SYNTHESIS AND ACID–BASE TRANSFORMATIONS OF 2-SUBSTITUTED 3-METHYLPYRIDO-[2,3-b]CHROMONES

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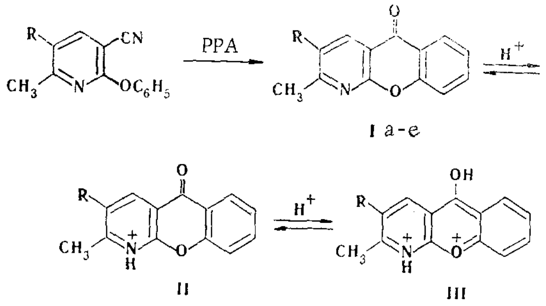
2-Substituted 3-methylpyrido[2,3-b]chromones were obtained by heating 5-substituted 6-methyl-2-phenoxynicotinonitriles in polyphosphoric acid. Their behavior in sulfuric acid solutions was studied by means of spectrophotometry.

We have previously synthesized pyrido[2,3-b]chromones with substituents in the benzene ring of the heterocyclic system and have studied their ionization constants [1]. In the present research in order to investigate the transmission of the electronic effects in compounds of this type through the protonated pyridine ring and to determine the range of applicability of the method of preparation we accomplished the synthesis of 2-substituted 3-methylpyrido[2,3-b]-chromones (Ia–e) by heating 5-substituted 6-methyl-2-phenoxynicotinonitriles [2] in polyphosphoric acid (PPA) (Table 1).



The structure of Ia–e was confirmed by the IR spectra, in which bands at 1670–1675 cm^{-1} (νCO) are observed but, in contrast to the spectra of the starting nitriles, the band of a nitrile group is absent. Maxima at 220, 260, 280, and 330–350 nm are observed in the UV spectra of solutions of these compounds in ethanol; the form of the spectra is similar to the form of the spectrum of pyrido[2,3-b]chromone [1].

A decrease in the intensity of the absorption, which is more pronounced for the bands at 220 and 330 nm and is evidently due to protonation of the starting compounds, occurs in the UV spectra of sulfuric acid solutions of Ia–e as the acid concentration is increased from 0 to 40%. It follows from a comparison of the pK values of pyridine [3] and xanthone [4], which are, respectively, 5.23 and –4.08 (55% sulfuric acid), that protonation of the nitrogen atom in Ia–e should precede protonation of the carbonyl group, i.e., ion II is produced in the first stage of ionization. The character of the spectrum remains virtually unchanged in solutions with acid concentrations from 40% to 80%. The intensity of the long-wave band increases commencing with 80% acid and as its percentage is increased. This change in the spectra is due to the development of doubly charged ions III.*

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*Compound Ic contains three centers that are capable of protonation. The nitrogen atoms of the pyridine ring and the amino group should be protonated initially (the pK of the first step in the ionization of 3-aminopyridine is 5.98 [5], while that of the second step is –1.5 [6]), after which the carbonyl group is protonated; the NH_3^+ group acts as a substituent in the 2 position of ions II and III in this case.

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TABLE 1. 3-Methylpyrido[2,3-b]chromones (I)

Compound	R	mp, °C	Found, %			Empirical formula	Calculated, %			Yield, %
			C	H	N		C	H	N	
Ia	H	129—131	73,7	4,1	6,5	$C_{13}H_9NO_2$	73,9	4,3	6,6	55
Ib	CH_3	184—186	74,9	4,9	6,2	$C_{14}H_{11}NO_2$	74,7	4,9	6,2	71
Ic	NH_2	262—264	69,0	4,5	12,4	$C_{13}H_{10}N_2O_2$	69,0	4,4	12,4	56
Id	Br	187—189	—	—	4,5	$C_{13}H_8BrNO_2$[a]	—	—	4,8	70
Ie	Cl	173—174	—	—	6,0	$C_{13}H_8ClNO_2$[b]	—	—	5,7	43

[a] Found: Br 27.3%. Calculated: Br 27.5%. [b] Found: Cl 14.4%. Calculated: Cl 14.5%.

TABLE 2. Acid–Base Properties and UV Spectra of 3-Methylpyrido[2,3-b]chromones (I)

Compound	λ_{max},[a] nm	lg ε	$-H_0$ range	$-a$[b]	$-b$[b]	$-pK_a$	r	s
Ia	332	4,38	7,92—9,15	7,978	0,926	8,61±0,09	0,986	0,07
Ib	336	4,37	7,47—9,85	9,186	1,116	8,23±0,07	0,992	0,03
Ic	338	4,23	9,05—10,17	8,648	0,917	9,43±0,08	0,974	0,08
Id	348	4,22	8,38—9,85	9,903	1,092	9,07±0,10	0,991	0,06
Ie	344	4,28	8,38—9,85	9,575	1,062	9,01±0,15	0,970	0,11

[a] For solutions of Ia-e in 96% sulfuric acid. [b] The parameters of the equation log Q = a + b·H_0.

