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Synthesis and reactivity of some Mannich bases. VIII. Studies on several Mannich bases derived from *ortho*-hidroxyacetophenones and their conversion into oximino derivatives

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The synthesis of several Mannich bases resulting from the reaction of 2-hydroxy-4-methylacetophenone with paraformaldehyde and secondary amines is reported. Another series of products was obtained from *N*,*N*-dimethyl substituted Mannich bases by replacing the amino group with pyrrolidine. Most of the Mannich bases were transformed into oximes by treatment with hydroxylamine hydrochloride in 10 % NaOH.

Keywords: *ortho*-phenolic ketones, Mannich bases, amine exchange reaction, Mannich bases oximes.

Alkyl aryl ketones belong to the most investigated group of substrates used in the Mannich reaction.[1,2] Among the variously substituted acetophenones employed for producing C-Mannich bases, the ones bearing a phenolic hydroxy group *ortho* to the carbonyl moiety are less studied.[3,4] In earlier papers, we have reported the synthesis of several -aminoketones **1** derived from 2-hydroxy-5-methylacetophenone[5] and 2-hydroxy-5-methylpropiophenone,[6] as well as the preparation[7] of the corresponding Mannich bases oximes methiodides **3**. The good anti-inflammatory activity of the former and the promissing action of the latter in reactivating cholinesterase inhibited by poisoning with organo-phosphorous compounds[8] urged us to undertake the present work. Moreover, the novel series of Mannich bases and their related oximes presented in this paper, mostly derived from 2-hydroxy-4-methylacetophenone, are valuable intermediates (Scheme 1) for the synthesis of 1,2-benzisoxazoles **4**, which are useful as acetylcholinesterase inhibitors.[9]

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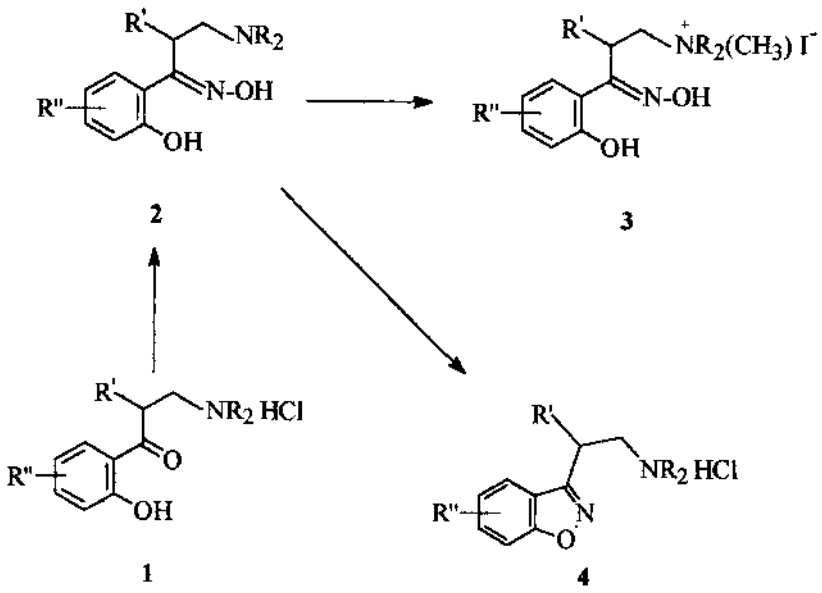


Scheme 1. Selected reactions of Mannich bases derived from *ortho*-hydroxyacetophenones.

EXPERIMENTAL

Melting points were determined on a Boetius apparatus and are uncorrected. IR spectra were taken on a SPECORD M80 spectrometer, whereas ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Gemini 200 and a Varian XL 300 spectrometers using D_2O or $CDCl_3$ as solvents and TMS as internal standard. The mass spectrum of **7b** was registered using a V.G. Micromass 7070 HS mass spectrometer.

