PREPARATION AND COVALENT HYDRATION OF 4H-IMIDAZOLE DERIVATIVES

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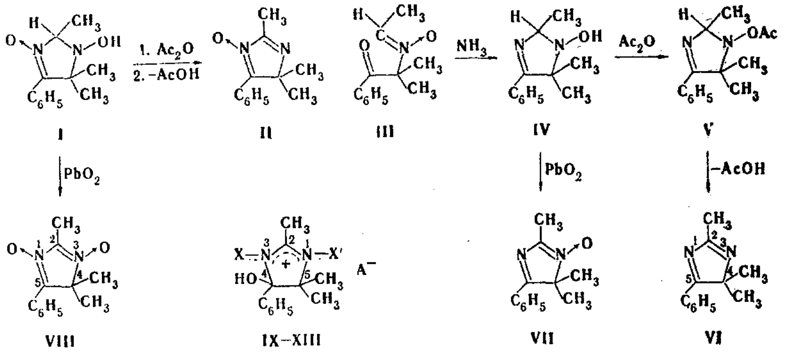
2,4,4-Trimethyl-5-phenyl-4H-imidazole, 4H-imidazole 3-oxide, and 4H-imidazole 1,3-dioxide were synthesized from 1-hydroxy-2,5,5-trimethyl-4-phenyl-3-imidazoline and 3-imidazoline 3-oxide. The action of hydrogen chloride on these compounds and on 2,4,4-trimethyl-5-phenyl-4H-imidazole 1-oxide gives products of the addition of water or alcohol – derivatives of 4-hydroxy-2-imidazolinium chlorides.

In a previous communication [1] we demonstrated that the acylation of 1-hydroxy-2,5,5-trimethyl-4-phenyl-3-imidazoline 3-oxide (I) and subsequent heating of the acetyl derivative leads to 2,4,4-trimethyl-5-phenyl-4H-imidazole 1-oxide (II). Similar products were obtained under the same conditions from other 5,5-disubstituted 3-imidazoline 3-oxides. The action of aqueous alkali on 4H-imidazole 1-oxides leads to cleavage of the heteroring and the formation of oximes of α-acylamino ketones.

Since the information on 4H-imidazoles and their N-oxides is limited [2-5], it seemed of interest to synthesize new derivatives of this series, including compounds that do not contain oxygen, N-oxides, and N,N-dioxides, and to study their properties. Convenient starting materials for the synthesis of 4H-imidazoles are α-hydroxylamino ketones and α-hydroxylamino oximes [1,6].

The condensation of α-hydroxylaminoisobutyrophenone with acetaldehyde proceeds smoothly to give N-(1-keto-2-methyl-1-phenyl-2-propyl)-α-methylnitrone (III) [6]. 1-Hydroxy-2,5,5-trimethyl-4-phenyl-3-imidazoline (IV) is formed in quantitative yield in the reaction of III with ammonia in anhydrous alcohol.

Treatment of IV with acetic anhydride in chloroform leads to 1-acetoxy-2,5,5-trimethyl-4-phenyl-3-imidazoline (V). When this compound is heated at 200°C in the presence of calcium oxide, a molecule of acetic acid is split out to give 2,4,4-trimethyl-5-phenyl-4H-imidazole (VI) (see [1]).



IX $X=X'=H$, $A=Cl$; X $X=H$, $X'=OH$, $A=Cl$; XI $X=OH$, $X'=H$, $A=Cl$; XII $X=X'=OH$, $A=Cl$; XIII $X=X'=H$, $A=B(C_6H_5)_4$

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TABLE 1. PMR Data and IR Spectra of the Compounds Obtained

Comp.	Chemical shifts (τ), ppm (in CD_3OD)			ν,[a] cm^{-1}
	2-CH_3	gem-$(CH_3)_2$	C_6H_5	
IV	8,54[b]	8,61; 8,64	2,26—2,69[c]	1620
V[d]	8,52[b]	8,54	2,31—2,72[c]	1620
VI	7,67	8,56	1,86—2,12[e] 2,46—2,66	1635
VII	7,60	8,34	2,02—2,29[e] 2,64—2,72	1640
VIII	7,60	8,21	1,39—1,63[e] 2,33—2,57	1635
IX	7,52	8,53; 9,26	2,62	1635
X	7,60	8,51; 9,25	2,54	1630
XI	7,54	8,49; 9,16	2,55	1630
XII	7,49	8,50; 9,09	2,54	1630
XIII	7,58	8,42; 9,12	2,35—2,85;	1620
XVII	7,58	8,54; 9,23	2,90—3,34[f]	1625
XVIII	7,57	8,21; 9,31	2,52 2,56	1630
XXI	7,76	5,4,4-$(CH_3)_3$— 8,53; 8,68; 8,76		1620
XXII	—	8,39; 9,08	2,01[g]	1630

