ISSN 1070-4280, Russian Journal of Organic Chemistry, 2018, Vol. 54, No. 4, pp. 593–600. © Pleiades Publishing, Ltd., 2018.
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Alternative Synthesis of Isoguvacine and Its *N*-(2-Aryl-2-hydroxyethyl) Derivatives

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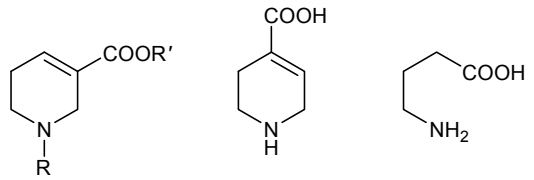
Received June 28, 2017

Abstract—Isonicotinic acid ethyl ester reacted with substituted phenacyl bromides to give the corresponding quaternary salts which were reduced with sodium tetrahydridoborate to ethyl 1-(2-aryl-2-hydroxyethyl)-1,2,3,6-tetrahydropyridine-4-carboxylates. The presence of an electron-donating substituent in the benzene ring of the latter is a necessary condition for their acid hydrolysis with cleavage of the C–N bond and formation of isoguvacine. Analogous derivatives with electron-withdrawing substituents are not converted to isoguvacine under similar conditions.

DOI: 10.1134/S1070428018040139

A number of tetrahydropyridine alkaloids, including arecoline (**1**), arecaidine (**2**), isoguvacine (**3**), guvacoline (**4**), and guvacine (**5**, 1,2,5,6-tetrahydronicotinic acid), have been isolated from the nuts of the *Areca catechu* palm growing in India, Ceylon, and the Philippines [1]. These compounds can be regarded as cyclic analogs of γ-aminobutyric acid (**6**, GABA) and are GABA receptor agonists [2], except for isoguvacine. The latter exhibits properties of GABA mimetic at a concentration of 3×10^{-6} to 3×10^{-5} M, causing inhibitory effect on spinal motor neurons (isolated cord) with simultaneous primary afferent depolarization [3, 4]. Guvacine, being an inhibitor of GABA neuronal seizure at a concentration of 10^{-6} to 10^{-3} M, reduces its absorption by cerebral cortex slices. Guvacine and isoguvacine are used in experimental medicines as tools for studying CNS functions [4].

Isoguvacine was synthesized for the first time in 1996 via a complicated three-step protocol starting from *N*-(*tert*-butoxycarbonyl)piperidin-4-one [5].



1, **2**, **4**, **5** **3** **6**

1, R = R′ = Me; **2**, R = Me, R′ = H; **4**, R = H, R′ = Me; **5**, R = R′ = H.

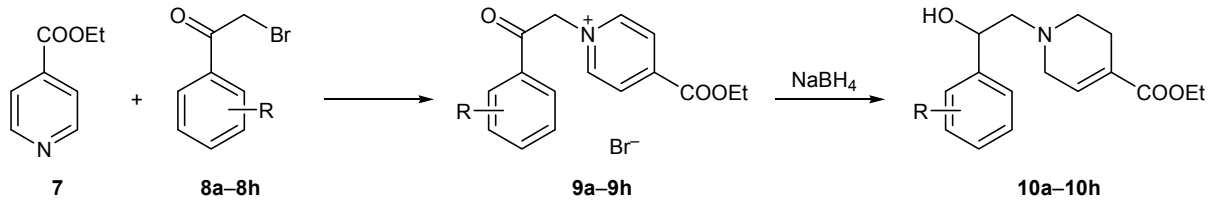
An alternative procedure utilizing difficultly accessible *N*-benzylpiperidine-2,6-dione derivative has been proposed later [6, 7].

Unfortunately, despite valuable pharmacological properties, isoguvacine is characterized by high toxicity, which stimulates search for its various biologically active low-toxic derivatives. A number of structurally complex derivatives of isoguvacine [8–10] and its esters [11, 12] have been synthesized and shown to act as GABA mimetics. All known methods of synthesis of isoguvacine and its derivatives are laborious, and the reactions require anhydrous inert media and highly expensive metal complex catalysts.

We have developed a new practical procedure for the synthesis of isoguvacine from accessible compounds and determined factors responsible for its formation. The starting compounds for the synthesis of isoguvacine (**3**) and its *N*-(2-aryl-2-oxoethyl) derivatives were isonicotinic acid ethyl ester (**7**) and phenacyl bromides **8a**–**8h** containing various substituents in the aromatic ring. The reaction of equimolar amounts of **7** and **8a**–**8h** in acetone at room temperature afforded quaternary salts **9a**–**9h** in 60–95% yield (Scheme 1).

Compounds **9a**–**9h** were isolated as colorless high-melting water-soluble solids. Their ^{1}H NMR spectra displayed signals from protons in the pyridinium fragment, methylene group (a singlet at δ 6.61–6.71 ppm), and aromatic ring. The carbonyl carbon signal was ob-

Scheme 1.



R = H (**a**), 4-Me (**b**), 4-Cl (**c**), 4-Br (**d**), 4-MeO (**e**), 3-MeO (**f**), 2-Br-4-MeO (**g**), 4-O_2N (**h**).

served in the ^{13}C NMR spectra of **9a**–**9h** at δ_C 188.5–190.8 ppm, and the neighboring methylene carbon atom resonated at δ_C 66.8–67.4 ppm.