2-Hydroxy-4-methylacetophenone (**5**) was obtained from *meta*-tolyl acetate by a Fries rearrangement. The desired isomer was separated from its mixture with 2-methyl-4-hydroxyacetophenone by steam distillation and then purified by distillation under reduced pressure. 3-Dimethylamino-1-(2'-hydroxy-5'-methylphenyl)-1-propanone and 3-dimethylamino-1-(2'-hydroxy-5'-methylphenyl)-2-methyl-1-propanone were prepared according to literature methods.[5,6]

*Mannich base hydrochlorides **6a-d** through direct aminomethylation*

General procedure. Ketone **5** (7.5 g, 0.05 mol), paraformaldehyde (3 g, 0.1 mol), amine hydrochloride (0.05 mol), 0.1 ml conc. HCl and 2-propanol (15–25 ml, depending on the amine) were refluxed with stirring for 4 h. In less than an hour the reactants had dissolved and sometimes the Mannich base hydrochloride started to separate from the reaction mixture as a solid after about 2 h when a small volume of 2-propanol was employed. After the reaction mixture had been kept in a freezer overnight, the crystals were filtered off, washed with acetone (or diethyl ether) and purified by recrystallization from ethanol.

3-Dimethylamino-1-(2'-hydroxyphenyl)-1-propanone (m.p. 174–175 ºC; lit.[10]: 175–176 ºC) and 1-(2'-hydroxyphenyl)-3-(4-morpholinyl)-1-propanone (m.p. 193–194 ºC; lit.[10]: 193–195 ºC) were obtained by applying the same method with 64 % and 56 % yields, respectively, and were converted into the corresponding oxime without further purification.

1-(2'-Hydroxy-4'-methylphenyl)-3-(4-morpholinyl)-1-propanone hydrochloride (**6a**). Anal. calcd. for $C_{14}H_{20}ClNO_3$: C, 58.84; H, 7.00, N, 4.90. Found: C, 58.62; H, 7.21; N, 4.68. M. p. 206–208 ºC. Yield 44 %. IR (KBr, cm^{-1}): 1640 ($_{CO}$). ^{1}H-NMR spectrum (D_2O), : 2.32 (*s*, 3H, CH_3Ar); 2.9–3.5 *s*, 4H, >$^{+}$N (CH_2–)$_2$]; 3.46 (*t*, 2H, $COCH_2$, *J* = 6.8 Hz); 3.79 (*t*, 2H, CH_2N^+, *J* = 6.8 Hz); 4.05–4.09 *m*, 4H,

O(CH_2–)$_2$]; 6.69–6.76 (*m*, 2H); 7.69 (*d*, 1H, *J* = 8.2 Hz). ^{13}C-NMR spectrum (D_2O), : 21.80 ($ArCH_3$); 35.45 ($COCH_2$); 53.46 and 53.52 $CH_2N^+H(CH_2–)_2$]; 66.76 O(CH_2–)$_2$]; 117.06; 117.44; 120.14; 129.62; 147.91; 162.49 (6 aromatic carbons); 200.39 (CO).

1-(2'-Hydroxy-4'-methylphenyl)-3-(1-piperidinyl)-1-propanone hydrochloride (**6b**). Anal. calcd. for $C_{15}H_{22}ClNO_2$: C, 63.49; H, 7.76; N, 4.93. Found: C, 63.21; H, 7.98; N, 4.70. M. p. 197–199 ºC. Yield 53 %.IR (KBr, cm^{-1}): 1645 ($_{CO}$). ^{1}H-NMR spectrum (D_2O), : 1.3–2.4 6H, $CH_2(CH_2–)_2$]; 2.27 (*s*, 3H, $ArCH_3$): 2.5–2.8 (*m*, 2H, $COCH_2$); 3.3–3.6 (*m*, 4H, $>^+N(CH_2–)_2$]; 3,76 (*t*, 2H, CH_2N^+, *J* = 7 Hz); 6.62–6.68 (*m*, 2H); 7.65 (*d*, 1H, *J* = 8 Hz). ^{13}C-NMR spectrum ($CDCl_3$), : 21.83 and 21.89 $CH_2(CH_2–)_2$]; 22.54 ($ArCH_3$): 32.62 ($COCH_2$); 53.53 and 53.61 $CH_2N^+H(CH_2–)_2$]; 116.31; 118.28; 120.74; 129.94; 149.00; 162.24 (6 aromatic carbons); 200.75 (CO).