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[a] The spectra of IV, V, VII, and VIII were recorded from KBr pellets, the spectrum of VI was obtained from a CCl_4 solution, while the remaining spectra are of mineral oil suspensions. [b] Doublet. The quartet of the corresponding methylidyne hydrogen atom is found at 5.50 ppm (J = 6.6 Hz) for IV and at 4.88 ppm (J = 6.5 Hz) for V. [c] Complex band. [d] CH_3CO at 7.94 ppm. [e] Two complex bands with an intensity ratio of 2 : 3. [f] Two complex bands of five phenyl protons. [g] Complex band of two phenyl groups.

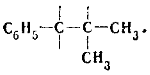
The oxidation of imidazoline IV with lead dioxide in benzene gives 2,4,4-trimethyl-5-phenyl-4H-imidazole 3-oxide (VII). Compound VII is an isomer of the previously described II [1] and differs from it only with respect to the position of the N-oxide oxygen in the ring. When it is oxidized under similar conditions, I forms 2,4,4-trimethyl-5-phenyl-4H-imidazole 1,3-dioxide (VIII).

The spectral characteristics of VI, VII, and VIII confirm their structures. An absorption band of a conjugated system of multiple bonds, including a benzene ring, with a maximum at 282 nm (log ε 4.0) is observed in the UV spectrum of VI. The maximum of the absorption band in the UV spectra of VII and VIII is found at 360 nm (log ε 3.94 and 4.07, respectively), which is characteristic for conjugated nitrones [7] and dinitrones [8]. The IR spectra of VI, VII, and VIII (Table 1) contain intense bands at 1560-1640 cm^{-1}, which correspond to the stretching vibrations of the C=N group in imines [9] and nitrones [7]. The singlet of a methyl group in the 2 position of the heteroring at 7.5-7.7 ppm, the singlet of two geminal methyl groups in the 4 position at 8.2-8.5 ppm, and two complex bands with an intensity ratio of 2 : 3 at 1.5-2.5 ppm from the five hydrogen atoms of the benzene ring [10, 11] are observed in the PMR spectra of these compounds (in CD_3OD) (Table 1).

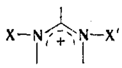
On passing from 4H-imidazole VI to N-oxides VII and VIII, one observes a sharp increase in the melting points and the appearance of a yellow coloration, which is apparently associated with the presence of the semipolar N-oxide grouping. Compounds VI, VII, and VIII are quite soluble in organic solvents (ether, benzene, and alcohol) and somewhat less soluble in water. They readily sublime on heating.

When hydrogen chloride is bubbled into ether solutions of VI, VII, VIII, and II, colorless crystalline IX-XII are formed in quantitative yields; these products correspond in composition to the products of the addition of one molecule of water to the hydrochlorides of the starting compounds. Compounds that differ from IX-XII are not obtained when the reaction is carried out in dry ether; traces of moisture are apparently sufficient for their formation. The molecule of water cannot be removed by prolonged drying of these compounds in vacuo. It should be noted that starting compound II is regenerated when solid product XI is added to aqueous alkali, which indicates retention of the heterocyclic skeleton.

The UV spectra of IX-XII differ sharply from the spectra of 4H-imidazoles. The fine structure characteristic for the unconjugated benzene ring is observed at 250-260 nm (log ε 2.0) in the UV spectrum of IX. In the UV spectra of X and XI, apart from the absorption of an unconjugated benzene ring, absorption maxima above 220 nm are absent, while the UV spectrum of XII contains an absorption band with λ_{max} 256 nm (log ε 3.83). These data indicate that products IX-XII are not 4H-imidazole hydrochlorides that contain a molecule of crystallization water.

