SYNTHESIS, ELECTRONIC STRUCTURE, AND ABSORPTION SPECTRA OF 9-HYDROXYPYRIDO[1,2-a]-PYRIMIDINIUM DERIVATIVES

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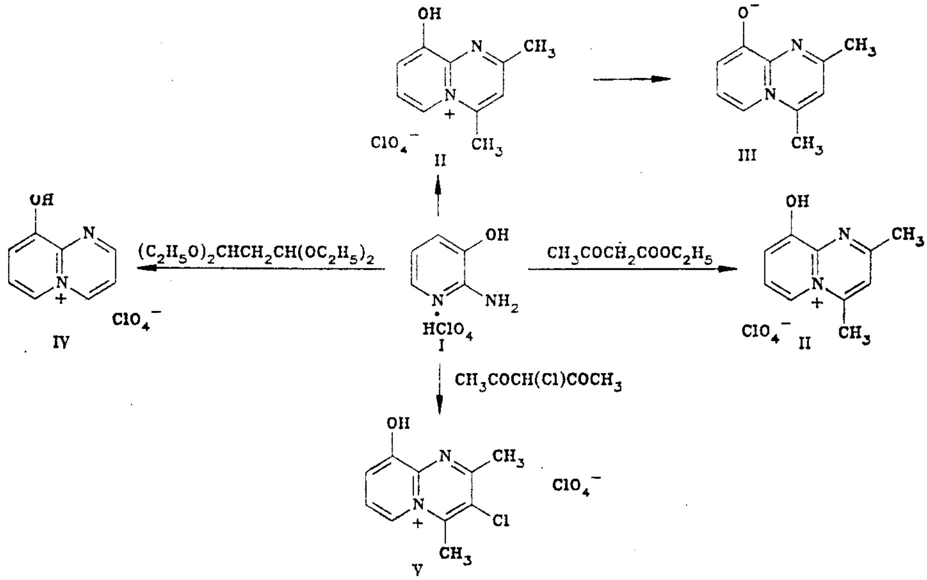
Pyrido[1,2-a]pyrimidinium salt derivatives have been prepared by condensation of 2-aminopyridinium salts with β-dicarbonyl compounds. The acid–base equilibrium dissociation constants for 2,4-dimethyl-9-hydroxypyrido[1,2-a]pyrimidinium perchlorate have been measured, and the spectroscopic characteristics of its neutral, anionic, and cationic forms have been determined; the electronic absorption spectra of the neutral and anionic forms of 2,4-dimethyl-9-hydroxypyrido[1,2-a]-pyrimidinium perchlorate have been interpreted based on this experimental and calculated data.

Developments and evolution in the chemistry of heterocyclic hydroxyl-containing antioxidants (3-hydroxypyridines, 5-hydroxypyrimidines) have stimulated interest in the synthesis of novel derivatives, whose structures might lead to the discovery of compounds in this series with interesting pharmacological properties; one such series involves nitrogen-containing bicyclic compounds with bridgehead nitrogen atoms.

The unusual behavior of acetoacetate ester upon condensation with 2-aminopyridinium perchlorate has been reported in the literature [1]. In the present paper we describe new experimental data relating to the synthesis and structure of pyrido[1,2-a]pyrimidinium salt derivatives prepared via this method. It was found that the condensation reaction could also be carried out using other 2-aminopyridine derivatives (in this case, 2-amino-3-hydroxypyridine). Thus, we have prepared 2,4-dimethyl-9-hydroxypyrido[1,2-a]pyrimidinium perchlorate (II) by condensation of the former with acetoacetate ester.



It is unclear, however, how and why acylacetate esters, containing four carbon atoms in the main chain, give the same condensation products with 2-aminopyridine salts as β-diketones [2], which represent five-carbon atom synthons.

