STRUCTURES AND REACTIVITIES OF 2-METHYL- AND 2-BENZYL-3-HYDROXYPYRIDINES AND THEIR N-OXIDES

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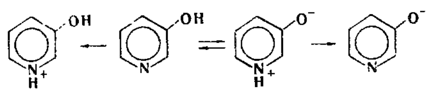
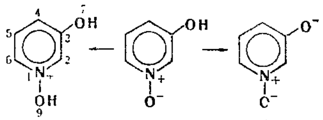
It was shown by UV spectroscopy that the introduction of CH_3 and CH_2Ph groups into the 2 position of 3-hydroxypyridine and its N-oxides does not have a substantial effect on the acid-base transformations of these compounds. The effect of methyl and benzyl groups on the electronic and energy characteristics of 3-hydroxypyridine and its N-oxide was studied by means of perturbation theory within the framework of the Hückel MO method. The reactivity indexes (RI) of 2-methyl- and 2-benzyl-3-hydroxypyridines and their N-oxides were calculated, and the RI were correlated with the experimentally observed regularity of the orientation of electrophilic substitution in the indicated compounds.

2-Methyl- and 2-benzyl-3-hydroxypyridines and their N-oxides were investigated in the present research by spectral and quantum-chemical methods for a systematic study of the structures and reactivities of 3-hydroxypyridine and its derivatives, which have a number of valuable biological properties [1, 2].

One of the peculiarities of 3-hydroxypyridine (I) and its N-oxide (II) is the possibility of their existence in neutral (N), dipolar (D), cationic (C), and anionic (A) forms, depending on the pH of the medium [3, 4].



I



II

Our comparison of the electronic absorption spectra [3, 4] of I and II with the spectra of 2-methyl- (III) and 2-benzyl-3-hydroxypyridines (IV) and their N-oxides (V, VI) showed that the introduction of CH_3 and CH_2Ph groups into the 2 position does not affect the acid–base transformations of I and II. In fact, it is apparent from Table I that III and IV have λ_{max} 282 and 284 nm of the longwave $\pi-\pi^*$ absorption bands characteristic for the H form of I [3]. However, the spectra of III and IV in water contain bands at 316 and 320 nm that characterize the B and N forms. As in the case of I [3], bathochromic shifts ($\Delta\lambda$) of the long-wave band of 24 and 22 nm are observed in the UV spectra of III and IV on passing from neutral to alkaline media, whereas bathochromic shifts of 6 and 8 nm are observed on passing from neutral (ethanol) to acidic media. The first shift is due to ionization of the OH group, whereas the second shift is due to protonation of the ring nitrogen [3]. As in the case of II [4], bathochromic shifts of the long-wave band (average $\Delta\lambda$ values of 9 and 25 nm, respectively), are observed in the spectra of V and VI on passing from acidic to neutral (ethanol) and alkaline media. This is due to loss of protons by the $>\overset{+}{N}-OH$ and OH^4 groups [4].

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TABLE 1. UV Spectra of III-VI

Compound	Medium	λ_{max}, nm				lg ε_{max}				ΔE	
										exptl.	calc.
III	Ethanol	220			282	3,62			3,66	1,80	1,80
	Water	220	249	290	316	3,62	3,61	3,49	3,60	1,61	1,61
	1 N HCl	224			288	3,44			3,82	1,76	1,76
	1 N KOH	220	245		306	3,42	3,90		3,72	1,66	1,66
IV	Ethanol				284				3,81	1,79	1,79
	Water	220	251	286	320					1,59	1,59
	1 N HCl	220			292	3,63			4,01	1,74	1,74
	1 N KOH	220	240		306	3,90	3,92		3,84	1,66	1,66
V	Ethanol	222	262		299	4,22	3,92		3,32	1,70	1,67
	Water	220	254		295	4,23	3,87		3,40		
	1 N HCl	220	255		291	3,92	3,42		3,66	1,75	1,75
	1 N KOH	235			316	4,34			3,75	1,61	1,61
VI	Ethanol	266	265		305	4,11	3,94		3,29	1,67	1,67
	Water	220	256		300						
	1 N HCl	220	258		295					1,72	1,72
	1 N KOH	235			320	4,45			3,85	1,59	1,59

