Chemistry of Heterocyclic Compounds, Vol. 33, No. 6, 1997

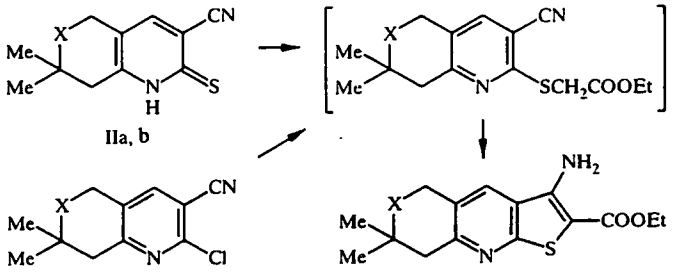
SYNTHESIS OF NEW CONDENSED THIENO[2,3-*b*]PYRIDINES CONTAINING PYRIMIDINE AND IMIDAZOLE RINGS

V. V. Dabaeva, A. S. Noravyan, V. N. Madakyan, and B. D. Enokyan

Two different convenient methods have been developed for the synthesis of condensed thieno[2,3-b]pyridines. The intramolecular cyclization of 3-amino-2-hydrazinocarbonyl-7,7-dimethyl-7,8-dihydo-5H-pyrano[3,4-e]-thieno[2,3-b]pyridine was carried out to give 7,7-dimethyl-2-oxo-1,2,6,7-tetrahydro-9H-pyrano[3',4'-e]-imidazo[4",5":2,3]thieno[5,4-b]pyridine, which is the first representative of a new heterocyclic system.

In a continuation of our study of thieno[2,3-*b*]pyridines, which hold interest as potential biologically active compounds [1] and intermediates for the synthesis of such compounds, we have synthesized new condensed heterocyclic systems containing pyrimidine and imidazole rings.

Two methods were developed for the synthesis of thieno[2,3-*b*]pyridines fused with dihydropyran, dihydrothiopyran, and tetrahydropyridine rings (Ia-Ic). The essence of the first method consists in the alkylation of condensed 3-cyano-2-pyridinethiones IIa and IIb at the sulfur atom [2]. Esters of chloroacetic acid were used as the alkylating reagent for the preparation of a compound with an active functional group. The alkylation products readily undergo Thorpe–Ziegler cyclization in the presence of excess alkali to give 3-amino-7,7-dimethyl-2-ethoxycarbonyl-7,8-dihydro-5H-pyrano- (Ia) or 3-amino-7,7-dimethyl-2-ethoxycarbonyl-7,8-dihydro-5H-thiopyrano[3,4-*e*]thieno[2,3-*b*]pyridines (Ib). The use of an ester of thioglycolic acid permitted us to obtain Ia, Ib, and 3-amino-7,7,8-trimethyl-2-ethoxycarbonyl-5,6,7,8-tetrahydro-thieno[2,3-*b*]-1,6-naphthyridine (Ic) directly from 2-chloro-3-cyano derivatives of the corresponding condensed pyridines IIIa-IIIc [3]. Thus, the cyanothione preparation step is shortened. In both cases, the cyclization proceeded smoothly with 70-75% yield.

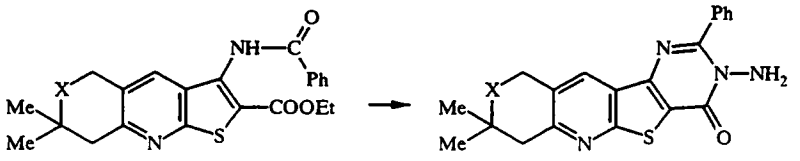


I—III a X = O, b X = S, c X = NMe

A study of the reactivity of the ester group of condensed thieno[2,3-*b*]pyridines showed that this group is rather active, while reactions involving the 3-amino group are hindered. Thus, an attempt to acylate the amino group succeeded only using benzoyl chloride. Heating products 3-benzoylamino-7,7-dimethyl-2-ethoxycarbonyl-7,8-dihydro-5H-pyrano-[3,4-*e*]-thieno-2,3-*b*]pyridine (IVa) and its 5H-thiopyrano analog (IVb) and 3-benzoylamino-7,7,8-tri-methyl-2-ethoxycarbonyl-5,6,7,8-tetrahydrothieno[2,3-*b*]-1,6-naphthyridine (IVc) with hydrazine hydrate at reflux in ethanol led to intramolecular cyclization and formation of the amino derivative of the corresponding condensed pyrimidines (Va-Vc).

