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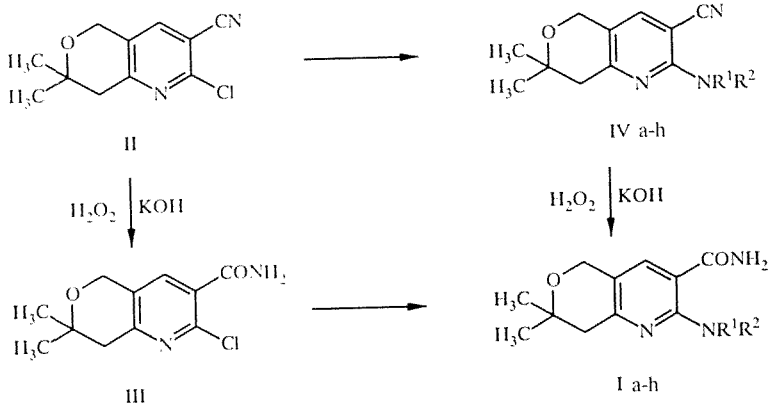
SYNTHESIS OF SUBSTITUTED DIHYDRO-5H-PYRANO[4,3-b]PYRIDIN-3-CARBOXAMIDES AND -3-CARBOXYLIC ACIDS

V. V. Dabaeva, S. G. Pilosyan, and A. S. Noravyan

Optimal conditions were established for the hydrolysis of 2-amino-3-cyanodihydropyranopyridines to give substituted dihydro-5H-pyrano-[4,3-b]pyridine-3-carboxylic acids. Two convenient routes also were developed for the synthesis of the 3-carboxamide derivatives of substi-tuted dihydro-5H-pyrano[4,3-b]pyridine from the corresponding 2-chlorocyano derivatives.

In a search for biologically active compounds in a series of condensed derivatives of a new heterocyclic system containing a pyridine ring in the same structure, we undertook the synthesis of substituted dihydro-5H-pyrano[4,3-b]pyridin-3-carboxamides and -3-carboxylic acids, which are condensed analogs of the biologically active 2-aminonicotinamide and 2-aminonicotinic acid [1, 2].

The synthesis of the desired amides (Ia-h) was accomplished by two routes: a) transformation of our earlier-obtained 2-chloro-3-cyanodihydro-5H-pyrano[4,3-b]pyridine (II) [3] by the action of hydrogen peroxide in the presence of potassium hydroxide into the 3-carboxamido-2-chloro derivative (III) and subsequent reaction of the latter by nucleophilic substitution with primary and secondary amines; b) partial hydrolysis by hydrogen peroxide in alkaline medium of the 2-NR^1R^2-nitriles (IVa-h) obtained from II. This second method is preferred over the first, since it provides more advantageous yields of the desired aminoamides Ia-h.



I, IV a $R^1 = R^2 = H$; b $R^1 = H$, $R^2 = CH_3$; c $R^1 = H$, $R^2 = C_2H_5$; d $R^1 = H$, $R^2 = i\text{-}C_3H_7$; e $R^1 = H$, $R^2 = CH_2C_6H_5$; f $R^1 = R^2 = CH_3$; g $R^1 + R^2 = -(CH_2)_5-$; h $R^1 + R^2 = -(CH_2)_2-O-(CH_2)_2-$

In order to synthesize the dihydro-5H-pyrano[4,3-b]pyridin-3-carboxylic acids, the possibility of the hydrolysis of the nitriles IVa-f with 5% aqueous potassium hydroxide was studied. However, under these conditions, only the 2-amino-3-cyanodihydropyrano[4,3-b]pyridine IVa saponified completely to form the amino acid (V), while the hydrolysis of the aminonitriles IVb-f stopped at the formation of the intermediate amides Ib-f.

A. L. Mndzhoyan Institute of Fine Organic Chemistry, National Academy of Sciences of the Republic of Armenia, Erevan, 375014. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 995-998, July, 1994. Original article submitted February 15, 1994.