The PMR spectra (in CD_3OD) of IX-XII (Table 1) are practically identical and contain four distinct singlets at 9.2, 8.5, 7.5, and 2.5 ppm, respectively, of three nonequivalent methyl groups and of a phenyl group. The shift of one of the signals of the geminal methyl groups to strong field can be explained by the anisotropic effect of the benzene ring attached to a saturated carbon atom. In this case, the carbocyclic fragment of the molecule can be represented as  $C_6H_5-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{CH_3}{C}}-CH_3$. The equivalence of the hydrogen atoms of the benzene ring is apparently due in this case to the electron-acceptor effect of the imine and N-oxide groupings [11].

The IR spectra of IX-XII (Table 1) contain an intense band at 1620-1630 cm^{-1}, which, for IX and X, is accompanied by an intense band at 1590-1600 cm^{-1}. On the basis of literature analogies [12], these data make it possible to assume the presence in the molecule of an amidinium grouping, where X and X' = H or OH.



Compounds IX-XII are apparently salts, since they are insoluble in nonpolar organic solvents but readily soluble in water. Salt XIII, which does not contain chlorine, is formed in the reaction of product IX with aqueous sodium tetraphenylborate. In addition to the signals of three methyl groups at 9.15, 8.42, and 7.58 ppm and two complex bands of five phenyl protons at 2.40-3.30 ppm, the PMR spectrum of salt XIII (in deuteroacetone) contains a distinct singlet of a hydroxyl group at 3.61 ppm and a broad signal of two NH groups centered at 0.29 ppm (when CD_3OD is added, the signals at 3.61 and 0.29 ppm vanish). Salts IX and XIII have similar IR spectra at 400-1800 cm^{-1}.

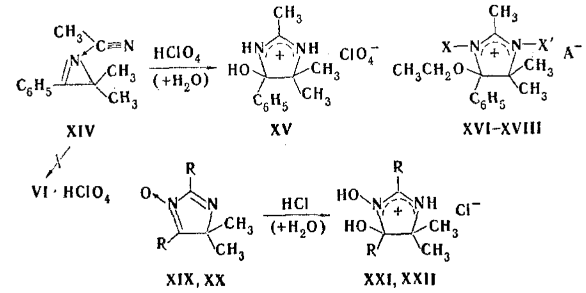
The data presented above make it possible to assign the 4-hydroxy- (IX), 1,4-dihydroxy- (X), 3,4-dihydroxy- (XI), and 1,3,4-trihydroxy-2,5,5-trimethyl-4-phenyl-2-imidazolinium chloride (XII) structures to the compounds formed in the reaction of HCl with the 4H-imidazole derivatives.

The literature contains a number of examples of the facile hydration of heterocyclic cations that is characteristic for compounds with a 1,3-orientation of the nitrogen atoms in the ring – quinazolines, pteridines, 1,2,4-triazines, etc. [13-16]. However, we were unable to find data on the hydration of imidazole derivatives. Nevertheless, we did find a compound that differs from salts IX and XIII only with respect to the anion. In a study of the ring-expansion reactions of azirine, Leonard [17] observed that the reaction of 3,3-dimethyl-2-phenyl-1-azirine (XIV) with acetonitrile in the presence of perchloric acid does not give the expected perchlorate of 4H-imidazole VI but rather the product of its covalent hydration – 4-hydroxy-2-imidazolinium salt XV. Salt XV has an IR spectrum that is close to the IR spectra of salts IX and XIII, while the PMR spectra of salts IX, XIII, and XV are practically identical in the region of the resonance absorption of the methyl groups. Compound VI was not obtained by Leonard and Zwanenburg [17].

A characteristic property of salt XV is the formation from it of 4-ethoxy derivative XVI on heating in alcohol for 5 h. When 3,4-dihydroxy-2-imidazolinium chloride (XI) is heated in alcohol for 30 min, 4-ethoxy-2,5,5-trimethyl-4-phenyl-2-imidazolinium chloride (XVII) is also formed. It is interesting that the products of the addition of alcohol (XVII and XVIII) are formed without heating in the reaction of hydrogen chloride with alcohol solutions of 4H-imidazole 1-oxide II and 4H-imidazole VI. The conversion of salts XV and XI to 4-ethoxy derivatives apparently proceeds through the initial formation of VI and II.

