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SYNTHESIS OF 3-HYDROXY-6-METHYL- AND 3-HYDROXY-2-(2-PHENYLETHYL)PYRIDINES AND THEIR SULFUR-CONTAINING AMINO AND HYDROXYMETHYL DERIVATIVES

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The aminomethylation of 3-hydroxy-6-methyl- and 3-hydroxy-2-(2-phenylethyl)pyridines by secondary amines has been investigated. It was shown that like 2-alkyl-3-hydroxypyridine aminomethylation is directed primarily to position 6 and then 4 of the pyridine ring. On heating the aminomethyl derivatives of 3-hydroxy-6-methyl- and 3-hydroxy-2-(2-phenylethyl)pyridines with acetic anhydride the corresponding acetoxy derivatives were obtained, which were converted on heating with hydrochloric or hydrobromic acids into hydroxy and bromomethyl derivatives. Isothioureidomethyl and benzimidazolylthiomethyl derivatives were synthesized by heating the bromomethyl-substituted derivative with thiourea or with 2-mercaptobenzimidazole. The structures of compounds were confirmed by data of ^{1}H NMR spectra.

Keywords: isothioureido and thiobenzimidazolyl derivatives, 3-hydroxy-2-(2-phenylethyl)pyridine, aminomethylation.

Among the known synthetic antioxidants significant interest is generated by derivatives of 3-hydroxypyridine (3-HP), close in structure to the vitamin B_6 group [1]. They possess an inhibiting action on free radical reactions, they change the structure–functional state of membranes, receptors, and membrane-bound enzymes [2].

As a result of systematic investigations of the pharmacological properties of 3-HP derivatives a series of effective medicinal preparations was revealed (emoxypine and mexidol), which opened broad possibilities in the search for promising new medicinal agents in the 3-HP series [3].

Analysis of structure–activity links in a series of 3-HP derivatives indicated that their biological activity is not determined by antiradical activity and lipophilic properties alone. A significant role in the development of pharmacological properties in 3-HP derivatives is played by the entry of pharmacophoric groups into their structure (aminomethyl, aralkyl, isothioureido, etc.) [2].

With the aim of searching for new bioantioxidants in this class of compounds we have therefore carried out the synthesis of isothioureido, benzimidazolethio, amino, and hydroxymethyl derivatives of 2-(2-phenylethyl)-3-HP (**1**) and of 6-methyl-2-(2-phenylethyl)-3-HP (**2**).

