SYNTHESIS OF AZA ANALOGS OF 2-AMINOCHROMONE

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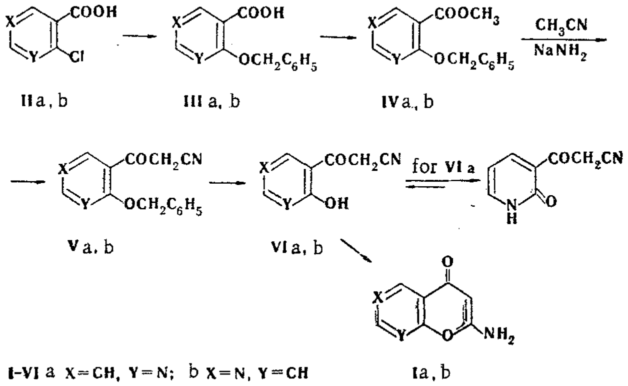
UDC 547.814.1'821 : 543.422.25.4

Aza analogs of 2-aminochromone – 2-amino-4-oxo-4H-pyrano [2,3-b]pyridine and 2-amino-4-oxo-4H-pyrano[3,2-c]pyridine – were synthesized. It was established from the PMR and IR spectra that these compounds exist in the amino ketone form.

It has been established [1] that some 2-aminochromone derivatives have a psychotropic effect. In this connection, we synthesized two aza analogs of 2-aminochromone – 2-amino-4-oxo-4H-pyrano[2,3-b]-pyridine (Ia) and 2-amino-4-oxo-4H-pyrano[3,2-c]pyridine (Ib).

Compound Ia was obtained from 2-benzyloxynicotinic acid (IIIa) via the following scheme:



The IR spectrum of Ia in the 1600-3500-cm^{-1} region is similar to the spectrum of 2-aminochromone. Vibrations of a $C \equiv N$ group are absent in the spectrum of Ia in dimethyl sulfoxide (DMSO) (the compound is insoluble in chloroform), but there is a broad absorption band at 3000-3300 cm^{-1}, which is related to a bonded NH_2 group; an intense band of NH_2 deformation vibrations appears at 1670 cm^{-1}, and, as in the case of 2-aminochromone [2], very intense and evidently subordinate stretching vibrations of the $C = O$ group are observed at 1630 cm^{-1}. Deuteration of Ia leads to the disappearance of NH_2 vibrations. The presence of vibations of a primary amino group provide evidence that Ia exists in the aminopyrone form rather than in the other possible tautomeric forms, for example, in one of the imino forms. The PMR spectrum of Ia contains the signals of pyridine-ring protons with the characteristic (for pyridines) chemical shifts and spin-spin splitting constants [3, 4]. A singlet 3-H signal appears at 5.2 ppm, and the signal of the two protons of the NH_2 group is identified by deuteration. The fundamental properties of the amino group in 2-aminochromones are markedly suppressed [2]. The amino group in Ia even has appreciable acidic properties (it dissolves in alkalis); Ia forms a hydrochloride, apparently through the pyridine ring nitrogen atom.

Another representative (Ib) of aza analogs of 2-aminochromone was synthesized in the same way as Ia from the known 4-chloronicotinic acid (IIb) [5]. Intermediate VIb could not be isolated because of its great tendency to undergo cyclization to Ib. As in the case of Ia, the structure of Ib is confirmed by the IR and PMR spectra (see the Experimental section). The deformation vibrations of the NH_2 group were identified by deuteration.

Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1616-1619, December, 1974. Original article submitted December 25, 1973.

We note that the UV spectrum of Ia, in contrast to the spectrum of Ib, contains a bathochromic shift, but both substances absorb at longer wavelengths than 2-aminochromone [2].

The mass spectra* of Ia and Ib contain only small differences in the relative intensities of the ions. The molecular ion peaks are the maximum peaks in the spectra. The principal pathways of fragmentation are to a certain degree similar to those in the disintegration of chromone [6] and consist in successive loss from the molecular ion of two CH groups (confirmed by the presence of the corresponding metastable ions). Another characteristic fragmentaion pathway is disintegration of the retrograde Diels–Alder type accompanied by migration of a hydrogen atom.

The establishment of the fine structure of potentially tautomeric V and VI seems of independent interest. The PMR and IR spectra attest to the presence of C=O, CH_2, and C≡N groupings, which is in agreement with the ketonitrile form of the side chain of V and VI. The heterocyclic portion of VIa has a pyridone rather than a hydroxypyridine form; this is typical for the usual 2-pyridones in solutions or in the crystalline state [3, 7]: the characteristic bands of stretching vibrations of a C=O group and of ring double bonds are observed in the IR spectra of a DMSO solution of VIa or of VIa crystals. The relatively large constant ($J_{\alpha\beta}$ = 7 Hz) is also in agreement with the pyridone rather than with the pyridine form [8].