A. D. Mndzhoyan Institute of Fine Organic Chemistry, Academy of Sciences of the Republic of Armenia, 375014 Yerevan. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 847-850, June, 1997. Original article submitted October 11, 1996.

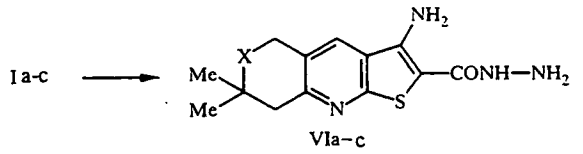
0009-3122/97/3306-0741$18.00



IV a-c V a-c

IV, V a X = O, b X = S, c X = NMe

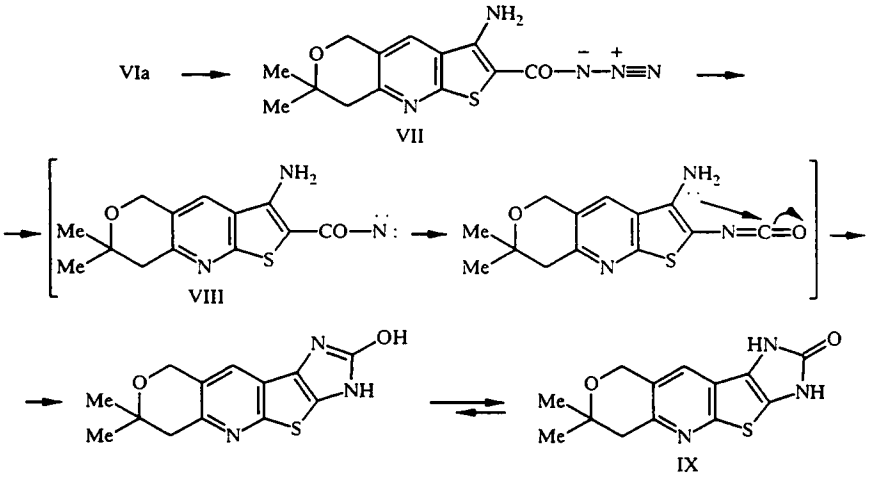
The ester group of Ia-Ic readily undergoes hydrazinolysis upon heating with concentrated hydrazine hydrate at 130°C to give the corresponding hydrazines VIa-VIc.



VIa-c

VI a X = O, a X = S, c X = NMe

Aminohydrazine VIa upon treatment with aqueous sodium nitrite in the presence of 10% acetic acid is converted to the acid azide VII, which undergoes the Curtius rearrangement upon heating in *m*-xylene to give the corresponding isocyanate. Intramolecular reaction of the isocyanate group with the amino group in this product gives a representative of a new heterocyclic system, namely, 7,7-dimethyl-2-oxo-1,2,6,7-tetrahydro-9H-pyrano[3′,4′-*e*]-imidazo[4″,5″:2,3]-thieno-[5,4-*b*]pyridine (IX).



VII

VIII

IX

The PMR spectrum of imidazothienopyridine IX has broad signals for the amide NH groups at 11.21-10.18 ppm, while its IR spectrum has a carbonyl group band at 1680 cm^{-1}, which is unequivocal evidence for the existence of IX as a lactam.

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrometer for Vaseline mulls, while the PMR spectra were taken on a Varian T-60 spectrometer. The mass spectra were taken on an MKh-1303 mass spectrometer with 70 eV ionizing voltage. The reaction course and purity of the products were monitored by thin-layer chromatography on plates coated with Brockmann Grade-III alumina with 3:1 ethyl acetate–hexane (a), 5:1 pyridine–butanol (b), 1:1 ethyl acetate–hexane (c), 1:3 pyridine–butanol, and 2:1 ethyl acetate–hexane (d) as the eluents. The plates were developed with iodine vapor.

The physical indices of I and IV-VI are given in Table 1.