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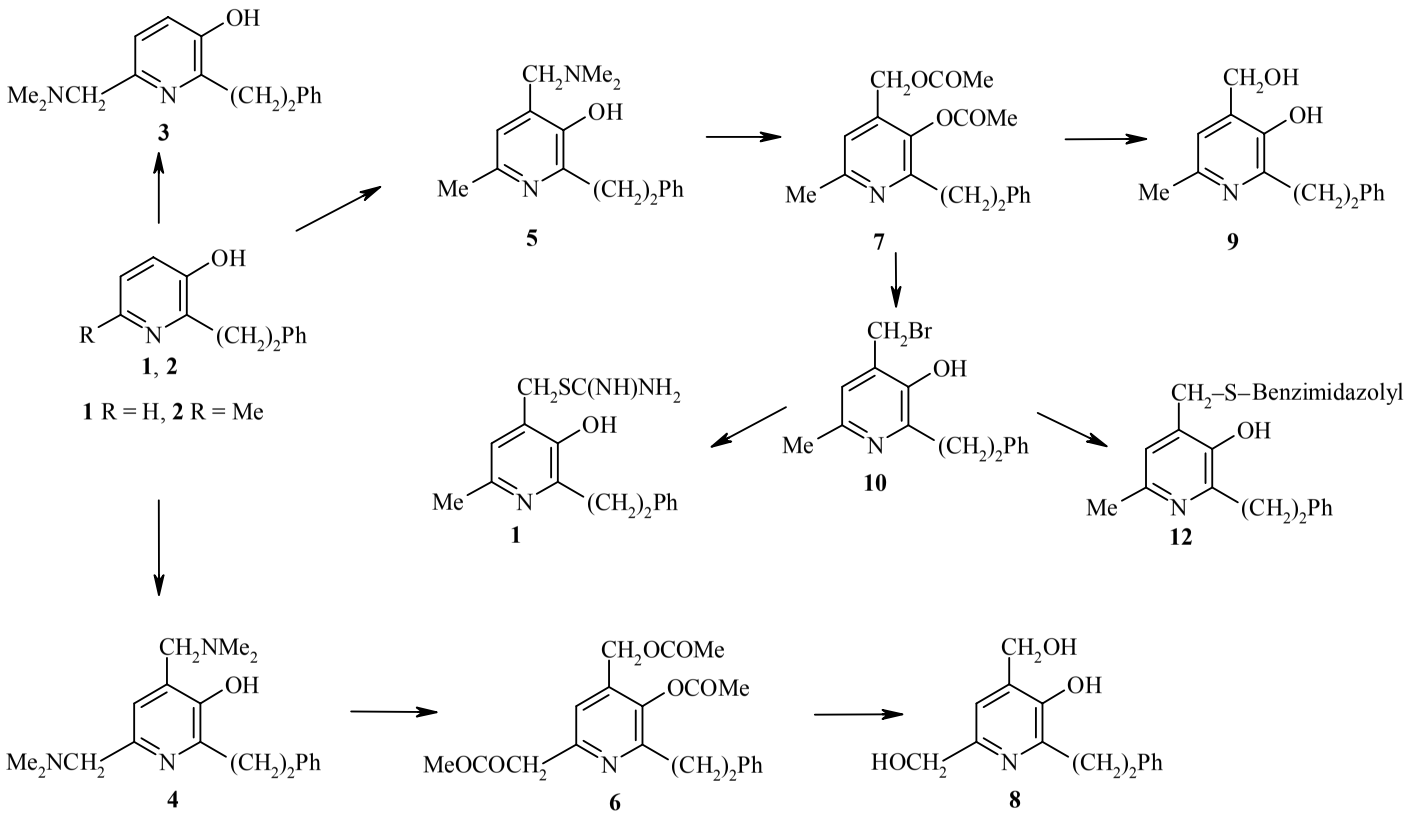
OH
Me2NCH2
N
(CH2)2Ph
3
R
1, 2
1 R = H, 2 R = Me
CH2NMe2
Me
5
CH2OCOMe
OCOMe
7
CH2OH
9
CH2Br
10
CH2SC(NH)NH2
1
CH2–S–Benzimidazolyl
12
4
MeOCOCH2
6
HOCH2
8

The synthesis of 4-isothioureidomethyl and benzimidazolylthiomethyl derivatives of 6-methyl- and 2-(2-phenylethyl)-3-HP was carried out by a scheme containing as initial step the aminomethylation of compounds **1** and **2** with subsequent replacement of the aminomethyl group by acetoxy and then by hydroxy and bromomethyl groups.

Previously we established the possibility of aminomethylating 3-HP at positions 2 and 6 of the ring, and in the case of a 2,6-dialkyl-3-HP at position 4 of the pyridine ring [4, 5]. We therefore investigated the aminomethylation of 2-phenylethyl-3-HP **1** and 6-methyl-2-(2-phenylethyl)-3-HP **2**. The initial 3-HP **1** and **2** were synthesized by the Leditschke reaction [6] by heating the appropriate furyl ketones with ammonium acetate at 220-250°C. Aminomethylation of pyridine **1** was carried out under analogous conditions to 2-alkyl-3-HP with the stoichiometric ratio of formaldehyde and secondary amine (dimethylamine). As a result, 6-mono- and 4,6-bis-substituted Mannich bases of 2-phenylethyl-3-HP **3-5** were obtained (Tables 1 and 2). The aminomethylation of compound **2** proceeded under analogous conditions leading to the formation of the 4-substituted Mannich base **5**. The structures of 3-HP **3-5** were confirmed by data of ^{1}H NMR spectra.

