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SYNTHESIS OF FUSED THIOPYRANS AND PYRIDINES ON THE BASE OF SIX-MEMBERED SATURATED CYCLIC KETONES

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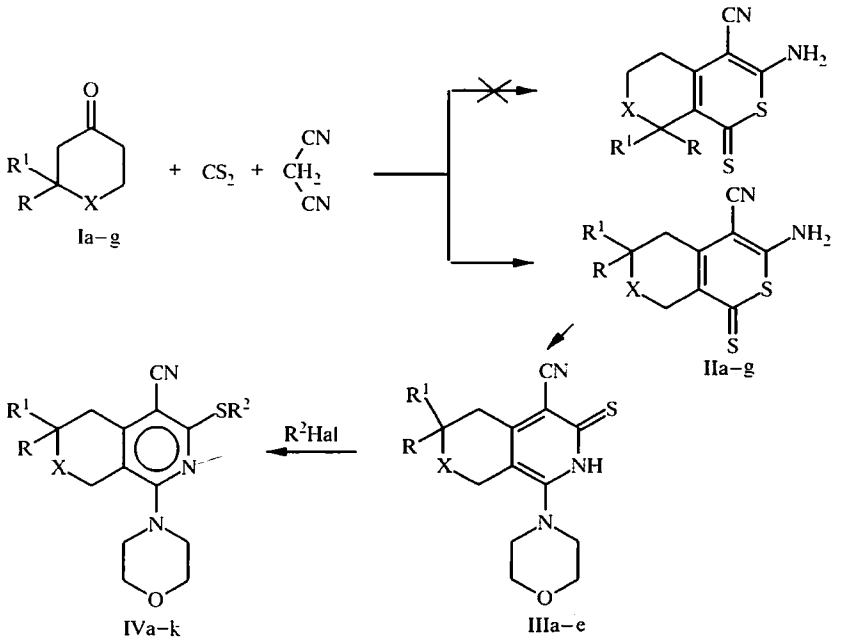
New heterocyclic systems consisting of condensed thiopyrans and several condensed pyridines based on them are synthesized. Opening of the tetrahydropyridine ring in substituted 2,7-naphthyridine is studied.

Compounds containing the thiopyranthione moiety are very reactive. In particular, the thiopyran ring opens and recyclizes when they react with amines [1, 2]. In the present work we synthesize previously unknown heterocyclic systems containing condensed thiopyrans and transform them into condensed pyridine systems.



I, IIa X = O, R = R¹ = Me; b X = O, R = Me, R¹ = C_2H_5; c X = S, R = R¹ = Me; d X = N–Me, R = R¹ = Me; e X = N–$CH_2CH{=}CH_2$, R = R¹ = Me; f X = N–Me, R = R¹ = H; g X = N–$CH_2C_6H_5$, R = R¹ = H.

IIIa X = O, R = R¹ = Me; b X = O, R = Me, R¹ = C_2H_5; c X = S, R = R¹ = Me; d X = N–Me, R = R¹ = Me; e X = CH_2, R = R¹ = H.

IVa X = O, R = R² = Me, R¹ = C_2H_5; b X = O, R = R¹ = Me, R² = C_2H_5; c X = O, R = R¹ = Me, R² = $CH_2C_6H_5$; d X = S, R = R¹ = Me, R² = C_2H_5; e X = S, R = R¹ = Me, R² = $CH_2C_6H_5$; f X = N–Me, R = R¹ = R² = Me; g X = N–Me, R = R¹ = Me, R² = C_2H_5; h X = N–Me, R = R¹ = Me, R² = $CH_2C_6H_5$; i X = CH_2, R = R¹ = H, R² = Me; j X = CH_2, R = R¹ = H, R² = C_2H_5; k X = CH_2, R = R¹ = H, R² = $CH_2C_6H_5$

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TABLE 1. Condensed Thiopyranes IIa-g

