Chemistry of Heterocyclic Compounds, Vol. 31, No. 2, 1995

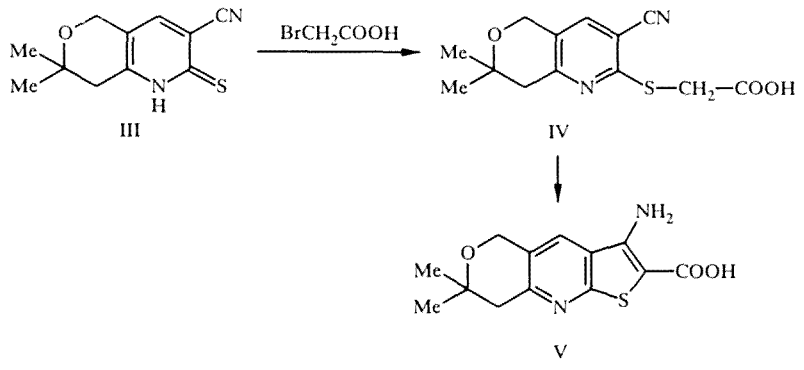
SYNTHESIS OF DIHYDRO-10H-PYRANO[3′,4′: 5,6]PYRIDO[3,2:4″,5″]-THIENO[3″,2″-d][3,1]OXAZINES AND PYRIMIDINES

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

Convenient methods have been developed for synthesizing dihydro-10H-pyrano[3′,4′:5,6]-pyrido-[3,2:4″,5″]thieno[3″,2″-d][3,1]-oxazines and -pyrimidines. Optimum conditions have been established for the chlorodeoxygenation of condensed thieno-pyrimidin-4-ones.

The synthesis of new condensed heterocyclic systems containing pyrimidine and oxazine rings has been effected with the aim of searching for biologically active compounds in the thieno[3,2-b]pyridine series. Some representatives are already used widely in medicine as effective drugs (ticlopidine, tinoridine [1]).

The 3-cyano-2-thio derivative (III) was used as starting material for the synthesis of thieno[2,3-b]pyridines condensed with a tetrahydropyran ring (Ia-c) and (IIa-c) since it is readily alkylated by bromoacetic acid. The resulting acid (IV) cyclizes in the presence of sodium alcoholate to 3-amino-7,7-dimethyl-7,8-dihydro-5H-pyrano[3,4-e]thieno[2,3-b]pyridine-2-carboxylic acid (V) in accordance with the rules of the Torp–Ziegler reaction.



The 2-methyl, ethyl, and phenyl substituted derivatives of oxazines (Ia-c) were synthesized by reacting the obtained aminoacid (V) with acetic, propionic, and benzoic anhydrides. The ease of replacing the endocyclic oxygen atom in the latter by a hydrazine residue is worthy of note. Fission of the lactone ring occurs on boiling the thieno-oxazines (Ia-c) with hydrazine hydrate in ethanol, with subsequent cyclization into 2-substituted 3-amino-4-oxo-3,4,7,8-tetrahydro-10H-pyrano-[3′,4′:5,6]pyrido[3,2:4″,5″]-thieno[3″,2″-d]pyrimidines (IIa-c).

Similarly the derivatives (VIa-c) are formed on reacting the condensed oxazines (Ia-c) with 25% ammonia solution. These same compounds are obtained by an alternate synthesis by heating the 3-aminopyrimidine derivatives with sodium nitrite in the presence of acetic acid.

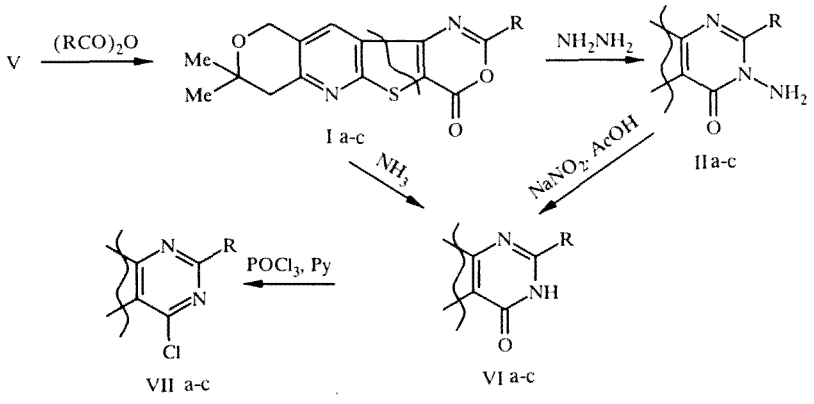
A. L. Mndzhoyan Institute of Fine Organic Chemistry, Armenian Academy of Sciences, Yerevan 375014. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 250-253, February, 1995. Original article submitted November 15, 1994.

