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ESR SPECTRA OF FREE RADICALS OF 3,3-DISUBSTITUTED 1,2,3,4-TETRAHYDROPYRIDINES PRODUCED DURING ELECTROCHEMICAL REDUCTION

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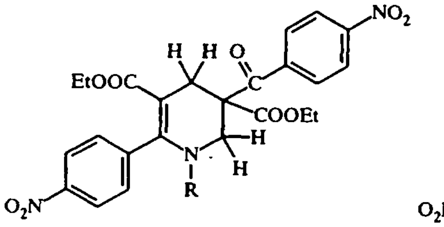
The polarographic properties (potentials, number of electrons, reversibility) of the electrochemical reduction of 3,5-diethoxycarbonyl-3-(p-nitrobenzoyl)-6-(p-nitrophenyl)-1,2,3,4-tetrahydropyridine and its derivatives in dimethylformamide have been determined. In the course of the electrochemical generation, ESR spectra of primary radical anions of p-nitrobenzoyl structure were obtained along with ESR spectra of nitrophenyl-p-substituted free radicals formed as a result of further reduction.

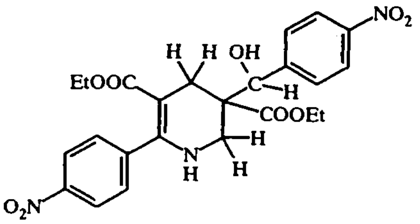
In an attempt to synthesize derivatives of 1,4-dihydropyridine by the Hantzsch reaction, it was found that the reaction of ethyl p-nitrobenzoylacetate with hexamethylenetetramine and ammonium acetate leads to the formation of 3,5-diethoxycarbonyl-3-(p-nitrobenzoyl)-6-(p-nitrophenyl)-1,2,3,4-tetrahydropyridine [1].

This paper presents the results of the electrochemical generation and an ESR study of the free radicals formed during electrochemical reduction of 3,5-diethoxycarbonyl-3-(p-nitrobenzoyl)-6-(p-nitrophenyl)-1,2,3,4-tetrahydropyridine (I), its derivatives (II-IV), and the model compounds (V, VI).

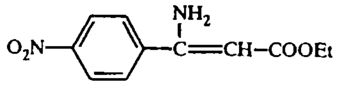


I-III

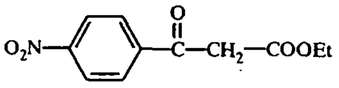
I R = H; II R = Me; III R = NO



IV



V



VI

During the course of the electrochemical reduction, several nitrobenzene-type free radicals of different structures were recorded for each of the compounds I-III. For purposes of their identification, we carried out the electrochemical generation of free radicals of compounds V, VI, which model the fragments of the molecule in the 3 and 6 positions of compounds I-IV. For compound V, electrochemical generation at a potential of −1.2 V leads to the formation of primary radical anions of the compound studied. This is indicated by the hyperfine structure of the ESR spectrum, caused by the interaction of the unpaired electron with the nitrogen nucleus of the nitro group, two different pairs of equivalent protons of the phenyl ring, and also the nucleus of the nitrogen atom and two equivalent protons of the amino group. At higher generation potentials, formation of sec-

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TABLE 1. Electrochemical Generation Potentials (E, V), Character and Constants (a, G) of the Hyperfine Interaction of the Unpaired Electron with the Atomic Nuclei in the Free Radicals

Compound	$-E$	Character of HFS	a_N	a_{2H}	a_{2H}	a_N	a_{2H}	a_H	a_H
I	1,0	$3_N\times3_H\times3_H$	5,15	2,57	0,33	—	—	—	—
	1,8	$3_N\times3_H\times3_H$	6,10	2,84	0,59	—	—	—	—
	1,8	$3_N\times3_H\times3_H$	9,64	3,23	1,03	—	—	—	—
II	0,7 1,2*	$3_N\times3_H\times3_H$	5,15	2,57	0,33	—	—	—	—
	1,2	$3_N\times3_H\times3_H$	9,64	3,27	1,03	—	—	—	—
III	0,8 1,2*	$3_N\times3_H\times3_H$	5,15	2,57	0,33	—	—	—	—
	1,2	$3_N\times3_H\times3_H$	9,70	3,27	1,06	—	—	—	—
IV	1,3	$3_N\times3_H\times3_H$	9,63	3,30	1,06				
V	1,2	$3_N\times3_H\times3_H\times3_N\times3_H$	7,45	3,10	0,79	0,79	0,33	—	—
	1,4	$3_N\times3_H\times3_H\times2_H$	9,37	3,33	1,02	—	—	0,33	—
VI	0,8	$3_N\times2_H\times2_H\times3_H\times3_H$	5,35	0,86	0,40	—	—	2,84	2,44
	1,0	$3_N x 3_H x 3_H x 2_H$	9,34	3,27	1,06	—	—	0,33	—

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*The nature of the hyperfine structure and constants of the ESR spectrum of the free radical were not determined.

