate starting materials there is a marked formation of 2-N′-thioureide derivatives of the condensed thiophenes.

Condensed derivatives of thioxothieno[2,3-d]pyrimidines are of great interest for the synthesis of new condensed heterocyclic systems and for the synthesis of new effective biologically active compounds based on them [2-4].

We have shown that the corresponding ethyl 2-methyl-2-ethyltetrahydro-4-pyranylidene(thiopyranylidene)cyanoacetates IIa and b are formed by the condensation of 2-methyl-2-ethyltetrahydropyran(thiopyran)-4-ones (I) [5, 6] with ethyl cyanoacetate. Reaction of IIa and b with sulfur gave 2-amino-5-methyl-5-ethyl-3-ethoxycarbonyl-4,5-dihydro-7H-thieno[2,3-d]pyran(thiopyran) (IIIa and b). The same thiophenes were obtained in a single step by the reaction of the heterocyclic ketones Ia and b with ethyl cyanoacetate and sulfur in the presence of diethylamine which facilitates greater yields of the desired products IIIa and b.



Reaction of the thiophenes IIIa and b with various isothiocyanates gave the corresponding 2-N′-thioureides of the thiophenes (IVa-f). This reaction belongs to the general class of nucleophilic addition reactions. The reaction slows with decreasing electron acceptor ability of the substituent on the nitrogen atom of the isothiocyanate starting materials (R–N=C=S) in the order C_6H_5–CO–N=C=S > C_6H_5–N=C=S > CH_3–N=C=S. While the condensation of thiophenes III a and b with benzoylisothiocyanate in methanol occurred in quantitative yield at 30-40°C, high yields of the thioureides from reactions with phenyl- and methylisothiocyanates required higher temperatures (78 and 117°C) and the reactions were carried out in ethanol and butanol respectively.

*For Communication 11 see [1].

A. A. Mndzhoyan Institute of Fine Organic Chemistry, National Academy of Sciences, Republic of Armenia, Erevan 375014. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1388-1391, October, 1998. Original article submitted October 21, 1997.

0009-3122/98/3410-1181$20.00

TABLE 1. Characteristics of the Synthesized Compounds IIa and b, IIIa and b, IVa-f and VIa-f

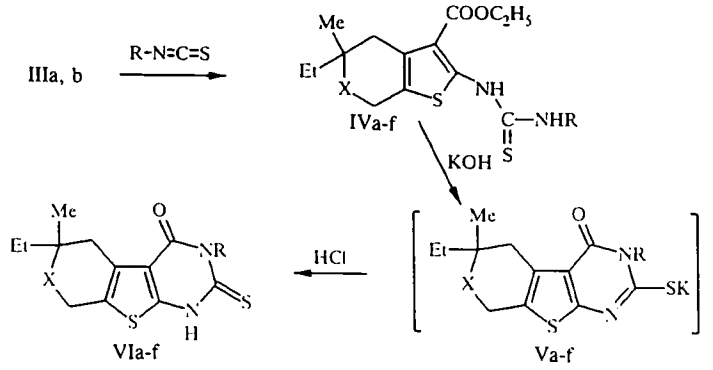
Compound	Molecular formula	Found, % / Calculated, %		mp, °C; bp\mm	R_f*	Yield, % (method)
		N	S			
IIa†	$C_{13}H_{19}NO_3$	6,0 5,9	—	135...137/1,5	0,63	80
IIb‡	$C_{13}H_{19}NO_2S$	6,1 5,8	12,3 12,6	140...142/1,5	0,62	81,5
IIIa	$C_{13}H_{19}NO_3S$	5,1 5,3	11,6 11,9	70...72	0,64	74,5 (A) 90,5 (B)
IIIb	$C_{13}H_{19}NO_2S_2$	4,5 4,9	22,1 22,5	85/86	0,55	75,5 (A) 91 (B)
IVa	$C_{21}H_{24}N_2O_4S_2$	6,7 6,5	14,8 14,5	184...185	0,63	83,5
IVb	$C_{21}H_{24}N_2O_3S_3$	6,0 6,3	21,8 21,4	189...190	0,60	84
IVc	$C_{20}H_{24}N_2O_3S_2$	7,2 6,9	15,5 15,8	155...157	0,58	75
IVd	$C_{20}H_{24}N_2O_2S_3$	6,6 6,7	22,6 22,8	163...165	0,62	76
IVe	$C_{15}H_{22}N_2O_3S_2$	8,1 8,2	18,4 18,7	184...186	0,64	64
IVf	$C_{15}H_{22}N_2O_2S_3$	7,3 7,7	26,2 26,8	150...151	0,60	63
VIa	$C_{12}H_{14}N_2O_2S_2$	10,3 9,9	22,6 22,7	252...254	0,49	96
VIb	$C_{12}H_{14}N_2OS_3$	9,3 9,4	32,5 32,2	288...290	0,45	94
VIc	$C_{18}H_{18}N_2O_2S_2$	7,6 7,8	17,6 17,9	245...247	0,62	96
VId	$C_{18}H_{18}N_2OS_3$	7,1 7,5	25,9 25,6	290...292	0,61	96
VIe	$C_{13}H_{16}N_2O_2S_2$	9,6 9,4	21,1 21,6	233...235	0,61	95
VIf	$C_{13}H_{16}N_2OS_3$	8,6 9,0	30,8 30,7	243...245	0,58	96