It is known that complex boron hydrides reduce quaternized pyridine derivatives with an electron-withdrawing substituent or fused aromatic ring to the corresponding tetrahydropyridines [13] with the remaining double bond localized at the carbon atom bearing electron-withdrawing substituent or at the fusion atom. Salts **9a**–**9h** were also reduced in this way. Treatment of **9a**–**9h** with excess sodium tetrahydridoborate in aqueous methanol at room temperature gave ethyl 1-(2-aryl-2-hydroxyethyl)-1,2,3,6-tetrahydropyridine-4-carboxylates **10a**–**10h** in 70–97% yield (Scheme 1). Compounds **10a**–**10h** are colorless or slightly colored solids melting at much lower temperatures than quaternary salts **9a**–**9h**. The ^1H NMR spectra of **10a**–**10h** lacked signals of pyridinium fragment, but broadened two-proton singlets appeared at δ 2.61–2.69, 2.46–2.48, and 2.55–2.61 ppm due to tetrahydropyridine ring. The DEPT-135 ^{13}C NMR spectra of **10a**–**10h** showed negative upfield signals of three methylene carbons at δ_C 49.4–51.7 (C^2H_2), 25.1–25.2 (C^3H_2), and 52.4–52.5 ppm (C^6H_2). The reduction of the pyridinium ring was accompanied by reduction of the carbonyl group to hydroxy. This followed from the ^1H NMR and ^{13}C DEPT-135 data. Protons of the exocyclic methylene group resonated as two symmetrical doublets at δ 3.39–3.43 and 3.19–3.22 ppm with a geminal coupling constant ^2J of 18.0–18.8 Hz, the C**H**OH proton resonated as a quartet at δ 2.71–2.91 ppm, and the hydroxy proton gave rise to a doublet at δ 4.71–4.78 ppm. In the DEPT-135 spectrum, a positive signal appeared as δ_C 68.2–69.1 ppm due to the CHOH carbon.

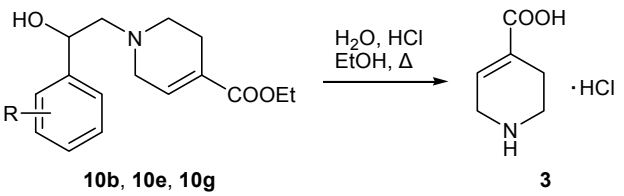
The acid hydrolysis of **10a**–**10h** followed two different paths. Heating of compounds **10b**, **10e**, and **10g** containing electron-donating substituents in the *para*-position of the benzene ring in aqueous–alcoholic HCl for 10–12 h resulted in not only hydrolysis of the ester group but also cleavage of the exocyclic C–N bond with formation of isoguvacine hydrochloride (yield 80–87%; Scheme 2). The product was isolated by evaporation of the reaction mixture to dryness and subsequent removal of tarry impurities by washing with anhydrous acetone and recrystallization from ethanol. The ^1H NMR spectrum of hydrochloride **3** contained a signal of the COOH proton at δ 12.77 ppm, a broadened singlet of the N^+H_2 protons (δ 9.53 ppm), a signal of the olefinic proton at δ 6.77 ppm, and a group of signals from the methylene protons at δ 3.15 (C^2H_2), 2.44 (C^3H_2), and 3.71 ppm (C^6H_2). Its ^{13}C NMR spectrum displayed signals of the carbonyl carbon atom (δ_C 166.9 ppm) and C^4 (δ_C 129.1 ppm). In the DEPT-135 spectrum of **3**, a positive peak of C^5H (δ_C 131.6 ppm) and three negative methylene carbon signals at δ_C 39.3 (C^2H_2), 21.2 (C^3H_2), and 41.4 ppm (C^6H_2) were observed in agreement with its structure.

Under analogous conditions, the acid hydrolysis of compounds **10a**, **10c**, **10d**, **10f**, and **10h** (R = H or electron-withdrawing substituent) involved only the ester group, and the products were the corresponding carboxylic acids **11a**, **11c**, **11d**, **11f**, and **11h** (Scheme 3) whose ^1H NMR spectra showed no signals of the ester ethoxy group.

The ^{13}C NMR and DEPT-135 spectra of carboxylic acids **11** showed signals (positive peaks in the DEPT-135 spectrum) of the carboxy group (δ_C 168.2–168.3 ppm), C^5 (δ_C 130.9–131.6 ppm), and CHOH (δ_C 66.8–66.9 ppm), as well as signals (negative peaks) at δ_C 60.9–61.3 (exocyclic methylene group), 39.5–40.0 (C^2H_2), 21.1–21.7 (C^3H_2), and 40.8–41.4 ppm (C^6H_2).

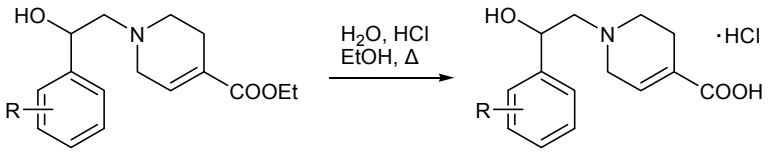
Presumably, the mechanism of acid hydrolysis of β-amino alcohols **10b**, **10e**, and **10g** involves two competing paths, "enamine" (*a*) and "glycol" (*b*)

Scheme 2.



R = 4-Me (**b**), 4-MeO (**e**), 2-Br-4-MeO (**g**).

Scheme 3.



10a, **10c**, **10d**, **10f**, **10h** **11a**, **11c**, **11d**, **11f**, **11h**

R = H (**a**), 4-Cl (**c**), 4-Br (**d**), 3-MeO (**f**), 4-O_2N (**h**).

(Scheme 4). These paths leading to the formation of substituted arylacetaldehyde which rapidly polymerizes under the given conditions were discussed in [14, 15] where the hydrolysis of β-amino alcohols was studied. Electron-donating substituents in the benzene ring favor the reaction to proceed along both paths, whereas path *a* predominates under more severe acidic conditions. The formation of glycol intermediate via nucleophilic substitution at C^2 (path *b*) is facilitated by intramolecular general base assistance of the hydroxy group in the corresponding transition state.

