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SYNTHESIS AND REACTIVITY OF SOME MANNICH BASES. IV. QUATERNARY AMMONIUM IODIDES FROM MANNICH BASES OXIMES

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Abstract: A series of oximes derived from some Mannich bases was transformed at into quaternary ammonium salts at the amine nitrogen atom. The reaction was accomplished on oximes generated from 1-(2'-hydroxy-5'-methylphenyl)-3-dialkylamino-1-propanone and its 4'-methylphenyl substituted isomer. Quaternization was performed with methyl iodide in tetrahydrofuran (THF) as well as in ethanol, at room temperature. The structure of the oximes' methiodides was investigated by IR, ^{1}H-NMR, ^{13}C-NMR and FAB spectra.

INTRODUCTION

Oximes, substances generically related with carbonylic compounds, play an important role in organic synthesis, as well as in modern therapeutics or various technical domains. There is a large number of pharmaceuticals containing an oximino group attached to a variable structure, frequently a heterocyclic one [1-3]. Other oxime derivatives present a fungitoxic and herbicide effect [4-6], or act as growth regulators for plants [7].

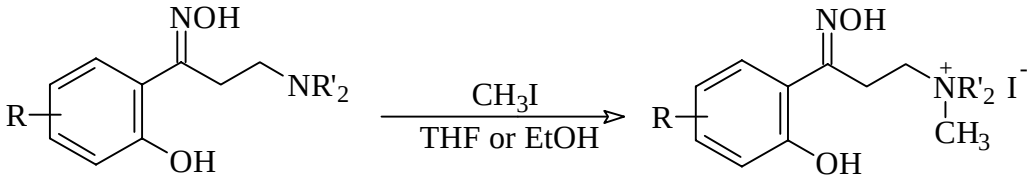
Mannich bases oximes have received little attention and these compounds' quaternization at the amine nitrogen atom was studied even lesser. Scott and MacConaill [8] described the preparation of such substances, subsequently used in the synthesis of some Δ^2-1,2-oxazoline derivatives. A series of methiodides has been obtained by other authors using as a substrate Mannich bases oximes generated from methyl styryl ketones [9].

Some studies on the 2-piridinaldoxime methylated at the heterocyclic nitrogen atom (2-PAM, pralidoxime) showed its remarkable activity as a reactivator of inhibited cholinesterase in poisonings with organo-phosphoric compounds [10,11]. Pralidoxime's activity is attributed to the presence of two active centers in these compounds' structure. The first active center - the oximino group - nucleophilically attacks the phosphorus atom from the inhibited enzyme, whereas the second one - the cationic quaternized nitrogen - is involved in the orientation of the molecule's remainder to the anionic centers of the enzyme. Since Mannich bases oximes having an exocyclic quaternized amino group met the above mentioned structural requirements, it seemed attractive to prepare a series of quaternary ammonium iodides from Mannich bases oximes in order to estimate their activity as reactivators of inhibited cholinesterase in poisonings with organo-phosphoric compounds. The evaluation is currently underway and will be reported elsewhere.

RESULTS AND DISCUSSION

This paper aims at transforming some Mannich bases into quaternary ammonium salts. The starting oximes, unlike the earlier investigated ones [12-14], resulted from ketonic Mannich bases with a phenolic hydroxyl in *ortho* to the carbonyl group. This new type of oximes has been recently described in some papers of ours [15-17], that emphasized the phenolic group's influence on both the synthesis and particular properties of these compounds.

Oximes **1a-e** were prepared from two series of ketonic Mannich bases, namely 1-(2'-hydroxy-5'-methylphenyl)-3-(dialkylamino)-1-propanone and 1-(2'-hydroxy-4'-methylphenyl)-3-(dialkylamino)-1-propanone. Quaternization with methyl iodide was attempted in several organic solvents such as dioxane, tetrahydrofuran, ethanol and chloroform.