3-Dimethylamino-1-(2'-hydroxy-4'-methylphenyl)-1-propanone hydrochloride (**6c**). Anal. calcd. for $C_{12}H_{18}ClNO_2$: C; 59.13; H, 7.39; N, 5.74. Found: C, 59.01; H, 7.59; N, 5.46. M.p. 183–185 ºC. Yield 47 %. IR (KBr, cm^{-1}): 1650 ($_{CO}$). ^{1}H-NMR spectrum (D_2O), : 2.08 (*s*, 3H, $ArCH_3$); 2.77 *s*, 6H, $^+N(CH_3)_2$]; 3.33 (*bs*, 4H, $COCH_2CH_2^+N$); 6.48 and 6.58 (*bs*. 2H) 7.44 (*d*, 1H). ^{13}C-NMR spectrum (D_2O), : 22.13 ($ArCH_3$); 33.63 ($COCH_2$); 44.04 $^+N(CH_3)_2$]; 53.58 (CH_2^+N); 117.39; 118.57; 122.26; 131.38; 150.71; 161.28 (6 aromatic carbons); 203.44 (CO).

3-Dimethylamino-1-(2'-hydroxy-4'-methylphenyl)-1-propanone hydrochloride (**6d**). Anal. calcd. for $C_{14}H_{22}ClNO_2$: C, 61.87; H, 6.18; N, 5.15. Found: C, 61.65; H, 6.31; N, 4.89. M.p. 122–123 ºC. Yield 32 %. IR (KBr, cm^{-1}): 1650 ($_{CO}$). ^{1}H-NMR spectrum (D_2O), : 1.34 (*t*, 6H, $>N^+(CH_2CH_3)_2$, *J* = 7.3 Hz ; 2.31 (*s*, 3H, $ArCH_3$); 3.28 q, 4H, $>N^+(CH_2CH_3)_2$, *J* = 7.3 Hz); 3.54 (*s*, 4H, $COCH_2CH_2N^+$); 6.76 (*bs*, 1H) 6.83 (*d*, 1H, *J* = 8.2 Hz); 7.70 (*d*, 1H, *J* = 8.2 Hz). ^{13}C-NMR spectrum (D_2O), : 9.68 $>N^+(CH_2CH_3)_2$]; 20.9 ($ArCH_3$); 34.10 ($COCH_2$); 47.98 and 49.39 $CH_2^+NH(CH_2–)_2$]; 118.89; 120.08; 121.27; 131.57; 139.7; 159.4 (6 aromatic carbons); 204.38 (CO).

Mannich base hydrochlorides ***7a-d*** *through N-alkylation of pyrrolidine*

General procedure. A Mannich base hydrochloride (0.02 mol) was dissolved with stirring in 50 ml water and treated with pyrrolidine (1.42 g, 1.65 ml; 0.02 mol). Stirring was continued for 3–4 h at room temperature and then the reaction mixture was extracted with diethyl ether. The organic layer was washed with water, dried over Na_2SO_4 and distilled under reduced pressure to remove the solvent. The oily residue was treated with ethanolic HCl whereby the Mannich base hydrochloride separated as a solid. Repeated recrystallizations were performed from ethanol. In an earlier attempt to carry out the reaction in ethanol-water (1:1), dilution with water prior to diethyl ether extraction was required. Heating, even to an insignificant extent, caused colouring of the reaction mixture up to reddish-brown.