Compound	Empirical formula	Found, % / Calculated, %		PMR spectrum (DMSO-d_6), δ, ppm	mp, °C	R_f	Yield, %
		N	S				
IIa	$C_{11}H_{12}N_2OS_2$	11.12 / 11.10	25.50 / 25.41	1.09 (6H, s, $2CH_3$); 2.54 (2H, s, 5-CH_2); 4.42 (2H, s, 8-CH_2); 8.85 (2H, br. s, NH_2)	268-269	0.68	80
IIb	$C_{12}H_{14}N_2OS_2$	10.46 / 10.51	24.11 / 24.07	0.86 (3H, t, J = 7 Hz, $CH_2\underline{CH_3}$); 1.15 (3H, s, CH_3); 1.41 (2H, q, J = 7 Hz, $C\underline{H_2}CH_3$) 2.48 (2H, s, 5-CH_2); 4.41 (2H, s, 8-CH_2); 8.8 (2H, br. s, NH_2)	220-221	0.72	70
IIc	$C_{11}H_{12}N_2S_3$	10.38 / 10.43	35.79 / 35.83	1.31 (6H, s, $2CH_3$); 2.85 (2H, s, 5-CH_2); 3.99 (2H, s, 8-CH_2); 9.0 (2H, br. s, NH_2)	233-234	0.70	53
IId	$C_{12}H_{15}N_3S_2$	15.86 / 15.83	24.13 / 24.16	1.05 (6H, s, $2CH_3$); 2.30 (3H, s, CH_3); 2.80 (2H, s, 5-CH_2); 3.90 (2H, s, 8-CH_2) 6.8 (2H, br. s, NH_2)	204-205	0.59	70
IIe	$C_{14}H_{17}N_3S_2$	14.47 / 14.41	22.04 / 22.00	1.09 (6H, s, $2CH_3$); 2.65 (2H, s, 5-CH_2); 3.2 (2H, d, J = 6 Hz, $CH{=}C\underline{H_2}$); 3.59 (2H, s, 8-CH_2) 4.9-6.01 (3H, m, $CH{=}CH_2$); 7.2 (2H, br. s, NH_2)	189-190	0.64	90
IIf	$C_{10}H_{11}N_3S_2$	17.66 / 17.70	27.09 / 27.01	2.2 (3H, s, CH_3); 2.32-2.69 (4H, m, $2CH_2$); 3.2 (2H, s, 8-CH_2); 6.2 (2H, br. s, NH_2)	201-202	0.53	92
IIg	$C_{16}H_{15}N_3S_2$	13.39 / 13.41	20.48 / 20.46	2.38-2.92 (4H, m, $2CH_2$); 3.53 (2H, s, 8-CH_2); 3.76 (2H, s, $C\underline{H_2}C_6H_5$); 7.42 (5H, s, C_6H_5) 8.8 (2H, br. s, NH_2)	219-220	0.53	29