TABLE 2. Potentials ($E_{1/2}$) of Polarographic Waves Relative to the Aqueous Saturated Calomel Electrode

Compound	$-E_{1/2}$*, V
I	0,80(0,8; +); 1,04(1,0; +); 1,30(0,9; -); 1,82(1,3; -)
II	0,82(1,0; +); 1,02(0,8; +); 1,30(1,3; -); 1,84(1,4; -)
III	0,78(1,0; +); 1,05(1,0; +); 1,33(0,7; +)
IV	0,92(0,4; -); 1,08(1,7; +); 1,78(1,8; -); 2,08(1,2; -)
V	0,95(1,0; +); 1,43(1,0; -); 1,55(1,0; -); 2,59(1,3; -)
VI	0,86(1,2; +); 1,30(0,8; +); 2,06(2,1; -)

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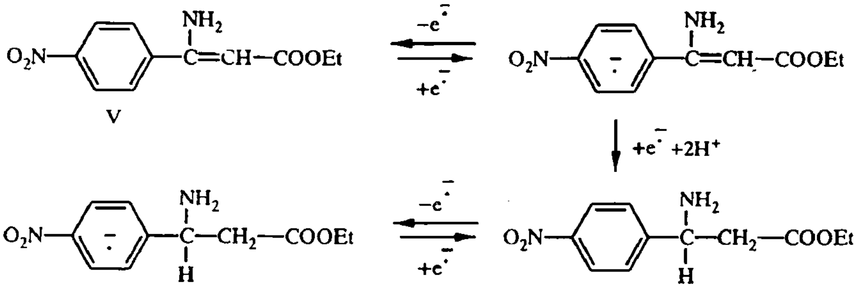
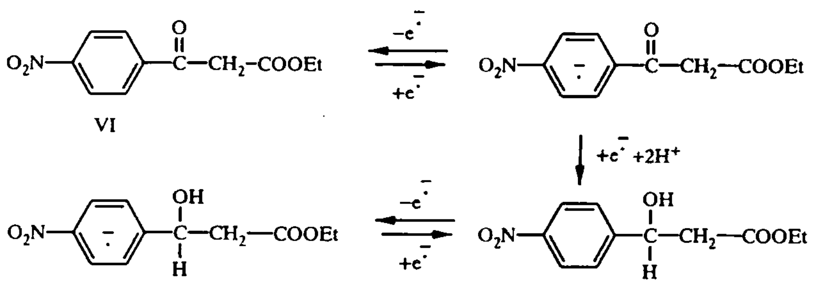
*Given in parentheses as values of the relative number (n) and reversibility (+) of the reaction of electron transfer at the individual stages of electrochemical reduction at a potential scanning speed of 100 mV·sec^{-1} for compounds I-VI in dimethyl formamide (base electrolyte, 0.1 M $(C_4H_9)_4NPF_6$).

ondary free radicals was recorded. The hyperfine structure of their ESR spectra was also determined by the interaction of the unpaired electron with the nitrogen nucleus of the nitro group and the protons of the phenyl fragment, but among the nuclei of the atoms in the p substituent in the hyperfine structure, only a single proton is manifested. This indicates a transformation of the structure of the p substituent. The values of the constant due to the interaction of the unpaired electron with the atomic nuclei of the nitrophenyl fragment of the secondary radical are higher than for the primary radical anion (Table 1). Hence, in the secondary free radical, the substituent has less electrophilic properties than in the initial compound, and in the course of electrochemical generation, after the primary one-electron reduction of the nitro group, what takes place is not its further reduction, but the reduction of the C=C double bond in the p substituent. The formation of the primary and secondary free radicals of compound V may be represented as follows:



The electrochemical generation of the free radicals of compound VI takes place approximately in the same way as in the case of compound V. Depending on the values of the generation potential, there may be formed both primary radical anions and secondary free radicals, in which the nitro group is also preserved. The density of the unpaired electron on the nitrophenyl fragment in the secondary radical is higher than in the primary one (Table 1). As in the case of compound V, the formation of the free radicals of compound VI may be similarly represented.