1-(2'-Hydroxyphenyl)-3-(1-pyrrolidinyl)-1-1-propanone hydrochloride (**7a**). Anal. calcd. for $C_{13}H_{18}ClNO_2$: C, 61.05; H, 7.04; N, 5.47. Found: C, 60.80; H, 7.29; N, 5.58. M.p. 162–163 ºC (lit.[26]: 161–162 ºC). Yield: 44 %. IR (KBr, $cm^–$): 1650 ($_{CO}$). ^{1}H-NMR spectrum (D_2O), : 1.90–2.08 (*bs*. 4H, CH_2CH_2); 2.77–2.78 (*t*, 2H, $COCH_2$); 3.36–3.44 *m*, 6H, $CH_2^+NH(CH_2–)_2$]; 6.78 (*d*, 1H), 6.83 (*dd*, 1H); 7.39 (*dd*, 1H); 7.65 (*d*, 1H). ^{13}C-NMR spectrum (D_2O), : 23.67 ($CH_2CH_2CH_2CH_2$); 35.14 ($COCH_2$); 50.63, 53.57 and 55.49 $CH_2^+NH(CH_2–)_2$]; 118.68; 119.88; 121.09; 131.59; 138.38; 161.12 (6 aromatic carbons); 204.17 (CO).

1-(2'-Hydroxy-5'-methylphenyl)-3-(1-pyrrolidinyl)-1-propanone hydrochloride (**7b**). Anal. calcd. for $C_{14}H_{20}ClNO_2$: C, 62.33; H, 7.42; N, 5.19. Found: C, 62.01; H, 7.60; N, 5.01. M.p. 181–183 ºC. Yield 48 %. IR (KBr, cm^{-1}): 1650 ($_{CO}$). ^{1}H-NMR spectrum (D_2O), : 1.99–2.07 (*m*, 4H, $CH_2CH_2CH_2CH_2$); 2.22 (*s*, 3H, $ArCH_3$); 2.88 (*bs*, $COCH_2$, *J* = 2.2 Hz); 3.34–3.54 *m*, 6H, $CH_2^+NH(CH_2–)_2$]; 6.81–6.87 (*dd*, 1H, *J* = 2.0 Hz); 7.35–7.39 (*d*, 1H, *J* = 8.5 Hz); 7.61 (*s*, 1H). ^{13}C-NMR spectrum (D_2O), : 19.40 ($ArCH_3$); 22.61 ($CH_2CH_2CH_2CH_2$); 42.96 ($COCH_2$); 49.57; 52.49; 54.42 $CH_2^+NH(CH_2–)_2$]; 117.47; 118.66; 129.75; 130.12; 138.27; 158.02 (6 aromatic carbons); 203.8 (CO).

1-(2'-Hydroxy-4'-methylphenyl)-3-(1-pyrrolidinyl)-1-propanone hydrochloride (**7c**). Anal. calcd. for $C_{14}H_{20}ClNO_2$: C, 62.33; H, 7.42; N, 5.19. Found: C, 62.09; H, 7.49; N, 5.27. M.p. 176–178

ºC. Yield 52 %. IR (KBr, cm^{-1}): 1650 ($_{CO}$). ^{1}H-NMR spectrum (D_2O), : 1.90–2.03 (*m*, 4H, CH_2CH_2); 2.12 (*s*, 3H, Ar(CH_3), 2.77 (*t*, 2H, $COCH_2$); 3.36–3.40 [(*m*, 6H, $CH_2^+NH(CH_2–)_2$]; 6.57 (*s*, 1H); 6.64 (*d*, 1H); 7.51 (*d*, 1H). ^{13}C-NMR spectrum (D_2O), : 22.13 ($ArCH_3$); 23,69 ($CH_2CH_2CH_2CH_2$); 34.87 ($COCH_2$); 50.73, 53.64 and 55.50 $CH_2^+NH(CH_2–)_2$]; 117.52; 118.63; 122.29; 131.43; 150.76; 161.35 (6 aromatic carbons); 203.52 (CO).

