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DERIVATIVES OF CONDENSED PYRIDOPYRIMIDINES. 3*. SYNTHESIS OF CONDENSED IMIDAZO[4,5-*b*]PYRIDINE AND ALSO 4-OXO- AND 2,4-DIOXO-PYRIDO[2,3-*d*]PYRIMIDINES

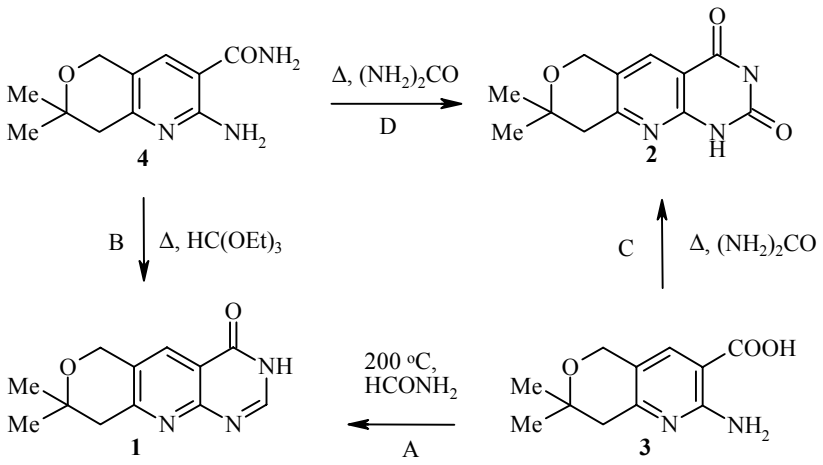
V. V. Dabaeva, S. G. Pilosyan, M. R. Bagdasaryan, V. N. Madakyan, and A. S. Novaryan

A convient methods has been developed for the synthesis of condensed imidazo[4,5-b]pyridine and also 4-oxo- and 2,4-dioxopyrido[2,3-d]pyrimidines. The optimum conditions for the Curtius rearrangement of 2-amino-3-azidocarbonyl derivative of pyrano[4,3-b]pyridine have been established.

Keywords: pyranoimidazopyridine, pyranopyridine, pyridopyrimidine.

In the present paper we consider variants of the synthesis of 4-oxo- and 2,4-dioxopyrimidines **1** and **2** starting from previously described [2] amino acid **3** and its amide **4** (see Scheme 1).

Scheme 1



* For part 2, see [1].

A. L. Mndzhoyan Institute of Fine Organic Chemistry, Armenian National Academy of Sciences, Erevan 375014, Armenia; e-mail: west@msrc.am. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, 971-974, July, 2001. Original article submitted June 16, 1999.

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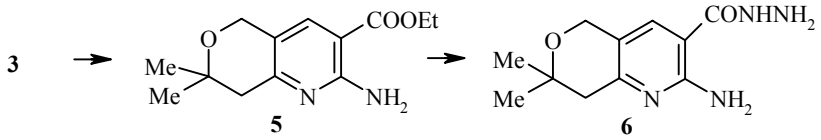
Compound **1** was obtained from the reaction of the amino acid **3** with an excess of formamide at 200°C (method A) or by refluxing the amino amide **4** with ethyl orthoformate in the presence of acetic anhydride (method B). Compound **2** was obtained by fusing amino acid **3** (method C) or the amino amide **4** with urea (method D).

In these cyclization reactions it is likely that the considerable nucleophilicity of the nitrogen atom of the amino group plays a major positive role despite the presence of the electron accepting pyridine ring.

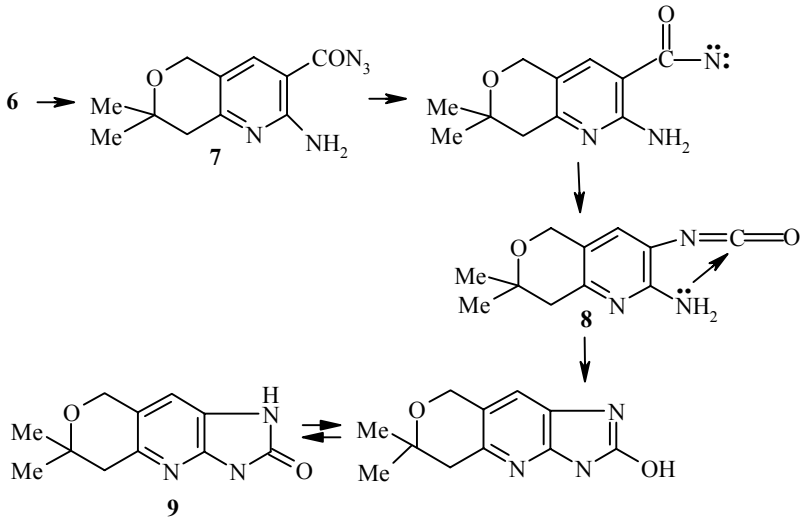
The ethyl ester **5** was synthesized by esterification of the amino acid **3**. The ester was converted into the hydrazide **6** with hydrazine hydrate (scheme 2).