The results of PM7 semiempirical quantum chemical calculations [16] (MOPAC2016 [17]) with full geometry optimization of the most energetically favorable conformations showed that variation of the R substituent causes the strongest change of effective charges on the C^1 and O^3 atoms and that increase of the electron-donating power of the R substituent is accompanied by increase of the electron density on O^3 (Table 1). The computational data are consistent with both enamine and glycol paths. In the two cases, introduction of an electron-withdrawing substituent into the benzene ring should strongly inhibits acid hydrolysis. In fact, this is confirmed experimentally by published data on the hydrolysis of β-amino alcohols [15], as well as by the results of the present study.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance II 400 spectrometer (400 MHz for ^1H and 100 MHz for ^{13}C) using tetramethylsilane as internal standard. The purity of the isolated compounds

Scheme 4.

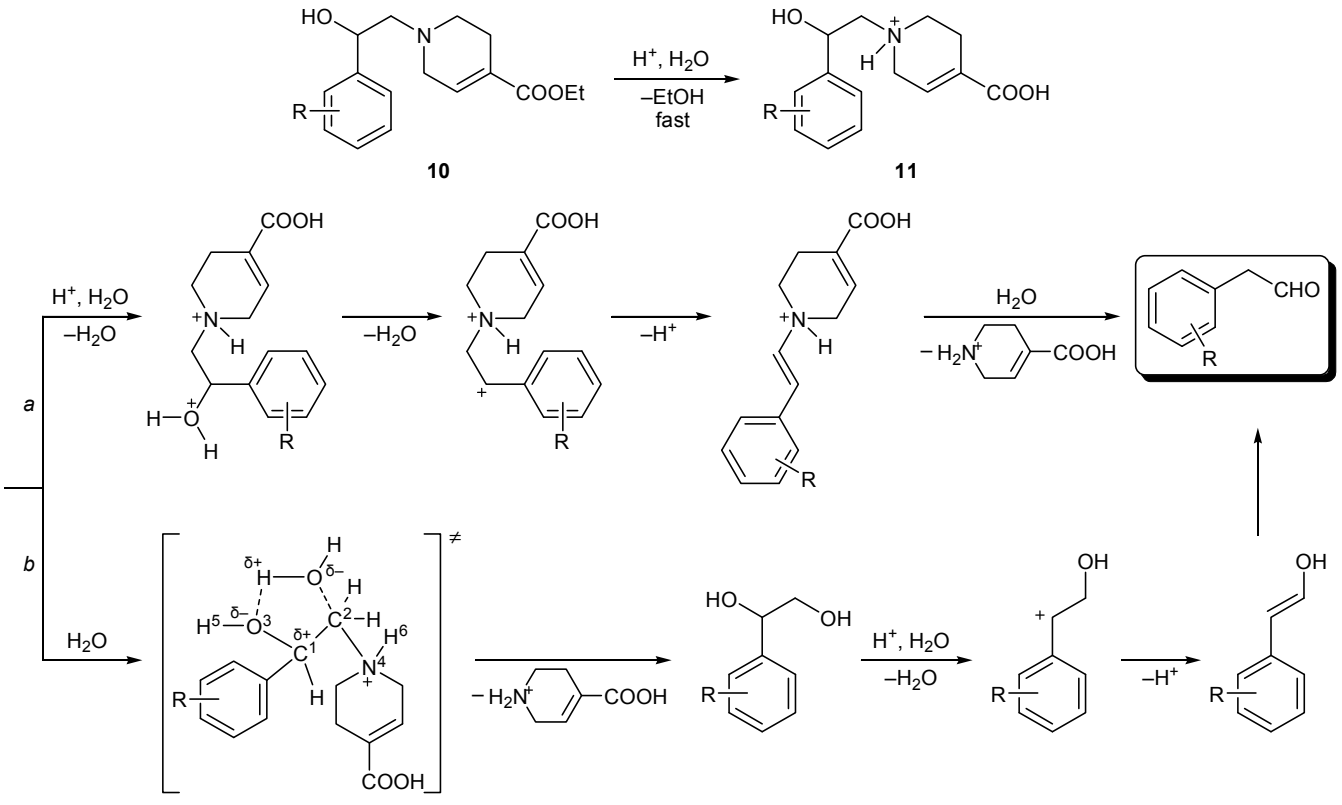
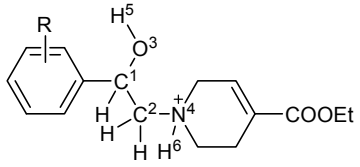


Table 1. Effective charges on some atoms of compounds **10a**–**10h** calculated for fully optimized geometry by the PM7 semiempirical approximation



R	σ^0	Effective charges, a.u.					
		C^1	C^2	O^3	N^4	H^5	H^6
4-MeO	–0.15	+0.172	–0.227	–0.626	–0.085	+0.374	+0.320
4-Me	–0.10	+0.157	–0.224	–0.620	–0.084	+0.373	+0.319
4-MeO-2-Br	–	+0.172	–0.222	–0.617	–0.085	+0.371	+0.318
H	0.00	+0.148	–0.224	–0.616	–0.083	+0.373	+0.319
3-MeO	0.08	+0.144	–0.221	–0.615	–0.083	+0.374	+0.319
4-Br	0.30	+0.151	–0.223	–0.614	–0.085	+0.373	+0.319
4-Cl	0.28	+0.152	–0.222	–0.614	–0.085	+0.373	+0.319
4-NO_2	0.81	+0.137	–0.222	–0.608	–0.086	+0.373	+0.319

was checked by TLC on Silufol UV-254 plates using methanol–chloroform (1 : 10) as eluent; spots were visualized by treatment with iodine vapor or under ultraviolet light.

Quaternary salts 9a–9h (*general procedure*). A solution of 11 mmol of substituted phenacyl bromide **8a**–**8h** in 10 mL of acetone was added to a solution of 10 mmol of ethyl pyridine-4-carboxylate (**7**) in 12 mL of acetone. The mixture was kept for 24 h at room temperature, and the precipitate was filtered off, washed with acetone, and recrystallized from ethanol.

