

lithium, obtained from 0.1 g (0.014 g-atom) of lithium and 1.45 g (9.2 mmole) of bromobenzene in 10 ml of ether, after which the mixture was stirred at room temperature for 1 h. The ether was removed by distillation, and the residual mixture was refluxed for 2 h. It was then treated with 50 ml of water, and the reaction products were extracted with benzene. The benzene extract was dried with sodium sulfate and worked up to give 1.1 g (85%) of colorless crystals of alcohol VII with mp 231-235° (from benzene-ligroin). IR spectrum: 3556 (associated OH group) and 703 cm⁻¹ (monosubstituted benzene ring). Found: C 84.9; H 6.7; N 4.0%. C₂₄H₂₃NO. Calculated: C 84.4; H 6.8; N 4.1%.

A mixture of 0.52 g (1.5 mmole) of alcohol VII, 2 g (15 mmole) of propionic anhydride, and 15 ml of pyridine was refluxed for 12 h, after which the pyridine and excess propionic anhydride were removed by vacuum distillation. The residual mixture was treated with 50 ml of water and made alkaline with sodium carbonate solution. The reaction products were extracted with ether. The ether extract was passed through a column filled with aluminum oxide (elution with ether) to give 0.32 g (53%) of colorless crystals of ester VIII with mp 175-181.5° (from heptane). Found: N 3.7%. C₂₇H₂₇NO₂. Calculated: N 3.5%.

LITERATURE CITED

1. N. Campbell and A. E. S. Fairfull, J. Chem. Soc., 1239 (1949).
2. R. S. Taylor and R. Connor, J. Org. Chem., 6, 696 (1941).
3. N. S. Prostakov, V. P. Shalimov, and V. P. Zvolinskii, Khim. Geterotsikl. Soedin., No. 11, 1668 (1972).
4. High-Resolution Nuclear Magnetic Resonance Spectra Catalog, Varian Associates, No. 79 (1962).

SYNTHESIS AND PROPERTIES OF CHROMONO[2,3-b]PYRIDINES

A. I. Mikhalev and M. E. Konshin

UDC 547.814.1'821.07:543.422.6

Chromono[2,3-b]pyridines were synthesized by cyclization of 2-phenoxy nicotinic acids. Their UV spectra are due to $\pi-\pi^*$ transitions and, in contrast to the spectrum of xanthone, are of high intensity. In concentrated sulfuric acid the chromono[2,3-b]pyridines form a doubly charged pyridinium-pyrylium ion, and the reaction is accompanied by an increase in the intensity of the long-wave bands (330-340 nm) in the UV spectrum. The spectrophotometrically determined pK_a values of 8-R-chromono[2,3-b]pyridines range from -8.62 to -9.81, depending on the substituent in the 8 position, and correlate with Hammett σ_p constants.

Practically no study has been devoted to chromono[2,3-b]pyridines. In the present research in order to ascertain the effect of the pyridine ring on the properties of the benzopyran fragment of these compounds and compare them with the properties of xanthones, we synthesized 8-R-chromono[2,3-b]pyridines (VI-X, Table 1) by cyclization of substituted 2-phenoxy nicotinic acids (I-V, Table 1) by means of phosphorus oxychloride or polyphosphoric acid (PPA). (See scheme on following page.)

In the case of VI it was shown that replacement of the carbonyl oxygen atom by a sulfur atom to give thiochromono[2,3-b]pyridine (XI) occurs in the reaction with phosphorus pentasulfide. Heating the same compound with an alcoholic potassium hydroxide solution is accompanied by cleavage of the pyran ring to give 3-(o-hydroxybenzoyl)-2-pyridone (XII). Cyclization to give chromono[2,3-b]pyridine in 73% yield is observed in turn when XII is

Perm Pharmaceutical Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii No. 9, pp. 1235-1238, September, 1976. Original article submitted July 22, 1975.

This material is protected by copyright registered in the name of Plenum Publishing Corporation, 227 West 17th Street, New York, N.Y. 10011. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, microfilming, recording or otherwise, without written permission of the publisher. A copy of this article is available from the publisher for \$7.50.