TABLE 2. Electronic Characteristics and Bond Lengths for the H Forms of III-VI

Compound and form	No. of the atom	g_r	r-s bond	P_{rs}	r_{rs}, Å
III N	1	1,082	1—2	0,658	1,331
	2	1,012	1—6	0,664	1,330
	3	0,974	2—3	0,644	1,400
	4	1,006	3—4	0,655	1,398
	5	1,004	4—5	0,667	1,395
	6	0,987	5—6	0,665	1,396
	7	1,961	3—7	0,197	1,363
	8	1,972	2—8	0,164	1.510
IV N	1	1,082	1—2	0,657	1,331
	2	1,012	1—6	0,664	1,330
	3	0,974	2—3	0,644	1,400
	4	1,006	3—4	0,655	1,398
	5	1,004	4—5	0,667	1,396
	6	0,987	5—6	0,665	1,396
	7	1,961	7—3	0,197	1,363
	8	1,963	8—2	0,165	1,510
	1′	1,033	1′—8	0,091	1,525
	2′	0,990	1′—2′	0,663	1,396
	3′	1,000	2′—3′	0,667	1,395
	4′	0,994	3′—4′	0,666	1.395
V N	1	1,125	1—2	0.629	1,336
	2	1,032	1—6	0.634	1,335
	3	0,972	2—3	0,652	1,399
	4	1,022	3—4	0,651	1,399
	5	1,002	4—5	0,664	1,396
	6	1,003	5—6	0,671	1,395
	7	1,961	7—3	0,197	1,363
	8	1,976	8—2	0,149	1,513
	9	1,808	9—1	0,282	1.368
VI N	1	1,125	1—2	0,629	1,335
	2	1,032	1—6	0,634	1,334
	3	0,972	2—3	0,651	1,399
	4	1,022	3—4	0,651	1,399
	5	1,002	4—5	0,664	1,396
	6	1,003	5—6	0,671	1,395
	7	1,961	7—3	0,197	1,363
	8	1,968	8—2	0,150	1,513
	9	1,808	9—1	0,282	1,368
	1′	1,033	1′—8	0,090	1,525
	2′	0,990	1′—2′	0,663	1,396
	3′	1,001	2′—3′	0,667	1,395
	4′	0,994	3′—4′	0,666	1,395

In order to evaluate the effect of methyl and benzyl groups on the electronic and energy characteristics of the various forms of I and II, we used the perturbation theory developed for the Hückel MO method by Coulson, Longuet–Higgins [5], and Dewar [6]. In addition, perturbation theory makes it possible to determine the numerical values of the coulombic and resonance parameters through the use of the long-wave absorption band in the UV spectra of various compounds [7].

A comparison of the calculated values [the π-electron density (g_r), the bond orders (P_{rs}), and bond

TABLE 3. Results of Calculations of the Energy Values in the Units Presented in [7] ($\beta = -2.44$ eV)

Compound and its form	Substituent in the 2 position									
	CH_3					CH_2-Ph				
	ΔΔEexp	ΔΔEcalc	ΔERS	ΔERS /K	ΔDER /n	ΔΔE exp	ΔΔEcalc	ΔERS	ΔERS/K	ΔDER/n
I N	0,04	0,04	0,186	0,093	0,264	0,05	0,05	0,217	0,027	0,028
I B	0,02	0,02	0,170	0,085	0,268	0,04	0,04	0,240	0,030	0,033
I C	0,04	0,04	0,180	0,090	0,260	0,06	0,06—	0,232	0,029	0,022
I A	0,05	0,05	0,300	0,150	0,266	0,05	0,05	0,304	0,038	0,028
II N	−0,01	0,01	0,164	0,082	0,228	0,01	0,01	0,240	0,030	−0,008
II C	0,02	0,02	0,178	0,089	0,216	0,05	0,05	0,208	0,026	−0,024
II A	0,01	0,01	0,321	0,161	0,234	0,03	0,03	0,376	0,047	0,14

TABLE 4. Reactivity Indexes for the Various Forms of III-VI

Compound and its form	r No. of the atom	Polarization step		π complex		σ complex
		Q_r	π_{rr}	f_r	S_r	L_r
III C	4	+0,008	0,404	0,043	0,817	2,542
	5	−0,013	0,398	0,300	0,807	2,582
	6	+0,034	0,403	0,452	0,825	2,542
III A	4	−0,011	0,410	0,092	0,926	2,456
	5	−0,019	0,400	0,172	0,920	2,515
	6	+0,010	0,406	0,326	0,930	2,462
IV C	4	+0,008	0,404	0,029	0,818	2,543
	5	−0,013	0,398	0,274	0,828	2,582
	6	+0,034	0,403	0,370	0,811	2,543
	2	+0,005	0,404	0,034	0,853	2,485
	3	0,000	0,398	0,012	0,830	0,539
	4	+0,003	0,399	0,072	0,846	2,490
IV A	4	−0,011	0,406	0,058	0,844	2,459
	5	−0,019	0,400	0,218	0,824	2,516
	6	+0,010	0,404	0,320	0,890	2,462
	2	+0,015	0,399	0,001	0,927	2,527
	3	−0,001	0,398	0,000	0,824	2,533
	4	+0,010	0,399	0,002	0,831	2,529
V C	4	+0,006	0,407	0,060	0,856	2,514
	5	−0,011	0,398	0,318	0,826	2,534
	6	+0,033	0,410	0,480	0,900	2,505
V A	4	−0,036	0,415	0.014	1,009	2,322
	5	−0,031	0,399	0,242	0,953	2,440
	6	−0,014	0,420	0,180	1,022	2,308
VI C	4	+0,006	0,407	0,022	0,860	2,516
	5	−0,011	0,398	0,302	0,828	2,532
	6	+0,033	0,410	0,320	0,843	2,508
	2	+0,004	0,402	0,056	0,874	2,490
	3	0,000	0,398	0,022	0,816	2,545
	4	+0,002	0,400	0,132	0,870	2,495
VI A	4	−0,036	0,415	0,064	1,008	2,320
	5	−0,031	0,400	0,060	0,949	2,434
	6	−0,014	0,420	0,433	1,017	2,310
VI A	2	+0,006	0,401	0,016	0,861	2,526
	3	0,000	0,398	0,002	0,838	2,532
	4	+0,003	0,399	0,026	0,857	2,530

