ISOLATION AND PROPERTIES OF THE PRODUCTS OF THE COVALENT HYDRATION OF 4H-IMIDAZOLES

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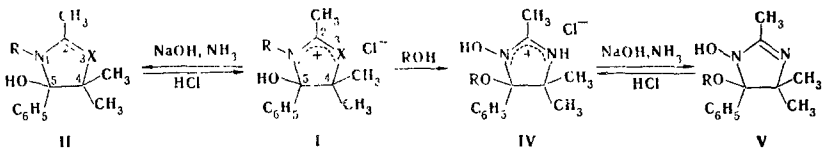
The neutralization of 5-hydroxy-4,4-dimethyl-2-imidazolinium chlorides yields in the free state the products of the covalent hydration of the corresponding 4H-imidazoles – 5-hydroxy-4,4-dimethyl-2-imidazolines. On being heated, the compounds obtained undergo various transformations, depending on the presence and position of oxygen-containing functions: 5-hydroxy-2-imidazoline gives 2-acetylamino-2-methyl-1-phenylpropan-1-ol; 3,5-dihydroxy-2-imidazoline dehydrates to 4H-imidazole 3-oxide; and 1,5-dihydroxy-2-imidazolines are converted into 2,3-dihydro-4H-1,2,5-oxadiazines.

It has been shown previously [1] that 4H-imidazole derivatives possess the capacity for adding a molecule of water or an alcohol under the action of hydrogen chloride with the formation of 2-imidazolinium salts, regardless of the presence and position of N-oxide oxygen and the nature of the radicals in positions 2 and 5 of the heterocycle. Although there are a number of examples in the literature of the ready hydration of heterocyclic cations [2, 5], there is no information on the isolation of the products of covalent hydration in the free state. The present paper describes the isolation of the products of the covalent hydration of 4H-imidazoles in the free state and discusses their properties.

The careful neutralization of 1,5-dihydroxy-2,4,4-trimethyl-5-phenyl-2-imidazolinium chloride (Ia) [1] with a small excess of a solution of caustic soda or ammonia in the cold gave the colorless crystalline (IIa), sparingly soluble in nonpolar organic solvents and soluble in alcohols, acetone, and water, and forming the product of the addition of a molecule of water to the molecule of a 4H-imidazole 1-oxide. The UV spectrum of (IIa), like the spectrum of the initial hydrochloride (Ia), has no absorption in the region above 220 nm. Its IR spectrum has bands at 1640 cm^{-1} (C=N) and 3600 cm^{-1} (OH).

In the PMR spectrum of compound (IIa) there are the signals of the protons of three nonequivalent methyl groups and of the protons of a phenyl ring. The signals of the geminal methyl groups in the PMR spectrum of compound (IIa) have shifted upfield by 0.27 and 0.20 ppm, and the signal of the methyl group in position 2 by 0.38 ppm as compared with the signals in the spectrum of the hydrochloride. The shift in the signals with no change in the nature of the spectrum may serve as an indication of the retention of the skeleton of the molecule [6]. On the basis of these facts, we assigned to compound (IIa) the structure of 1,5-dihydroxy-2,4,4-trimethyl-5-phenyl-2-imidazoline, with the hydroxy groups apparently in the trans position with respect to one another, since its IR spectrum lacks the vibrations of an intramolecular hydrogen bond [7].



II I IV V

I a) R=OH, X=NH, b) R=H, X=NOH; c) R=OH, X=NOH; d) R=H, X=NH.
II a) R=OH, X=N; b) R=H, X=N→O; c) R=OH, X=N→O. d) R=H, X=N.
IV a) $R=C_2H_5$; b) $R=CH_3$. V a) $R=C_2H_5$, b) $R=CH_3$