Hence, the mechanism of formation of the primary radical anions of compounds V and VI is expressed by a reversible one-electron reduction of the initial molecules, as represented by the one-electron reversible wave on the polarograms. However, the sequence of elementary steps in the process of formation of secondary free radicals of these compounds may be different. This is indicated by the results of the study of their electrochemical reduction (Table 2). Although the first step is of the same character for both compounds, reduction of the radical anion of compound V subsequently takes place in three irreversible one-electron steps, whereas the radical anion of compound VI is reduced in two stages reflected in the polarograms, the first, reversible step being similar to a one-electron step, and the second being a two-electron step and irreversible. The density of the impaired electron on the nitrophenyl fragment of the free radicals of compound VI is lower than that of compound V (Table 1); this can be explained by the increased electrophilicity of the p substituent of the nitrophenyl in the primary radical anion and by the decreased electron-donor properties of the substituent in the secondary radical of compound VI as compared with compound V.

During the electrochemical generation of free radicals of compound I at a potential of -1.0 V relative to the platinum reference electrode, free radicals are formed whose hyperfine structure of the ESR spectrum is determined by the interaction of the unpaired electron with the single nucleus of the nitrogen atom and two different pairs of equivalent protons (Fig. 1). The character of the hyperfine structure ($3_N \times 3_H \times 3_H$) and the values of the constants of the ESR spectrum indicate (see Table 1) delocalization of the unpaired electron over the nitrophenyl fragment. It is more probable that this is a fragment of the p nitrobenzoyl substituent of compound I in the 3 position, having the most electrophilic reaction center in the molecule under consideration. This hypothesis is confirmed by the similarity of the values of the hyperfine structure constants of the ESR spectra of the primary free radicals of compounds I and VI, determined by the interaction of the unpaired electron with the nitrogen nucleus of the nitro group.

As the generation potential is raised, the primary radical anions disappear, and when a potential of -1.8 V is reached, secondary free radicals of a p-substituted nitrobenzene of a different structure are formed. The character of the hyperfine structure of the ESR spectrum of the secondary free radicals is the same as that of the primary free radicals, but the values of the hyperfine structure constants (a) are somewhat higher and indicate that the substituent in the p position of the nitrophenyl fragment of the secondary radical is less electrophilic than in the primary free radicals of compound I and VI. The values of the constants of the ESR spectrum of the secondary free radical of compound I are lower than those for the secondary radicals of compound VI (see Table 1). Hence, the secondary free radical was formed, not by the reduction of the C=O double bond