TABLE 2. Condensed Pyridines IIIb,d and IVa-k

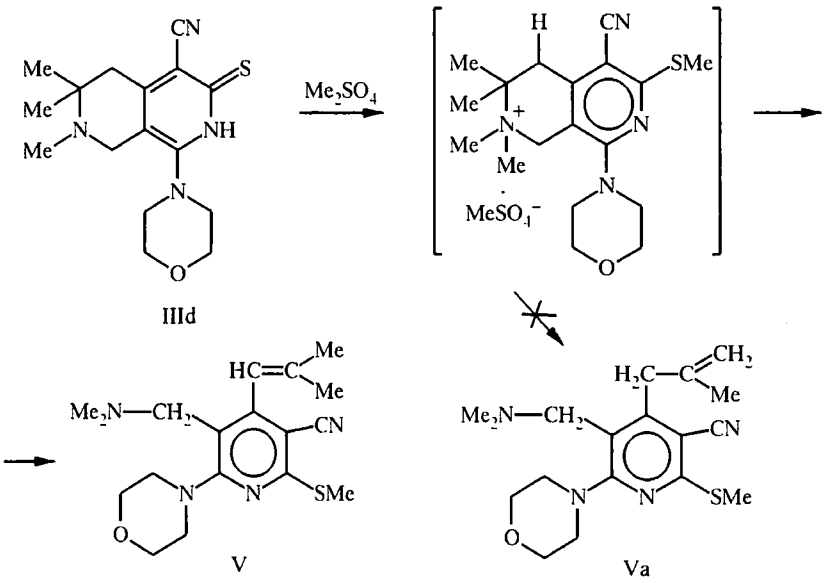
Compound	Empirical formula	Found, % / Calculated, % N	Found, % / Calculated, % S	PMR spectrum (DMSO-d_6), δ, ppm	mp, °C	R_f	Yield, %
IIIb	$C_{16}H_{21}N_3O_2S$	13.09 / 13.15	10.03 / 10.11	0.78-1.1 (6H, m, $2CH_3$); 1.43 (2H, q, J = 7 Hz, $C\underline{H}_2CH_3$); 2.6 (2H, s, 5-CH_2) 3.05-3.37 (4H, m, $2CH_2$); 3.65-3.9 (4H, m, $2CH_2$); 4.45 (2H, s, 8-CH_2); 10.2 (1H, s, NH)	218-220	0.61	59
IIId	$C_{16}H_{22}N_4OS$	17.62 / 17.59	10.09 / 10.07	1.16 (6H, m, $2CH_3$); 2.38 (3H, s, 7-CH_3); 2.68 (2H, s, 5-CH_2); 3.0-3.39 (4H, m, $2CH_2$) 3.44-3.85 (6H, m, $3CH_2$); 10.42 (1H, s, NH)	247-248	0.71	69
IVa	$C_{17}H_{23}N_3O_2S$	12.59 / 12.61	9.65 / 9.61	0.72-1.0 (3H, t, J = 7 Hz, $CH_2C\underline{H}_3$); 1.05 (3H, s, CH_3); 1.48 (2H, q, J = 7 Hz, $C\underline{H}_2CH_3$) 2.48 (3H, s, CH_3); 2.65 (2H, s, 5-CH_2); 3.05-3.38 (4H, m, $2CH_2$); 3.58-3.9 (4H, m, $2CH_2$) 4.4 (2H, s, 8-CH_2)	88-90	0.62	79
IVb	$C_{17}H_{23}N_3O_2S$	12.63 / 12.61	9.57 / 9.61	1.18-1.6 (9H, m, $3CH_3$); 2.73 (2H, s, 5-CH_2); 3.0-3.43 (6H, m, $3CH_2$) 3.62-3.89 (4H, m, $2CH_2$); 4.51 (2H, s, 8-CH_2)	120-121	0.62	69
IVc	$C_{22}H_{25}N_3O_2S$	10.67 / 10.62	8.13 / 8.11	1.23 (6H, s, $2CH_3$); 2.69 (2H, s, 5-CH_2); 3.08-3.27 (4H, m, $2CH_2$); 3.59-3.8 (4H, m, $2CH_2$) 4.42 (2H, s, $C\underline{H}_2C_6H_5$); 4.52 (2H, s, 8-CH_2); 7.71-7.38 (5H, m, C_6H_5)	126-127	0.57	73
IVd	$C_{17}H_{23}N_3OS_2$	11.96 / 12.02	18.37 / 18.34	1.22-1.58 (9H, m, $3CH_3$); 2.91 (2H, s, 5-CH_2); 3.05-3.42 (6H, m, $3CH_2$); 3.61 (2H, s, 8-CH_2) 3.71-3.96 (4H, m, $2CH_2$)	143-144	0.74	67
IVe	$C_{22}H_{25}N_3OS_2$	11.10 / 11.07	15.32 / 15.44	1.35 (6H, s, $2CH_3$); 2.85 (2H, s, 5-CH_2); 3.06-3.37 (4H, m, $2CH_2$); 3.6 (2H, s, 8-CH_2) 3.65-3.89 (4H, m, $2CH_2$); 4.43 (2H, s, $C\underline{H}_2C_6H_5$); 7.11-7.42 (5H, m, C_6H_5)	114-115	0.62	75
IVf	$C_{17}H_{24}N_4OS$	16.79 / 16.85	9.58 / 9.64	1.15 (6H, s, $2CH_3$); 2.35 (3H, s, CH_3); 2.56 (3H, s, CH_3); 2.72 (2H, s, 5-CH_2) 3.15-3.4 (4H, m, $2CH_2$); 3.5 (2H, s, 8-CH_2); 3.7-3.96 (4H, m, $2CH_2$)	147-148	0.64	72
IVg	$C_{18}H_{26}N_4OS$	16.21 / 16.17	9.31 / 9.35	1.13 (6H, s, $2CH_3$); 1.31 (3H, t, J = 7 Hz, $CH_2C\underline{H}_3$); 2.29 (3H, s, CH_3); 2.62 (2H, s, 5-CH_2) 3.0-3.51 (8H, m, $4CH_2$); 3.61-3.95 (4H, m, $2CH_2$)	123-124	0.71	87
IVh	$C_{23}H_{28}N_4OS$	13.69 / 13.71	7.87 / 7.84	1.09 (6H, s, $2CH_3$); 2.28 (3H, s, CH_3); 2.67 (2H, s, 5-CH_2); 3.1-3.39 (4H, m, $2CH_2$) 3.43 (2H, s, 8-CH_2); 3.63-3.87 (4H, m, $2CH_2$); 4.4 (2H s, $C\underline{H}_2C_6H_5$); 7.1-7.38 (5H, m, C_6H_5)	154-155	0.61	74
IVi	$C_{15}H_{19}N_3OS$	14.54 / 14.52	11.10 / 11.07	1.48-1.9 (4H, m, $2CH_2$); 2.3-2.55 (5H, m, CH_2CH_3); 2.6-2.91 (2H, m, 7-CH_2) 3.21-3.5 (4H, $2CH_2$); 3.62-3.95 (4H, m, $2CH_2$)	172-173	0.59	75
IVj	$C_{16}H_{21}N_3OS$	13.87 / 13.84	10.53 / 10.56	1.4 (3H, t, J = 7 Hz, $CH_2C\underline{H}_3$); 1.6-1.91 (4H, m, $2CH_2$); 2.39-2.61 (2H, m, 6-CH_2) 2.63-3.0 (2H, m, 7-CH_2); 3.12-3.4 (6H, m, $3CH_2$); 3.63-3.96 (4H, m, $2CH_2$)	122-123	0.58	68
IVk	$C_{21}H_{23}N_3OS$	11.16 / 11.19	8.49 / 8.53	1.49-1.83 (4H, m, $2CH_2$); 2.31-2.58 (2H, m, 6-CH_2); 2.62-2.9 (2H, m, 7-CH_2); 3.11-3.37 (4H, m, $2CH_2$); 3.58-3.8 (4H, m, $2CH_2$); 4.4 (2H, s, $C\underline{H}_2C_6H_5$); 7.08-7.4 (5H, m, C_6H_5)	113-115	0.59	71