The corresponding acetoxy derivatives of **6** and **7** were obtained by heating aminomethyl derivatives **4** and **5** with acetic anhydride. Then by heating the acetoxy derivatives with hydrochloric or hydrobromic acids the hydroxymethyl-3-HP **8** and **9** and the bromomethyl derivative of 3-HP **10** were synthesized. The isothioureidomethyl and the benzimidazolylthiomethyl-substituted **11** and **12** were synthesized by heating bromomethyl derivative **10** with thiourea or with 2-mercaptobenzimidazole as in the Scheme. Their structures were confirmed by data of ^{1}H NMR spectra.

The synthesized sulfur-containing derivatives **11** and **12** displayed marked antihypoxic and actoprotective properties [7].

TABLE 1. Physicochemical Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %		mp, ºC	Yield, %
		C	H		
1	$C_{13}H_{13}NO$	78.36 / 78.35	6.62 / 6.58	203.5-204.5	52
2	$C_{14}H_{15}NO$	78.82 / 78.87	7.06 / 7.04	231-232	72
3	$C_{16}H_{20}N_2O{\cdot}2HCl$	58.27 / 58.31	6.62 / 6.74	206-207	90
4	$C_{19}H_{27}N_3O{\cdot}3HCl$	53.95 / 53.92	7.13 / 7.16	166-167	85
5	$C_{17}H_{22}N_2O{\cdot}2HCl{\cdot}0.5H_2O$	57.88 / 57.94	6.85 / 7.15	119-120	89
6	$C_{21}H_{23}NO_6$	65.20 / 65.45	5.87 / 5.97	—*	75
7	$C_{19}H_{21}NO_4$	69.45 / 69.67	6.52 / 6.48	—*[2]	80
8	$C_{15}H_{17}NO_3{\cdot}HCl{\cdot}H_2O$	57.67 / 57.36	6.64 / 6.37	196-197	58
9	$C_{15}H_{17}NO_2{\cdot}HCl$	64.71 / 64.36	6.35 / 6.50	221-222	70
10	$C_{15}H_{17}Br_2NO$	46.47 / 46.49	4.36 / 4.39	169-171	85
11	$C_{16}H_{19}N_3OS{\cdot}2HCl$	51.35 / 51.30	5.62 / 5.66	190-192	72
12	$C_{22}H_{21}N_3OS{\cdot}2HCl{\cdot}H_2O$	56.48 / 56.65	5.32 / 5.39	190-192	85

* Bp 170-172°C (2-3 mm Hg).

*[2] Bp 175-178°C (1-3 mm Hg).

TABLE 2. ^{1}H NMR Spectra of Amino, Acetoxy, and Hydroxymethyl Derivatives of 2-Phenylethyl-3-HP