IR Spectra. Compound II is an 8-hydroxyquinoline analog. In a series of papers [3-8] it has been demonstrated that the quinoline ring vibrations in the IR spectra of 8-substituted quinolines give rise to 8 bands in the 1623-1358 cm^{-1} region [cf. Table 1] [5], while the other remaining bands can be assigned to CH and OH group vibrations (Table 1). A large degree of similarity has been observed in a comparison of the IR spectra of

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TABLE 1. IR Absorption Spectra of 9-Hydroxypyrido[1,2-a]pyrimidinium Derivatives

Compound	Vibrational frequency, cm^{-1}*								
	$\nu_{OH}+$ $+\nu_{H_2O}$	ν_{OH}	ν_{CH}	ν_{CH_3}	ν_1^r	ν_2^r	ν_3^r	ν_4^r	ν_5^r
X**		3159 br	3045 w		1623±5 m	1598±8 s	1577±6 s	1503± ±6 vs	1466± ±8 s
II		3295 s 3220 sh	3026 sh 3083 w	2860 2930 sh	1645 vs	1580		1505 vs	1470+ s
III		3384 s 3238 sh	3038 m	2856 sh 2920 sh	1643 vs	1585/1569	1550/ 1535 vs	1495 vs	1459+ vs
IV	3434 ms [sic]		3026 w 3067 m	2860 s	1632 s	1577 m	1531 s		1469+ w
V	3407 s	3257 s	3030 m		1633 m/ 1616 m	1568	1534 s	1502 w	1474+ w

*+) Overlapped or obscured; vs) very strong; s) strong; m) medium; w) weak; vw) very weak; sh) shoulder; br) broad. $\nu_1{}^r$-$\nu_8{}^r$ are the 1-8 ring vibrational bands.
**X) 8-Substituted quinoline.

hydroxypyrido[1,2-a]pyrimidinium derivatives with the spectra of 8-substituted quinolines (Table 1). For example, there are seven or eight intense bands, in the same regions as noted by Katritzky [3, 4], in the range of heterocyclic ring vibrations (cf. Table 1). The bands characteristic of 8-substituted quinolines in the region 1589-1505 cm^{-1} are missing, however, in the IR spectra of compound II (Table 1). This band does appear in the spectra of its anionic forms (Fig. 1). It follows, therefore, that this band can be used as a criterion to assess the deprotonation of compound II. The maximum for the high-frequency ring vibration band in the IR spectra of compound II (Table 1) is 10-45 cm^{-1} higher than in the spectrum of 8-substituted quinolines. This suggests that there is strong perturbation of the ring due to the presence of the quaternary nitrogen atom. The second and third ring vibrational bands in the IR spectra of derivatives of II appear in the form of doublets, which are shifted toward lower frequency relative to their position in the IR spectra of 8-hydroxyquinoline. In the spectrum of the deprotonated form the $\nu_{C=N^+}$ band at 1643 cm^{-1} is retained, and a new band also appears at 1550/1565 cm^{-1}.

The IR spectra of compound II in the crystalline state contain a band at 3295, with a shoulder at 3220 cm^{-1}, in the hydroxyl group stretching vibration region. Bands at 3434-3407 cm^{-1} are assigned apparently to overlapping OH group and water molecule stretching vibration bands. The observed ν_{OH} bands are shifted 320 cm^{-1} relative to the free band in naphthols [7], which suggests the existence of strong intermolecular hydrogen bonding. This is furthermore consistent with the observed position of the ν_{OH} band in the IR spectrum of a very dilute solution of compound II in chloroform, where it appears as a doublet at 3640 (vw) and 3580 (m) cm^{-1}. The band splitting can be attributed to trans- and cis-orientations of the OH group.

An intense C−O stretching vibration band is observed in the range 1234-1322 cm^{-1}, and is shifted toward higher frequency upon deprotonation of the OH group.

The antisymmetric stretching vibrations for the anion $\nu_3(F_2)_{ClO_4^-}$ appear in the form of a band which is weakly resolved or split into several components, indicating that the symmetry of the perchlorate anion is distorted in the salt (Table 1).