1-(2'-Hydroxy-5'-methylphenyl)-2-methyl-3-(1-pyrrolidinyl)-1-propanone hydrochloride (**7d**) Anal. calcd. for $C_{15}H_{22}ClNO_2$: C, 63.49; H, 7.76; N, 4.93. Found: C, 63.12; H, 7.91; N, 4.73. M.p. 180–181 ºC. Yield 41 %. IR (KBr, cm^{-1}): 1650 ($_{CO}$).

Mannich base oximes ***8a-g***

General procedure. To a well-stirred solution of a Mannich base hydrochloride (5 mmol) in 10 % aqueous NaOH (1 g, 25 mmol), hydroxylamine hydrochloride (0.695 g, 10 mmol) dissolved in a small amount of water was added dropwise. The reaction mixture was stirred for another 6 h or it was left overnight. After filtration, the ice-cold solution was carefully brought up to pH 6.5–7.0 with 20 % aqueous acetic acid. At lower pH values, a considerable decrease of the amount of precipitate and even dissolution of the oxime were noticed. The precipitate was filtered off, thoroughly washed with ice-cold water and recrystallized from 50–80 % aqueous ethanol or from hexane.

1-(2-Hydroxy-4'-methylphenyl)-3-(4-morpholinyl)-1-propanone oxime (**8a**). Anal. calcd. for $C_{14}H_{20}N_2O_3$: C, 63.63; H, 7.57; N, 10.60. Found: C, 63.70; H, 7.60; N, 10.42. M.p. 148–149 ºC. Yield 75 %. IR (KBr, cm^{-1}): 1620 ($_{C=N}$). ^{1}H-NMR spectrum ($CDCl_3$), : 2.29 (*s*, 3H, $ArCH_3$); 2.61–2.70 *m*, 6H, $CH_2N(CH_2–)_2$; 3.03–3.1 *m*, 2H, C(=NOH)CH_2]; 3.75 *t*, 4H, $O(CH_2–)_2$, J = 4.6 Hz ; 6.69 (*s*, 1H); 6.67 (*d*, 1H); 7.22–7.26 (*d*, 1H, J = 6 Hz).

1-(2-Hydroxy-4'-methylphenyl)-3-(1-piperidinyl)-1-propanone oxime (**8b**). Anal. calcd. for $C_{15}H_{22}N_2O_2$: C, 68.70; H, 8.39; N, 10.68. Found: C, 68.46; H, 8.59; N, 10.80. M.p. 182–184 ºC. Yield 76 %. IR (KBr, cm^{-1}): 1630 ($_{C=N}$). ^{1}H-NMR spectrum ($CDCl_3$), : 1.3–1.8 *m*, 6H, $CH_2(CH_2–)_2$]; 2.27 (s, 3H, $ArCH_3$); 2.5–2.68 *m*, 6H, $CH_2(CH_2–)_2$]; 3.05 *t*, 2H, C(=NOH)CH_2; J = 6.9 Hz ; 6.65 (*dd*, 1H); 6.75 (*s*, 1H); 7.19 (*d*, 1H, J = 8 Hz).

3-Dimethylamino-1-(2-hydroxy-4'-methylphenyl)-1-propanone oxime (**8c**). Anal. calcd. for $C_{12}H_{18}N_2O_2$: C, 64.86; H, 8.10; N, 12.61. Found: C, 64.59; H, 8.31; N, 12.41. M.p. 176–178 ºC. Yield 81 %. IR (KBr, cm^{-1}): 1630 ($_{C=N}$). ^{1}H-NMR spectrum ($CDCl_3$), : 2.27 *s*, 3H, $ArCH_3$); 2.39 *s*, 6H, $N(CH_3)_2$; 2.62 *t*, 2H, C(=NOH)CH_2]; 3.04 (*t*, 2H, CH_2N); 6.65 and 6.74 (*m*, 2H); 7.22 (*d*, 1H). ^{13}C-NMR spectrum ($CDCl_3$), : 21.25 ($ArCH_3$); 23.48 C(=NOH)CH_2]; 45 and 56.15 [$CH_2N(CH_3)_2$]; 115.45; 117.93; 119.91; 126.80; 141.04; 158.26 (6 aromatic carbons); 160.68 (C=N).