TABLE 1. 2-Phenoxynicotinic Acids (I-V) and Chromono[2,3-b]pyridines (VI-X)

Compound	R	mp, °C	Empirical formula	Found, %				Calc., %				Yield, %	IR spectrum, ν_{CO} , cm^{-1}
				C	H	N	Hal	C	H	N	Hal		
I	H	179-180 ¹	$\text{C}_{12}\text{H}_9\text{NO}_3$	—	—	—	—	—	—	—	—	81	
II	CH_3	167-168	$\text{C}_{13}\text{H}_{11}\text{NO}_3$	68,2	4,8	6,2	—	68,1	4,8	6,1	—	76	
III	Br	170-171	$\text{C}_{12}\text{H}_8\text{BrNO}_3$	62,2	2,8	4,7	27,1	62,1	2,7	4,8	27,2	78	
IV	Cl	157-158	$\text{C}_{12}\text{H}_8\text{ClNO}_3$	57,8	3,3	5,7	14,3	57,8	3,2	5,6	14,2	72	
V	F	179-180	$\text{C}_{12}\text{H}_8\text{FNO}_3$	66,9	3,8	5,9	—	67,0	3,8	6,0	—	75	
VI	H	182-183 ¹	$\text{C}_{12}\text{H}_7\text{NO}_2$	—	—	—	—	—	—	—	—	63	1672
VII	CH_3	171-172	$\text{C}_{13}\text{H}_9\text{NO}_2$	73,9	4,3	6,7	—	73,9	4,3	6,6	—	61	1660
VIII	Br	195-196	$\text{C}_{12}\text{H}_6\text{BrNO}_2$	52,3	2,2	5,1	28,9	52,2	2,2	5,1	29,0	54	1655
IX	Cl	201-202	$\text{C}_{12}\text{H}_6\text{ClNO}_2$	62,2	2,7	5,9	15,2	62,2	2,6	6,0	15,3	50	1665
X	F	181-182	$\text{C}_{12}\text{H}_6\text{FNO}_2$	61,9	3,5	6,6	—	61,8	3,4	6,5	—	56	1663

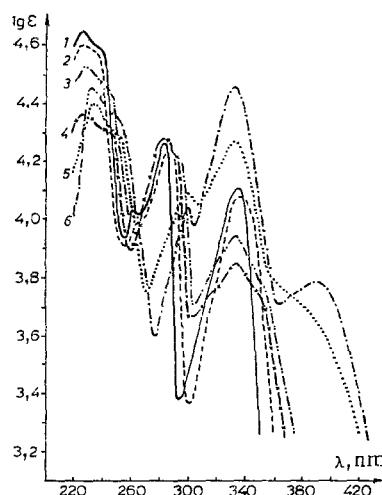
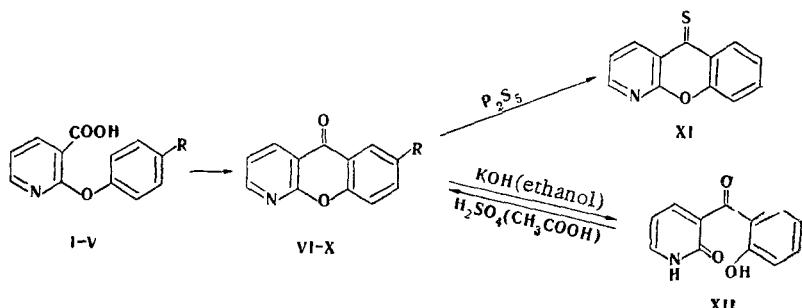


Fig. 1. UV spectra of VI-X: 1) in hexane; 2) in ethanol; 3) in H_2SO_4 (at a base-to-acid ratio of 1:1); 4, 5, 6) in 40, 90, and 96% sulfuric acid, respectively.



heated in glacial acetic acid in the presence of sulfuric acid. The structures of VI-X were confirmed by their IR spectra, which contain ν_{CH} bands at 3080 ν_{CO} bands at 1655-1672 cm^{-1} , and four bands due to the stretching vibrations of benzene and heterocyclic rings at 1620, 1600, 1580, and 1570 cm^{-1} .