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The neutralization of 3,5-dihydroxy-, 1,3,5-trihydroxy-, and 5-hydroxy-2,4,4-trimethyl-5-phenyl-2-imidazolinium chlorides (Ib,c,d) under similar conditions led to the colorless crystalline products (IIb-d), respectively. Compound (IId), like (IIa), has no absorption in the UV spectrum in the region above 220 nm. The UV spectra of compounds (IIb) and (IIc) have absorption at 258 and 263 nm (log ε 3.79 and 3.95), respectively, which is characteristic for compounds containing the $>C=N\rightarrow O$ grouping [8]. The existence of absorption in the UV spectra of (IIb) and (IIc) and its absence in the spectra of (IIa) and (IId) enables compounds (IIb-d) to be assigned the structures of 5-hydroxy- and 1,5-dihydroxy-2,4,4-trimethyl-5-phenyl-2-imidazoline 3-oxides (IIb and c) and 5-hydroxy-2,4,4-trimethyl-5-phenyl-2-imidazoline (IId), respectively.

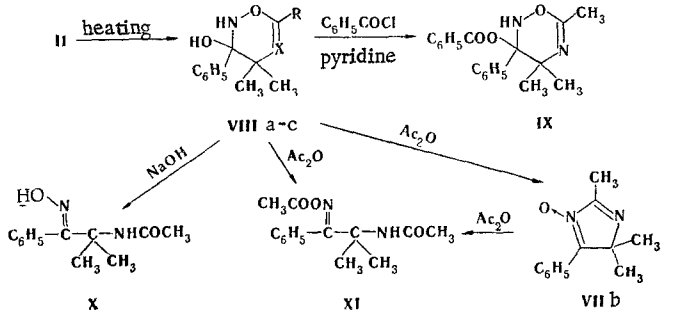
The action of hydrogen chloride on solutions of compounds (IIa-d) regenerates the initial imidazolinium chlorides (Ia-d), and the action of acetic acid on (IId) forms 2-imidazolinium acetate (III), the PMR spectrum of which is close to that of the hydrochloride (Id).

In the preceding communication [1], the formation from the hydrochloride (Ia) of the hydrochloride of the ethoxy derivative (IVa) was described. The hydrochloride of the methoxy derivative (IVb) is formed under similar conditions. The neutralization of (IVa) and (IVb) under conditions similar to those for the neutralization of the hydrochloride (Ia) led to compounds (Va) and (Vb). A comparison of the PMR spectra of compounds (IIa), (Va), and (Vb) (Table 1) shows the retention of a common structure for these compounds. The IR spectra of (Va) and (Vb) lack absorption bands in the region of the vibrations of the NH group and show the absorption of OH groups, at 3620 and 3580 cm^{-1}, respectively. A comparison of the IR, UV, and PMR spectra of compounds (Va), (Vb), and (IIa) refutes a structure including an NH group and permits compounds (Va) and (Vb) to be ascribed the structures of 1-hydroxy-5-ethoxy- and 1-hydroxy-5-methoxy-2,4,4-trimethyl-5-phenyl-2-imidazolines, respectively.

The imidazolines (IIa-d) and (Va,b) are comparatively stable compounds, the direction of the transformations of which depends on the presence and position of oxygen-containing functions. Compound (IId) proved to be the most stable; boiling it in a mixture of ethyl acetate and ethanol (10:1) for 30 min did not lead to changes, and when its aqueous solution was boiled for a few minutes cleavage of the heterocycle took place with the formation of 2-acetylamino-2-methyl-1-phenylpropan-1-ol (VI) [9]. On standing or on being heated, compound (IIb) readily dehydrates with the formation of 2,4,4-trimethyl-5-phenyl-4H-imidazole 3-oxide (VIIa) [1]. Under prolonged heating, the compounds (Va) and (Vb) split off a molecule of alcohol and form the 4H-imidazole 1-oxide (VIIb). Finally, when a solution of (IIa) is heated briefly or is allowed to stand for several hours at 20°C, it is converted completely into the new compound (VIIIa). Under the same conditions compound (IIc) gives (VIIIb).