3-Dimethylamino-1-(2-hydroxy-4'-methylphenyl)-1-propanone oxime (**8d**). Anal. calcd. for $C_{14}H_{22}N_2O_2$: C, 67.20; H, 8.80; N, 11.20. Found: C, 67.01; H, 8.99; N, 11.35. M.p. 122–123 ºC. Yield 63 %. IR (KBr, cm^{-1}): 1620 ($_{C=N}$). ^{1}H-NMR spectrum ($CDCl_3$), : 1.13 *t*, 6H, $N(CH_2CH_3)_2$]; 2.26 (*s*, 3H, $ArCH_3$); 2.71 *q*, 4H, $N(CH_2CH_3)_2$]; 2.79 [*t*, 2H,C(=NOH)CH_2]; 3.05 (*t*, 2H, CH_2N); 6.63 and 6.74 (*m*, 2H); 7.24 (*d*, 1H). ^{13}C-NMR spectrum ($CDCl_3$), : 10.95 $N(CH_2CH_3)_2$; 21.23 ($ArCH_3$); 22.01 C(=NOH)CH_2]; 46.73 and 48.74 $CH_2N(CH_2–)_2$]; 115.58; 117.77; 119.91; 126.64; 140.75; 158.20 (6 aromatic carbons); 160.18 (C=N).

3-Dimethylamino-1-(2'-hydroxyphenyl)-1-propanone oxime (**8e**). Anal. calcd. for $C_{11}H_{16}N_2O_2$: C, 63.46; H, 7.69; N, 13.46. Found: C, 63.50; H, 7.81; N, 13.42. M.p. 137–139 ºC. Yield 75 %. IR (KBr, cm^{-1}): 1620 ($_{C=N}$). ^{1}H-NMR spectrum ($CDCl_3$), : 2.43 *s*, 6H, $N(CH_3)_2$]; 3.12 (*t*, 2H, CH_2N); 6.8 (*d*, 1H); 6.87 (*dd*, 1H); 7.17 (*dd*, 1H); 7.35 (*d*, 1H). ^{13}C-NMR spectrum ($CDCl_3$), : 22.60 C(=NOH)CH_2]; 44.74 and 55.29 $CH_2N(CH_3)_2$]; 117.27; 118.03; 118.94; 126.81; 130.19; 158.20 (6 aromatic carbons); 160.68 (C=N).

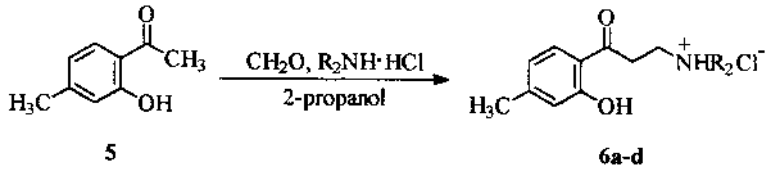
1-(2'-Hydroxyphenyl)-3-(4-morpholinyl)-1-propanone oxime (**8f**). Anal. calcd. for $C_{13}H_{18}N_2O_3$: C, 62.40; H, 7.20; N, 11.20. Found: C, 62.18; H, 7.43; N, 11.39. M.p. 182–183 ºC. Yield 74 %. IR (KBr, cm^{-1}): 1620 ($_{C=N}$). ^{1}H-NMR spectrum ($CDCl_3$), : 2.5–2.8 *m*, 6H, $CH_2N(CH_2–)_2$]; 3.0–3.2 *s*, 2H, C(=NOH)CH_2]; 3.6–3.8 *m*, 4H, $O(CH_2–)_2$]; 6.8–7.0 (2*dd*, 2H); 7.2 (*d*, 1H); 7.36 (*d*, 1H, J = 7.9 Hz).