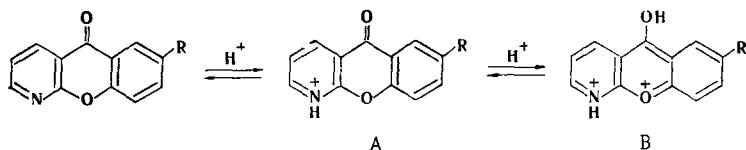
The chromono[2,3-p]pyridines dissolve in concentrated sulfuric acid to give yellow solutions. In order to study the transformations that accompany this phenomenon, we obtained the spectra of hexane, ethanol, and sulfuric acid solutions of VI-X of varying concentrations. The spectrum of VI is presented in Fig. 1 as an example.

TABLE 2. Log Q - H_o Regression Parameters and pK_a Values of Chromono[2,3-b]pyridines (VI-X)

Compound	R	λ_{max} , nm	$\lg \epsilon$	- H_o interval	-a	-b	- pK_a	r	s
VI	H	332	4.462	10.4-7.60	9.04	0.994	9.09 ± 0.02	0.998	0.044
VII	CH ₃	341	4.532	10.4-8.04	8.56	0.993	8.62 ± 0.01	0.995	0.011
VIII	Br	340	4.544	10.4-7.72	9.72	0.992	9.81 ± 0.01	0.999	0.029
IX	Cl	340	4.580	10.4-8.04	9.59	0.994	9.65 ± 0.01	0.999	0.026
X	F	338	4.483	10.4-7.72	9.13	0.978	9.34 ± 0.02	0.999	0.028

*The data for solutions of VI-X in 96% sulfuric acid are presented.

Maxima are observed in the UV spectrum of a hexane solution of VI at 225, 236, 260, 282, and 336 nm, and it is similar to the spectrum of xanthone [2] in the same solvent but differs from it with respect to its higher intensity. The bathochromic shift on passing to an ethanol solution of VI provides evidence that the spectrum of VI is determined by $\pi-\pi^*$ transitions. A decrease in the intensity of the absorption in the maximum, which is more strongly expressed for the shortwave band and is only slight for the long-wave band, is observed in the spectra of sulfuric acid solutions of VI up to an acidity of -1.01 H_o . This change in the spectrum is probably associated with protonation of the heterocyclic nitrogen atom and development of ion A, since the pK values of pyridine [3] and xanthone [4] are, respectively, 5.23 and -4.08 units, and, because of this, protonation of the nitrogen atom in VI should precede protonation of the carbonyl group.



Within the limits of acidities of the medium from -1.01 to -5.65 H_o units the character of the spectrum of VI remains practically unchanged. The intensity of the long-wave band increases as an acid concentration of 80% is reached ($H_o = -6.97$) and as the acidity increases further. This occurs owing to protonation of the carbonyl group and the development of doubly charged ion B. Since VI-X behave like primary Hammett bases, one must use the H_o acidity function [5] for the quantitative characterization of the acid-base equilibrium of the ions A \rightleftharpoons B) and must calculate the pK_a values from the equation $pK_a = H_o + \log (B)/[A]$.

The linear dependence of the logarithms of the indicator ratios (log Q) on H_o for the sulfuric acid-water system, which is satisfied with a slope close to unity, confirms the correctness of the selection of the H_o acidity function as a measure of the acidity of the medium. The pK_a values of VI-X (Table 2), which range from -8.62 to -9.81, depend on the substituents in the benzene ring, and correlate with the Hammett σ_p constants ($r = 0.996$, $\rho = -2.78$, calculated $pK_a = -9.11$, and $s = 0.04$), were calculated from the equation presented above. The correlation of the pK_a values with the σ_p constants but not with the σ_p^+ constants ($r = 0.508$) constitutes evidence for the absence of direct polar conjugation between the substituents and the reaction center. This is apparently due to the fact that the positive charge on ion B is not concentrated on the oxygen atom of the pyran ring but rather is delocalized due to interaction with the π -electron system of the pyran and benzene rings. The decrease in the pK_a value of chromono[2,3-b]pyridine by five units as compared with the pK_a of xanthone [4] is associated with the manifestation of electron-acceptor properties on the part of the protonated pyridine ring.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The UV spectra were recorded with a Spektro MOM-202 spectrophotometer. The ionization constants in a sulfuric acid-water system were determined spectrophotometrically with the same spectrophotometer ($2-5 \cdot 10^{-5}$ M solutions at $20 \pm 1^\circ$). The analytical wavelengths corresponded to the maximum at 332-341 nm. In connection with the fact that the

basicities of VI-X are low and do not make it possible to obtain 100% ionized solutions, the maximum optical densities were calculated from the formula proposed in [6]. The parameters of the $\log Q - H_0$ dependence were calculated by the method of least squares. The pK_a values were calculated with respect to seven to eight points at a fixed reliability of 0.98.