Compound (VIIIa) has the same composition as (IIa) and has no absorption maxima in its UV spectrum above 220 nm (Table 2). Its IR spectrum has bands at 920 and 980, 1065 and 1100, 1535 and 3430, and 1640 and 3600 cm^{-1}, which correspond to the absorption of N–O, C–O, NH [10-12], C=N, and OH groups. The passage from the imidazoline (IIa) to compound (VIIIa) is accompanied by considerable changes in the PMR spectrum. Thus, while in the case of compounds (Ia) and (IIa) the distance between the signals of the protons of the geminal methyl groups is 0.74 ppm, in compound (VIIIa) it is only 0.25 ppm. These results show a change in the skeleton of compound (VIIIa) as compared with the skeleton of compound (IIa). The treatment of (VIIIa) with benzoyl chloride in pyridine leads to the monobenzoyl derivative (IX), the IR spectrum of which lacks a band at 3600 cm^{-1} and retains the absorption of the NH group at 3370 cm^{-1} (in KBr) and 3440 cm^{-1} (in CCl_4).

On the basis of these facts, we have suggested that (VIIIa) has the structure of 3-hydroxy-4,4,6-trimethyl-3-phenyl-2,3-dihydro-4H-1,2,5-oxadiazine.



VIII a $R=CH_3$, $X=N$; b $R=CH_3$, $X=N\rightarrow O$; c $R=C_6H_5$, $X=N$

TABLE 1. Spectral Characteristics of the Imidazolines

Compound	PMR spectra (in deuteromethanol)			IR spectra (in KBr), ν, cm^{-1}				UV spectra (in ethanol)	
	signals of the methyl groups		phenyl protons	C=N	NH	OH	N→O	λ_{max}, nm	log ε
	2	4 (gem)							
Ie	—	1,61 0,92	8,00[a]	1620	3365	—	—	229	3,88
IIa	2,08	1,31 0,57	7,40	1640	—	3600[b]			
IIb	2,14	1,44 0,71	7,39	1660	3380	—	1220	258	3,79
IIc	2,22	1,46 0,80	7,49	1650	—	—	1220	263	3,95
IId	2,38	1,40 0,64	7,39	1615	3380				
III	1,89	1,51 0,77	7,47	1630	3370				
IVb[c]	2,47	1,47 0,74	7,48	1630	3375				
Va[d]	2,12	1,34 0,56	7,48	1645	—	3580[b]			
Vb[e]	2,14	1,32 0,57	7,44	1640	—	3620[b]			

[a]Center of a multiplet with an intensity of 10 H. [b]In CCl_4, c 0.025%, d = 5 cm. [c]Signal of the protons of an OCH_3 group – 3.44δ. [d]Centers of the triplet and quartet of an OC_2H_5 group 1.12 and 3.64δ, respectively. [e]Signal of the protons of the OCH_3 group – 3.39δ.

TABLE 2. Spectral Characteristics of the Oxadiazines

Compound	PMR spectra (in deuteromethanol)			IR spectra (KBr), ν, cm^{-1}			UV spectra (in ethanol)	
	signals of the methyl groups		phenyl protons	C=N	NH	OH	λ_{max}, nm	log ε
	4 (gem)	6						
VIIIa	0,94 1,19	1,87	7,36	1640	3370 [a]	3600 [b]		
VIIIa·HCl	1,07 1,29	2,24	7,49	1670	3380	[c]		
VIIb[d]	1,01 1,20	1,99	7,74	1620	3370	[c]	252	3,60
VIII c	1,04 1,29	—	7,53 [e]	1660	3370	3590	260	3,49
IX[e]	0,97 1,41	1,81	7,74 [e]	1630	3370 [g]		231	4,24
IX·HCl[h]	1,09 1,52	2,18	7,88 [e]	1670	3370 [g]		228	4,18

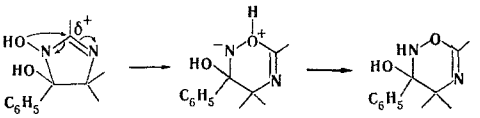
[a]In CCl_4 (c 0.25%, d = 5 cm) this band shifts to 3430 cm^{-1}. [b]In CCl_4, c 0.025%, d = 5 cm. [c]Not determined – the spectrum was recorded only in KBr. [d]In the IR spectrum, band of the N → O group at 1220 cm^{-1}. [e]Intensity of the signal 10 H. [f]Bands of an ester grouping in the IR spectrum at 1280 and 1730 cm^{-1}. [g]In CCl_4 (c 0.025%, d = 2 cm) this band shifts to 3440 cm^{-1}. [h]Bands of an ester grouping in the IR spectrum at 1270 and 1750 cm^{-1}.