Electronic Absorption Spectra. The electronic absorption spectrum of compound II in ethanol solution exhibits a long-wavelength band at 347 nm with a shoulder at 370 nm (Table 2). The presence of a shoulder can be

TABLE 1 (continued)

Vibrational frequency, cm^{-1}									
$\nu_6 r$	$\nu_7 r$	$\nu_8 r + \delta_{CH_3}$	$\beta_{CH} + \nu_{C-OH}$	ν_{C-OH}	$\nu^{as}_{ClO_4^-}$	$\beta_{CH} + \nu^{as}_{ClO_4^-}$	$\delta^{as}_{ClO_4^-}$	β	δ_{CH}
1433±11 s	1398± ±19 s	1358± ±10 m	1304± ±18 s			1069± ±12		1131± ±4 w	822± ±5 vs
1436/1420 vs	1390 s	1377+	1307 w	1258 s	1177, 1140 sh 1117 sh 1103 s	1067+ vs	620 s 591 w	1035, 978 sh 933 w	890, 861 w 747 s 729 w 668 w
1422 s	1382+ vs	1354/ 1340+ s	1309 vw	1275 vs				1034 m 982 m 926 w	863 m 735 s 725 s
1454 s	1403 w	1372+ vs	1305 s	1322 sh 1247 w	1181 w 1149 w 1115 vs	1089+ vs 1072+ sh	626 vs	1031 sh 941 w	898 w 823 s 801 w 789 w 775 m 728 m
1442 m	1414 s	1360+ s	1320 w	1300 w 1234	1187 m 1150 vs 1120 vs	1088+ vs	627 vs	1050, 1028 m 971 m 940 w	902 m 860 w 790 w 775 m 751

rationalized in terms of the existence of the following ionic equilibrium in solution: II ⇄ III + H^+.

As the solvent polarity for this solution is increased the intensity of the long-wavelength band increases, suggesting that the ionic equilibrium is shifted in favor of the dissociated form under these conditions.

In order to obtain more detailed information concerning the dissociation process for compound II we have recorded its electronic spectrum at different pH values (Fig. 2). The spectra exhibit several isosbestic points, which provide evidence for the existence of two compounds in solution. The acid dissociation constant for compound II measured potentiometrically gives a value of $pK_a = 4.73 \pm 0.04$. The dissociation constant for 8-hydroxyquinoline, on the other hand, is $pK_a = 9.89$ [3].

It should be noted in this regard that the electronic spectra of compound II differ markedly from the spectrum of the model compound, 8-hydroxyquinoline. For example, λ_{max} for the neutral form of 8-hydroxyquinoline (317 nm) is shifted 30 nm toward shorter wavelength relative to the position of this band in the spectrum of compound II (347 nm). Upon proton abstraction in basic solution the absorption maximum for 8-hydroxyquinoline is shifted toward longer wavelength, beyond the absorption maximum for compound II.

The long-wavelength band observed in the electronic absorption spectrum of compound II in ethanol solution exhibits λ_{max} 347 nm, but the band is asymmetric toward the shorter wavelength side. Based on our calculations we conclude that this band corresponds to two electronic transitions, at 353 and 334 nm, which are oriented at an angle of 80° relative to one another (Table 3). Since the oscillator strength (F) for the 353 nm transition is twice as great as for the 334 nm transition, the long-wavelength bands overlap one another and are observed in the form of an asymmetric band. The complex 353 and 334 nm transitions are due to electron density redistribution from the HOMO (ψ_n) to LUMO (ψ_m), 65% in the case of the 353 nm band, 38% in the case of the 334 nm band, as well as to $\psi_n \rightarrow \psi_{m+1}$, to the extent of 26% for the 353 nm transition and 50% for the 334 nm band ($n = 6$, $m = 7$). The 353 nm transition is furthermore due to an electron density shift to the pyrimidine ring $\Delta Q_\pi = 0.55e$ from the rest of the molecule (Fig. 3). In the case of the 334 nm transition the C═N bond in the pyrimidine ring is the primary or predominant electron acceptor, while in the case of the 353 nm transition it is the $C{=}N^+$ bond. Upon molecular deprotonation the bands due to these transitions are shifted toward the red, while retaining the overall characteristics