1a-e **2a-e**

	R	R’	R’
a	5-CH_3	$CH_2CH_2OCH_2CH_2$	
b	5-CH_3	$CH_2(CH_2)_3CH_2$	
c	5-CH_3	CH_3	CH_3
d	5-CH_3	C_2H_5	C_2H_5
e	4-CH_3	$CH_2CH_2OCH_2CH_2$	

Reaction scheme for converting Mannich bases oximes into quaternary ammonium iodides

Dioxane was employed as a solvent for the quaternization of **1b** in an earlier stage of this work**.** The oily product that separated on treatment with hexane became solid after being placed in a freezer overnight, but it proved to be the starting oxime. An attempt to produce the desired quaternary salt in chloroform led to an impure product in low chemical yield (36%). Good results were obtained using THF, in which the oximes are highly soluble; the methiodides separated almost quantitatively when a diminished volume of solvent was employed. Ethanol also provided access to highly pure oxime methiodides, but the chemical yields were lower when compared to those obtained when THF was used as solvent. This fact is presumably due to the larger amount of ethanol required for the reaction to take place in a homogenous phase, as the oximes’ solubility in this solvent is smaller than in THF. Table 1 presents comparatively the chemical yields for the reaction products after the work-up in THF and ethanol. Taking into account the iodomethane's volatility at room temperature, the reactions were performed in a stoppered flask. The resulting products were purified from ethanol; if the synthesis was conducted in the same solvent, they separated purely enough to pass the elemental analysis.

Table 1. Comparative yields of oxime methiodides in THF and ethanol

Compound	Yield in THF, %	Yield in ethanol, %
2a	90	52
2b	95	65
2c	98	78
2d	96	70
2e	93	61

Table 2. Some characteristics of the quaternized oximes

Compound	M.p. °C	Formula	Analysis			IR, $\nu_{C=N}$ cm^{-1}
			C	H	N	
2a	178	$C_{15}H_{23}IN_2O_3$ (406)	44.33 44.50	5.66 5.80	6.89 6.66	1630
2b	172	$C_{16}H_{25}IN_2O_2$ (404)	47.52 47.35	6.18 6.40	6.93 6.73	1630
2c	183	$C_{13}H_{21}IN_2O_2$ (364)	42.83 42.62	5.76 5.89	7.69 7.51	1630
2d	182	$C_{15}H_{25}IN_2O_2$ (392)	45.91 45.77	6.37 6.50	7.14 7.02	1630
2e	181	$C_{15}H_{23}IN_2O_3$ (406)	44.33 44.05	5.66 5.38	6.89 6.69	1630

The structure of compounds was minutely investigated by means of spectroscopy. IR spectra exhibit the $\nu_{C=N}$ absorption band at 1630 cm^{-1} (see Table 2). The aliphatic C-H bonds' absorption localized in the 2875-2960 cm^{-1} region is quite distinct, as well as the one generated by the hydroxyl groups at 3200-3300 cm^{-1}. ^{1}H-NMR spectra showed the adequate signals for each type of protons present in the molecule. Phenolic and oximino hydroxyl protons appeared in off set at about 10.6 and 11.8 ppm, respectively. Different methyl groups' protons could be easily discriminated, due to the higher chemical shift value induced by the positive charge on the nitrogen atom. The same effect was observed in the case of the two nonequivalent methylenic groups.

Discussions on the E or Z configuration of the oximes **1** can be extended for the quaternary iodides **2a-e** as both of them include in their structure the same oximino

group. It has already been shown that *ortho*-phenolic oximes adopt preferentially the E configuration due to its stabilization through an intramolecular hydrogen bond (Fig. 1) [18]. This configuration was confirmed for oximes **1** as well as for quaternary iodides **2a-e** by NMR spectra. Thus, the peak at 10.6 ppm attributed to the phenolic proton proved the hydroxyl's involvement in a hydrogen bond.