2-Phenoxy nicotinic Acids (I-V). A 50-g sample of the corresponding phenol was added to a solution of sodium ethoxide (5 g of Na in 100 ml of C_2H_5OH), the alcohol was vacuum evaporated, 50 g of 2-chloronicotinic acid was added, and the mixture was heated at 170-180° for 5 h. It was then cooled, treated with 200 ml of 10% hydrochloric acid, and extracted with ether. The extract was treated with 10% hydrochloric acid solution, and the resulting precipitate was removed by filtration and crystallized from benzene.

Chromono[2,3-b]pyridines (VI-X). A 5-ml (0.05 mole) sample of phosphorus oxychloride was added to 0.01 mole of the corresponding 2-phenoxy nicotinic acid, and the mixture was heated at 105-110° for 5 h, after which it was cooled and poured into cold water. The aqueous mixture was neutralized with 10% sodium hydroxide solution, and the precipitated bases VI-X were removed by filtration and crystallized from benzene.

Chromono[2,3-p]pyridine (VI). A mixture of 0.01 mole of 2-phenoxy nicotinic acid and 10 ml of polyphosphoric acid was heated at 160° for 6 h, after which it was cooled, treated with water, and neutralized with 10% sodium hydroxide solution. The resulting precipitate was crystallized from benzene to give 0.75 g (38%) of VI. No melting-point depression was observed for a mixture of this product with the product obtained in the preceding experiment.

Thiochromono[2,3-b]pyridine (XI). A mixture of 0.01 mole of VI and 2 g of phosphorous pentasulfide in 20 ml of xylene was heated at 140° for 5 h, after which the hot solution was filtered, and the filtrate was evaporated to dryness. The residue was crystallized from ethanol to give 1.71 g (78%) of long green acicular crystals with mp 170°. Found: N 6.62; S 14.77%. $C_{12}H_9NOS$. Calculated: N 6.57; S 15.04%.

3-(o-Hydroxybenzoyl)-2-pyridone (XII). A mixture of 0.01 mole of VI and 3 g of potassium hydroxide in 20 ml of ethanol was refluxed for 3 h, after which it was cooled and poured into 100 ml of cold water. The aqueous mixture was acidified with 10% hydrochloric acid, and the mixture was worked up to give 1.33 g (62%) of XII with mp 229-230° (ethanol). Found: N 6.60; C 66.90; H 4.27%. $C_{12}H_9NO_5$. Calculated: N 6.51; C 66.97; H 4.22%.

Cyclization of 3-(o-Hydroxybenzoyl)-2-pyridone. A solution of 0.01 mole of XII in 5 ml of glacial acetic acid and 1 ml of concentrated sulfuric acid was heated at 100° for 20 min, after which it was cooled and poured into cold water. The aqueous mixture was neutralized with 10% sodium hydroxide solution, and the resulting precipitate was removed by filtration to give 1.44 g (73%) of VI with mp 183° (benzene). No melting-point depression was observed for a mixture of this product with a sample of VI obtained by cyclization of 2-phenoxy nicotinic acid.

LITERATURE CITED

1. F. G. Mann and I. H. Turnbull, J. Chem. Soc., 761 (1951).
2. R. N. Nurmuhametov, L. A. Mileshina, and D. N. Shigorin, Opt. Spektrosk., 22, 740 (1967).
3. A. Albert, in: Physical Methods in the Chemistry of Heterocyclic Compounds (ed. by A. R. Katritzky), Academic Press (1963).
4. A. N. Tolmachev, L. M. Shulezhko, and A. A. Kiselenko, Zh. Obshch. Khim., 35, 1707 (1965).
5. L. Hammett, Physical Organic Chemistry, McGraw-Hill, New York (1940).
6. O. F. Ginzburg and N. S. Mel'nikova, Zh. Obshch. Khim., 25, 1156 (1955).