*IIa ($CHCl_3$–ether, 2:1); IIb, IIIb ($CHCl_3$–hexane, 1:2); IIIa (CCl_4–hexane, 1:2); IVa and b (acetone–hexane, 1:2); IVc ($CHCl_3$–CCl_4, 1:2); IVd-f (CCl_4–acetone, 2:1); VIa, d, f ($CHCl_3$–CCl_4, 2:1); VIe (CCl_4–acetone, 1:1).

†n_D^{20} 1.4899.

‡n_D^{20} 1.5022.

Treatment of compounds IVa-f with aqueous alcoholic potassium hydroxide caused intramolecular cyclization with formation of the potassium salts of 4-oxo-2-thioxothieno[2,3-d]pyrimidines with a condensed six-membered heterocycle (Va-f). The parent 2-thioxothienopyrimidines VIa-f were isolated by acidification of aqueous solutions of Va-f.



IV a X = O, R = COPh; b X = S, R = COPh;
VI a X = O, R = H; b X = S, R = H;
IV, VI c X = O, R = Ph; d X = S, R = Ph;
e X = O, R = Me; f X = S, R = Me

EXPERIMENTAL

IR spectra of Nujol mulls were recorded with a UR-20 spectrometer, ^{1}H NMR spectra were recorded with a Varian T-60 instrument, TLC was carried out on Silufol UV-254 strips, with development with iodine vapor.

Characteristics of the synthesized compounds II-IV and VI are cited in Table 1.

Ethyl 2-Methyl-2-ethyltetrahydro-4-pyranyl(thiopyranyl)cyanoacetates (IIa, b). Esters IIa, b.p. 135-137°C and IIb, b.p. 140-142°C were obtained from a mixture of ketones Ia or Ib (0.01 mol), ethyl cyanoacetate (11.3 g, 0.01 mol), glacial acetic acid (1 ml) and ammonium acetate (1 g) in dry benzene (30 ml) by a method described in [6]. IR spectra of compounds IIa and b: 1620 (C=C), 1690 (C=O), 2250 cm^{-1} (CN). ^{1}H NMR spectrum of ester IIa (CCl_4): 4.26 (2H, q, J = 7 Hz, $COO\underline{CH_2}-CH_3$), 3.73 (2H, q, J = 5 Hz, 6-CH_2-), 3.0 (1H, t, J = 5 Hz, 5-$CH_{(e)}$), 2.67 (1H, t, J = 5 Hz, 5-$CH_{(a)}$), 2.58 (2H, 3-CH_2-), 1.44 (2H, q, J = 7 Hz, 2-$\underline{CH_2}CH_3$), 0.75-1.20 ppm (9H, m, 2-CH_3, 2-$CH_2-\underline{CH_3}$, $COOCH_2-\underline{CH_3}$).

