AZOLE- AND Δ^2-AZOLINECARBALDEHYDE OXIMES AND THEIR DERIVATIVES

I. SYNTHESIS

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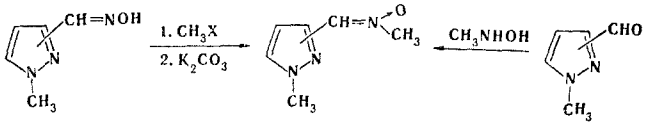
The production of 1-methyl-substituted pyrazole-, imidazole-, Δ^2-pyrazoline-, and Δ^2-imidazolinecarbaldehyde oximes is described. The alkylation of 1-methylimidazole- and 1-methyl-Δ^2-pyrazolinecarbaldehyde oximes with methyl iodide and α,ω-dihalogenoalkanes forms quaternary and bisquaternary ammonium derivatives, respectively. The quaternary derivatives of 1-methylpyrazolecarbaldehyde oximes are obtained by the oximation of the corresponding quaternary derivatives of the aldehydes; the direct methylation of these oximes either does not take place or leads to the formation of nitrones.

Continuing an investigation of carbaldehyde oximes of nitrogen-containing heterocycles [1], which are of practical importance [2], we have effected the synthesis of aldoximes of carbaldehyde derivatives of 1-methylpyrazole (I-III), 1-methylimidazole (IV-VII), 1-methyl-Δ^2-pyrazoline (VIII), and 1-methyl-Δ^2-imidazoline (IX) (Table 1) and their quaternary (X-XI) and bisquaternary (XVI-XVIII) ammonium derivatives (Table 2).*

We have described the pyrazole- and pyrazolinecarbaldehydes necessary for the synthesis of the oximes previously [5]. The 1-methylimidazolecarbaldehydes and their diethyl acetals were obtained by the reaction of 1-methylimidazol-2-ylmagnesium and 1-methylimidazol-5-ylmagnesium halides [6, 7] with dimethylformamide and orthoformic ester, and the diethyl acetal of 1-methyl-Δ^2-imidazoline-2-aldehyde by the method of Iversen and Lund [11].



XIX, XX

X = I, CH_3SO_4

Position of CH=N(O)CH, XIX — 3, XX — 4

The oximation of the aldehydes was performed both in acid (method A) and in neutral (weakly alkaline) (method B) media; in some cases, the latter promotes the formation of a less stable isomer [9]. Because of the instability of the corresponding aldehyde [8], the oxime (IX) was obtained by the simultaneous hydrolysis and oximation of the acetal in an acid medium. Some oximes had melting points which varied according to the method of oximation (I, II) or unsharp melting points (IA, IIB, VII), which sometimes (IIB) changed when the sample was stored. This indicated the formation of mixtures of isomers and their mutual transformation, which was confirmed by PMR spectra. However, it must be mentioned that in the majority

*While the present communication and subsequent ones were being prepared for printing, a paper [3] appeared in which the synthesis and some properties of the oximes (VII), (XII), and (XIV) are described. The oxime (IV) was known previously [4].

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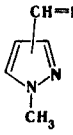
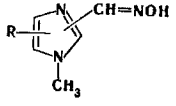
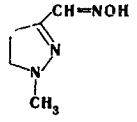
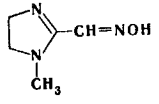
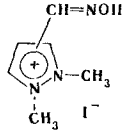
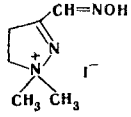
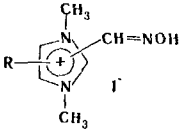
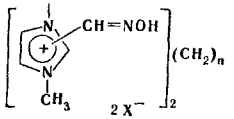
TABLE 1. Characteristics of the 1-Methyl-Substituted Azolecarbaldehyde and Δ^2-Azolinecarbaldehyde Oximes[a]

Compound	Formula	Position of oxime group	R	Method of preparation	mp, °C	Empirical formula	Found, % C	Found, % H	Found, % N	Found, % Cl	Calc., % C	Calc., % H	Calc., % N	Calc., % Cl	Yield, %
I		3	—	A	110—119[b]	$C_5H_7N_3O$	48,2	5,7			48,0	5,6	33,6		80
				B	80—81[b,c]		48,1	5,6	33,5						81
II		4	—	A	113—114[b]	$C_5H_7N_3O$	48,2	5,8	33,5		48,0	5,6	33,6		87
				B	85—90[d]		47,9	5,4	33,5						89
III		5	—	A, B	164,5—165,5[e,f]	$C_5H_7N_3O \cdot HCl$				21,7				21,6	85
IV		2	H	A, B	176—177 [g,h]										75
V		2	4-Cl	A	194—195 [i]	$C_5H_6ClN_3O$			26,3				26,3		~100
VI		2	5-Cl	A	200—202 [i]	$C_5H_6ClN_3O$			26,4				26,3		~100
VII		5	H	A, B	169—173 [g,j]	$C_5H_7N_3O$			33,5				33,6		89
VIII		3	—	B	187 [e,k]	$C_5H_9N_3O \cdot HCl$				21,6				21,7	78
IX		2	—	A	157 [l]	$C_5H_9N_3O$	47,2	7,3			47,2	7,1			23