EXPERIMENTAL

The UV spectra of alcohol solutions were recorded with SF-4 and Perkin–Elmer-402 spectrophotometers. The IR spectra of mineral oil suspensions or DMSO or chloroform solutions were obtained with a UR-10 spectrometer. The PMR spectra of DMSO solutions were recorded with a Varian T-60 spectrometer. The mass spectra were obtained with an MKh-1303 spectrometer with a system for direct introduction of the samples into the ion source at 200° and an ionizing voltage of 50 V.

4-Benzyloxynicotinic Acid (IIIb). A 10.8-g (0.1 mole) sample of benzyl alcohol and (in small portions) 15.45 g (0.1 mole) of 4-chloronicotinic acid (IIb) [5] were added successively with water cooling to a suspension of 6 g (0.25 mole) of NaH in 50 ml of anhydrous DMSO, after which the mixture was heated at 70° for 1 h. It was then acidified to pH 5 with acetic acid, and the resulting precipiate was removed by filtration to give 2.3 g of acid IIIb. The filtrate was vacuum evaporated almost to dryness to give an additional 8 g of IIIb. The overall yield of product with mp 150-151° (dec., from alcohol) was 10.3 g (45%). Found: C 68.1; H 4.9; N 6.2%. $C_{13}H_{11}NO_3$. Calculated: C 68.1; H 4.8; N 6.1%.

Methyl 2-Benzyloxynicotinate (IVa). A total of 25.8 g (0.11 mole) of acid IIIa was added to an ether solution of diazomethane (from 30 g of nitrosomethylurea), after which the mixture was allowed to stand for 16 h. Workup yielded 20.8 g (85.5%) of ester IVa with bp 151-153° (2 mm) and n_D^{20} 1.5705. Found: C 69.1; H 5.4; N 5.8%. $C_{14}H_{13}NO_3$. Calculated: C 69.1; H 5.4; N 5.8%.

Methyl 4-Benzyloxynicotinate (IVb). A mixture of 12.3 g (0.054 mole) of acid IIIb in 350 ml of anhydrous dioxane and diazomethane (from 15 g of nitrosomethylurea) in 150 ml of ether was allowed to stand for 16 h, after which it was evaporated to give 11.1 g (85.5%) of IVb with mp 101-102° (from alcohol). Found: C 68.8; H 5.4; N 5.9%. $C_{14}H_{13}NO_3$. Calculated: C 69.1; H 5.4; N 5.8%.

2-Benzyloxy-3-cyanoacetylpyridine (Va). A solution of 6.8 g (0.165 mole) of acetonitrile in 10 ml of absolute ether and a solution of 20.79 g (0.0825 mole) of ester IVa in 20 ml of absolute ether were added to a suspension of sodium amide [from 4.92 g (2.14 g-atom) of Na] in 350 ml of liquid ammonia, after which the mixture was allowed to stand overnight to evaporate the solvents. The residue was dissolved in 400 ml of water, and the filtrate was acidified with acetic acid to give 21.6 g (100%) of ketonitrile Va with mp 74-75° (from alcohol). The product gave a dark-red coloration with an alcohol solution of $FeCl_3$. UV spectrum: λ_{max} 298-304 nm (log ε 3.95). IR spectrum (in $CHCl_3$, c 10^{-1} M, d 0.6 mm), cm^{-1}: 2264 (C≡N), 1700 (C=O; at 1684 cm^{-1} in mineral oil), 1589 (aromatic). PMR spectrum, δ, ppm: 4.4 (s,† CH_2CN), 5.4 (s, OCH_2), 6.9-7.5 (m, 5-H and C_6H_5), 8.1 (two d, J_1=8 Hz, J_2=2 Hz, 4-H), 8.3 (two d, J_1=5.5 Hz, J_2=2 Hz, 6-H). Found: C 71.6; H 4.8; N 11.1%. $C_{15}H_{12}N_2O_2$. Calculated: C 71.4; H 4.8; N 11.1%.

4-Benzyloxy-3-cyanoacetylpyridine (Vb). A solution of 4.1 g (0.1 mole) of acetonitrile in 10 ml of absolute ether and a solution of 12.4 g (0.51 mole) of ester IVb in 50 ml of anhydrous benzene were added successivly to a suspension of sodium amine [from 2.94 g (0.126 g-atom) of Na] in 250 ml of liquid ammonia,

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* The mass spectra were studied by D. V. Zagorevskii.

† The following abbreviations are used here and subsequently: s is singlet, d is doublet, t is triplet, and m is multiplet.

and the mixture was cooled and stirred for 1 h, after which it was allowed to stand overnight to evaporate the solvents. The residue was dissolved in 400 ml of water, and the aqueous solution was separated and acidified to pH ~5 with acetic acid. The resulting oil was separated by decantation and dissolved in alcohol. The solution was vacuum evaporated, anhydrous benzene was added, and the mixture was evaporated to give 8 g (57.6%) of ketonitrile Vb with mp 89-99° (from benzene). The product gave a dark-red coloration with an alcohol solution of $FeCl_3$. UV spectrum (c 10^{-4} M), λ_{max}, nm (log ε): 234-238 (3.93), 276-278 (3.55), and 310 (inflection at 2.95). IR spectrum (in mineral oil), cm^{-1}: 2250 ($C\equiv N$), 1675 ($C=O$), and 1584 (aromatic). PMR spectrum, δ, ppm: 4.5 (s, CH_2CN), 5.3 (s, OCH_2), 7.2-7.7 (m, C_6H_5 and 5-H), 8.4-8.8 (m, 2-H and 6-H). Found: C 71.5; H 4.8; N 11.5%. $C_{15}H_{22}N_2O_2$. Calculated: C 71.4; H 4.8; N 11.1%.