4-(Ethoxycarbonyl)-1-(2-oxo-2-phenylethyl)-pyridinium bromide (9a). Yield 69%, mp 189–190°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.38 t (3H, $CH_2C\mathbf{H}_3$, J = 7.1 Hz), 4.46 q (2H, $C\mathbf{H}_2CH_3$, J = 7.0 Hz), 6.67 s (2H, CH_2CO), 7.66 t (2H, 3′-H, 5′-H, J = 7.6 Hz), 7.79 t (1H, 4′-H, J = 7.3 Hz), 8.07 d (2H, 2′-H, 6′-H, J = 7.6 Hz), 8.65 d (2H, 3-H, 5-H, J = 6.1 Hz), 9.25 d (2H, 2-H, 6-H, J = 6.2 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 14.4 ($CH_2\mathbf{C}H_3$), 63.5 ($\mathbf{C}H_2CH_3$), 67.2 ($\mathbf{C}H_2CO$), 127.4, 128.8, 129.6, 133.9, 135.2, 145.1, 148.3, 162.3 (OCO), 190.8 ($CH_2\mathbf{C}O$). Found, %: C 54.72; H 4.63; N 3.97. $C_{16}H_{16}BrNO_3$. Calculated, %: C 54.87; H 4.61; N 4.00.

4-(Ethoxycarbonyl)-1-[2-(4-methylphenyl)-2-oxoethyl]pyridinium bromide (9b). Yield 75%, mp 196–198°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.40 t (3H, $CH_2C\mathbf{H}_3$, J = 6.3 Hz), 2.44 s (3H, CH_3), 4.46 q (2H, $C\mathbf{H}_2CH_3$, J = 6.7 Hz), 6.61 s (2H, CH_2CO), 7.48 d (2H, 3′-H, 5′-H, J = 7.0 Hz), 7.97 d (2H, 2′-H, 6′-H, J = 7.2 Hz), 8.64 d (2H, 3-H, 5-H, J = 4.6 Hz), 9.23 d (2H, 2-H, 6-H, J = 4.8 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 14.4 ($CH_2\mathbf{C}H_3$), 21.8 (CH_3), 63.4 ($\mathbf{C}H_2CH_3$), 67.0 ($\mathbf{C}H_2CO$), 127.4, 128.9, 130.3, 131.4, 145.1, 145.9, 148.3, 162.5 (OCO), 190.2 ($CH_2\mathbf{C}O$). Found, %: C 56.00; H 5.01; N 3.78. $C_{17}H_{18}BrNO_3$. Calculated, %: C 56.06; H 4.98; N 3.85.

1-[2-(4-Chlorophenyl)-2-oxoethyl]-4-(ethoxycarbonyl)pyridinium bromide (9c). Yield 65%, mp 183–185°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.39 t (3H, $CH_2C\mathbf{H}_3$, J = 6.9 Hz), 4.46 q (2H, $C\mathbf{H}_2CH_3$, J = 6.9 Hz), 6.66 s (2H, CH_2CO), 7.75 d (2H, 3′-H, 5′-H, J = 8.1 Hz), 8.08 d (2H, 2′-H, 6′-H, J = 8.2 Hz), 8.65 d (2H, 3-H, 5-H, J = 5.7 Hz), 9.24 d (2H, 2-H, 6-H, J = 5.9 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 14.4 ($CH_2\mathbf{C}H_3$), 63.5 ($\mathbf{C}H_2CH_3$), 67.1 ($\mathbf{C}H_2CO$), 127.4, 129.8, 130.7, 132.7, 140.0, 145.2, 148.3, 162.5 (OCO), 190.0 ($CH_2\mathbf{C}O$). Found, %: C 49.87; H 4.01; N 3.72. $C_{16}H_{15}BrClNO_3$. Calculated, %: C 49.96; H 3.93; N 3.84.

1-[2-(4-Bromophenyl)-2-oxoethyl]-4-(ethoxycarbonyl)pyridinium bromide (9d). Yield 88%, mp 200–203°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.38 t (3H, $CH_2C\mathbf{H}_3$, J = 7.0 Hz), 4.46 q (2H, $C\mathbf{H}_2CH_3$, J = 6.9 Hz), 6.61 s (2H, CH_2CO), 7.89 d (2H, 3′-H, 5′-H, J = 8.1 Hz), 7.99 d (2H, 2′-H, 6′-H, J = 8.1 Hz), 8.65 d

(2H, 3-H, 5-H, J = 5.8 Hz), 9.21 d (2H, 2-H, 6-H, J = 5.7 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 14.4 ($CH_2\mathbf{C}H_3$), 63.4 ($\mathbf{C}H_2CH_3$), 67.1 ($\mathbf{C}H_2CO$), 127.4, 129.3, 130.7, 132.7, 133.0, 145.2, 148.3, 162.5 (OCO), 190.2 ($CH_2\mathbf{C}O$). Found, %: C 44.70; H 3.61; N 3.22. $C_{16}H_{15}Br_2NO_3$. Calculated, %: C 44.78; H 3.52; N 3.26.

4-(Ethoxycarbonyl)-1-[2-(4-methoxyphenyl)-2-oxoethyl]pyridinium bromide (9e). Yield 80%, mp 186–188°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.39 t (3H, $CH_2C\mathbf{H}_3$, J = 7.0 Hz), 2.44 s (3H, OCH_3), 4.46 q (2H, $C\mathbf{H}_2CH_3$, J = 6.9 Hz), 6.62 s (2H, CH_2CO), 7.47 d (2H, 3′-H, 5′-H, J = 7.8 Hz), 7.97 d (2H, 2′-H, 6′-H, J = 7.8 Hz), 8.65 d (2H, 3-H, 5-H, J = 6.0 Hz), 9.23 d (2H, 2-H, 6-H, J = 6.1 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 14.4 ($CH_2\mathbf{C}H_3$), 56.3 (OCH_3), 63.5 ($\mathbf{C}H_2CH_3$), 67.0 ($\mathbf{C}H_2CO$), 114.9, 127.4, 128.9, 130.1, 131.4, 146.0, 148.3, 162.5 (OCO), 190.3 ($CH_2\mathbf{C}O$). Found, %: C 53.64; H 4.79; N 3.51. $C_{17}H_{18}BrNO_4$. Calculated, %: C 53.70; H 4.77; N 3.68.