[a]The oximes (IV-VI) and (VIII, IX) were individual stereoisomers and the others were mixtures of the E (syn) and Z (anti) isomers in various ratios. [b]From benzene. [c]Falls on repeated crystallizations. A mixture of the products obtained by methods A and B gives a depression. [d]On recrystallization or storage for several days at room temperature, the mp gradually rises to 110-112°C. [e]From ethanol. [f]Hydrochloride. For the base, 166-168°C. Samples of the base obtained by different methods were identical in mp, IR spectra, and PMR spectra. [g]From water. [h]Identical samples regardless of the method of oximation. According to the literature [4], mp 176°C. [i]Washed with water. [j]According to the literature [3], mp of the E isomer 191-193°C. [k]Hydrochloride; the base is noncrystalline. [l]From acetone.

TABLE 2. Characteristics of the Quaternary and Bisquaternary Ammonium Derivatives of 1-Methyl-Substituted Azolecarbaldehyde and Δ^2-Azolecarbaldehyde Oximes[a]

Compound	Formula	Position of oxime group	R	Method of preparation	mp, °C	Empirical formula	Found, %		Calc., %		Yield, %
							I	N	I	N	
X		3(5)	—	B	175—177[b]	$C_6H_{10}IN_3O$	47,9	15,6	47,6	15,7	63
XI		4	—	B	182—185[c]	$C_6H_{10}IN_3O$	48,7	16,1	47,6	15,7	75
XII		2	H	C	202—204[d,e]	$C_6H_{10}IN_3O$	47,3	15,2	47,6	15,7	66
XIII		2	4(5)-Cl	C	242—243[d]	$C_6H_9ClIN_3O$	41,2		42,2		82
XIV		5	H	C	183—185[f,g]	$C_6H_{10}IN_3O$	47,6	15,7	47,6	15,7	60
XV		3	—	C	187[h]	$C_6H_{12}IN_3O$	47,4	15,7	47,2	15,6	94
XVI		2	3[i]	C	252—254	$C_{13}H_{20}Br_2N_6O_2$[j]					30
XVII		2	4[i]	C	256—258	$C_{14}H_{22}I_2N_6O_2$	46,0		45,3		53
XVIII		5	4[i]	C	248—250	$C_{14}H_{22}I_2N_6O_2$	44,8		45,3		36

[a]The oximes (XII, XIII, and XV-XVII) were individual stereoisomers and the oximes (X, XI, XIV, and XVIII) mixtures of the E and Z isomers in various ratios. [b]From isobutyl alcohol. [c]From isopropyl alcohol. [d]Washed with acetone. [e]According to the literature [3], mp 223-224°C, [f]From propyl alcohol. [g]According to the literature [3], mp of the Z isomer 185-187°C. [h]From ethanol. [i]The number n is shown. X = Br (XVI) or I (XVII, XVIII). [j]Found, %: Br 35.9. Calculated, %: Br 35.4.

of cases the melting point is not a criterion of the configurational individuality of an oxime. Compounds (III, X, XI, XIV, and XVIII), just like (I) and (II) are mixtures of stereoisomers but they melt within a two-degree range. It is likely that at high temperatures [all the oximes mentioned apart from (I) and (II) melt above 150°C] isomerization and destruction processes take place in the solid phase and the temperature recorded does not reflect the initial state of the substance.

In attempts to quaternize the oximes (I) and (II) with methyl iodide and dimethyl sulfate, the corresponding nitrones (XIX, XX) were isolated, their structures being confirmed by independent syntheses.

Under the same conditions, the oxime (III) proved to be inert with respect to methylating agents. A preferential alkylation of the nitrogen of the oxime group as compared with the nitrogen of the ring was observed for 6-methylpyridine-2-carbaldehyde oxime [10]. Apparently, an increase in steric hindrance adjacent to the pyridine-like nitrogen atom and a fall in its basicity leads to a change in the ratio of the nucleophilic properties of the ring and the oxime nitrogen atoms in favor of the latter. In the absence of competing nucleophilic centers – in the corresponding aldehydes – quaternization of the ring takes place without complications. Consequently, the oximes (X) and (XI) were obtained by the oximation of quaternary derivatives of the aldehydes. The quaternary and bisquaternary derivatives (XII-XVIII) are readily formed during the normal quaternization of the oximes (IV-VIII) with methyl iodide, 1,3-dibromopropane, and 1,4-diiodobutane (method C).* Attempts to quaternize the oxime (IX) proved unsuccessful, which is apparently due to features of its structure.

EXPERIMENTAL

1-Methylimidazole-2-carbaldehyde. At room temperature, 5.4 ml of dimethylformamide was added to a solution of 1-methylimidazol-2-ylmagnesium bromide in tetrahydrofuran obtained from 4.6 g (0.056 mole) of 1-methylimidazole [6], and the mixture was boiled for 3 h. On the following day, it was decomposed with hydrochloric acid; the aqueous solution was washed with ether, saturated with anhydrous potassium carbonate, and repeatedly extracted with ether. After the elimination of the ether and distillation, 3.77 g (65%) of the aldehyde was obtained with bp 90-93°C (11 mm) [11].