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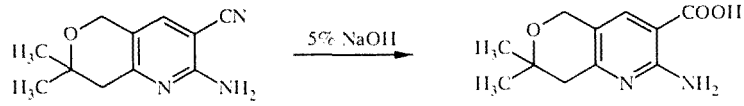
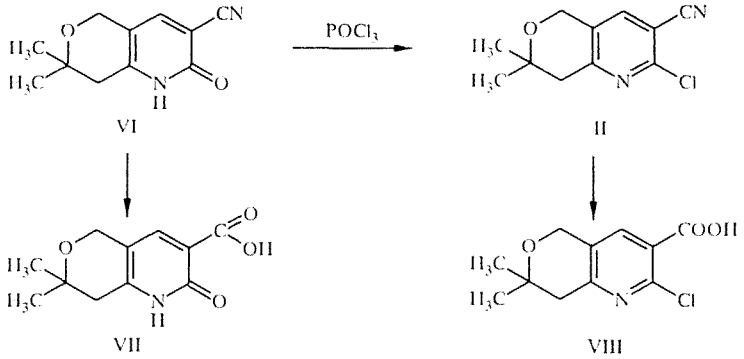


All attempts at the transformation of the aminonitriles IVb-f into the corresponding acids both in strongly-acidic (conc. HCl, H_2SO_4) and in concentrated sodium hydroxide solution did not go to successful completion. This presumably is connected with significantly lowered reactivity of the formed amide as a result of the influence of the electronic as well as the steric effect of the alkyl substituents of the amino groups. This suggestion is claimed to be useful in examples of the successful saponification of compounds containing electron acceptor groups in position 2 of the pyridine ring. Thus, 2-oxo-3-cyanodihydro-5H-pyranopyridine (VI) [3] and the 2-chloro derivative II were transformed into the corresponding 3-carboxylic acids (VII and VIII) in high yields under the conditions indicated above.



EXPERIMENTAL

The IR spectra were recorded with a UR-20 spectrometer in Vaseline oil, the ^1H NMR were obtained with a Varian T-60 instrument, and the mass spectra with an MX-1303 instrument with ionization voltage 70 eV. TLC was carried out on Silufol UV-254 plates with visualization by iodine vapor.

Elemental analysis data for compounds I, IV, V, VII, and VIII corresponded with the calculated values.

The characteristics of compounds I, IV, V, VII, and VIII are presented in Table 1.

7,7-Dimethyl-2-chloro-7,8-dihydro-5H-pyrano[4,3-b]pyridine-3-carboxamide (III). To a mixture of 2.2 g (0.01 mole) of nitrile II and 0.6 g (0.01 mole) of potassium hydroxide in 25 ml of absolute ethanol was added dropwise with stirring at 60-70°C over 30 min 30 ml of 30% hydrogen peroxide solution. The resulting mixture was kept at the same temperature for 1 h and then the solvent was evaporated. The crystalline residue was washed with water and ether and dried. IR spectrum: 1550, 1590, 1620 (arom), 1660 (amide C=O), 3180, and 3359 cm^{-1} (NH_2), ^1H NMR spectrum (DMSO-d_6): ppm: 7.93 (^1H, bs, CH), 7.63 (2H, s, NH_2), 4.70 (2H, t, 5-CH_2), 2.73 (2H, t, 8-CH_2), 1.23 (6H, s, 7-$(CH_3)_2$). Yield, 2.2 g.

2-NR^{1}R^2-7,7-Dimethyl-3-cyano-7,8-dihydro-5H-pyrano[4,3-b]pyridines (IVa-h). A. A reaction mixture composed of 0.01 mole of chloride II and 20 ml of 25% alcoholic amine solution in a glass ampule was kept in a waterbath at 90°C for 18 h. The solvent was evaporated and water was added to the residue. The resulting crystals were filtered off, washed with water, dried, and recrystallized from a mixture of ethanol and water.