lengths (r_{rS}) for the N form of III-VI (Table 2)] with the analogous values [4, 7] of the N form of I and II, respectively, indicates the weak effect of CH_3 and CH_2Ph groups on the electronic characteristics of the β-pyridol ring. For this reason, the nonuniform distribution of the π-electron density on the carbon atoms in the hydroxypyridine ring of III-VI molecules is associated primarily with the effect of the ring nitrogen atom and the OH group.

The transition energies (ΔE) found from the difference in the energies of the lower vacant molecular orbital and the higher occupied molecular orbital for the maximum of the long-wave absorption band (Table 1) and the calculated values (ΔΔE) (Table 3), which characterize the effect of CH_3 and CH_2Ph groups on the ΔE values of I and II are in good agreement with the experimental data.

A measure of the interaction or conjugation of a substituent (S) with a π-ring system (R) is energy $\Delta\varepsilon^{rS}$, which is equal to the difference in the π energies of conjugated system rS and the energies of the isolated RS and S systems. The calculations show (Table 3) that the energy of conjugation of the CH_3 group is less than the energy of conjugation of the CH_2Ph group with the hydroxypyridine ring in III–VI. Energy $\Delta\varepsilon^{RS}$ enters into the delocalization energy per π electron ($DE^{RS}/n+K$) of system RS, characterizing the change in the stability DE^R/n of system R. As a consequence of this, the newly obtained RS compound will be more stable than the starting compound under the condition

$$\Delta\varepsilon^{RS}/k > DE^R/n - DE^S/k = \Delta DE^R/n,$$

where DE^R and DE^S are the delocalization energies, and n and k are the number of π electrons in isolated systems R and S, respectively.

From an analysis of Table 3 it can be concluded that the addition of a CH_3 group lowers the stability of I and II, whereas the addition of a CH_2Ph group somewhat increases their stability. The destabilizing effect of the CH_3 group was established during a mass-spectroscopic investigation of I and III, according to which transition from 3-hydroxypyridine to 2-methyl-3-hydroxypyridine was accompanied by a decrease in the stability with respect to electron impact from 28 to 22.6%, respectively [8].

In the theoretical examination of substitution reactions within the framework of the MO method the most important reactivity indexes (RI) are the π-electron charge (Q_r), the atomic self-polarizability (π_{rr}) in the polarization step, the boundary electron density (f_r), the hyperdelocalizability (S_r) in the π complex of the transition state, and the localization energy (L_r) in the σ complex.

According to the data in [9-12], electrophilic substitution in III and V proceeds at the 6 and 4 positions in alkaline and acidic media. The phenyl ring has the highest reactivity in IV and VI in acidic media, whereas the hydroxypyridine ring has the highest reactivity in alkaline media [9-12]. The coulombic and resonance parameters found by means of perturbation theory made it possible to calculate the RI for III–VI (Table 4); these RI accurately predict the direction of electrophilic substitution in 2-methyl-3-hydroxypyridine and its N-oxide and confirm the established regularity of orientation of electrophilic substitution as a function of the medium in 2-benzyl-3-hydroxypyridine and its N-oxide.

The best agreement between the calculations and the experiments was found when the localization energies (L_r) were used as the RI, whereas the π-charge distribution (Q_r) does not determine the direction of electrophilic attack.

EXPERIMENTAL

The UV absorption spectra (Table 1) were recorded with an SF-8 spectrophotometer.

The following were used in the calculations of III–VI by means of perturbation theory within the framework of the Hückel MO method: a heteroatomic model of the CH_3 group with coulombic parameter h = 2, the coulombic and resonance parameters for the nitrogen and oxygen atoms of the OH and N–O groups that we found in [4, 7], resonance parameters $R_{C-CH_3} = 0.54$, 0.47, 0.50, and 0.80 for the $C-CH_3$ bond, $R_{C-CH_2} = 0.3$, 0.5, 0.4, and 0.1 for the $C-CH_2Ph$ bond in the H, B, C, and A forms of III and IV, $R_{C-CH_3} = 0.5$, 0.45, and 0.85, and $R_{C-CH_2} = 0.3$, 0.5, and 0.4 in the H, C, and A forms of V and VI. The auxiliary inductive parameter for the carbon atoms adjacent to the CH_3 and CH_2-Ph groups (h) was assumed to be 0.1.

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