Scheme 2



Treatment of the hydrazide **6** with aqueous sodium nitrite solution in the presence of 10% acetic acid gave the azide **7**, which on heating in *m*-xylene underwent the Curtius rearrangement to give the corresponding isocyanate **8**, which cyclized intramolecularly to give the new heterocyclic system, 6,6-disubstituted 2-oxo-1,2,5,6-tetrahydro-8H-pyrano[3,4-*e*]imidazo[4,5-*b*]pyridine (**9**) (scheme 3).

Scheme 3



In the ^{1}H NMR spectrum of compound **9**, recorded in DMSO-d_6, broad signals for the protons of the amide group are present at 11.13 and 10.67 ppm proving unambiguously that compound **9** exists as the lactam tautomer. Characteristics of the compounds synthesized, **1**, **2**, **5-7**, and **9**, are cited in Table 1.

TABLE 1. Characteristics of the Synthesized Compounds **1**, **2**, **5-7**, and **9**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	R_f (solvent system)	Yield, % (method)
		C	H	N			
1	$C_{12}H_{13}N_2O_2$	61.8 62.4 62.3	5.6 5.9 5.7	18.5(A) 18.1(B) 18.2	344-345	0.69 (**a**)	37.9 (A) 47.6 (C)
2	$C_{12}H_{13}N_3O_3$	58.8 58.5 58.3	5.6 5.4 5.3	17.4 (C) 17.2 (D) 17.0	290-291	0.74 (**b**)	36.4 (C) 42.8 (D)
5	$C_{13}H_{18}N_2O_3$	62.2 62.4	7.5 7.2	12.0 11.2	132-133	0.52 (**c**)	60.5
6	$C_{11}H_{16}N_4O_2$	55.7 55.9	7.0 6.8	23.9 23.7	150-151	0.52 (**d**)	97.3
7	$C_{11}H_{13}N_5O_2$	53.5 53.4	5.0 5.3	28.5 28.3	330-331	0.71 (**e**)	76.8
9	$C_{11}H_{13}N_3O_2$	60.5 60.3	5.9 6.0	19.4 19.2	315-316	0.63 (**e**)	91.2

EXPERIMENTAL

IR spectra of nujol mulls were recorded with a UR-20 instrument, ^{1}H NMR spectra were recorded on a Varian T-60 spectrometer, and mass spectra with an MX-1303 machine with an ionizing voltage of 70 eV. TLC was carried out on Silufol-254 plates with the following solvent systems: (**a**) 4:5 ethyl acetate–methanol, (**b**) 5:4 ethyl acetate–methanol, (**c**) 1:2:0.5 ethyl acetate–chloroform–ethanol, (**d**) 1:5 pyridine–butanol, and (**e**) 1:3 pyridine–butanol; developer – iodine vapor.

8,8-Dimethyl-4-oxo-3,4,8,9-tetrahydro-6H-pyrano[3′,4′:5,6]pyrido[2,3-*d*]pyrimidine (1). A. A mixture of acid **3** (2.2 g, 0.01 mol) and formamide (3.6 g, 0.08 mol) was kept at 200°C for 2 h, then cooled and ether (20 ml) was added. The crystals of product **1** were filtered off, washed with water and ethanol, and dried. Yield 0.9 g. ^{1}H NMR spectrum (CF_3COOD), δ, ppm, *J* (Hz): 9.05 (1H, s, 2-H); 8.80 (1H, s, 5-H); 5.28 (2H, t, *J* = 2, 6,6-H_2); 3.42 (2H, t, *J* = 2, 9,9-H_2); 1.57 (6H, s, 8,8-Me_2). Mass spectrum, *m/z*: 231 (M^+), 216, 202, 174, 173, 147, 120. IR spectrum (thin layer), ν, cm^{-1}: 1570, 1620 (arom), 1700 (C=O, amide), 3040, 3200 (NH).

B. A mixture of amide **4** (2.2 g, 0.01 mol), acetic anhydride (14 ml), and ethyl orthoformate (14 ml) was refluxed for 4 h. The reaction mixture was cooled, the crystals of product **1** were filtered off, washed with water and ether, and dried. Yield 1.1 g. A mixed sample of compounds synthesized by methods A and B did not give a melting point depression.

8,8-Dimethyl-2,4-dioxo-1,2,3,4,8,9-hexahydro-6H-pyrano[3′,4′:5,6]pyrido[2,3-*d*]pyrimidine (2). C. Amide **4** (2.2 g, 0.01 mol) and urea (2.4 g, 0.04 mol) were kept in a Wood's metal bath for 5 min at 150°C. The temperature was then raised stepwise to 210°C and kept there for 10 min, after which it was cooled. The solid mass was dissolved with heating in 2 N sodium hydroxide solution (25 ml) and then neutralized with concentrated hydrochloric acid. The precipitated crystals of **2** were filtered off, washed with water and ethanol, and dried. Yield 0.9 g. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 10.00 (2H, br. s, 2NH); 7.90 (1H, s, 5-H); 4.67 (2H, t, *J* = 2, 6,6-H_2); 2.73 (2H, t, *J* = 2, 9,9-H_2); 1.23 (6H, s, 8,8-Me_2). IR spectrum (thin layer), ν, cm^{-1}: 1600, 1630 (arom), 1700, 1720 (C=O, amide), 3080, 3170 (NH).