4-(Ethoxycarbonyl)-1-[2-(3-methoxyphenyl)-2-oxoethyl]pyridinium bromide (9f). Yield 95%, mp 214–216°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.39 t (3H, $CH_2C\mathbf{H}_3$, J = 6.5 Hz), 3.86 s (3H, OCH_3), 4.46 q (2H, $C\mathbf{H}_2CH_3$, J = 6.7 Hz), 6.66 s (2H, CH_2CO), 7.38 d (1H, 4′-H, J = 6.5 Hz), 7.55–7.61 m (2H, 2′-H, 5′-H), 7.67 d (1H, 6′-H, J = 6.4 Hz), 8.66 d (2H, 3-H, 5-H, J = 5.0 Hz), 9.23 d (2H, 2-H, 6-H, J = 4.9 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 14.4 ($CH_2\mathbf{C}H_3$), 56.1 (OCH_3), 63.5 ($\mathbf{C}H_2CH_3$), 67.2 ($\mathbf{C}H_2CO$), 113.4, 121.0, 121.2, 127.4, 130.9, 135.2, 145.2, 148.2, 160.0, 162.5 (OCO), 190.7 ($CH_2\mathbf{C}O$). Found, %: C 53.61; H 4.82; N 3.53. $C_{17}H_{18}BrNO_4$. Calculated, %: C 53.70; H 4.77; N 3.68.

1-[2-(2-Bromo-4-methoxyphenyl)-2-oxoethyl]-4-(ethoxycarbonyl)pyridinium bromide (9g). Yield 60%, mp 217–220°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.39 t (3H, $CH_2C\mathbf{H}_3$, J = 6.9 Hz), 4.00 s (3H, OCH_3), 4.46 q (2H, $C\mathbf{H}_2CH_3$, J = 6.9 Hz), 6.55 s (2H, CH_2CO), 7.38 d (1H, 5′-H, J = 8.5 Hz), 8.09 d (1H, 6′-H, J = 8.6 Hz), 8.25 s (1H, 3′-H), 8.64 d (2H, 3-H, 5-H, J = 5.9 Hz), 9.17 d (2H, 2-H, 6-H, J = 6.2 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 14.4 ($CH_2\mathbf{C}H_3$), 57.5 (OCH_3), 63.5 ($\mathbf{C}H_2CH_3$), 66.8 ($\mathbf{C}H_2CO$), 111.6, 113.2, 127.5, 127.8, 130.7, 133.5, 145.2, 148.2, 160.7, 162.5 (OCO), 188.5 ($CH_2\mathbf{C}O$). Found, %: C 44.39; H 3.75; N 3.01. $C_{17}H_{17}Br_2NO_4$. Calculated, %: C 44.47; H 3.73; N 3.05.

4-(Ethoxycarbonyl)-1-[2-(4-nitrophenyl)-2-oxoethyl]pyridinium bromide (9h). Yield 72%, mp 188–190°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.39 t (3H, $CH_2C\mathbf{H}_3$, J = 7.1 Hz), 4.47 q (2H, $C\mathbf{H}_2CH_3$, J = 7.0 Hz), 6.71 s (2H, CH_2CO), 8.30 d (2H, 2′-H, 6′-H, J = 8.5 Hz), 8.47 d (2H, 3′-H, 5′-H, J = 8.5 Hz), 8.68 d (2H, 3-H, 5-H, J = 6.1 Hz), 9.24 d (2H, 2-H, 6-H, J = 6.2 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 14.4 ($CH_2\mathbf{C}H_3$), 63.5 ($\mathbf{C}H_2CH_3$), 67.4 ($\mathbf{C}H_2CO$), 124.6, 127.5, 130.3, 138.7, 144.2, 145.3, 148.3, 162.5 (OCO), 190.2 ($CH_2\mathbf{C}O$). Found, %: C 48.52; H 3.87; N 7.04. $C_{16}H_{15}BrN_2O_5$. Calculated, %: C 48.63; H 3.83; N 7.09.

Reduction of quaternary salts 9a–9h (*general procedure*). Sodium tetrahydridoborate, 30 mmol, was added in portions over a period of 2 h to a solution of 10 mmol of quaternary salt **9a**–**9h** in 70 mL of aqueous methanol (1 : 1) with stirring at room temperature. The reduction product was filtered off and recrystallized from aqueous ethanol.

Ethyl 1-(2-hydroxy-2-phenylethyl)-1,2,3,6-tetrahydropyridine-4-carboxylate (10a). Yield 70%, mp 77–80°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.30 t (3H, $CH_2C\mathbf{H}_3$, J = 7.0 Hz), 2.48 br.s (2H, 3-H), 2.61 br.s (2H, 2-H), 2.63 br.s (2H, 6-H), 2.91 q (1H, C**H**OH, J = 16.0 Hz), 3.22 d and 3.42 d (1H each, 1-CH_2, J = 18.4 Hz), 4.23 q (2H, $C\mathbf{H}_2CH_3$, J = 7.1 Hz), 4.80 d (1H, OH, J = 8.2 Hz), 6.92 br.s (1H, 5-H), 7.30–7.39 m (5H, Ph). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.3 ($CH_2\mathbf{C}H_3$), 25.1 (C^3), 49.5 (C^2), 52.5 (C^6), 60.5 ($\mathbf{C}H_2CH_3$), 65.6 (1-CH_2), 69.1 (CHOH), 125.8, 127.6, 128.4, 128.8, 136.3 (C^5), 141.9, 167.0 (C=O). Found, %: C 69.71; H 7.72; N 5.03. $C_{16}H_{21}NO_3$. Calculated, %: C 69.79; H 7.69; N 5.09.