0009-?122/95/3102-0219$12.50

TABLE 1. Characteristics of Compounds (Ia-c), (IIa-c), (IV), (V), (VIa-c) and (VIIa-c)

Compound	Empirical formula	mp, °C	R_f*	Yield, % (method)
I a	$C_{15}H_{14}N_2O_3S$	242...244	0,78	73,3
I b	$C_{16}H_{16}N_2O_3S$	197...198	0,56	59,4
I c	$C_{20}H_{16}N_2O_3S$	207...208	0,77	60,7
II a	$C_{15}H_{16}N_4O_2S$	181...182	0,51	46,7
II b	$C_{16}H_{18}N_4O_2S$	201...202	—	63,6
II c	$C_{20}H_{18}N_4O_2S$	271...273	0,71	55,7
IV	$C_{13}H_{14}N_2O_3S$	225...227	0,52	80,0
V	$C_{13}H_{14}N_2O_3S$	204...206	0,56	85,0
VI a	$C_{15}H_5N_3O_2S$	> 300 (decomp.)	—	56,7 (A), 53,6 (B)
VI b	$C_{16}H_{17}N_3O_2S$	> 300 (decomp.)	—	57,1 (A), 52,3 (B)
VI c	$C_{20}H_{17}N_3O_2S$	> 300 (decomp.)	—	63,7 (A), 51,3 (B)
VII a	$C_{15}H_{14}ClN_3OS$	200...202	0,71	87,5
VII b	$C_{16}H_{16}ClN_3OS$	186...187	0,72	90,9
VII c	$C_{20}H_{16}ClN_3OS$	294...295	—	84,2

*In the system pyridine–butanol, 1:3; (Ia) ethyl acetate–hexane, 3:1; (VIIa) ethyl acetate–hexane, 2:1; (IV) pyridine–butanol, 1:1.



I, II, VI, VII a R = CH_3, b R = C_2H_5, c R = C_6H_5

Study of the chlorodeoxygenation reaction of condensed pyrimidin-4-ones has shown that the reaction goes smoothly under the action of phosphorus oxychloride in the presence of pyridine.

EXPERIMENTAL

The IR spectra were taken on a UR-20 instrument in Nujol mulls, PMR spectra were obtained on a Varian T-60 instrument, and mass spectra were taken on a MX-1303 instrument at an ionizing potential of 70 eV. Thin layer chromatography was carried out on Silufol 254 plates, visualizing with iodine vapor.

The data of elemental analysis of compounds (I), (II), and (IV)-(VII) corresponded to calculated values.

The characteristics of compounds (I), (II), and (IV)-(VII) are given in Table 1.

3-Cyano-7,7-dimethyl-7,8-dihydro-5H-pyrano[4,3-b]-2-pyridylthioacetic Acid (IV). A 10% solution (5.6 ml) of KOH in water was added to a mixture of the thione (III) (2.2 g: 0.01 mole) in DMF (20 ml). Monobromoacetic acid (1.4 g: 0.01 mole) was added with vigorous stirring to the solution obtained. The reaction mixture was stirred at room temperature for 2-3 h, the 10% acetic acid solution (15 ml) was poured in. The precipitated solid was filtered off, washed with water and with alcohol, and dried. The yield of compound (III) was 2.2 g. PMR spectrum (DMSO): 7.90 (1H, s, −CH); 4.38-4.17 (4H, m, 5-CH_2, S−CH_2); 2.50 (2H, t, 8-CH_2); 1.20 ppm [6H, s, 7-$(CH_3)_2$]. IR spectrum: 1570, 1620 (C=C, conj.), 1710 (C=O), 2220 (C=N), 3580 cm^{-1} (OH).

3-Amino-7,7-dimethyl-7,8-dihydro-5H-pyrano[3,4-e]thieno[2,3-b]pyridine-2-carboxylic Acid (V). The acid (IV) (2.8 g, 0.01 mole) was added to a solution of sodium ethylate obtained from Na (0.5 g, 0.02 g-atom) and ethyl alcohol (70 ml). The mixture was boiled with stirring for 3 h. After cooling, the reaction mixture was diluted with acetic acid until an acid reaction was obtained, the precipitated solid was filtered off, washed with water and with alcohol, and recrystallized from dioxane. The yield of acid (V) was 2.3 g. IR spectrum: 1560, 1590, 1610 (arom.), 1660 (C=O), 3200, 3340, 3430 cm^{-1} (NH_2, OH).

3-Substituted 8,8-Dimethyl-4-oxo-7,8-dihydro-10H-pyrano[3′,4′:5,6]pyrido[3,2:4″,5″]thieno[3″,2″-d][3,1]-oxazines (Ia-c). A. A mixture of acid (V) (2.8 g: 0.01 mole) and the appropriate acid anhydride (20 ml) was boiled for 1 h. The reaction mixture was cooled and the precipitated solid was filtered off, washed with ether and with water, and dried to give compounds (Ia-c). PMR spectrum of (Ia) ($CDCl_3$): 8.11 (1H, s, 11-H); 4.98 (2H, s, 10-CH_2); 3.05 (2H, s, 7-CH_2); 2.55 (3H, s, 2-CH_3); 1.35 ppm [6H, s, 8-$(CH_3)_2$]; of (Ib) ($CDCl_3$): 2.70 (2H, q, J = 7 Hz, $\underline{CH_2}$−CH_3); 1.46-1.20 ppm [9H, m, −CH_2−CH_3, 8-$(CH_3)_2$]. The chemical shifts of the remaining protons were practically no different from those in the PMR spectrum of compound (Ia).