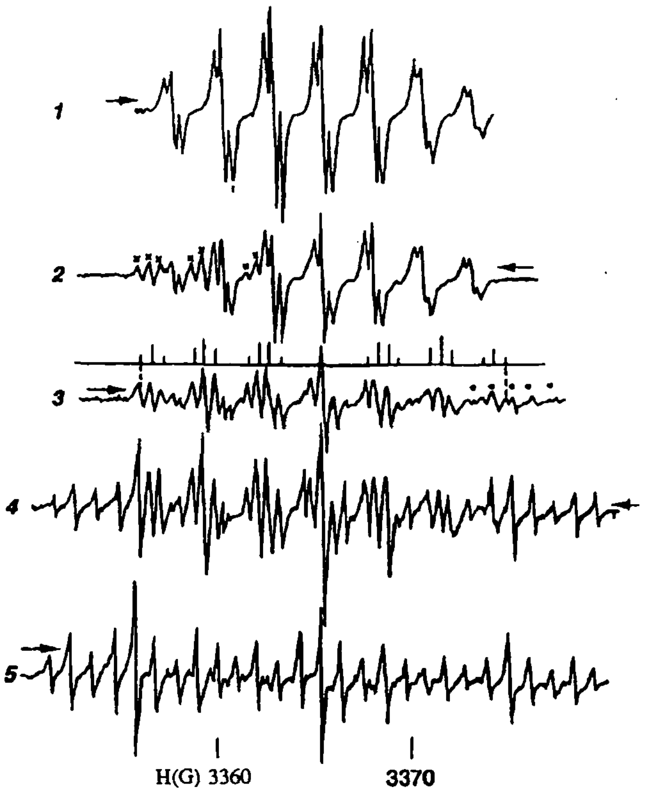


Fig. 1. ESR spectra of electrochemically generated radical anions of compound I in DMFA in a base electrolyte of 10^{-1} mole/liter of tetrabutylammonium hexafluorophosphate: 1) ESR spectrum of primary radical anions of compound I at a generation potential of -1.0 V; 2) transition from primary to secondary free radicals in the course of electrochemical generation at a potential of -1.8 V (crosses denote the ESR signals of the second radical); 3) most distinct ESR spectrum of secondary radicals at a generation potential of -1.8 V and its linear reconstruction (points — signals of the third radical in the high-polar region); 4) sum of ESR spectra of the second and third radicals during their electrochemical generation at a potential of -1.8 V; 5) ESR spectrum of the third type of free radicals at a potential of -1.8 V. Recording time for each spectrum, 30 min; arrows denote the scanning direction of the magnetic field.

in the substituent of the 3 position, but as a result of one-electron reduction of the nitrophenyl substituent in the 6 position of the compound studied.

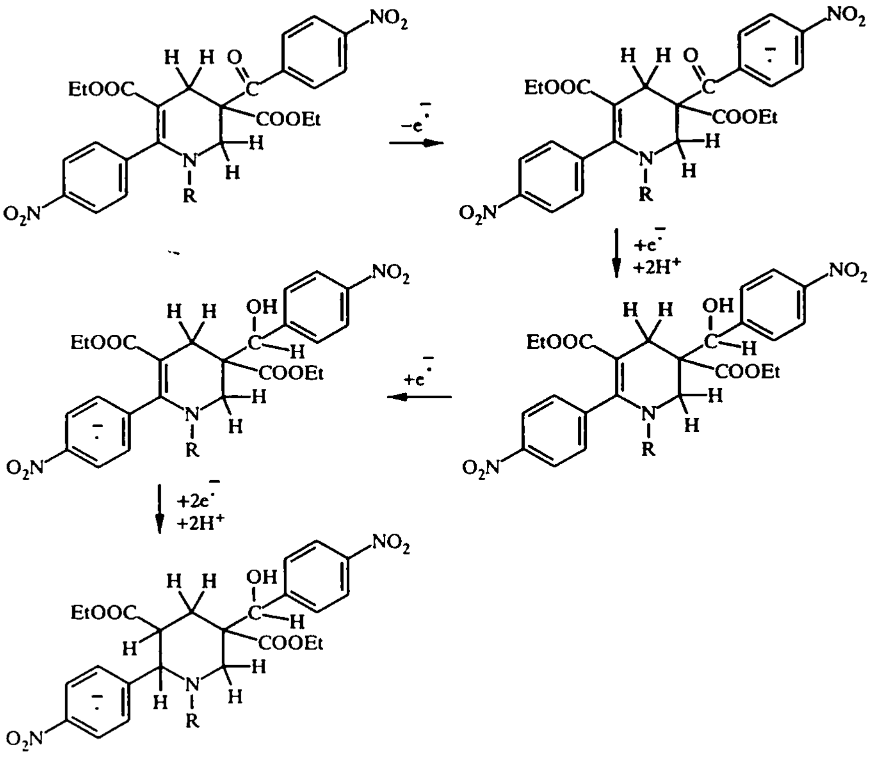
During the generation, the concentration of secondary radicals decreases, and after ~0.5 h, the radicals disappear; simultaneously at the same generation potential, new radicals appear. The character of the hyperfine structure of the ESR spectrum of all three radicals is the same ($3_N \times 3_H \times 3_H$), characteristic of a nitrophenyl-type radical anion. The values of the hyperfine structure constants of the ESR spectrum indicate (see Table 1) that in the radical obtained, as in the secondary radicals of model compounds V and VI, the nitrophenyl in the para position has an aliphatic substituent. Since the values of the constants of the secondary radicals of model compounds V and VI are quite similar, the structure of the aliphatic substituent is difficult to establish by comparing the constants of this radical with the constants of model compounds V and VI, although the value of the constant due to the nitrogen nucleus of the nitro group is closer to the value of the constant for the secondary radical of compound V. Hence, it may be postulated that the third free radical of compound I was formed as a result of a one-electron reduction of the nitrophenyl substituent in the 6 position of the compound with a reduced double bond in the heterocycle. This hypothesis is consistent with the generation potentials of these radicals: the generation potential of the third free radicals of compound I is closer to that of the secondary radicals of model compound V then to the generation potential of those of compound VI.