Convenient starting materials for synthesis the former are the heterocyclic ketones Ia-g [3, 4]. The condensed thiopyranthiones IIa-g are synthesized from these in high yields *via* a one-step condensation with malonodinitrile and CS_2 in the presence of triethylamine. The thiopyranthiones II are produced regiospecifically owing to the presence in the starting ketones of two methyl groups on $C_{(2)}$, which hinder attack at $C_{(3)}$.

The thiopyranthione moiety of II reacts with morpholine in a rearrangement similar to the one described in the literature [5]. This produces the condensed pyridines III.

Alkylation of pyridines III by alkyl halides, as expected, occurs in alkaline medium also regiospecifically [6] to give exclusively alkylthiopyridines IVa-k.

Previously it was shown that methylation of 3-thioxopyridines IIIa,c with dimethylsulfate occurs analogously to methylation with methyl iodide to give thiomethyl derivatives [5]. The reaction of naphthyridine IIId with dimethylsulfate in alkaline medium proceeds exhaustively on the nitrogen atom of the tetrahydropyridine ring. This breaks the N–$C_{(6)}$ bond, releasing the proton on $C_{(5)}$ and producing 4-isobutenylpyridine V according to the scheme:



The destruction of onium salts usually proceeds *via* the Hoffman decomposition if the resulting olefin is not conjugated [7]. In our instance the PMR spectra clearly indicate that only 4-isobutenylpyridine V forms (a styrene analog). The signal of the vinyl proton in the PMR spectrum of V appears as a multiplet near 6.25 ppm whereas the signals of the methyl groups on the vinyl carbon atom affected by the neighboring pyridine ring appear as two doublets at 1.6 and 1.95 ppm (J = 1.2 Hz).

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument in vaseline oil. PMR spectra were measured on a Varian T-60 instrument with TMS internal standard. Mass spectra were obtained on a MX-1303 mass spectrometer using direct-probe sample introduction. The purity of the compounds was monitored using TLC on Silufol UV-254 plates with butanol–acetic acid–water (4:2:5) (IIa,b and IIIb), $CHCl_3$–ether (1:3) (IIc-g, IIId, and IVb), pyridine–ethanol (1:4) (IVa,f,g), ether–heptane (2:1) (IVc,e), and ethanol–$CHCl_3$ (3:1) (IVd,h-k).