2-Amino-3-ethoxycarbonyl-5-methyl-5-ethyl-4,5-dihydro-7H-thieno[2,3-c]pyran(thiopyran) (IIIa, b). A. Compounds IIIa and b were obtained from a mixture of the ester IIa or b (0.1 mol), powdered sulfur (3.2 g, 0.1 mol), 96% ethanol (80 ml) and diethylamine (10 ml) by a method described in [7].

B. A mixture of the ketone Ia or b (0.1 mol), ethyl cyanoacetate (11.3 g, 0.1 mol), glacial acetic acid (1 ml) and ammonium acetate (1 g) in 96% ethanol (100 ml) was boiled for 3 h. The mixture was cooled to 55°C and powdered sulfur was added (3.2 g, 0.1 mol), the mixture was stirred and diethylamine (10 ml) was added dropwise. Stirring was continued at 60°C until the sulfur had dissolved completely. Further work up was as in A. IR spectra of compounds IIIa and b: 1680 (C=O), 3330, 3440 cm^{-1} (NH_2). ^{1}H NMR spectrum of compound IIIa ($CDCl_3$): 5.96 (2H, s, NH_2), 4.46 (2H, s, 7-CH_2), 4.23 (2H, q, J = 7 Hz, $COO\underline{CH_2}-CH_3$), 2.63 (2H, s, 4-CH_2), 1.26-1.95 (5H, m, 5-$\underline{CH_2}-CH_3$, $COOCH_2-\underline{CH_3}$), 1.20 (3H, s, 5-CH_3), 0.93 ppm (3H, t, J = 7 Hz, 5-$CH_2-\underline{CH_3}$). ^{1}H NMR spectrum of compound IIIb ($CDCl_3$): 5.83 (2H, s, NH_2), 4.23 (2H, q, J = 7 Hz, $COO\underline{CH_2}$-CH_3), 3.50 (2H, s, 7-CH_2), 2.86 (2H, s, 4-CH_2), 1.22-1.85 (5H, m, 5-$\underline{CH_2}-CH_3$, $COOCH_2-\underline{CH_3}$), 1.20 (3H, s, 5-CH_3), 0.97 ppm (3H, t, J = 7 Hz, 5-$CH_2-\underline{CH_3}$).

2-(N′-Benzoylthioureido)-5-methyl-5-ethyl-3-ethoxycarbonyl-4,5-dihydro-7H-thieno[2,3-c]pyran(thiopyran) (IVa, b). Benzoylisothiocyanate (3.2 g, 0.02 mol) was added to a stirred solution of amine IIIa or b (0.02 mol) in methanol (50 ml) at 35°C. Stirring was continued for 2h. The precipitated crystals were filtered off, washed with ether and recrystallized from ethanol. IR spectra of compounds IVa and b: 1680 (C=O amide), 1710 (C=O) , 3350 cm^{-1} (NH). ^{1}H NMR spectrum of thiopyran IVb ($CDCl_3$): 9.10 (2H, br. S, NH), 7.38-8.0 (5H, m, C_6H_5), 4.52 (2H, q, J = 7 Hz, $COO-\underline{CH_2}-CH_3$), 3.78 (2H, s, 7-$CH_2$), 3.02 (2H, s, 4-$CH_2$), 1.44-1.98 (5H, m, 5-$\underline{CH_2}-CH_3$, $COO-CH_2-\underline{CH_3}$), 1.40 (3H, s, 5-$CH_3$), 1.05 ppm (3H, t, J = 7 Hz, 5-$CH_2-\underline{CH_3}$).

2-(N′-Phenylthioureido)-5-methyl-5-ethyl-3-ethoxycarbonyl-4,5-dihydro-7H-thieno[2,3-c]pyran(thiopyran) (IVc and d). A mixture of amine IIIa or b (0.02 mol), phenylisothiocyanate (2.7 g, 0.02 mol) and ethanol (60 ml) was boiled for 7 h and left overnight. The precipitated crystals were filtered off, washed with ether and recrystallized from ethanol. IR spectra of compounds IVc and d: 1670 (C=O), 3200 cm^{-1} (NH). ^{1}H NMR spectra of the thioureides IVc and d ($CDCl_3$): 12.06 (1H, s, NH), 8.46 (1H, s, $\underline{NH}-C_6H_5$), 7.40 ppm (5H, s, C_6H_5). The chemical shifts of the remaining protons were practically the same as those for compounds IIIa and b.