Electrochemical generation of free radicals of compound II at a potential of −0.7 V leads to the formation of free radicals whose type and values of the hyperfine structure constants of the ESR spectrum indicate a p-nitrobenzoyl structure, i.e., the unpaired electron is localized on the substituent on the 3-position of compound II. As the generation potential is raised to −1.2 V relative to the platinum electrode, formation of two kinds of free radicals of different structures is observed. One of them, whose ESR spectrum contains a complex hyperfine structure and which could not be identified, was apparently formed by a one-electron reduction of the nitrophenyl substituent in the 6 position of tetrahydropyridine II. The complexity of the hyperfine structure is probably due to delocalization of the unpaired electron over both the nitrophenyl and the heterocycle. The hyperfine structure of the ESR spectrum of radicals of the third kind has a $3_N \times 3_H \times 3_H$ character peculiar to nitrophenyl-type free radical anions. Judging from the hyperfine structure constants [2], this is the nitrophenyl radical anion, which has been replaced by an aliphatic substituent in the p position. For the same reasons, as in the case of the third type of free radicals of compound I, this radical may be assumed to have been formed by one-electron reduction of the nitrophenyl substituent in the 6 position of the heterocycle with a reduced double bond between the carbon atoms in the 5 and 6 positions.

The introduction of a nitroso group at the N atom in the heterocycle (compound III) does not appreciably affect the value of the polarographic potential of the first wave and does not produce an additional wave on the polarogram, since the compound may be assumed to be an N-nitrosamine, which is reduced at potentials [3] inaccessible under these conditions. During the electrochemical generation of the five radicals of compound III, ESR spectra of three kinds of nitrophenyl-type free radicals were recorded. As the generation potential increases, there are successively formed free radicals of the p-nitrobenzoyl substituent in the 3 position, p-nitrophenyl substituent in the 6 position, and p-nitrophenyl substituent in the 6 position of compound III with a reduced C=C double bond in the heterocycle. The hyperfine structure constants of the ESR spectrum of the second could not be determined.

For compound IV, the free radical of the p-nitrophenyl substituent in the 6 position of the compound with a reduced double bond of the heterocycle was recorded.

Consequently, during the electrochemical reduction of the 1,2,3,4-tetrahydropyridines discussed, the ESR method was used to detect three kinds of p-nitrophenyl-type free radicals. Neglecting conjugation with chemical side reactions of a different kind, the sequence of formation of the free radicals with increasing generation potential may be represented as follows:



Primary radical anions of the compounds and the secondary radical of compound I were identified more reliably.

Free radicals of the third kind were referred to the nitrophenyl fragment in the 6 position of the heterocycle with a reduced double bond, not to the nitrophenyl fragment in the 3 position of the heterocycle. This conclusion is confirmed by the fact that the values of the hyperfine structure constants of the ESR spectra of the third kind of radical are sensitive to changes in the structure of the R substituent of the heterocycle. For the radical with localization of the unpaired electron in the substituent of the 3 position of the heterocycle, the influence of the R substituent at the nitrogen atom of the heterocycle is not manifested, and the primary radical anions of compounds I-III are identical (see Table 1). Thus, free radicals of the third kind are generated, not on further reduction of the primary free radicals, but in the transformation of the secondary radical by reduction of the double bond of the heterocycle. Thus, during the electrochemical generation of free radicals of compounds I-IV, there are formed primary radical anions studied by the ESR method, owing to the delocalization of the unpaired electron in the substituent of the 3 position and two kinds of free radicals with delocalization of the unpaired electron in the substituent of the 6 position. Formation of such semistable radicals – products of further reduction of primary radical anions having delocalization of the unpaired electron the substituent of the 3 position – was not observed.

EXPERIMENTAL

The electrochemical reduction of compounds I-VI ($c = 5 \cdot 10^{-4}$ mole/liter) was carried out in anhydrous DMFA [4] in tetrabutylammonium hexafluorophosphate base electrolyte ($c = 10^{-1}$ mole/liter). Classical polarograms and cyclic current–voltage curves were recorded on a PAR-170 polarograph using a three-electrode cell. The cathode was a dropping mercury electrode with forced separation of the drop ($t = 0.5$ sec, $m = 0.90$ mg/sec), the anode was platinum wire, and the reference electrode was an aqueous saturated calomel electrode provided with a transition bridge for work in nonaqueous solvents. The cyclic current–voltage curves were recorded on a glassy-carbon electrode with a cycle scanning speed of 0.1 V/sec.