TABLE 3. Elementary Analyses, Melting Points, and Yields of the Imidazolines and Oxadiazines

Compound	mp, °C	Empirical formula	Found, %				Calc., %				Yield, %
			C	H	Cl	N	C	H	Cl	N	
Ie	160—161[a]	$C_{17}H_{18}N_2O_2 \cdot HCl$	64,1	6,0	11,0	8,7	64,0	6,0	11,1	8,8	98
IIa	144—146[b]	$C_{12}H_{16}N_2O_2$	65,4	7,2	—	12,9	65,5	7,3	—	12,7	60
IIb	93—95[b]	$C_{12}H_{16}N_2O_2$	65,4	7,4	—	12,3	65,5	7,3	—	12,7	72
IIc	114—115[b]	$C_{12}H_{16}N_2O_3$	61,2	6,9	—	11,7	61,1	6,8	—	11,8	72
IId	153—154[b]	$C_{12}H_{16}N_2O$	70,5	7,8	—	13,7	70,6	7,9	—	13,7	87
III	163—165[a]	$C_{14}H_{20}N_2O_3$	64,0	7,2	—	11,1	63,6	7,6	—	10,6	60
IVb	138—140[a]	$C_{13}H_{18}N_2O_2 \cdot HCl$	57,6	7,1	13,1	10,3	57,7	7,0	13,1	10,3	95
Va	111—113[d]	$C_{14}H_{20}N_2O_2$	67,4	8,1	—	11,3	67,7	8,1	—	11,3	90
Vb	116—118[a]	$C_{13}H_{18}N_2O_2$	66,8	7,7	—	12,0	66,7	7,7	—	12,0	95
VIIIa	158—160[e]	$C_{12}H_{16}N_2O_2$	65,5	7,3	—	12,8	65,5	7,3	—	12,7	98
VIIIa·HCl	162—163	$C_{12}H_{16}N_2O_2 \cdot HCl$	56,5	6,8	13,9	11,0	56,3	6,7	13,7	10,9	95
VIIIb	109—111[e]	$C_{12}H_{16}N_2O_3$	61,0	7,0	—	11,5	61,1	6,8	—	11,8	70
VIIIc	148—150[c]	$C_{17}H_{18}N_2O_2$	72,3	6,5	—	10,0	72,3	6,4	—	9,9	80
IX	192—193[c]	$C_{19}H_{20}N_2O_3$	70,3	6,3	—	8,8	70,3	6,2	—	8,7	30
IX·HCl	128—130	$C_{19}H_{20}N_2O_3 \cdot HCl$	63,2	5,5	9,4	7,4	63,4	5,7	9,7	7,8	50

[a]From acetonitrile. [b]Without crystallization. [c]From ethanol. [d]From methanol. [e]From ethyl acetate.

Compound (IIa) readily rearranges with the expansion of the ring in the same way as has been observed for derivatives of 8H-xanthine 7N-oxide [13, 14], and nicotine N-oxide [15]. The expansion of the heterocycle apparently begins with an attack of position 2 of the imidazoline ring by the oxygen of the N–OH group.



Heating (VIIIa) in alkali leads to the opening of the heterocycle and the formation of 2-acetylamino-2-methyl-1-phenylpropan-1-one oxime (X) [16]. The treatment of (X) with concentrated hydrochloric acid or hydrogen chloride regenerates the imidazolinium chloride (Ia).