B. A mixture of acid (V) (2.8 g, 0.01 mole), benzoic anhydride (3.2 g, 15 mmole), and absolute ethanol (30 ml) was boiled for 4 h. The solvent was distilled off, ether (20 ml) was added to the residue, the precipitated crystals were filtered off, washed with water, and dried. In all cases (methods A and B) the reaction products were recrystallized from ethanol. PMR spectrum (Ic) ($CDCl_3$): 8.11 (1H, s, 11-CH); 7.43 (5H, s, C_6H_5); 4.98 (2H, s, 10-CH_2); 3.05 (2H, s, 7-CH_2); 1.35 ppm [6H, s, 8-$(CH_3)_2$]. IR spectrum (Ia-c): 1560, 1590, 1620 (arom., C=C, C=N), 1750 cm^{-1} (C=O, lactone).

2-Substituted 3-Amino-8,8-dimethyl-4-oxo-3,4,7,8-tetrahydro-10H-pyrano[3′,4′:5,6]pyrido[3,2:4″,5″]thieno-[3″,2″-d]pyrimidines (IIa-c). A mixture of (Ia-c) (0.01 mole), hydrazine hydrate (5 ml) and absolute ethanol (30 ml) was boiled for 5 h. The solvent was evaporated to dryness, the residue treated with water (20 ml), the precipitated crystals were filtered off, washed with ether, dried, and compounds (IIa-c) were obtained. IR spectrum (IIa-c): 1540, 1590, 1610 (arom., C=C, C=N), 1680 (C=O), 3180, 3200, 3310 cm^{-1} (NH_2).

2-Substituted 8,8-Dimethyl-4-oxo-3,4,7,8-tetrahydro-10H-pyrano[3′,4′:5,6]pyrido[3,2:4″,5″]thieno[3″,2″-d]pyrimidines (VIa-c). A. A mixture of (Ia-c) (0.01 mole), 25% aqueous ammonia solution (20 ml), and dioxan (40 ml) was heated for 2 h at 25°C. After cooling, the precipitated crystals were filtered off, washed with water and with ethanol, and dried. Compounds (VIa-c) were obtained by recrystallization from DMSO. IR spectrum (VIa-c): 1550, 1600, 1620 (arom., C=C, C=N, conj.), 1680 (C=O), 3110 cm^{-1} (NH).

B. Sodium nitrite (1.0 g: 15 mmole) dissolved in water (10 ml) was added dropwise to a suspension of (IIa-c) (0.01 mole) in 50% acetic acid (30 ml) at 50°C. Heating was continued until evolution of nitrogen dioxide had ceased. The precipitated crystals were filtered off, washed with water, and dried. Compounds (VIa-c) were obtained by recrystallization from DMSO.

2-Substituted 4-Chloro-8,8-dimethyl-7,8-dihydro-10H-pyrano[3′,4′:5,6]pyrido[3,2:4″,5″]thieno[3″,2″-d]pyrimidines (VIIa-c). A mixture of (VIa-c) (0.01 mole), absolute pyridine (2 ml), and phosphorus oxychloride (30 ml) was heated at 105°C for 4 h. The excess phosphorus oxychloride was distilled off in vacuum, and ice water (20 ml) was added dropwise with cooling to the residue. The mixture was then neutralized with 25% aqueous ammonia solution, the precipitated crystals were filtered off, washed with water, and dried. Compounds (VIIa-c) were obtained by recrystallization from ethanol. IR spectrum (VIIa-c): 1520, 1560, 1660 cm^{-1} (arom., C=C, C=N, conj.). PMR spectrum of (VIIa) ($CDCl_3$): 8.65 (1H, s, 2-CH); 8.38 (1H, s, 11-CH); 4.84 (2H, s, 10-CH); 3.12 (2H, s, 7-CH_2); 2.82 (3H, s, 2-CH_3); 1.22 ppm [6H, s, 8-$(CH_3)_2$]; of (VIIb) ($CDCl_3$): 3.23-2.84 (4H, m, 7-CH_2); 1.58-1.25 ppm, [9H, m, 8-$(CH_3)_2$, CH_2−CH_3]; of (VIIc) ($CDCl_3$): 7.45 ppm (5H, s, C_6H_5). The chemical shifts of the remaining protons of compounds (VIIb) and (VIIc) were practically the same as those in the spectrum of compound (VIIa).

REFERENCES

1. M. Negwer, Organische Chemische Arzneimittel und Synonyma, Berlin (1978), Vol. 1, p. 606 and Vol. 2, p. 1215.
2. S. P. Pilosyan, V. V. Dabaeva, and A. S. Noravyan, Arm. Khim. Zh., **44**, 479 (1991).