Other 4H-imidazole derivatives react with hydrogen chloride to give products with similar structures. Thus 2,4,4,5-tetramethyl- (XIX) and 4,4-dimethyl-2,5-diphenyl-4H-imidazole 1-oxide (XX) give 3,4-dihydroxy-2,4,5,5-tetramethyl- (XXI) and 3,4-dihydroxy-5,5-dimethyl-2,4-diphenyl-2-imidazolinium chloride (XXII). (See scheme on following page.)

Thus, regardless of the presence and position of an N-oxide oxygen and the character of the groups in the 2 and 5 positions, 4H-imidazole derivatives have a capacity for covalent hydration on reaction with hydrogen chloride and give 2-imidazolinium salts. The structures and transformations of the products of the neutralization of these salts will be examined in subsequent communications.



XVI X=X′=H, A=ClO$_4$; XVII X=OH, X′=H, A=Cl; XVIII X=X′=H, A=Cl;
XIX R=CH$_3$; XX R=C$_6$H$_5$; XXI R=CH$_3$; XXII R=C$_6$H$_5$

EXPERIMENTAL

The IR spectra of KBr pellets (0.25%, pellet thickness 1 mm), mineral oil suspensions, and CCl$_4$ solutions (5%) were recorded with a UR-10 spectrometer. The UV spectra of alcohol solutions were recorded with a Unicam SP-700C spectrometer. The PMR spectra of 5-7% solutions in CD$_3$OD and in (CD$_3$)$_2$CO were recorded with a Varian A-56-60A spectrometer. Hexamethyldisiloxane (9.96 ppm) was used as the internal standard, and the chemical shifts are presented on the τ scale in parts per million. The yields, melting points, results of elementary analysis, and IR and PMR spectral data are presented in Tables 1 and 2.

1-Hydroxy-2,5,5-trimethyl-4-phenyl-3-imidazoline (IV). A 12.5-ml sample of concentrated ammonium hydroxide was added to a solution of 13.0 g (0.063 mole) of N-(1-keto-2-methyl-1-phenyl-2-propyl)-methylnitrone (III) [6] in 90 ml of anhydrous alcohol. The solution was held at 20° for 2 days, and the alcohol was evaporated. Trituration of the residual oil in diethyl ether precipitated crystalline IV. UV spectrum: λ_{max} 240 nm (log ε 4.01).

1-Acetoxy-2,5,5-trimethyl-4-phenyl-3-imidazoline (V). A 2.8-ml (0.032 mole) sample of acetic anhydride was added to a solution of 4.3 g (0.019 mole) of IV in 25 ml of chloroform, and the mixture was refluxed for 10 min. The solution was washed with 3% aqueous sodium carbonate solution and water and dried over magnesium sulfate. The chloroform was evaporated, and the residual oil was triturated in ether to give crystalline V. UV spectrum: λ_{max} 242 nm (log ε 4.03).

2,4,4-Trimethyl-5-phenyl-4H-imidazole (VI). A 2.0-g (8.1 mole) sample of V was triturated with 2.0 g of calcium oxide, and the mixture was heated in a sublimator at 190-200° for 30 min. The reaction mixture sublimed at 180° (10-20 mm). The sublimed oily product was chromatographed on aluminum oxide with ether. Removal of the ether and cooling of the oil to 0° gave crystalline VI. UV spectrum: λ_{max} 282 nm (log ε 3.99).

2,4,4-Trimethyl-5-phenyl-4H-imidazole 3-Oxide (VII) and 1,3-Dioxide (VIII). A suspension of 3.0 g (0.015 mole) of IV and 24.0 g (0.105 mole) of lead dioxide and 90 ml of benzene was stirred for 24 h. The