1-(2'-Hydroxy-5'-methylphenyl)-3-(1-pyrrolidinyl)-1-propanone oxime (**8g**). Anal. calcd. for $C_{14}H_{20}N_2O_2$: C, 67.74; H, 8.06; N, 11.29. Found: C, 67.55; H, 8.12; N, 11.11. M.p. 148–149 ºC. Yield 69 %. IR (KBr, cm^{-1}): 1620 ($_{C=N}$). ^{1}H-NMR spectrum ($CDCl_3$), : 1.87 *bs*, 4H, CH_2CH_2); 2.23 (*s*, 3H, $ArCH_3$); 2.74–2.81 *m*, 6H, $CH_2N(CH_2–)_2$]; 3.15 *t*, 2H, C(=NOH)CH_2]; 6.8 (*d*, 1H); 6.97 (*d*, 1H); 7.14 (*s*, 1H). ^{13}C-NMR spectrum ($CDCl_3$), : 20.71 ($ArCH_3$); 22.67 C(=NOH)CH_2]; 23.36 (CH_2CH_2); 52.37; 53.8 and 55.43 $CH_2N(CH_2–)_2$]; 116.97; 117.74; 127.03; 127.77; 130.77; 155.94 (6 aromatic carbons); 159.23 (C=N).

RESULTS AND DISCUSSION

The investigated reaction pathway is presented in Scheme 2.

Compound **5** can undergo aminomethylation at the C -atom to the carbonyl group or the *ortho* position to the phenolic hydroxyl.[11] In order to obtain ketonic Mannich bases, the reaction was conducted at low pH values, in the presence of concentrated hydrochloric acid. 2-Propanol was found to be a better solvent than ethanol.[3,5] *ortho*-Hydroxyacetophenone was subjected to aminomethylation with morpholine hydrochloride and dimethylamine hydrochloride under the same experimental conditions.



5 **6a-d**

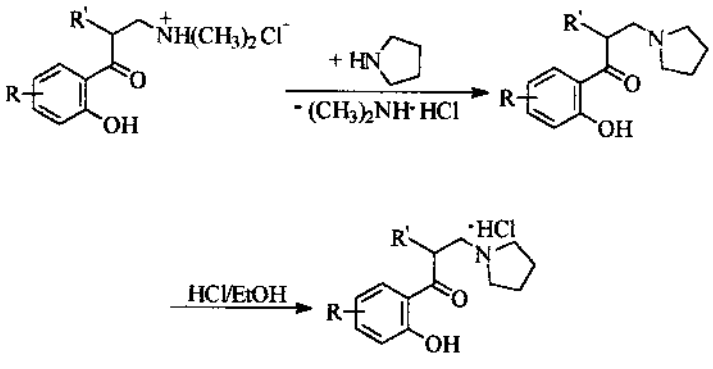
	R	R
6a	$CH_2CH_2OCH_2CH_2$	
6b	$CH_2(CH_2)_3CH_2$	
6c	CH_3	CH_3
6d	C_2H_5	C_2H_5

Scheme 2. Reaction scheme for converting 2-hydroxy-4-methylacetophenone into Mannich bases.

Several -pyrrolidinyl Mannich bases of *ortho*-hydroxyaryl alkyl ketones were also prepared through an indirect pathway. It is well known that one of the most interesting properties of Mannich bases is their ability to undergo amino group substitution, and within this particular type, *N*-alkylations are among the most intensively investigated. Thus, the easily leaving *N*,*N*-dialkylamino moiety from a -amino-*ortho*-hydroxypropiophenone has been successfully replaced by another *N*,*N*-dialkylamino group[3,4] or even by a *N*-arylamino group[12] in an amine exchange reaction under appropriate reaction conditions.

The amine exchange reaction between pyrrolidine and several Mannich bases derived from *ortho*-hydroxyacetophenones is described in Scheme 3.