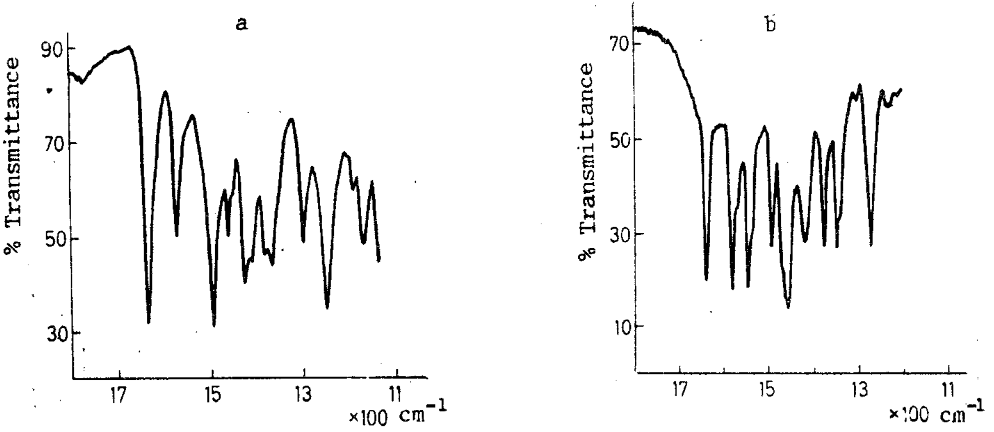

Fig. 1. IR absorption spectra: a) perchlorate II; b) oxide III.

of the neutral molecules (Table 3).

The experimental λ_{max} 241 nm band corresponds, based on our calculations, to two electronic transitions at 240 and 236 nm, and their F values are 1.5-times higher than those for the 353 and 334 nm transitions (Table 3). This ratio is corroborated experimentally at least qualitatively (Fig. 2). The 240 and 236 nm transitions, which are polarized at an angle of 95° relative to one another, are also complex or compound transitions. The 240 transition corresponds to 51% $\psi_{n-1} \rightarrow \psi_n$ and 14% $\psi_n \rightarrow \psi_{m+2}$. The C(3) and C(7) atoms appear to be the strongest electron acceptors in this transition, and the electron accepting capacity of the N and N^+ atoms seems to be two times lower than that of the above-mentioned carbon atoms. The 236 nm transition corresponds to $\psi_n \rightarrow \psi_{m+2}$ (65%) and $\psi_m \rightarrow \psi_{m+1}$ (9%). The oxygen (ΔQ = 0.152e) and C(2) atoms (ΔQ = 0.152e) are the strongest donor atoms in this transition, while the C(4) (ΔQ = 0.154e) and C(8) atoms (ΔQ = 0.072e) function as electron acceptor traps.

The experimentally observed λ_{max} 217 nm band is also due to two electronic transitions, at 217 and 212 nm (cf. Table 2 for their assignments).

π-Electronic Structure. It is clear from the molecular diagram depicted in Fig. 3 that there are three equivalent (strength) CN^+ bonds about the N^+ atom. This is characteristic as well of the three carbon–nitrogen bonds in the same positions in the molecular structure of 8-hydroxyquinoline. The quaternary nitrogen atom in compound II is a 1.6-times stronger π-electron acceptor than the nitrogen atom in the C=N bond (Fig. 3). The positive charge on N^+ is compensated (or balanced) to the extent of 0.42 e in this manner. The oxygen atom acts as an electron donor in both the ground and first excited states. In both compound II and 8-hydroxyquinoline the primary π-acceptor in the transition to the first excited state is the heterocyclic ring, while the benzene ring and hydroxyl group act as π-donors. The π-bonds in these molecules are thus significantly delocalized.

EXPERIMENTAL

IR spectra were recorded using a Specord IR-75 spectrophotometer (for KBr pellets and solutions in $CHCl_3$), with KBr cuvettes (5 mm cell length). Electronic absorption spectra were measured on a Specord UV-VIS spectrophotometer in the 200-700 nm wavelength range (using aqueous solutions or solutions in organic solvents). pH changes accompanying potentiometric titration were measured on an EV-74 potentiometer for aqueous solutions at 22°C, using a glass ESP-43-07 electrode as the operating electrode, and an EVP-IM3 silver chloride electrode as the reference electrode. Ionization constants were calculated according to a literature procedure [8].

Quantum mechanical calculations for the neutral and anionic forms of compound II were carried out based on the Pariser–Parr–Pople method, and the Dewar variation [9]. PMR spectra were obtained on Varian T-60 and Bruker AC-250 spectrometers using 0.2 mole/liter solutions in CD_3OD, DMSO-D_6, versus HMDS as internal standard. The results of C, H, N elemental analysis for all the newly synthesized compounds agreed with calculations.