Compound	Chemical shifts, δ, ppm (*J*, Hz)*
1	2.85 (4H, m, CH_2–CH_2); 6.95-7.25 (5H, m, H arom.); 7.70-8.30 (3H, m, H pyrid.)
2	2.40 (3H, s, CH_3); 3.30 (4H, m, CH_2–CH_2); 6.95-7.25 (5H, m, H arom.); 7.70-8.30 (2H, m, H pyrid.)
3	2.87 (6H, s, $N(CH_3)_2$); 3.30 (4H, m, $(CH_2)_2$); 4.60 (2H, s, N–CH_2); 7.2-7.5 (5H, m, H arom.); 7.88 (1H, d, *J* = 9.0, H-5); 8.05 (1H, d, *J* = 9.0, H-4)
4	2.75 (6H, s, $N(CH_3)_2$); 2.88 (6H, s, $N(CH_3)_2$); 3.20 (4H, m, $(CH_2)_2$); 4.35 (2H, s, N–CH_2); 4.41 (2H, s, N–CH_2); 6.95-7.20 (5H, m, H arom.); 7.45 (1H, s, H-5)
5	2.48 (3H, s, CH_3); 2.80 (6H, s, $N(CH_3)_2$); 3.5 (4H, m, $(CH)_2$); 4.40 (2H, s, N–CH_2); 6.80-7.20 (5H, m, H arom.); 7.45 (1H, s, H-5)
6	1.98 (3H, s, $COCH_3$); 2.03 (3H, s, $COCH_3$); 2.20 (3H, s, $COCH_3$); 2.90 (4H, m, $(CH_2)_2$); 4.90 (2H, s, OCH_3); 5.15 (2H, s, OCH_3); 7.00-7.20 (5H, m, H arom.); 7.10 (1H, s, H-5)
7	1.83 (3H, s, $COCH_3$); 2.09 (3H, s, $COCH_3$); 2.38 (3H, s, CH_3); 2.81 (4H, m, $(CH_2)_2$); 4.90 (2H, s, OCH_2); 6.85 (1H, s, H-5); 7.10 (5H, m, H arom.)
8	3.26 (4H, m, $(CH_2)_2$); 4.81 (2H, s, CH_2OH); 4.83 (2H, s, CH_2OH); 7.15-7.30 (5H, m, H arom.); 7.88 (1H, s, H-5)
9	2.65 (3H, s, CH_3); 3.22 (4H, m, $(CH_2)_2$); 4.85 (2H, s, CH_2OH); 7.10-7.30 (5H, m, H arom.); 7.62 (1H, s, H-5)
10	2.59 (3H, s, CH_3); 3.22 (4H, m, $(CH_2)_2$); 4.86 (2H, s, CH_2Br); 7.0-7.5 (5H, m, H arom.); 7.60 (1H, s, H-5)
11	2.39 (3H, s, CH_3); 3.0 (4H, m, $(CH_2)_2$); 4.66 (2H, s, CH_2S); 6.70-7.20 (5H, m, H arom.); 7.30 (1H, s, H-5)
12	2.50 (3H, s, CH_3); 3.05 (4H, m, $(CH_2)_2$); 4.71 (2H, s, CH_2S); 6.70-7.30 (5H, m, H arom.); 7.65 (1H, s, H-5)

* Spectra were recorded in CD_3OD (compound **1**), D_2O (compounds **2-7**, **10-12**), and $CDCl_3$ (compounds **8** and **9**).

EXPERIMENTAL

The ^{1}H NMR spectra were obtained on a Bruker AC-250 (250 MHz) spectrometer, internal standard was HMDS (δ 0.05 ppm). The physicochemical and spectral characteristics are given in Tables 1 and 2.

3-Hydroxy-2-(2-phenylethyl)pyridine (1). A mixture of 1-(2-furyl)-3-phenylpropan-1-one (6.0 g, 0.03 mol) and ammonium acetate (6.9 g, 0.09 mol) was heated in an autoclave at 220-225°C for 14 h, cooled to room temperature, H_2O (100 ml) was added, the solid residue was filtered off, and dissolved with heating on a water bath in 2 N NaOH (1000 ml). The solution was cooled to 20°C, filtered, and neutralized by passing in gaseous CO_2 or diluting with 10% H_2SO_4 to pH 7. The precipitated solid was separated, dried, sublimed at high vacuum, and 3-HP **1** was obtained.

3-Hydroxy-6-methyl-2-(2-phenylethyl)pyridine (2) was obtained analogously to compound **1** from 1-(5-methylfur-2-yl)-3-phenylpropan-1-one (6.9 g, 0.03 mol) and ammonium acetate (6.9 g, 0.09 mol).

Dihydrochloride of 6-Dimethylaminomethyl-3-hydroxy-2-(2-phenylethyl)pyridine (3). Aqueous 33% dimethylamine (3 ml, 0.022 mol) and aqueous 30% formaldehyde solution (2.2 ml, 0.022 mol) were added to a solution of compound **1** (4.2 g, 0.02 mol) in alcohol (20 ml) with constant stirring. The mixture was heated for 28 h on a water bath, the solvent was removed in vacuum, the residue, a viscous oil, was dissolved in anhydrous alcohol, and the solution saturated with gaseous HCl. Compound **3** was obtained.