B. A mixture containing 0.01 mole of chloride II and 0.02 mole of amine in 20 ml of absolute ethanol was boiled for 18 h and then worked up according to Method A. IR spectra of IVa-e: 1520, 1590, 1620 (arom), 2230 C=N), 3350-3380 cm^{-1} (NH). IR spectra of IVf-h: 1550, 1590 (arom), 2230 cm^{-1} (C=N). ^1H NMR spectrum of IVa (pyridine-d_5): 7.50 (2H, bs, NH_2), 7.40 (1H, s, CH), 4.65 (2H, t, 5-CH_2), 2.77 (2H, t, 8-CH_2), 1.25 (6H, s, 7-$(CH_3)_2$). ^1H NMR spectrum of IVe (CD_2Cl_2): 7.28 (5H, s, C_6H_5), 4,57 ppm (2H, d, $CH_2C_6H_5$). The chemical shifts for the remaining protons were practically indistinguishable from those of compound IVa. Mass spectrum of IVa, *m/z* (%): 203(31) (M^+), 188(12), 174(6), 146(34), 145(100), 119(5).

2-NR^{1}R^2-7,7-Dimethyl-7,8-dihydro-5H-pyrano[4,3-b]pyridine-3-carboxamides (Ia-h). A. The products Ia-d and f were obtained by Method A described above from the chloride III and the corresponding amine.

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Emprical formula	mp, °C	R_f (System)	Yield, % (Method)
Ia	$C_{11}H_{15}N_3O_2$	252...253	0,53 Ethyl acetate:petroleum ether: ethanol, 5:1:4	56(A), 72 (C)
Ib	$C_{12}H_{17}N_3O_2$	203...204	0,75 Pyridine:butanol, 1:2	40 (A), 65 (C), 50 (D)
Ic	$C_{13}H_{19}N_3O_2$	218...220	0,77 Chloroform: methanol, 4:5	43 (A), 57 (C), 44 (D)
Id	$C_{14}H_{21}N_3O_2$	220...221	0,73 Ethyl acetate:methanol 5:4	41 (A), 59 (C), 46 (D)
Ie	$C_{18}H_{21}N_3O_2$	175...176	0,70 Ethyl acetate:methanol 5:4	53 (B) 77(C), 46 (D)
If	$C_{19}H_{19}N_3O_2$	195...196	0,67 Chloroform:methanol 1:5	47 (A), 70(C), 49 (D)
Ig	$C_{15}H_{21}N_3O_3$	193...194	0,66 Pyridine:butanol 1:2	50 (B) 74(C)
Ih	$C_{16}H_{23}N_3O_2$	196...197	0,76 Pyridine:butanol 1:2	75 (B) 85 (C)
III	$C_{11}H_{13}ClN_2O_2$	178...179	0,70 Pyridine:butanol 1:2	91
IVa	$C_{11}H_{13}N_3O$	222...223	0,51 Ethyl acetate:petroleum ether, 5:2	51
IVb	$C_{12}H_{15}N_3O$	113...114	0,74 Ethyl acetate:petroleum ether 1:1	34
IVc	$C_{13}H_{17}N_3O$	118...119	0,78 Ethyl acetate:petroleum ether, 1:1	71
IVd	$C_{14}H_{19}N_3O$	122...123	0,71 Benzene:ether, 3:1	73
IVe	$C_{18}H_{19}N_3O$	118...119	0,79 Ethyl acetate:petroleum ether, 3:5	66
IVf	$C_{13}H_{17}N_3O$	86...87	0,80 Acetone:chloroform, 5:3	90
IVg	$C_{15}H_{19}N_3O$	107...108	0,50 Ethyl acetate:petroleum ether 3:5	82
IVh	$C_{16}H_{21}N_3O$	71...72	0,62 Ethylacetate:petroleum ether 3:5	61
V	$C_{11}H_{14}N_2O_3$	350	0,73 Chloroform:methanol: acetone, 4:5:1	76
VII	$C_{11}H_{13}NO_4$	350	—	90
VIII	$C_{11}H_{12}ClNO_3$	170...172	0,76 Chloroform:methanol, 1:5	79

B. The products Ie, g, h were synthesized according Method B described above from chloride III and the corresponding amine.