2,4-Dimethyl-9-hydroxypyrido[1,2-a]pyrimidinium Perchlorate (II, $C_{10}H_{11}ClN_2O_6$). A. A mixture of 2.1 g (10 mmoles) 2-amino-3-hydroxypyridine perchlorate (I) with 1.3 g (13 mmoles) acetylacetone was heated at 140-160°C (in a bath) for 2 h. The reaction mixture was cooled, and the resulting precipitate was removed by filtration and washed with a small amount of alcohol or acetone. Evaporation of the filtrate gave an additional amount of product, which was combined with the first portion, and dried in a vacuum desiccator over $CaCl_2$. mp 192-193°C (from alcohol). PMR spectrum (DMSO-D_6): 2.82 (3H, s, 2-CH_3); 2.95 (3H, s, 4-CH_3); 7.91 (2H, m, 7.8-H); 8.04 (1H, s, 3-H); 8.69 ppm (1H, d, 6-H). Yield 1.78 g (68%).

B. A mixture of 2.1 g (10 mmoles) compound I and 1.95 g (15 mmoles) acetoacetate ester was heated at 160-170°C (in a bath) for 5-6 h; the reaction mixture was cooled, and the precipitate was separated by filtration,

TABLE 2. Electronic Absorption Spectra

Compound	Solvent	λ_{max}, nm (log ε)
II	Water	213 (4,28); 239 (4,29); 342 (3,86); 371 (3,70)
	Alcohol	217 (4,33); 241 (4,32); 260 (3,53); 347 (3,87); 370 (3,53)
	DMF	350 (3,54); 402 (3,77)
	2n NaOH	212 (4,32); 224 (4,28); 247 (4,11); 371 (3,94)
IV	Water	214 (4,43); 230 (4,40); 245 (4,33); 254 (4,30); 264 (4,21); 357 (4,24); 423 (4,01)
V	Water	224 (4,43); 237 (4,42); 268 (4,36); 372 (4,22); 424 (4,00)

TABLE 3. Calculated Electronic Absorption Spectra

Compound	λ_{max}, nm	F*	Polarization, deg relative to the x axis	MO Configuration interaction matrix
II	353	0,264	20,71	0,810 (6—7); −0,52 (6—8)
	334	0,137	−59,49	0,74 (6—8); 0,54 (6—7); 0,32 (5—7)
	240	0,289	−35,48	0,73 (5—7); −0,38 (6—8)
	236	0,326	−59,65	0,81 (6—9); 0,30 (6—8); 0,30 (6—8)
	214	0,709	37,73	0,83 (5—8); −0,30 (6—9)
	208	0.182	21,49	0,71 (4—7); −0,43 (6—10); 0,42 (4—8)
III	365	0,254	32,47	0,92 (6—7); −0,32 (6—8)
	343	0,176	−44,11	0,86 (6—8); 0,33 (6—7); −0,33 (5—7)
	245	0,165	−85,37	0,93 (6—9)
	242	0,424	−45,14	0,77 (5—7); 0,37 (4—8); 0,30 (6—8)
	217	0,462	38,34	0,83 (5—8); −0,38 (4—7)
	211	0,141	35,79	0,67 (4—7); −0,47 (6—10); 0,41 (4—8)

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*F) Oscillator strength.

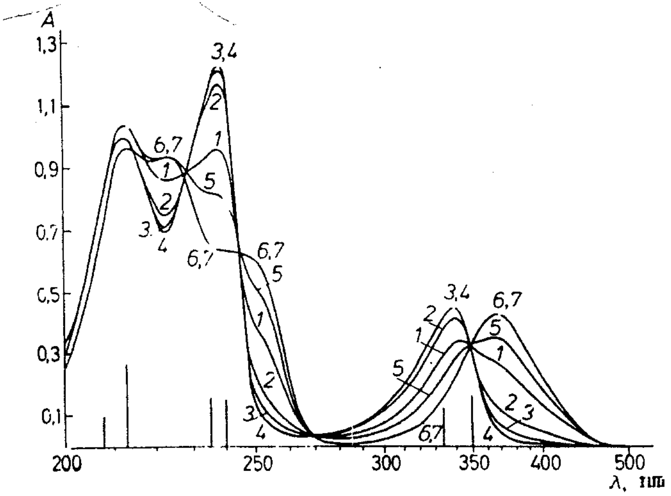

Fig. 2. Electronic absorption spectra of perchlorate II at different pH values: 1, 2, 3, 4) in water−HCl (1, pH 3.80; 2, pH 3.45; 3, pH 2.95; 4, pH 2.46); 5) in water (pH 4.25); 6, 7) in water−KOH (5, pH 8.35; 6, pH 8.89).