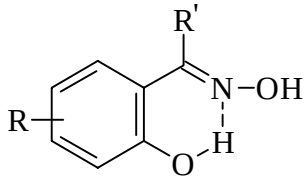


Fig.1. Intramolecular hydrogen bond formation.

^{13}C-NMR spectra interpreted by DEPT technique showed for the methylenic carbon in α to the oximino group a signal at about 20.1 ppm, that suggests a *syn*-alkyl disposition of oxime's hydroxyl [19].

Mass spectra non-equivocally confirmed the methiodides' structure. Because of these compounds' slight volatility, FAB (Fast Atom Bombardment) technique was rather used. The base peaks were at the same time the ones for the molecular ions, the mass of which were in full agreement with those of the N-methylated oximes' cations.

EXPERIMENTAL

Melting points were taken on a Boetius melting point microscope and are uncorrected. Elemental analyses were performed at “Petru Poni” Institute of Macromolecular Chemistry, Iasi. IR Spectra were registered on a SPECORD M80 spectrometer, while ^{1}H- and ^{13}C-NMR spectra were recorded in deuterated dimethylsulfoxide on a VARIAN XL-300 apparatus at 100 MHz. Mass spectra were determined on a V.G. Micromass 7070 HS mass spectrometer.

Oximes **1** were prepared from the corresponding ketonic Mannich bases by treatment with hydroxylamine hydrochloride in a 10% NaOH aqueous solution, at room temperature. To separate them, aqueous acetic acid was added dropwise to the cooled solutions, until pH reached 6.8-7.2 [14-15].

Oximes' methiodides were prepared through one of the below mentioned procedures:

Oxime (10 mmol), dissolved in 35 mL ethanol, was treated with methyl iodide (1.42 g; 0.62 mL; 10 mmol). The reaction mixture was stirred at room temperature for about 2 hours and then left in a refrigerator. The solid methiodide was filtered off and washed with diethyl ether.

Oxime (10 mmol), dissolved in the minimum amount of THF, was treated with methyl iodide (1.42 g; 0.62 mL; 10 mmol) with good stirring. Although a solid product separated from the very first minutes, stirring at room temperature continued for another 90 min. The reaction mixture was left overnight in a refrigerator, then the precipitate was filtered off and washed with a little THF. The raw products were recrystallized from ethanol.

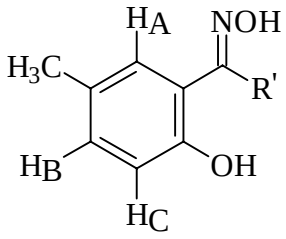


Fig. 2. Types of protons in the aromatic ring of compounds **2a-d**.

1-(2'-Hydroxy-5'-methylphenyl)-3-(4-morpholinyl)-1-propanone oxime methiodide **2a**

^{1}H-NMR spectrum (ppm): 2.10 (s, 3H, $ArCH_3$); 3.11 (s, 3H, H_3C^+N); 3.15-3.19 [t, 2H, $C(=NOH)CH_2$]; 3.37-3.41 [m, 4H, $>^+N(CH_2\text{-})_2$]; 3.52-3.56 [t, 2H, CH_2^+N]; 3.87 [s, 4H, $O(CH_2\text{-})_2$]; 6.72-6.74 (d, H_C); 7.03 (d, H_B); 7.05 (s, H_A); 10.6 (1H, ArOH); 11.8 (1H, =NOH).

1-(2'-Hydroxy-5'-methylphenyl)-3-(1-piperidinyl)-1-propanone oxime methiodide **2b**

^{1}H-NMR spectrum (ppm): 1.53 and 1.77 [m, 2H and 4H, $CH_2(CH_2\text{-})_2$]; 2.23 (s, 3H, $ArCH_3$); 3.13 (s, 3H, H_3C^+N); 3.19-3.21 [2H, t, $C(=NOH)CH_2$]; 3.45 (b.s, 6H, $CH_2^+N(CH_2\text{-})_2$]; 6.75-6.79 (d, H_C, $J_{1,2}$= 8.2 Hz); 7.01-7.06 (d, H_B, J=8.3 Hz); 7.25 (s, H_A); 10.6 (1H, ArOH); 11.8 (1H, =NOH).