C. Compounds Ia-h were prepared analogously to chloride III by treatment of nitriles IVa-h with hydrogen peroxide in alcoholic potassium hydroxide.

D. A mixture of 0.01 mole of nitrile IVb-f in 50 ml of 5% aqueous sodium hydroxide was boiled for 8 h. After cooling, the crystalline product Ib-f was filtered off, washed with water, and dried. In all cases (see also Methods A-D) the

reaction products were recrystallized from ethanol. IR spectra of Ia-e: 1500, 1580, 1620 (arom), 1670 (C=O, amide), 3190, 3350 cm^{-1} (NH, NH_2). IR spectra of If-h: 1510, 1560, 1620 (arom), 1660 (C=O, amide), 3150, 3350 cm^{-1} (NH_2). ^1H NMR spectrum of Ie (DMSO-d_6): 7.67 (1H, s, CH), 7.30 (4H, bs, $2NH_2$), 4.52 (2H, t, 5-CH_2), 2.53 (2H, t, 8-CH_2), 1.20 ppm (16H, s, 7-$(CH_3)_2$). ^1H NMR spectrum of Ie (DMSO-d_6): 8.83 (1H, t, J = 5 Hz, NH), 7.76-7.08 (7H, m, NH_2, C_6H_5), 4.63 (2H, d, J = 5 Hz, $CH_2C_6H_5$). ^1H NMR spectrum of Ig (DMSO-d_6): 7.47 (2H, s, NH_2), 3.63 (4H, m, $-CH_2-O-CH_2-$), 3.22 (4H, m, $-CH_2-N-CH_2-$).

The chemical shifts for the remaining protons were practically indistinguishable from those of compound Ia. Mass spectrum of I*a*, *m/z* (%): 211(50) (M^+), 163(44), 37(100).

2-Amino-7,7-Dimethyl-7,8-dihydro-5H-pyrano[4,3-b]pyridine-3-carboxylic Acid (V). A mixture of 2.0 g (0.01 mole) of aminonitrile IVa and 50 ml of 5% aqueous sodium hydroxide was boiled for 8 h, cooled, and then treated with concentrated HCl to neutral. The resulting crystals were filtered off, washed with water and ethanol, and dried to give 1.7 g. IR spectrum: 1580, 1620 (arom), 1720 (C=O), 1670, 3100, 3320 (NH_2), 3580 cm^{-1} (OH).

7,7-Dimethyl-2-oxo-1,2,7,8-tetrahydro-5H pyrano[4,3-b]pyridine-3-carboxylic Acid (VII). A mixture of 2.0 g (0.01 mole) of nitrile VI and 50 ml of 5% aqueous sodium hydroxide was boiled for 8 h and worked up as described for acid Va. The crystalline product was washed with water and ethanol and dried to give 2.0 g. IR spectrum: 1570, 1620 (C=C, conj), 1670 (C=O, amide), 1730 (C=O), 3030, 3120, 3280 (NH), 3580 cm^{-1} (O-H). ^1H NMR spectrum (DMSO-d_6): 8.10 (1H, s, CH), 4.53 (2H, t, 5-CH_2), 2.63 (2H, t, 8-CH_2), 1.23 ppm (6H, s, 7-$(CH_3)_2$).

7,7-Dimethyl-2-chloro-7,8-dihydro-5H-pyrano[4,3-b]pyridine-3-carboxylic Acid (VIII). A mixture of 2.2 g (0.01 mole) of nitrile II and 50 ml of 5% aqueous sodium hydroxide was boiled for 10 h and worked up as described for acid V. The crystalline product was washed with water and ether and dried to give 1.9 g. IR spectrum: 1570, 1600, 1640 (arom), 1700 (C=O), 3100-3500 cm^{-1} (O-H). ^1H NMR spectrum (DMSO-d_6): 7.97 (1H, s, CH), 6.20 (1H, bs, OH), 4.68 (2H, t, 5-CH_2), 2.73 (2H, t, 8-CH_2), 1.17 ppm (6H, s, 7-$(CH_3)_2$).

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