The free radicals were generated in a steady state in a three-electrode arrangement on the surface of a platinum electrode placed in a TM_{110}-type cylindrical cavity of an SE/X 2547 ESR spectrometer equipped with an MP-102 spectrum analyzer (OPP Radiopan, Poland) (Mikropan-Poznan) using the method of [5, 6]. The scanning of the magnetic field was calibrated against the ESR spectrum of nitrobenzene radical anions generated electrochemically in accordance with the method of [7]. Use was made of $5 \cdot 10^{-4}$-10^{-3} mole/liter solutions of compounds I-VI in anhydrous DMFA, and the solution contained 10^{1} mole/liter of tetrabutylammonium hexafluorophosphate.

The PMR spectra were recorded on Bruker WH instrument (90 MHz) in $CDCl_3$, and the chemical shifts were determined in ppm relative to TMS. The IR spectra were recorded on a Perkin-Elmer 580B spectrometer for samples consisting of suspensions of the compound in Nujol. The mass spectra were recorded on an AE/MS-59 instrument.

Ethyl p-nitrobenzoylacetate (VI) was synthesized in accordance with the well-known method of [8].

3,5-Diethoxycarbonyl-3-(p-nitrobenzoyl)-6-(p-nitrophenyl)-1,2,3,4-tetrahydropyridine(I), 3,5-diethoxycarbonyl-3-(p-nitrobenzoyl)-1-nitroso-6-(p-nitrophenyl)-1,2,3,4-tetrahydropyridine (III) and 3-(α-hydroxy-p-nitrobenzyl)-3,5-diethoxycarbonyl-6-(p-nitrophenyl)-1,2,3,4-tetrahydropyridine (IV) were synthesized in accordance with the method of [1].

Ethyl-3-nitrophenyl-3-aminopropen-2-oate (V). A solution of 2.38 g (10 mmole) of ethyl p-nitrobenzoylacetate and 1.9 g (20 mmole) of ammonium acetate were boiled in 20 ml of ethanol for 1 h. After cooling, the precipitate was filtered off and crystallized from ethanol. Yield, 2.34 g (98%), mp, 97°C. Found, %: C 55.9; H 5.1; N 11.9. $C_{11}H_{12}N_2O_4$. Calculated, %: C 55.9; H 5.1; N 11.5. IR spectrum: 1655, 3320, 3340 cm^{-1}. PMR spectrum: 1.24 (3H, t, $OCH_2\underline{CH_3}$); 4.14 (2H, q, $O\underline{CH_2}CH_3$); 4.95 (1H, s, 2-H); 6.44 (2H, br.s, NH_2); 7.55-8.35 ppm (4H, m, $C_6H_4NO_{2\text{-}p}$). Mass spectrum, *m/z*, M^+ 236.

3,5-Diethoxycarbonyl-3-(p-nitrobenzoyl)-6-(p-nitrophenyl)-1-methyl-1,2,3,4-tetrahydropyridine (II). We mixed 1.5 ml of a 36% formaldehyde solution and 1.5 ml of a 25% aqueous methylamine solution and left the mixture standing for 1 h at 0°C. A solution of 1.19 g (5 mmole) of ethyl p-nitrobenzoylacetate in 10 ml of ethanol was added to the cooled mixture of formaldehyde and methylamine, then the combined mixture was boiled for 1 h. The reaction mixture was cooled, and the oil was triturated with methanol. The precipitate was crystallized from methanol. Yield, 1.0 g (39%), mp 130-131°C. Found, %: C 56.8; H 4.9; N 8.1. $C_{25}H_{25}N_3O_9$. Calculated, %: C 58.7; H 4.9; N 8.2. IR spectrum: 1685, 1740 cm^{-1}. PMR spectrum: 0.75 and 1.15 (6H, t, $OCH_2\underline{CH_3}$); 2.55 (3H, s, $N-CH_3$); 3.12 (2H, s, 4-H_2); 3.65 (4H, m, $O\underline{CH_2}CH_3{}^+$, $N-CH_2$); 4.20 (2H, q, $O\underline{CH_2}CH_3$); 7.85-8.35 (8H, m, arom.). The course of the reaction and the purity of the synthesized compounds were monitored on Merck Kieselgel 60 F_{254} plates, 0.25 mm. The solvent systems were 9:7:1 chloroform–hexane–acetone and 20:1 benzene–ethyl acetate.

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