3-Cyanoacetyl-2-pyridone (VIa). A solution of 3.8 g (0.015 mole) of ketonitrile Va in 100 ml of glacial acetic acid was hydrogenated over 1.0 g of 10% Pd on $BaSO_4$ until 470 ml (0.02 mole) of hydrogen had been absorbed. The resulting precipitate was removed by filtration and recrystallized from acetic acid to give 1.7 g (70%) of pyridone VIa with mp 221-222° (dec., from alcohol). The product gave a violet coloration with an alcohol solution of $FeCl_3$. UV spectrum, λ_{max}, nm (log ε): 240-244 (3.78), 348-350 (3.95). IR spectrum (in DMSO, c 4 10^{-4} M, d 0.07 mm), cm^{-1}: 2220, 1690, 1670, 1602, and 1550. PMR spectrum, δ, ppm: 4.4 (s, CH_2CN), 6.5 (t, J = 7 Hz, 5-H), 7.7 (two d, J_1 = 8 Hz, J_2 = 3 Hz, 4-H), and 8.1 (two d, J_1 = 8 Hz, J_2 = 3 Hz, 6-H). Found: C 59.3; H 3.7; N 17.6%. $C_8H_6N_2O_2$. Calculated: C 59.3; H 3.7; N 17.3%.

2-Amino-4-oxo-4H-pyrano[2,3-b]pyridine (Ia). A solution of 13.5 g (0.0535 mole) of ketonitrile Va in 250 ml of acetic acid was hydrogenated over 1.5 g of 10% Pd on $BaSO_4$ until 0.0535 mole of H_2 had been absorbed. The reaction mixture was then heated to the boiling point, the hot solution was filtered, and the filtrate was refluxed for 30 min, vacuum evaporated almost to dryness, and cooled. Workup gave 8.2 g (93.5%) of Ia with mp 215-216° (dec., from acetic acid, alcohol). UV spectrum (c 2.5 10^{-5} M), λ_{max}, nm (log ε): 237-238 (3.83), 287-288 (4.05). IR spectrum (in mineral oil), cm^{-1}: 3000-3300 (ν_{NH_2}) 1680 (δ_{NH_2}), 1610 (broad intense $C=O$ band). PMR spectrum, δ, ppm: 5.2 (s, 3-H), 7.36 (two d, J_1 = 8 Hz, J_2 = 5 Hz, 6-H), 7.7 (s, NH_2), 8.2 (two d, J_1 = 8 Hz, J_2 = 2 Hz, 5-H), 8.4 (two d, J_1 = 5 Hz, J_2 = 2 Hz 7-H). Mass spectrum, m/e (intensities in percent of the maximum peak): 162 (100), 134 (26), 122 (36), 106 (9), 105 (8), 95 (33), 94 (26) 79 (19), 78 (9). Found: C 59.0; H 3.8; N 17.4%. $C_8H_6N_2O_2$. Calculated: C 59.3; H 3.7; N 17.3%. The hydrochloride had mp 214-215° (dec., from alcohol). Found: C 48.4; H 3.5; Cl 17.5; N 14.2%. $C_8H_6N_2O_2 \cdot HCl$. Calculated: C 48.4; H 3.6; Cl 17.9; N 14.1%.

2-Amino-4-oxo-4H-pyrano[3,2-c]pyridine (Ib). A solution of 7.4 g (0.023 mole) of Vb in 120 ml of acetic acid was hydrogenated over 1 g of Pd on $BaSO_4$ until 0.029 mole of H_2 had been absorbed. The mixture was then heated to the boiling point, the hot solution was filtered, and the filtrate was vacuum evaporated to give 3.2 g (70.5%) of Ib with mp 235-236° (dec., from alcohol). UV spectrum (c 2.5 10^{-5} M, d 10 mm): λ_{max} 296-298 nm (log ε 4.11). IR spectrum (in DMSO, c 0.05 M, d 0.04 mm), cm^{-1}: 3000-3400 (broad bands, ν_{NH_2}), 1660 (δ_{NH_2}; the band vanishes after the addition of D_2O), 1629 ($C=O$). PMR spectrum, δ, ppm: 5.2 (s, 3-H), 7.4 (d, J = 6 Hz, 8-H), 7.8 (broad s, NH_2), 8.7 (d, J = 6 Hz, 7-H), 9.1 (s, 5-H). Mass spectrum, m/e (intensity in percent of the maximum peak): 106 (9), 105 (10), 95 (54), 94 (53), 79 (12), and 78 (11). Found: C 59.0; H 3.8; N 17.1%. $C_8H_6N_2O_2$. Calculated: C 59.3; H 3.7; N 17.3%.

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