A characteristic reaction for some oxadiazines is the contraction of the heterocycle under the action of acetic [17] or hydrochloric [18] acid. However, the treatment of (VIIIa) and (IX) with hydrogen chloride led to hydrochlorides of oxadiazines – (VIIIa · HCl) and (IX · HCl) – the neutralization of which regenerated the initial compounds.

It is possible to bring about the contraction of the oxadiazine ring into an imidazole ring by treating compound (VIIIa) with acetic anhydride in chloroform. However, heating with acetic anhydride in the absence of a solvent leads to the opening of the heterocyclic ring and to the formation of the known 1-acetoxyimino-2-acetylamino-2-methyl-1-phenylpropane (XI) [16]. The acylation of thr 4H-imidazole 1-oxide (VIIb) under similar conditions leads to the same diacetyl derivative (XI).

It has been possible to extend the ring-expanding reaction of 1-hydroxy-2-imidazoline to compounds having different substituents in positions 2 and 3. By analogy with (VIIIa), for the compounds obtained by heating the products of the neutralization of the hydrochlorides (Ic) and (Ie) we have proposed the structures of 3-hydroxy-4,4,6-trimethyl-3-phenyl-2,3-dihydro-4H-1,2,5-oxadiazine 5-oxide (VIIIb), and 3-hydroxy-4,4-dimethyl-3,6-diphenyl-2,3-dihydro-4H-1,2,5-oxadiazine (VIIIc).

Thus, in the present work it has been shown that the products of the covalent hydration of 4H-imidazoles can be isolated in the free state and have the structure of 5-hydroxy-2-imidazolines. When a hydrogen atom is present in position 1 of the imidazoline ring, these compounds readily undergo dehydration, and when a hydroxy group is present in this position the expansion of the heterocyclic ring apparently takes place.

EXPERIMENTAL

The IR spectra were taken on a UR-20 instrument in KBr (concentration 0.25%, thickness of the tablets 1 mm) and in CCl_4 (concentration 1%, saturated solutions). The UV spectra were taken on a Unicam Sp 700c instrument in ethanol, and the PMR spectra on a Varian A-56-60A instrument using 5-7% solutions in deuteromethanol. Hexamethyldisiloxane was used as the internal standard, and the chemical shifts are given in the δ scale in ppm. The yields, melting points, and elementary analyses of the compounds are given in Table 3. The identity of the products was established by comparing IR, UV, and PMR spectra and by mixed melting points with authentic samples. The synthesis of compounds (Ia-d) and (VIIc) has been described previously.

Hydroxy Derivatives of 2,2,4-Trimethyl-5-phenyl-2-imidazolines (IIa-d). a) To a solution of 6 mmoles of ammonia in absolute ethanol was added a solution of 4 mmoles of (Ia) or (Ic) in absolute ethanol at −5°C. The suspension was diluted with dry ether, the precipitate of ammonium chloride was filtered off, and the filtrate was evaporated. Trituration of the resulting oil with ether gave a crystalline precipitate of (IIa) or (IIc).

b) An aqueous solution of 2 mmoles of (Ia, b, or d) was treated with a 5-7% solution of caustic soda at 0°C to give pH 7.5-8.0. When the solution was left to stand for a few minutes, a precipitate of (IIa, b, or d) precipitated, and this was filtered off and washed with cold water. When ethanolic solutions of compounds (IIa-d) were treated with hydrogen chloride at −5°C, the hydrochlorides (Ia-d) were obtained, and the action of acetic acid at 20°C on (IId) gave the acetate (III).

The neutralization of the hydrochlorides (IVa) and (IVb) under the same conditions led to 1-hydroxy-5-ethoxy- and 1-hydroxy-5-methoxy-2,4,4-trimethyl-5-phenyl-2-imidazolines (Va and b), respectively.

2-Acetylamino-2-methyl-1-phenylpropan-1-one (VI). A solution of 0.2 g (1.14 mmole) of (IId) in 5 ml of water was boiled for 3 min. On cooling, a crystalline precipitate of (VI) deposited.