TABLE 2. Synthesized Compounds

Comp.	mp, °C	Empirical formula	Found, %				Calc., %				Yield, %
			C	H	Cl	N	C	H	Cl	N	
IV	105—107[a]	$C_{12}H_{16}N_2O$	70,5	7,8	—	13,7	70,5	7,8	—	13,7	98
V	65—67[a]	$C_{14}H_{18}N_2O_2$	68,4	7,4	—	11,2	68,3	7,4	—	11,3	81
VI	15—17	$C_{12}H_{14}N_2$	77,6	7,6	—	14,6	77,5	7,5	—	15,0	66
VII	138—140[a]	$C_{12}H_{14}N_2O$	71,2	7,1	—	13,8	71,4	7,0	—	13,8	88
VIII	138—140[a]	$C_{12}H_{14}N_2O_2$	66,6	6,4	—	13,0	66,2	6,4	—	12,9	90
IX	220—222[b]	$C_{12}H_{17}ClN_2O$	60,4	7,5	15,0	11,6	60,0	7,8	14,8	11,7	95
X	168—170[c]	$C_{12}H_{17}ClN_2O_2$	56,7	6,7	13,6	10,9	56,3	6,7	13,8	10,9	94
XI	153—154[d]	$C_{12}H_{17}ClN_2O_2$	55,7	6,6	13,9	11,2	56,3	6,7	13,8	10,9	90
XII	149—150[d]	$C_{12}H_{17}ClN_2O_3$	52,9	6,2	13,0	10,3	52,9	6,3	13,0	10,3	90
XIII	147—148	$C_{36}H_{37}N_2OB$	82,4	6,9	—	5,2	82,5	7,1	—	5,4	81
XVII	124—125[d]	$C_{14}H_{21}ClN_2O_2$	59,1	7,4	12,8	10,1	59,1	7,4	12,3	9,9	80
XVIII	164—166[e]	$C_{12}H_{21}N_2O$	62,3	7,8	—	10,7	62,5	7,8	13,3	10,5	94
XXI	145—146[d]	$C_7H_{15}ClN_2O_2$	43,3	7,7	18,4	14,4	43,2	7,7	18,3	14,4	90
XXII	160—161[d]	$C_{17}H_{19}ClN_2O_2$	64,1	6,0	11,0	8,7	64,0	6,0	11,1	8,8	90

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[a] From cyclohexane. [b] From 10% HCl. [c] From alcohol–ether. [d] From acetonitrile. [e] From chloroform–ether.

filtered solution was evaporated, and the residual oil was triturated in ether to give crystalline VII. UV spectrum: λ_{max} 360 nm (log ε 3.94). Oxidation of 3-imidazoline 3-oxide (I) [1] under similar conditions gave VIII. UV spectrum: λ_{max} 360 nm (log ε 4.07).

4-Hydroxy-2,5,5-trimethyl-4-phenyl-2-imidazolinium Chloride (IX). Hydrogen chloride was passed into an ether solution of 1.5 g (0.081 mole) of VI for 1 min. Crystalline IX precipitated. 3,4-Dihydroxy-2,5,5-trimethyl-4-phenyl-2-imidazolinium chloride (XI) was formed under similar conditions.

1,4-Dihydroxy-2,5,5-trimethyl-4-phenyl-2-imidazolinium Chloride (X). A 0.4-g (0.002 mole) sample of VII was dissolved in 50 ml of ether, and hydrogen chloride was bubbled through the solution until it was decolorized. The ether was evaporated, and the residue was crystallized from acetonitrile. 1,3,4-Trihydroxy-2,5,5-trimethyl-4-phenyl-2-imidazolinium chloride (XII), 3,4-dihydroxy-2,4,5,5-tetramethyl-2-imidazolinium chloride (XXI), and 3,4-dihydroxy-5,5-dimethyl-2,4-diphenyl-2-imidazolinium chloride (XXII) were similarly obtained.

4-Hydroxy-2,5,5-trimethyl-4-phenyl-2-imidazolinium Tetraphenylborate (XIII). An aqueous solution of 0.2 g (0.001 mole) of IX was added to an aqueous solution of 0.32 g (0.001 mole) of sodium tetraphenylborate, and crystalline XIII precipitated from the solution.

3-Hydroxy-4-ethoxy-2,5,5-trimethyl-4-phenyl-2-imidazolinium Chloride (XVII). A 0.3-g (0.001 mole) sample of XI was dissolved in 5 ml of anhydrous alcohol, and hydrogen chloride was bubbled into the solution for 1 min. The mixture was then refluxed for 30 min. The solvent was removed by distillation, the residue was treated with acetonitrile, and the precipitated XVII was removed by filtration. A 0.2-g (0.001 mole) sample of II was dissolved in 3 ml of anhydrous alcohol, and hydrogen chloride was bubbled into the solution for 3 min. The solvent was removed by distillation, the residue was treated with acetonitrile, and the precipitated XVII was removed by filtration. Under similar conditions, 4-ethoxy-2,5,5-trimethyl-4-phenyl-2-imidazolinium chloride (XVIII) was formed from VI.

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