Diethyl Acetal of 1-Methylimidazole-5-carbaldehyde. To a solution of 1-methylimidazol-5-ylmagnesium chloride obtained from 5.84 g (0.059 mole) of 5-chloro-1-methylimidazole [7] in 45 ml of tetrahydrofuran was added 65 ml of dry benzene, and 75 ml of the solvent was distilled off; 8 g of orthoformic ester in 10 ml of benzene was added to the residue and the mixture was stirred at 100-115°C for 2 h 30 min. The cooled mixture was decomposed with a saturated solution of ammonium chloride, the organic layer was separated off, the aqueous layer was saturated with anhydrous potassium carbonate and extracted with ether. After the elimination of the solvent from the combined extracts and distillation, 4.05 g (45%) of the acetal was obtained; bp 116.5°C (4 mm); n_D^{20} 1.4730. Found, %: C 58.7; H 8.6; N 14.9. $C_5H_7N_3O$. Calculated, %: C 58.7; H 8.7; N 15.2.

1-Methylimidazole-5-carbaldehyde was formed in quantitative yield by the acid hydrolysis of the acetal. mp 47-52°C [12].

4-Chloro-1-methylimidazole-2-carbaldehyde (mp 74-77°C) and 5-chloro-1-methyl-2-carbaldehyde (oil) were obtained with yields of 50-60% from 4-chloro- and 5-chloro-1-methylimidazoles [13], respectively, as for the preparation of 1-methylimidazole-2-carbaldehyde. They were characterized in the form of the oximes (Table 1).

1,2-Dimethyl-3(5)- and -4-formylpyrazolium iodides were obtained by heating 1-methylpyrazole-5- and -4-carbaldehydes [5] in an excess of methyl iodide at 100°C for 13 and 3 h, respectively. The salts formed, with mp 162-163°C (about 100%) and 168-170°C (85%), respectively, were characterized through the oximes (Table 2).

Oximation of the Aldehydes. A. A small excess of a concentrated aqueous solution of hydroxylamine hydrochloride was added to an acidified solution of one of the aldehydes. After 2-3 h, the mixture was made alkaline with 50% potassium carbonate solution and the oxime was filtered off or was extracted with chloroform. In the preparation of the oxime (IX), 1.1 g of the acetal of the corresponding aldehyde [8] and 0.43 g of hydroxylamine hydrochloride were dissolved in 5 ml of 3 N hydrochloric acid, the solution was boiled for 3 h and was saturated with anhydrous potassium carbonate to a porridge-like consistency, and the oxime was extracted with chloroform 10-12 times.

*In these oximes the basicity of the ring is higher or considerably higher than in the oximes (I-III).

B. To a solution of the aldehyde in ethanol was added a filtered ethanolic solution of free hydroxylamine obtained by neutralizing its hydrochloride with the calculated amount of sodium ethoxide. After 2-3 h, the ethanol was evaporated off and the oxime was obtained. In the preparation of (VIII), to a solution of the aldehyde [5] in a small amount of water was added a solution of hydroxylamine hydrochloride (15% excess) previously neutralized to pH 8, the reaction mixture was left in an atmosphere of argon for 30 min, a solution of potassium carbonate was added to pH 10, the oxime was extracted with ether, the solvent was driven off, and the oil so obtained was converted into the crystalline hydrochloride by means of an ethanolic solution of hydrogen chloride.

For the preparation of the methiodides of the oximes, the corresponding bases were treated with an excess of methyl iodide in ethanol at room temperature (XV); in a mixture of acetone and alcohol (2 : 1) at the boil for 4 h (XII, XIV); or in acetone at 100°C for 4 h (XIII). In the preparation of the bis(quaternary ammonium) derivatives a mixture of the corresponding free oxime and of a dihalogenoalkane (molar ratio 2 : 1) was heated in dimethylformamide at 100°C for 3 h (XVI), 7 h (XVII), or 13 h (XVIII).

The Nitrones (XIX and XX). The oximes (I) and (II) were treated with an excess of methyl iodide at 100°C or with dimethyl sulfate at room temperature. The resulting salts, unstable in an acid medium, were made alkaline with potassium carbonate solution and subjected to extraction with chloroform. This gave the crystalline nitrones with mp 102-110°C (from carbon tetrachloride) (XIX) and 115-117°C (from carbon tetrachloride) (XX). For (XX): found, %: C 52.2; H 7.0; N 30.3. $C_6H_9N_3O$. Calculated, %: C 51.8; H 6.5; N 30.1. Both nitrones were also obtained from the corresponding aldehydes and N-methylhydroxylamine under the conditions for the formation of oximes (method B for VIII). A mixture of samples obtained by different methods melted without depression, and the samples had identical IR spectra. After treatment by the method described, the oxime (III) was recovered unchanged.

The melting points were determined on a Kofler block.

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