D. Compound **2** (1.8 g) was obtained from a mixture of acid **3** (2.2 g, 0.01 mol) and urea (2.4 g, 0.04 mol) as described above. A mixed sample of compounds prepared by methods C and D gave no depression of the melting point.

2-Amino-3-ethoxycarbonyl-7,7-dimethyl-7,8-dihydro-5H-pyrano[4,3-b]pyridine (5). A mixture of acid **3** (2.2 g, 0.01 mol) and concentrated sulfuric acid (2.8 g) in ethanol (6 ml) was refluxed for 6 h, then cooled and poured into water. The precipitated crystals of **5** were filtered off, washed with water and dried. Yield 1.5 g.

^{1}H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 7.73 (1H, s, 4-H); 6.43 (2H, br. s, NH_2); 4.60 (2H, t, *J* = 2, 5,5-H_2); 4.25 (2H, q, *J* = 7, $C\underline{H}_2$–CH_3); 2.62 (2H, t, *J* = 2, 8,8-H_2); 1.30 (3H, t, *J* = 7, CH_2–$C\underline{H}_3$); 1.27 (6H, s, 7,7-$(CH_3)_2$). IR spectrum (thin film), ν, cm^{-1}: 1560, 1590, 1620 (arom), 1680 (C=O), 3130, 3280, 3440 (NH_2).

2-Amino-3-hydrazinocarbonyl-7,7-dimethyl-7,8-dihydro-5H-pyrano[4,3-*b*]pyridine (6). A mixture of ester **5** (2.5 g, 0.01 mol) and concentrated hydrazine hydrate (50 ml) was kept at 130°C for 1 h. The excess of hydrazine hydrate was evaporated and the residue was ground with hexane. The precipitated crystals were filtered off, washed with ether, and dried. Yield 2.3 g. ^{1}H NMR spectrum (pyridine-d_5), δ, ppm, *J*, Hz): 7.67 (1H, s, 4-H); 7.48 (2H, br. s, 2-CH_2); 4.93 (3H, br. s, NH–NH_2); 4.57 (2H, t, *J* = 2, 5,5-H_2); 2.70 (2H, s, 8,8-H_2); 1.13 (6H, s, 7,7-$(CH_3)_2$). IR spectrum (thin film), ν, cm^{-1}: 1580, 1610 (arom.), 1650 (C=O), 3130, 3290, 3380 (NH–NH_2).

2-Amino-3-azidocarbonyl-7,7-dimethyl-7,8-dihydro-5H-pyrano[4,3-*b*]pyridine (7). A solution of sodium nitrite (0.7 g, 0.01 mol) in water (7 ml) was added at 0°C to a solution of hydrazide **6** (2.4 g, 0.01 mol) in acetic acid (60 ml, 10%). The mixture was stirred for 1 h at 0°C. The precipitated crystals were filtered off, washed with water, and dried. Yield 1.9 g. ^{1}H NMR spectrum (pyridine-d_5), δ, ppm, *J* (Hz): 7.70 (1H, s, 4-H); 4.83 (2H, br. s, NH_2); 4.67 (2H, t, *J* = 2, 5,5-H_2); 2.80 (2H, s, 8,8-H_2); 1.23 (6H, s, 7,7-$(CH_3)_2$). IR spectrum (thin film): ν, cm^{-1}: 1550, 1590, 1620 (arom.), 1660 (C=O), 2130 (N_3), 3120, 3270, 3490 (NH_2).

6,6-Dimethyl-2-oxo-1,2,5,6-tetrahydro-8H-pyrano[3,4-*e*]imidazo[4,5-*b*]pyridine (9). A solution of azide **7** (2.5 g, 0.01 mol) in *m*-xylene (20 ml) was kept on a water bath at 80°C for 1 h and was then heated at 140°C for 10 min. The precipitated crystals were filtered off, washed with ether, and dried. Yield 2.0 g. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 11.13 (1H, br. s, 3-NH); 10.67 (1H, br. s, 1-NH); 6.93 (1H, s, 4-H); 4.63 (2H, t, *J* = 2, 8,8-H_2); 2.67 (2H, t, *J* = 2, 5,5-H_2); 1.20 (6H, s, 6,6-$(CH_3)_2$). Mass spectrum, *m/z*: 219 (M^+), 204, 162, 161. IR spectrum (thin film), ν, cm^{-1}: 1560, 1600 (arom.), 1680 (C=O, amide), 3050, 3320 (NH).

REFERENCES

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