3-Amino-7,7-dimethyl-2-diethoxycarbonyl-7,8-dihydro-5H-pyrano- (Ia) and 3-amino-7,7-dimethyl-2-diethoxy-carbonyl-7,8-dihydro-5H-thiopyrano[3,4-*e*]thieno[2,3-*b*]pyridines (Ib). A mixture of 1.2 ml ethyl thioglycolate and 0.01

TABLE 1. Physical Indices of Products Ia-Ic, IVa-IVc, Va-Vc, and VIa-VIc

Compound	Chemical formula	Found, % / Calculated, %		mp,* °C	R_f	Yield, %
		N	S			
Ia	$C_{15}H_{18}N_2O_3S$	9.0 9,1	10.3 10,5	187...188	0,66 (a)	71,0
Ib	$C_{15}H_{18}N_2O_2S_2$	8.9 8,7	19.8 19,9	238...238	0,70 (a)	78,7
Ic	$C_{16}H_{21}N_3O_2S$	13.0 13,2	19.9 20,0	214...215	0,51 (b)	68,8
IVa	$C_{22}H_{22}N_2O_4S$	6.7 6,8	7.4 7,8	187...189	0,68 (c)	73,2
IVb	$C_{22}H_{22}N_2O_3S$	6.0 6,4	14.8 15.0	175...176	—	79,7
IVc	$C_{23}H_{25}N_3O_3S$	9.9 9,6	7.6 8,0	168...169	—	57,1
Va	$C_{20}H_{18}N_4O_2S$	14.5 14,8	8.0 8,5	271...273	0,71 (d)	55,7
Vb	$C_{20}H_{18}N_4OS_2$	14.6 14,2	15.9 16,3	260...261	—	74,4
Vc	$C_{21}H_{21}N_5OS$	17.8 17,9	7.9 8,2	260...261	—	60,0
VIa	$C_{13}H_{16}N_4O_2S$	19.4 19,2	11.2 11,0	286...287	0,72 (d)	75,9
VIb	$C_{13}H_{16}N_4OS_2$	17.9 18,2	20.6 20,8	296...297	0,51 (e)	80,7
VIIc	$C_{14}H_{19}N_5OS$	22.7 22,9	10.3 10.5	270...271	—	64,7

*Recrystallization solvents: aqueous ethanol for Ia-Ic and Va-Vc and 5:1 hexane–ethyl acetate for IVa-IVc and VIa-VIc.

mole 7,7-dimethyl-2-chloro-3-cyano-7,8-dihydro-5H-pyrano- (IIa) or 7,7-dimethyl-2-chloro-3-cyano-7,8-dihydro-5H-thiopyrano[4,3-*b*]pyridine (IIb) was added dropwise with stirring to sodium ethylate obtained from 0.23 g (0.01 mole) metallic sodium and 25 ml absolute ethanol. The reaction mixture was heated at reflux with stirring for 6 h. The solvent was distilled off and water was added. The crystalline precipitate was filtered off, washed with water and ethanol, and dried to give Ia or Ib. PMR spectrum of Ia in $CDCl_3$: 7.52 (1H, s, 4-CH), 5.83 (2H, s, NH_2), 4.80 (2H, s, 5-CH_2), 4.28 (2H, q, J = 7 Hz, O–$C\underline{H}_2$–CH_3), 2.92 (2H, s, 8-CH_2), 1.42-1.20 ppm (9H, m, O–CH_2–$C\underline{H}_3$, 7-$(CH_3)_2$). PMR spectrum for Ib in C_5D_5N: 7.95 (1H, s, 4-CH), 4.85 (2H, s, NH_2), 4.22 (2H, q, J = 7 Hz, O–$C\underline{H}_2$–CH_3), 3.78 (2H, s, 5-CH_2), 3.15 (2H, s, 8-CH_2), 1.34-1.0 ppm (9H, m, 7-$(CH_3)_2$, O–CH_2–$C\underline{H}_3$). IR spectrum of Ia and Ib: 1540, 1580 (arom), 1680 (C=O), 3180, 3280, 3410 cm^{-1} (NH_2).