2,4,4-Trimethyl-5-phenyl-4H-imidazole 1-Oxide (VIIb). A solution of 0.11 g (0.55 mmole) of (Va) in absolute ethanol was boiled for 30 min. The solvent was distilled off and the residue was recrystallized from cyclohexane, giving (VIIb). Compounds (Va) and (Vb) sublime at 130-140°C (2-3 mm), giving (VIIb).

3-Hydroxy-4,4,6-trimethyl-3-phenyl-2,3-dihydro-4H-1,2,5-oxadiazine (VIIIa). A mixture of 0.55 g (0.25 mmole) of (IIa) and 6 ml of ethyl acetate was boiled. After 3.5 min, the solution deposited a precipitate of (VIIIa). Compound (VIIIb) was obtained similarly. The treatment of (VIIIa) with concentrated hydrochloric acid or of its ethanolic solution with hydrogen chloride led to the hydrochloride (VIIIa · HCl).

3-Hydroxy-4,4-dimethyl-3,6-diphenyl-2,3-dihydro-4H-1,2,5-oxadiazine (VIIIc). A solution of 0.8 g (0.25 mmole) of the hydrochloride (Ie) [obtained from 4,4-dimethyl-2,5-diphenyl-4H-imidazole 1-oxide (VIIc)] in 5 ml of water at 20°C was neutralized with 10% caustic soda solution to pH 7.0. The precipitate that deposited was filtered off and recrystallized from ethanol to give (VIIIc).

3-Benzoyloxy-4,4,6-Trimethyl-3-phenyl-2,3-dihydro-4H-1,2,5-oxadiazine (IX). A solution of 0.95 g (0.43 mmole) of the oxadiazine (VIIIa) in 10 ml of pyridine was treated with 0.73 g (0.52 mmole) of benzoyl chloride, and the mixture was shaken for 15 min and was left at 20°C for 30 min. The reaction mixture was poured into 25 ml of cold water, and the resulting precipitate of (IX) was filtered off and washed with water (5 × 5 ml).

A solution of (IX) in ethyl acetate was treated with hydrogen chloride, giving the hydrochloride (IX · HCl). The neutralization of (VIIIa · HCl) and (IX · HCl) with gaseous ammonia led to the regeneration of the initial compounds.

2-Acetylamino-2-methyl-1-phenylpropan-1-one Oxime (X). A solution of 0.1 g (0.45 mmole) of (VIIIa) in 3 ml of a 10% solution of caustic soda was boiled for 15 min. On cooling, (X) deposited.

1,5-Dihydroxy-2,4,4-trimethyl-5-phenyl-2-imidazolinium Chloride (Ia). Hydrogen chloride was passed into a solution of 0.1 g (0.45 mole) of (X) in 4 ml of ethyl acetate. The solvent was distilled off, leaving a residue of compound (Ia). When 0.1 g (0.45 mmole) of (X) was dissolved in 3 ml of concentrated hydrochloric acid, the solution was kept at 20°C for 1 h 30 min and was then evaporated without heating; and when the resulting residue was treated with acetonitrile, compound (Ia) was obtained again.

Contraction of the 2,3-Dihydro-4H-1,2,5-oxadiazine Ring. A mixture of 0.2 g (0.91 mmole) of (VIIIa), 5 ml of chloroform, and 1 ml of acetic anhydride was boiled for 10 min. Then it was washed with a 3% solution of sodium bicarbonate to give pH 7.0. The chloroform solution was dried over magnesium sulfate, the solvent was distilled off, and the residue was treated with 1.5 ml of ether. On standing, compound (VIIb) precipitated.

1-Acetoxyimino-2-acetylamino-2-methyl-1-phenylpropane (XI). A solution of 0.05 g (0.23 mmole) of (VIIIa) or (VIIb) in 1 ml of acetic anhydride was boiled for 5 min. The red-yellow solution was poured into water and the water was distilled off. The residual oil was dried in a vacuum desiccator and dissolved in ether. On standing, the solution deposited a crystalline precipitate of (XI).

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