A study of the II ⇄ III equilibrium in the sulfuric acid–water system showed that ions II behave like primary Hammett bases, and their basicities can be characterized by the H_0 acidity function [7]. This is confirmed by the dependence of the logarithms of the indicator ratios (log [III]/[II] = log Q) on H_0 with a slope close to unity. The pK_a values that characterize the II ⇄ III equilibrium (Table 2) correlate well with the σ_p constants of the substituents [7] ($r = 0.998$, $\rho = -2.032$, $pK_a{}^{\circ}{}_{calc} = -8.59$, and $s = 0.032$).* The ρ value shows that protonation of the pyridine ring in ions II transmits the electronic effects of the substituents to the benzopyran fragment, which is the reaction center, with the same ease as the benzene ring of the latter [1].

EXPERIMENTAL

The IR spectra of solutions in CCl_4 were recorded with a UR-20 spectrometer. The UV spectra were recorded with an SF-16 spectrophotometer. The ionization constants in sulfuric acid–water were determined spectrophotometrically with the same spectrophotometer at 20 ± 1 °C. The analytical wavelength corresponded to the maximum at 332-348 nm. In connection with the low basicities of Ia-e and the impossibility of obtaining a 100% ionized solution, the maximum optical densities were calculated from the formula (see [8]) $D_{max} = D' \cdot D''(1 - n)/D'' - n \cdot D'$, where D' and D" are the optical densities of solutions of Ia-e at two different H_0 values, and n is the algorithm of the difference in these H_0 values taken with the opposite sign. The parameters of the dependence of log Q on H_0 were calculated by the method of least squares. The pK_a values were calculated from the equation $pK_a = H_0 + \log[III]/[II]$ from seven points at a predesignated reliability of 0.98 (Table 2).

3-Methylpyrido[2,3-b]chromones (Ia-e). A mixture of 30 g of PPA and 0.01 mole of the corresponding 6-methyl-2-phenoxynicotinonitrile was heated at 170°C for 6 h, after which it was poured into water, and the aqueous mixture was neutralized with 10% NaOH solution. The precipitate was removed by filtration. Compounds Ib,d,e were crystallized from ethanol, Ia was crystallized from benzene, and Ic was crystallized from hexane.

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*The pK_a value of Ic was not used in the correlation.

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SYNTHESIS OF 2-HYDROXYMETHYLENE- AND 2-DIMETHYLAMINOMETHYLENE-3-OXOQUINUCLIDINES AND THEIR REACTIONS WITH NUCLEOPHILIC REAGENTS

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The reaction of 3-oxoquinuclidine with ethyl formate in the presence of sodium and with dimethylformamide diethylacetal was used to synthesize 2-hydroxymethylene- and 2-dimethylaminomethylene-3-oxoquinuclidines, which upon reaction with amines from N-substituted 2-aminomethylene-3-oxoquinuclidines and upon reaction with hydrazine hydrate give pyrazolo[3,4-b]quinuclidines. The reaction of 2-aryl- and 2-heteroarylmethylene-3-oxoquinuclidines with hydrazine hydrate and thiourea, which led to the synthesis of pyrazolo[3,4-b]- and pyrimido[5,4-b]quinuclidines with aryl or heteroaryl substituents in the resulting ring, was studied.

One of the methods for the synthesis of condensed quinuclidine derivatives is the conversion of 3-oxoquinuclidine (I) to 2-methylene- and 2-arylidene-3-oxoquinuclidines with subsequent reaction of these compounds of their derivatives with bifunctional nucleophilic reagents [1-5]; new partially or completely hydrogenated rings condensed with the quinuclidine ring are formed as a result of the reaction of the binucleophiles with both the carbonyl group and the olefinic bond of the indicated α,β-unsaturated ketones. It seemed of interest to study the possibility of the synthesis of quinuclidines condensed with unsaturated heterorings on the basis of 2-hydroxymethylene- (II) and 2-dimethylaminomethylene-3-oxoquinuclidines (III), with which nucleophilic reagents should react not only at the olefinic bond but also at the hydroxy or dimethylamino group.

Compounds II and III have not been described in the literature. We obtained 2-hydroxymethylene-3-oxoquinuclidine (II) in 67% yield by the reaction of 3-oxoquinuclidine (I) with ethyl formate in the presence of an equimolar amount of sodium metal, and we prepared 2-dimethylaminomethylene-3-oxoquinuclidine (III) in 58% yield by prolonged refluxing of ketone I in a solution of dimethylformamide diethylacetal with simultaneous removal of the resulting ethanol.

The structures of II and III were confirmed by the ^{1}H and ^{13}C NMR spectra. In the ^{1}H NMR spectra (Table 1) the singlets at 8.89 (ketone II) and 6.91 ppm (ketone III) correspond to the protons attached to the exocyclic double bond; in the ^{13}C NMR spectra (Table 2) of these compounds the signals at 180.0 and 137.6 ppm, respectively, correspond to the exocyclic carbon atom.

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