^{13}C-NMR spectrum (ppm): 19.36 and 19.58 [$CH_2(CH_2\text{-})_2$]; 20.15 ($ArCH_3$);20.44 [$C(=NOH)CH_2$]; 46.86 (H_3C^+N); 57.93 and 59.85 [$CH_2^+N(CH_2\text{-})_2$]**;**116.37; 118.85; 127.77, 128.48; 131.15; 155.18 (6 aromatic carbons); 154.39 (C=N). **Mass spectrum**: m/z = 277.24.

1-(2'-Hydroxy-5'-methylphenyl)-3-dimethylamino-1-propanone oxime methiodide **2c**

^{1}H-NMR spectrum (ppm): 2.22 (s, 3H, $ArCH_3$); 3.14-3.23 [9H, $^+N(CH_3)_3$]; 3.36-3.37 (b.s, 2H, $C(=NOH)CH_2$]; 3.43-3.47 (t, 2H, $CH_2{}^+N$); 6.75-6.80 (dd, H_B, $J_{1,2}$=8,24 Hz; $J_{1,3}$=2 Hz); 7.03-7.07 (d, H_C, J=8.2 Hz); 7.21 (s, H_A); 10.65 (1H, ArOH); 11.87 (1H, =NOH).

^{13}C-NMR spectrum (ppm): 20.19 ($ArCH_3$); 20.52 [$C(=NOH)CH_2$]; 52.09 ($^+N(CH_3)_3$]; 60.98 ($CH_2{}^+N$); 116.45; 118.96; 127.78; 128.55; 131.19; 155.10 (6 aromatic carbons); 154.44 (C=N). **Mass spectrum**: m/z = 237.23.

1-(2'-Hydroxy-5'-methylphenyl)-3-diethylamino-1-propanone oxime methiodide **2d**

^{1}H-NMR spectrum (ppm): 1.20-1.26 (t, 6H, $CH_2C\underline{H}_3$); 2.22 (s, 3H, $ArCH_3$); 3.00 (s, 3H, H_3C^+N); 3.08-3.15 [t, $C(=NOH)CH_2$]; 3.36-3.44 (m, 6H, $CH_2{}^+N(CH_2\text{-})_2$]; 6.76-6.81 (dd, H_B, $J_{1,2}$=8.24 Hz; $J_{1,3}$=2.15 Hz); 7.03-7.07 (d, H_C, J=8.24 Hz); 7.19 (s, H_A); 10.59 (1H, ArOH); 11.87 (1H, =NOH).

^{13}C-NMR spectrum (ppm): 7.49 ($CH_2\underline{C}H_3$); 20.13 ($ArCH_3$); 20.13 [$C(=NOH)CH_2$]; 46.57 (H_3C^+N); 54.78 and 55.50 [$CH_2{}^+N(CH_2\text{-})_2$]; 116.37; 119.37; 127.71; 128.63; 131.14; 154.69 (6 aromatic carbons); 154.28 (C=N). **Mass spectrum**: m/z = 265.26.

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POVZETEK

Vrsto oksimov, pripravljenih iz Mannichovih baz, smo pretvorili v amonijeve soli. Uporabili smo oksime, pripravljene iz 1-(2'-hidroksi-5'-metilfenil)-3-dialkilamino-1-propanona in njegovega 4'-metilfenil izomera. Kvaternizacijo smo izvedli z metil jodidom v THF oziroma etanolu pri sobni temperaturi. Strukture produktov smo potrdili z IR, ^{1}H NMR, ^{13}C NMR in FAB MS spektri.