Trihydrochloride of 4,6-Bis(dimethylaminomethyl)-3-hydroxy-2-(2-phenylethyl)pyridine (4). Aqueous 33% dimethylamine (6 ml, 0.042 mol) and aqueous 30% formaldehyde solution (4 ml, 0.042 mol) were added to a solution of compound **1** (4.2 g, 0.02 mol) in alcohol (20 ml) with constant stirring. The mixture

was heated on a boiling water bath for 28 h. At the end of the reaction the solvent was removed in vacuum, the residue, a viscous oil, was dissolved in anhydrous alcohol, and the solution was saturated with gaseous HCl. Compound **4** was obtained.

Dihydrochloride of 4-Dimethylaminomethyl-3-hydroxy-6-methyl-2-(2-phenylethyl)pyridine (5). Aqueous 33% dimethylamine solution (4.5 ml, 0.032 mol) and aqueous 30% formaldehyde solution (3 ml, 0.032 mol) were added with constant stirring to a solution of compound **2** (4.44 g, 0.02 mol) in alcohol (30 ml). The mixture was heated on a boiling water bath for 28 h. At the end of the reaction the solvent was removed in vacuum, the residual viscous oil was dissolved in anhydrous alcohol, and the solution saturated with gaseous HCl. Compound **5** was obtained.

3-Acetoxy-4,6-bis(acetoxymethyl)-2-(2-phenylethyl)pyridine (6). A solution of compound **4** (0.05 mol) in freshly distilled $(MeCO)_2O$ was boiled for 6 h. The solvent was removed in vacuum and the residue fractionated at high vacuum. Compound **6** was obtained.

3-Acetoxy-4-acetoxymethyl-6-methyl-2-(2-phenylethyl)pyridine (7) was obtained analogously to compound **6**.

Hydrochloride of 3-Hydroxy-4,6-bishydroxymethyl-2-(2-phenylethyl)pyridine (8). A solution of compound **6** (0.026 mol) in 2 N HCl (100 ml) was boiled on a water bath for 7 h. The solvent was removed, the residue was washed with dry acetone, and recrystallized from alcohol. Compound **8** was obtained.

Hydrochloride of 3-Hydroxy-4-hydroxymethyl-6-methyl-2-(2-phenylethyl)pyridine (9) was obtained analogously to compound **8** from acetoxy derivative **7**.

Hydrobromide of 4-Bromomethyl-3-hydroxy-6-methyl-2-(2-phenylethyl)pyridine (10). A solution of compound **7** (3.27 g, 0.01 mol) in 48% HBr (50 ml) was boiled for 3-4 h, and the solvent distilled off in vacuum. The residue was triturated with a mixture of *i*-PrOH and ether, and the solid separated. Compound **10** was obtained.

Dihydrochloride of 3-Hydroxy-4-isothioureidomethyl-6-methyl-2-(2-phenylethyl)pyridine (11). A mixture of hydrobromide **10** (3.87 g, 0.01 mol), thiourea (0.76 g, 0.01 mol), and absolute ethanol (50 ml) was boiled under reflux for 7 h . The solvent was distilled off to dryness, the residue was dissolved in water (20 ml), the solution neutralized with aqueous 10% KOH solution to pH 7, the solvent removed, the residue washed with water, dried, and an alcohol solution of HCl was added. Compound **11** was obtained.

Dihydrochloride of 4-(2-Benzimidazolylthiomethyl)-3-hydroxy-6-methyl-2-(2-phenylethyl)pyridine (12). Sodium hydroxide (0.4 g, 0.02 mol) in ethanol (50 ml) and 2-mercaptobenzimidazole (1.5 g, 0.01 mol) were mixed and heated on a water bath until solution was complete. Hydrobromide **10** (3.87 g, 0.01 mol) in ethanol (50 ml) was added dropwise with stirring and heating, and the mixture was heated for 1-2 h. The solvent was evaporated to dryness, the residue was washed with water, dried, and an alcohol solution of HCl was added. Compound **12** was obtained.

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