Ethyl 1-[2-hydroxy-2-(4-methylphenyl)ethyl]-1,2,3,6-tetrahydropyridine-4-carboxylate (10b). Yield 72%, mp 59–60°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.30 t (3H, $CH_2C\mathbf{H}_3$, J = 6.9 Hz), 2.36 s (3H, CH_3), 2.47 br.s (2H, 3-H), 2.61 br.s (4H, 2-H, 6-H), 2.89 q (1H, C**H**OH, J = 11.2 Hz), 3.20 d (1H, J = 18.4 Hz) and 3.43 d (1H, J = 18.3 Hz) (1-CH_2), 4.23 q (2H, $C\mathbf{H}_2CH_3$, J = 6.8 Hz), 4.77 d (1H, CHO**H**, J = 5.6 Hz), 6.91 br.s (1H, 5-H), 7.17 d (2H, 3′-H, 5′-H, J = 6.5 Hz), 7.28 d (2H, 2′-H, 6′-H, J = 7.2 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.2 ($CH_2\mathbf{C}H_3$), 21.0 (CH_3), 25.2 (C^3), 51.7 (C^2), 52.4 (C^6), 60.3 ($\mathbf{C}H_2CH_3$), 65.6 (1-CH_2), 68.9 (CHOH), 125.8, 129.0, 135.9, 136.3 (C^5), 137.2, 138.9, 166.5 (C=O). Found, %: C 70.52; H 8.03; N 4.79. $C_{17}H_{23}NO_3$. Calculated, %: C 70.56; H 8.01; N 4.84.

Ethyl 1-[2-(4-chlorophenyl)-2-hydroxyethyl]-1,2,3,6-tetrahydropyridine-4-carboxylate (10c).

Yield 87%, mp 63–65°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.31 t (3H, $CH_2C\mathbf{H}_3$, J = 7.1 Hz), 2.47 br.s (2H, 3-H), 2.60 br.s (2H, 2-H), 2.63 br.s (2H, 6-H), 2.89 q (1H, C**H**OH, J = 11.2 Hz), 3.19 d and 3.41 d (1H each, 1-CH_2, J = 18.4 Hz), 4.22 q (2H, $C\mathbf{H}_2CH_3$, J = 7.1 Hz), 4.76 d (1H, CHO**H**, J = 7.6 Hz), 6.90 br.s (1H, 5-H), 7.32 s (4H, 2′-H, 3′-H, 5′-H, 6′-H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.3 ($CH_2\mathbf{C}H_3$), 25.1 (C^3), 49.5 (C^2), 52.5 (C^6), 60.5 ($\mathbf{C}H_2CH_3$), 65.5 (NCH_2), 68.4 (CHOH), 127.2, 128.5, 133.2, 135.8, 136.1 (C^5), 140.5, 166.4 (C=O). Found, %: C 61.97; H 6.55; N 4.48. $C_{16}H_{20}ClNO_3$. Calculated, %: C 62.03; H 6.51; N 4.52.

Ethyl 1-[2-(4-bromophenyl)-2-hydroxyethyl]-1,2,3,6-tetrahydropyridine-4-carboxylate (10d). Yield 97%, mp 68–70°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.31 t (3H, $CH_2C\mathbf{H}_3$, J = 7.1 Hz), 2.47 br.s (2H, 3-H), 2.61 br.s (2H, 2-H), 2.64 br.s (2H, 6-H), 2.88 q (1H, C**H**OH, J = 11.4 Hz), 3.20 d (1H, J = 18.0 Hz) and 3.40 d (1H, J = 18.4 Hz) (1-CH_2), 4.21 q (2H, $C\mathbf{H}_2CH_3$, J = 7.1 Hz), 4.75 d (1H, CHO**H**, J = 10.0 Hz), 6.90 br.s (1H, 5-H), 7.27 d (2H, 2′-H, 6′-H, J = 8.0 Hz), 7.48 d (2H, 3′-H, 5′-H, J = 8.0 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 15.8 ($CH_2\mathbf{C}H_3$), 25.1 (C^3), 49.5 (C^2), 52.5 (C^6), 60.6 ($\mathbf{C}H_2CH_3$), 66.9 (1-CH_2), 68.5 (CHOH), 122.8, 127.5, 130.6, 131.5, 135.7 (C^5), 142.5, 168.0 (C=O). Found, %: C 54.20; H 5.72; N 3.93. $C_{16}H_{20}BrNO_3$. Calculated, %: C 54.25; H 5.69; N 3.95.

Ethyl 1-[2-hydroxy-2-(4-methoxyphenyl)ethyl]-1,2,3,6-tetrahydropyridine-4-carboxylate (10e). Yield 73%, mp 83–85°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.31 t (3H, $CH_2C\mathbf{H}_3$, J = 7.1 Hz), 2.46 br.s (2H, 3-H), 2.58 br.s (2H, 2-H), 2.63 br.s (2H, 6-H), 2.89 q (1H, C**H**OH, J = 11.6 Hz), 3.20 d and 3.40 d (1H each, 1-CH_2, J = 18.4 Hz), 3.90 s (3H, OCH_3), 4.23 q (2H, $C\mathbf{H}_2CH_3$, J = 6.9 Hz), 4.76 d (1H, CHO**H**, J = 10.6 Hz), 6.89 d (2H, 3′-H, 5′-H, J = 8.4 Hz), 6.91 br.s (1H, 5-H), 7.30 d (2H, 2′-H, 6′-H, J = 8.4 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.3 ($CH_2\mathbf{C}H_3$), 25.2 (C^3), 49.5 (C^2), 52.4 (C^6), 55.2 (OCH_3), 60.5 ($\mathbf{C}H_2CH_3$), 65.7 (1-CH_2), 68.8 (CHOH), 113.9, 127.1, 129.1, 134.0, 135.9 (C^5), 159.1, 166.5 (C=O. Found, %: C 66.83; H 7.64; N 4.55. $C_{17}H_{23}NO_4$. Calculated, %: C 66.86; H 7.59; N 4.59.