Preparation of Substituted Tetrahydropyrano(thiopyrano or pyrido)[3,4-*c*]thiopyranes (IIa-g). A mixture of ketone Ia-g (0.1 mol), CS_2 (12 ml), and methanol (12 ml) is treated with stirring in portions with malonodinitrile (6.6 g, 0.1 mole). Then triethylamine (5 ml) is added to the mixture with stirring. The mixture is held at room temperature (20°C) for 48 h. The crystals formed are filtered off, washed with methanol, dried, and recrystallized from propanol (Table 1). IR spectrum: 3100-3500 (NH_2), 2210-2220 (CN), 1630-1650 (NH def.),

1580-1600 (C=C ar.), 1090-1120 cm^{-1} (C=S). Mass spectra, *m/z* (I_{rel}, %): (compound IIa) M^+ 252 (100), 237 (54), 234 (98), 219 (95), 191 (90); (compound IId) M^+ 265 (72), 250 (14), 232 (100), 217 (21), 205 (16), 199 (31), 174 (26).

Substituted Tetrahydropyrano(thiopyrano)[3,4-*c*]pyridin- and 2,7-Naphthyrindinethiones (IIIa,c,e) were prepared according to the literature [1, 5]. Compounds IIIb,d were prepared analogously (Table 2). IR spectrum: IIIb 3550-3630 (NH), 2225 (CN), 1580-1600 ($C=C_{ar}$), 1120-1160 cm^{-1} (C=S). Mass spectrum, *m/z* (I_{rel}, %): (compound IIId) M^+ 318 (46), 303 (100), 289 (4), 274 (17), 260 (23), 245 (14), 231 (12), 216 (14).

Preparation of Substituted Tetrahydropyrano(thiopyrano)[3,4-*c*]pyridines, -2,7-naphthyridines, and -isoquinolines (IVa-k). A solution of sodium ethoxide prepared from sodium (0.23 g, 0.01 mol) and absolute ethanol (50 ml) is treated with IIIa-e (0.01 mol). The corresponding alkyl halide (0.01 mol) is added dropwise after the solids dissolve. The mixture is stirred at 60°C for 2 h. Water (100 ml) is added to the cooled mixture. The crystals formed are filtered off, washed with water, dried, and recrystallized from ethanol (Table 2). IR spectrum: 2220 (CN), 1580-1600 cm^{-1} ($C=C_{ar}$).

5-Dimethylaminomethyl-2-methylthio-6-morpholino-4-isobutenylpyridin-3-carbonitrile (V). Compound IIId (0.64 g, 0.002 mol) is dissolved in aqueous KOH (20%, 10 ml). Dimethylsulfate (2 ml) is added dropwise to the stirred solution. The mixture is heated on a water bath at 60°C for 30 min. The crystals formed after cooling are filtered off, washed with water, and dried. Yield of V 0.5 g (71%); mp 125-126°C (ethanol). R_f 0.61 (ethanol–$CHCl_3$–ether, 1:1:1). IR spectrum: 2230 (CN), 1610 cm^{-1} (C=C). Mass spectrum, *m/z* (I_{rel}, %), M^+ 346 (25), 331 (5), 302 (47), 301 (65), 287 (21), 286 (100), 256 (22). PMR spectrum: 1.6 (3H, d, J = 1.2 Hz, CH_3); 1.95 (3H, d, J = 1.2 Hz, CH_3); 2.17 [6H, s, $N(CH_3)_2$]; 2.6 (3H, s, SCH_3); 3.31 [2H, s, $CH_2N(CH_3)_2$]; 3.42-3.98 (8H, m, $4CH_2$); 6.25 (1H, m, CH). Found, %: C 62.44; H 7.51; N 16.16; S 9.28. $C_{18}H_{26}N_4OS$. Calculated, %: C 62.39; H 7.56; N 16.17; S 9.25.

REFERENCES

1. K. Gewald, M. Buchwalder, and M. Peukert, *J. Prakt. Chem.*, **315**, 679 (1973).
2. S. Leistner, G. Wagner, and E. Iffland, *Z. Chem.*, **12**, 289 (1972).
3. *Syntheses of Heterocyclic Compounds* [in Russian], Erevan (1969), No. 8, p. 30.
4. S. A. Vartanyan, A. S. Noravyan, and V. N. Zhamagortsyan, *Izv. Akad. Nauk Arm. SSR*, No. 18, 124 (1965).
5. E. G. Paronikyan, G. V. Mirzoyan, A. S. Noravyan, D. A. Avakimyan, and Yu. Z. Ter-Zakharyan, *Khim.-Farm. Zh.*, No. 11, 29 (1993).
6. A. F. Pozharskii, *Theoretical Principles of Heterocyclic Chemistry* [in Russian], Khimiya, Moscow (1985), p. 159.
7. J. March, *Organic Chemistry* [Russian translation], Vol. 4, (1988), p. 51.