General Procedure for the Preparation of Ia-Ic. A sample of 10 ml 10% aq. sodium hydroxide was added with stirring to a mixture of 0.01 mole IIIa-IIIc in 20 ml dimethylformamide. Then, 1.8 g (0.015 mole) ethyl chloroacetate was added dropwise. Stirring was continued at room temperature for 1 h. After adding 20 ml water, the crystalline precipitate was filtered off, washed with water and ethanol, and dried to give Ia-Ic. PMR spectrum of Ic in $CDCl_3$: 7.47 (1H, s, 4-CH), 5.89-5.72 (2H, br.s, NH_2), 4.22 (2H, q, J = 7 Hz, O-$C\underline{H}_2$-CH_3), 3.69 (2H, s, 5-CH_2), 2.81 (2H, s, 8-CH_2), 2.25 (3H, s, N–CH_3), 1.25 (3H, t, J = 7 Hz, O–CH_2–$C\underline{H}_3$), 1.05 ppm (6H, s, 7-$(CH_3)_2$). IR spectrum: 1570, 1600, 1620 (arom), 1665 (C=O), 3160, 3260, 3400 cm^{-1} (NH_2).

3-Benzoylamino-7,7-dimethyl-2-ethoxycarbonyl-7,8-dihydro-5H-pyrano- (IVa), 3-Benzoylamino-7,7-dimethyl-2-ethoxycarbonyl-7,8-dihydro-5H-thiopyrano[2,3-*b*]pyridines (IVb), and 3-Benzoylamino-6,7,7-trimethyl-2-ethoxycarbonyl-5,6,7,8-tetrahydrothieno[2,3-*b*]naphthyridine (IVc). A mixture of 0.01 mole Ia-Ic, 2.1 g (0.015 mole) benzoyl chloride, and 5 ml dry triethylamine in 50 ml absolute benzene was heated at reflux with stirring for 6 h. Benzene was distilled off and water was added. The crystalline precipitate was filtered off, washed with water and ethanol, and dried to give IVa-IVc. PMR spectrum of IVa in C_5D_5N: 8.48-7.72 (7H, m, C_6H_5, NH, 4-CH), 4.89 (2H, s, 5-CH_2), 4.31 (2H, q, J = 6 Hz, OCH_2), 3.05 (2H, s, 8-CH_2), 1.33-1.05 ppm (9H, m, CH_2–$C\underline{H}_3$, 7-$(CH_3)_2$). PMR spectrum of IVb in $CDCl_3$: 10.75 (1H, s, NH), 8.41 (1H,s, 4-CH), 8.10-7.38 (5H, m, C_6H_5), 4.38 (2H, q, J = 7 Hz, OCH_2) 3.93 (2H, s, 5-CH_2), 3.18 (2H, s, 8-CH_2), 1.58-1.23 ppm (9H, m, O–CH_2–$C\underline{H}_3$, 7-$(CH_3)_2$). PMR spectrum of IVc in $CDCl_3$: 10.71 (1H, s,

NH), 8.24 (1H, s, 4-CH_2), 7.89-7.39 (5H, m, C_6H_5), 4.22 (2H, q, J = 6 Hz, O−CH_2), 3.77 (2H, s, 5-CH_2), 2.93 (2H, s, 8-CH_2), 2.36 (3H, s, N−CH_3), 1.42-1.00 ppm (9H, m, O−CH_2−CH_3, 7-$(CH_3)_2$). IR spectrum of IVa-IVc: 1550, 1580 (arom), 1680 (C=O, amide), 1710 (C=O, ester), 3250 cm^{-1} (NH).

Tetrahydro-10H-pyrano- (Va) and Tetrahydro-10H-thiopyrano[3′,4′:5,6]pyrido[3,2:″,5″]thieno[3″,2″-*d*]pyrimidines (Vb) and Hexahydropyrimido[2,3:3′,2′]thieno[5′,4′-*b*]naphthyridine (Vc). A mixture of 0.01 mole IVa-IVc , 10 ml concentrated hydrazine hydrate, and 30 ml absolute ethanol was heated at reflux for 12 h. After cooling, the crystalline precipitate was filtered off, washed with water, and dried to give Va-Vc. PMR spectrum of Va in C_5D_5N: 8.27-7.11 (8H, m, 11-CH, $NH_2C_6H_5$), 4.68 (2H, s, 10-CH_2), 2.91 (2H, s, 7-CH_2), 1.15 ppm (6H, s, 8-$(CH_3)_2$).