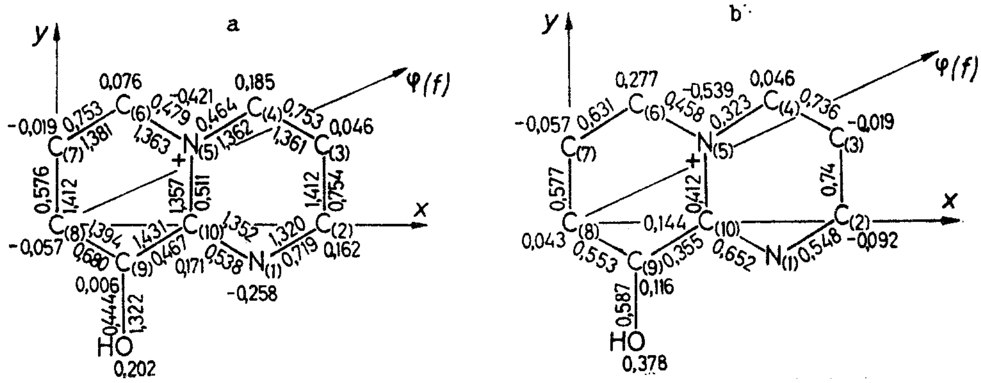

Fig. 3. Molecular diagram: a) ground state; b) first excited state.

washed with ether, and recrystallized from alcohol. Yield 45%. The compound was identical with a sample prepared as in Part A above.

2,4-Dimethyl[1,2-a]pyrimidine-9-oxide (III, $C_{10}H_{10}N_2O$). Prepared by passing an aqueous solution containing 1 g perchlorate II through a column with 5 g Dowex 50W × 2 resin (in its H^+ form), eluting with 20% aqueous ammonia (monitored by TLC using 6:1 alcohol–ammonia as the eluting system). The solution was evaporated to give yellow-green crystals, which were then recrystallized from alcohol and air-dried. Quantitative yield; mp 150-152°C. PMR spectrum (DMSO-D_6): 2.59 (3H, s, 2-CH_3); 2.71 (3H, s 4-CH_3); 7.76 (1H, br.s, 3-H); 8.38 ppm (3H, ms, 7.8-H).

9-Hydroxypyrido[1,2-a]pyrimidinium Perchlorate (IV, $C_8H_7ClN_2O_5$). A mixture of 2.1 g (10 mmoles) compound I with 7.1 ml 1,1,3,3-tetraethoxypropane in 25 ml alcohol was refluxed for 2 h, cooled, and the resulting precipitate was removed by filtration, washed with a small amount of alcohol, and recrystallized from alcohol and dried in a vacuum desiccator; mp 202-205°C. PMR spectrum (DMSO-D_6): 7.93 (1H, d, 8-H), 8.04 (1H, t, 7-H); 8.15 (1H, s, m, 3-H); 8.81 (1H, d, 6-H); 9.41 (1H, d, 2-H); 9.60 ppm (1H, d, 4-H). Yield 1.3 g (55%).

2,4-Dimethyl-3-chloro-9-hydroxypyrido[1,2-a]pyrimidinium Perchlorate (V, $C_{10}H_{10}Cl_2N_2O_5$). A mixture of 0.21 g (1 mmole) perchlorate I with 2.69 g (2 mmoles) 3-chloroacetylacetone in 3 ml alcohol was refluxed for 3 h. The reaction mixture was cooled, and the resulting crystals were removed by filtration and recrystallized from alcohol and dried in a vacuum desiccator; mp 244-246°C. PMR spectrum (CD_3OD): 2.91 (3H, s, 2-CH_3); 3.10 (3H, s, 4-CH_3); 7.88 (2H, m, 7.8-H); 8.54 ppm (1H, d, m, 6-H). Yield 1.65 g (57%).

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