Ethyl 1-[2-hydroxy-2-(3-methoxyphenyl)ethyl]-1,2,3,6-tetrahydropyridine-4-carboxylate (10f). Yield 95%, mp 42–45°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.31 t (3H, $CH_2C\mathbf{H}_3$, J = 7.0 Hz), 2.46 br.s (2H, 3-H), 2.59 br.s (2H, 2-H), 2.64 br.s (2H, 6-H), 2.88 q (1H, C**H**OH, J = 16.0 Hz), 3.20 d (1H, J = 18.4 Hz) and 3.40 d (1H, J = 18.8 Hz) (1-CH_2), 3.82 s (3H, OCH_3), 4.22 q (2H, $C\mathbf{H}_2CH_3$, J = 6.8 Hz), 4.77 d (1H, CHO**H**, J = 9.2 Hz), 6.82 d (1H, 4′-H, J = 8.0 Hz), 6.90 br.s (1H, 5-H), 6.95 t (1H, 5′-H, J = 7.5 Hz), 6.97 s (1H, 2′-H), 7.27 d (1H, 6′-H, J = 7.1 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.3 ($CH_2\mathbf{C}H_3$), 25.1 (C^3), 49.5 (C^2), 52.5 (C^6), 55.1 (OCH_3), 60.6 ($\mathbf{C}H_2CH_3$), 65.5 (1-CH_2), 68.9 (CHOH), 111.2, 112.9, 118.2, 129.3, 130.9, 135.9 (C^5), 137.8, 145.3, 161.3 (C=O). Found, %: C 66.80; H 7.63; N 4.54. $C_{17}H_{23}NO_4$. Calculated, %: C 66.86; H 7.59; N 4.59.

Ethyl 1-[2-(2-bromo-4-methoxyphenyl)-2-hydroxyethyl]-1,2,3,6-tetrahydropyridine-4-carboxylate (10g). Yield 70%, mp 108–110°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.31 t (3H, $CH_2C\mathbf{H}_3$, J = 6.9 Hz), 2.46 br.s (2H, 3-H), 2.58 br.s (2H, 2-H), 2.62 br.s (2H, 6-H), 2.88 q (1H, C**H**OH, J = 11.6 Hz), 3.20 d (1H, J = 18.4 Hz) and 3.39 d (1H, J = 18.8 Hz) (1-CH_2), 3.90 s (3H, OCH_3), 4.22 q (2H, $C\mathbf{H}_2CH_3$, J = 6.9 Hz), 4.71 d (1H, CHO**H**, J = 9.6 Hz), 6.87 br.s (1H, 5-H), 6.88 d (1H, 5′-H, J = 8.8 Hz), 7.28 d (1H, 6′-H, J = 8.0 Hz), 7.58 s (1H, 3′-H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.2 ($CH_2\mathbf{C}H_3$), 25.1 (C^3), 49.5 (C^2), 52.5 (C^6), 56.2 (OCH_3), 60.5 ($\mathbf{C}H_2CH_3$), 65.5 (1-CH_2), 68.2 (CHOH), 111.7, 111.8, 126.0, 130.8, 130.9, 135.6, 135.8 (C^5), 155.3, 166.5 (C=O). Found, %: C 53.08; H 5.81; N 3.63. $C_{17}H_{22}BrNO_4$. Calculated, %: C 53.14; H 5.77; N 3.65.

Ethyl 1-[2-hydroxy-2-(4-nitrophenyl)ethyl]-1,2,3,6-tetrahydropyridine-4-carboxylate (10h). Yield 80%, mp 100–102°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.31 t (3H, $CH_2C\mathbf{H}_3$, J = 7.1 Hz), 2.48 br.s (2H, 3-H), 2.55 br.s (2H, 2-H), 2.69 br.s (2H, 6-H), 2.71 q (1H, C**H**OH, J = 12.4 Hz), 3.22 d and 3.42 d (1H each, 1-CH_2, J = 18.0 Hz), 4.23 q (2H, $C\mathbf{H}_2CH_3$, J = 7.1 Hz), 4.88 d (1H, CHO**H**, J = 10.4 Hz), 6.90 br.s (1H, 5-H), 7.57 d (2H, 2′-H, 6′-H, J = 8.4 Hz), 8.22 d (2H, 3′-H, 5′-H, J = 8.5 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.3 ($CH_2\mathbf{C}H_3$), 25.1 (C^3), 49.4 (C^2), 52.5 (C^6), 60.6 ($\mathbf{C}H_2CH_3$), 65.0 (1-CH_2), 68.3 (CHOH), 123.7, 126.5, 129.2, 135.5 (C^5), 147.4, 149.6, 166.4 (C=O). Found, %: C 59.92; H 6.33; N 8.70. $C_{16}H_{20}N_2O_5$. Calculated, %: C 59.99; H 6.29; N 8.74.

Isoguvacine hydrochloride (3) and 1-(2-aryl-2-hydroxyethyl)-1,2,3,6-tetrahydropyridine-4-carboxylic acids 11a, 11c, 11d, 11f, and 11h (*general procedure***).** Compound **10a**–**10h**, 1 mmol, was dissolved in

5 mL of ethanol, 5 mL of concentrated aqueous HCl was added, and the mixture was refluxed for 10 h. The solvent was distilled off under reduced pressure, and the residue was thoroughly washed with acetone and recrystallized from ethanol.

1,2,3,6-Tetrahydropyridine-4-carboxylic acid (isoguvacine) hydrochloride (3). Yield 80–87%, mp 278–280°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.43 br.s (2H, 3-H), 3.17 br.s (2H, 2-H), 3.71 br.s (2H, 6-H), 6.76 br.s (1H, 5-H), 9.53 br.s (2H, NH_2^+), 12.77 br.s (1H, COOH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 21.2 (C^3), 40.0 (C^2), 41.4 (C^6), 129.1, 131.6 (C^5), 166.8 (C=O). Found, %: C 44.01; H 6.22; N 8.52. $C_6H_{10}ClNO_2$. Calculated, %: C 44.05; H 6.16; N 8.56.