2-(N′-Methylthioureido)-5-methyl-5-ethyl-3-ethoxycarbonyl-4,5-dihydro-7H-thieno[2,3-c]pyran(thiopyran) (IVe and f). A mixture of amine IIIa or b (0.02 mol), methylisothiocyanate (1.46 g, 0.01 mol) and butanol (50 ml) was boiled for 12 h and kept overnight. The precipitated crystals were filtered off, washed with ether and dried. IR spectra of compounds IVe and f: 1680 (C=O), 3300 cm^{-1} (NH). ^{1}H NMR Spectra of thioureides IVe and f ($CDCl_3$): 10.8 (1H, s, NH), 6.90 1H, s, $\underline{NH}$-CH_3), 3.06 ppm (3H, d, J = 5 Hz, $HN-\underline{CH_3}$). The chemical shifts of the remaining protons were practically the same as those for compounds IIIa and b.

3-Substituted-6-methyl-4-oxo-2-thioxo-6-ethyl-5,6-dihydro-8H-pyrano(thiopyrano)[4′,3′:4,5]thieno[2,3-d]pyrimidines (VIa-f). A mixture of a thioureides IVa-f (0.01 mol), potassium hydroxide (1.12 g, 0.02 mol) and 50% aqueous ethanol (50 ml) was boiled for 2 h. After cooling, the mixture was treated with 10% hydrochloric acid until weakly acidic. The precipitated crystals were filtered off, washed with water, dried and recrystallized from butanol. IR spectra of compounds VIa-f: 1690 (C=O), 3400-3200 cm^{-1} (NH). ^{1}H NMR spectrum of compound VIa (pyridine-D_5): 12.1 (1H, s, NH), 4.70 (2H, s, 8-CH_2), 3.06 (2H, s, 5-CH_2), 1.38 (2H, q, J = 7 Hz, 6-$\underline{CH_2}-CH_3$), 1.28 (3H, s, 6-CH_3), 1.05 ppm (3H, t, J = 7 Hz, 6-$CH_2-\underline{CH_3}$). ^{1}H NMR spectrum of compound VIe (pyridine-D_5): 11.5 (1H, s, NH), 4.72 (2H, s, 8-CH_2), 3.46

(3H, s, 3-$NHCH_3$), 3.10 (2H, s, 5-CH_2), 1.40 (2H, q, J = 7 Hz, 6-$\underline{CH_2}$—CH_3), 1.21 (3H, s, 6-CH_3), 1.07 (3H, t, J = 7 Hz, 6-$CH_2-C\underline{H_3}$).

REFERENCES

1. A. Sh. Oganisyan, A. S. Noravyan, and G. M. Avetisyan, Khim. Geterotsikl. Soedin., No. 6, 803 (1998)
2. A. S. Noravyan, A. P. Mkrtchyan, I. A. Dzhagatspanyan, R. A. Akopyan, N. E. Akopyan, and S. A. Vartanyan, Khim.-farm. Zh., No. 9, 38 (1977).
3. A. P. Mkrtchyan, S. G. Kazaryab, A. S. Noravyan, S. A. Vartanyan, I. A. Dzhagatspanyan, N. E. Akopyan, and I. M. Nazaryan, Khim.-farm. Zh., No. 4, 451 (1984).
4. A. P. Mkrtchyan, S. G. Kazaryan, A. S. Noravyan, R. A. Akopyan, I. A. Dzhagatspanyan, N. E. Akopyan, and A. G. Akopyan, Khim.-farm. Zh., No. 5, 557 (1985).
5. I. N. Nazarov, I. V. Torgov, and L. N. Terekhova, Izv. Akad Nauk SSSR, Otd. Khim. Nauk, No. 1, 50 (1943).
6. I. N. Nazarov and A. I. Kuznetsov, Izv. Akad Nauk SSSR, Otd. Khim. Nauk, No. 1, 118 (1948).
7. A. S. Noravyan, A. P. Mkrtchyan, I. A. Dzhagatspanyan, I. M. Nazaryan, N. E. Akopyan, and S. A. Vartanyan, Khim.-farm. Zh., No. 8, 20 (1977).