When involved in transamination reactions, highly basic aliphatic secondary amines, such as pyrrolidine, also cause a partial removal of the hydrochloric acid from



7a-d

	R	R·
7a	4-CH_3	H
7b	H	H
7c	5-CH_3	H
7d	5-CH_3	CH_3

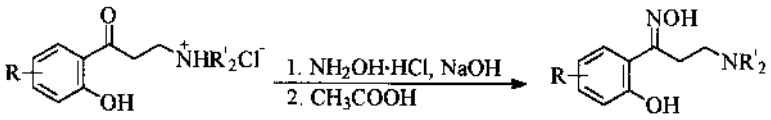
Scheme 3. Reaction scheme for obtaining Mannich bases **7a-d** trhough amine-exchange reaction.

the less basic tertiary Mannich base hydrochloride. As the resulting free base fraction no longer takes part in the amine exchange reaction, the raw product is usually a mixture that requires repeated recrystallizations up to the final obtainment of an analytically pure substance, and thus the yield of the purified product is lowered.

The formation of ketonic Mannich bases oximes is not a very common reaction. Besides a few typical oximations,[13,14] a literature survey provided a quite unusual example according to which the steps were surprisingly inverted: first the oxime was obtained which subsequenlly underwent to a Mannich condensation.[15] A modification of the method developed by Kalkote and Goswami for obtainig *ortho*-hydroxyacetophenone oximes[16] was considered to be the most convenient of all the preparation of Mannich bases oximes derived from *ortho*-hydroxyacetophenones. The considered reaction scheme is depicted in Scheme 4.

The IR spectra of Mannich bases exhibit an intense absorption at 1640–1650 cm^{-1} due to the involvement of the carbonyl group in an intramolecular hydrogen bond with the neighboring phenolic hydroxy group. A less intense $_{C=N}$ absorption at lower frequencies (1620–1630 cm^{-1}) was observed in the spectra of Mannich base oximes.

The oximes obtained under alkaline conditions displayed in their ^{13}C-NMR spectrum a diagnostic peak at around 20 ppm, which is characteristic for the -methylene of the *E* (*syn*-alkyl) geometrical isomer of the oxime double bond.[17] The preservation of the *E* configuration around the oxime carbon nitrogen double bond was crucial for the anticipated cyclization step to the benzisoxazoles **4**. The *Z*-isomer (*anti*-alkyl)



8a-g

	R	R'	R'
8a	4-CH_3	$CH_2CH_2OCH_2CH_2$	
8b	4-CH_3	$CH_2(CH_2)_3CH_2$	
8c	4-CH_3	CH_3	CH_3
8d	4-CH_3	C_2H_5	C_2H_5
8e	H	CH_3	CH_3
8f	H	$CH_2CH_2OCH_2CH_2$	
8g	5-CH_3	$CH_2(CH_2)_2CH_2$	

Fig. 4. Reaction scheme for converting Mannich bases into oximes **8a-g**.

has a non-planar conformation due to steric hindrance with the hydroxyl group in the *ortho* position and would not cyclize. On the contrary, the *E* isomer is stabilized by intramolecular hydrogen bonding with the hydroxyl group in the *ortho* position and the cyclization reaction is highly favourable.[18]

The FAB mass spectrum of the slightly volatile Mannich base hydrochloride **7b** was recorded. The spectrum exhibited an intense peak at *m*/*z* = 234.2 (100 %), which represents the precise value for the mass of the cation of the hydrochloride.

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СИНТЕЗА И РЕАКТИВНОСТ НЕКИХ MANNICH-ОВИХ БАЗА. ПРОУЧАВАЊА НЕКОЛИКО MANNICH-ОВИХ БАЗА ИЗВЕДЕНИХ ИЗ *орто*-ХИДРОКСИАЦЕТОФЕНОНА И ЊИХОВО ПРЕТВАРАЊЕ У ОКСИМИНО-ДЕРИВАТЕ

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Описана је синтеза неколико Mannich-ових база које постају при реакцији 2-хидрокси-4-метилацетофенона са параформалдехидом и секундарним аминима. Осим тога, једна серија производа добивена је из *N,N*-диметил супституисаних Mannich-ових база заменом њихових амино-група пиролидином. Већина добивених Mannich-ових база

трансформисана је у оксиме дејством хидроксиламин-хидрохлорида у 10 % раствору NaOH.

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