General Procedure for the Preparation of VIa-VIc. A mixture of 0.01 mole Ia-Ic in 25 ml concentrated hydrazine hydrate was heated at 130°C for 6 h. Excess hydrazine hydrate was distilled off and 15 ml ethanol was added to the residue. The crystalline precipitate was filtered off, washed with water and ether, and dried to give VIa-VIc. PMR spectrum of VIa in DMSO: 8.04 (1H, s, 4-CH), 6.94 (2H, s, NH_2), 4.68 (2H, s, 5-CH_2), 3.61-4.09 (3H, br.s, NH−NH_2), 2.77 (2H, s, 8-CH_2), 1.16 ppm (6H, s, 7-$(CH_3)_2$). PMR spectrum of VIb in DMSO: 8.51 (1H, s, 4-CH), 7.31 (2H, s, NH_2), 4.26 (2H, s, 5-CH_2), 4.05-3.72 (3H, br.s, NH−NH_2), 3.31 (2H, s, 8-CH_2), 1.46 ppm (6H, s, 7-$(CH_3)_2$). IR spectrum of VIa-VIc: 1660 (C=O), 3180, 3310, 3420 cm^{-1} (NH−NH_2).

3-Amino-2-azidocarbonyl-7,7-dimethyl-7,8-dihydro-5H-pyrano[3,4-*e*]thieno[2,3-*b*]pyridine (VII). A sample of 0.7 g (0.01 mole) sodium nitrite dissolved in 10 ml water was added dropwise to a solution of 2.4 g (0.01 mole) VIa in 60 ml 40% aq. acetic acid at 0°C. The mixture was stirred for 0.5 h at 10°C. The crystalline precipitate was filtered off, washed with water, and dried to give 2.1 g (67.7%) VII, mp 170-171°C, R_f 0.73 (1:3 pyridine−butanol). Found: N, 22.9; S, 10.2%. Calculated for $C_{13}H_{13}N_5O_2S$: N, 23.1; S, 10.6%. PMR spectrum in DMSO: 8.26 (1H, s, 4-CH), 7.82 (2H, s, NH_2), 4.84 (2H, s, 5-CH_2), 2.82 (2H, s, 8-CH_2), 1.36 ppm (6H, s, 7-$(CH_3)_2$). IR spectrum: 1580, 1600 (arom), 1650 (C=O), 2130 ($N^-−N^+≡N$), 3200, 3300, 3400 cm^{-1} (NH_2).

7,7-Dimethyl-2-oxo-1,2,6,7-tetrahydro-9H-pyrano[3′,4′-*e*]imidazo[4″,5″:2,3]thieno[5,4-*b*]pyridine (IX). A solution of 3.0 g (0.01 mole) VII in 20 ml *m*-xylene was heated on a water bath at 90°C for 0.5 h. The mixture was then heated at reflux at 140°C for 10 min. The crystalline precipitate was filtered off, washed with ether, and dried to give 2.2 g (80%) IX, mp 313-314°C. Found: N, 15.3; S, 11.4%. Calculated for $C_{13}H_{13}N_3O_2S$: N, 15.3; S, 11.6%. PMR spectrum in DMSO: 11.21-10.18 (2H, br.s, 1-NH, 3-NH), 7.51 (1H, s, 10-CH), 4.75 (2H, s, 9-CH_2), 2.74 (2H, s, 6-CH_2), 1.18 ppm (6H, s, 7-$(CH_3)_2$). IR spectrum: 1680 (C=O), 3450 cm^{-1} (NH).

REFERENCES

1. M. Negwer, Organische Chemische Arzneimettel und Synonyma, Vol. 1, Berlin (1978), p. 606; Vol. 2, Berlin (1978), p. 1215.
2. S. G. Pilosyan, V. V. Dabaev, and A. S. Noravyan, Arm. Khim. Zh., **44**, 479 (1991).
3. S. G. Pilosyan, V. V. Dabaev, B. D. Enokyan, É. A. Abgaryan, and A. S. Noravyan, Arm. Khim. Zh., **41**, 687 (1988).