1-(2-Hydroxy-2-phenylethyl)-1,2,3,6-tetrahydropyridine-4-carboxylic acid hydrochloride (11a). Yield 78%, mp 215–217°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.52 br.s (2H, 3-H), 3.28 br.s (2H, 2-H), 3.70 br.s (2H, 6-H), 4.06 br.s (2H, 1-CH_2), 5.22 d (1H, C**H**OH, J = 6.1 Hz), 6.27 br.s (1H, CHO**H**), 6.77 br.s (1H, 5-H), 7.28–7.41 m (5H, Ph). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 21.3 (C^3), 39.8 (C^2), 41.2 (C^6), 61.3 (1-CH_2), 66.7 (CHOH), 123.4, 127.2, 130.1, 131.6 (C^5), 142.6, 168.3 (C=O). Found, %: C 59.20; H 6.41; N 4.90. $C_{14}H_{18}ClNO_3$. Calculated, %: C 59.26; H 6.39; N 4.94.

1-[2-(4-Chlorophenyl)-2-hydroxyethyl]-1,2,3,6-tetrahydropyridine-4-carboxylic acid hydrochloride (11c). Yield 63%, mp 223–225°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.54 br.s (2H, 3-H), 3.28 br.s (2H, 2-H), 3.72 br.s (2H, 6-H), 4.05 br.s (2H, 1-CH_2), 5.21 br.s (1H, C**H**OH), 6.37 br.s (1H, CHO**H**), 6.78 br.s (1H, 5-H), 7.46 s (4H, 2′-H, 3′-H, 5′-H, 6′-H), 9.37 br.s (1H, NH), 10.59 br.s (1H, COOH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 21.2 (C^3), 39.9 (C^2), 41.4 (C^6), 61.3 (1-CH_2), 66.8 (CHOH), 128.4, 128.8, 131.6 (C^5), 133.1, 134.3, 142.7, 168.4 (C=O). Found, %: C 52.78; H 5.43; N 4.36. $C_{14}H_{17}Cl_2NO_3$. Calculated, %: C 52.84; H 5.39; N 4.40.

1-[2-(4-Bromophenyl)-2-hydroxyethyl]-1,2,3,6-tetrahydropyridine-4-carboxylic acid hydrochloride (11d). Yield 91%, mp 235–238°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.57 br.s (2H, 3-H), 3.29 br.s (2H, 2-H), 3.40 br.s (2H, 6-H), 4.06 br.s (2H, 1-CH_2), 5.22 d (1H, C**H**OH, J = 8.0 Hz), 6.38 br.s (1H, CHO**H**), 6.77 br.s (1H, 5-H), 7.39 d (2H, 2′-H, 6′-H, J = 8.0 Hz), 7.58 d (2H, 3′-H, 5′-H, J = 8.0 Hz), 10.72 br.s (1H, COOH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 21.7 (C^3), 39.5 (C^2), 40.8 (C^6), 61.3 (1-CH_2), 66.9 (CHOH), 122.8, 128.7, 130.9 (C^5), 131.7, 132.4, 143.2, 168.2 (C=O). Found, %: C 46.30; H 4.75; N 3.84. $C_{14}H_{17}BrClNO_3$. Calculated, %: C 46.37; H 4.72; N 3.86.

1-[2-Hydroxy-2-(3-methoxyphenyl)ethyl]-1,2,3,6-tetrahydropyridine-4-carboxylic acid hydrochloride (11f). Yield 53%, mp 205–210°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.53 br.s (2H, 3-H), 3.28 br.s (2H, 2-H), 3.55 br.s (2H, 6-H), 3.74 s (3H, OCH_3), 4.09 br.s (2H, NCH_2), 5.22 br.s (1H, C**H**OH), 6.32 br.s (1H, CHO**H**), 6.77 br.s (1H, 5-H), 6.86–7.01 m (3H, 4′-H, 5′-H, 6′-H), 7.28 s (1H, 2′-H). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 23.3 (C^3), 40.0 (C^2), 41.4 (C^6), 57.1 (OCH_3), 62.7 (1-CH_2), 69.0 (CHOH), 112.0, 113.6, 115.2, 118.6, 120.1, 130.0, 130.5 (C^5), 145.5, 168.2 (C=O). Found, %: C 57.40; H 6.45; N 4.44. $C_{15}H_{20}ClNO_4$. Calculated, %: C 57.42; H 6.42; N 4.46.

1-[2-Hydroxy-2-(4-nitrophenyl)ethyl]-1,2,3,6-tetrahydropyridine-4-carboxylic acid hydrochloride (11h). Yield 81%, mp 233–235°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.59 br.s (2H, 3-H), 3.31 br.s (2H, 2-H), 3.40 br.s (2H, 6-H), 4.08 br.s (2H, 1-CH_2), 5.40 d (1H, C**H**OH, J = 5.2 Hz), 6.62 br.s (1H, CHO**H**), 6.79 br.s (1H, 5-H), 7.73 d (2H, 2′-H, 6′-H, J = 7.6 Hz), 8.26 d (2H, 3′-H, 5′-H, J = 7.6 Hz), 10.77 br.s (1H, COOH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 21.7 (C^3), 40.0 (C^2), 41.2 (C^6), 60.9 (1-CH_2), 66.9 (CHOH), 125.5, 129.4, 130.9 (C^5), 132.5, 149.0, 151.4, 168.3 (C=O). Found, %: C 51.11; H 5.24; N 8.49. $C_{14}H_{17}ClN_2O_5$. Calculated, %: C 51.15; H 5.21; N 8.52.

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