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SOME TRANSFORMATIONS OF N-ETHOXYCARBONYL-METHYLPYRIDINIUM BROMIDES WITH A PYRIDYL OR 1,4-DIHYDROPYRIDYL SUBSTITUENT AT POSITION 3

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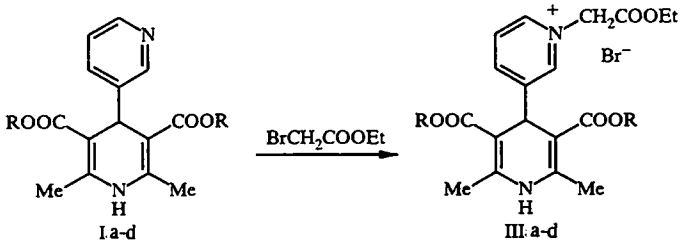
The direction of the reaction of derivatives of N-ethoxycarbonylmethylpyridinium bromide with chalcone in the presence of bases depends on the substituent at position 3 of the pyridine ring. In the presence of a pyridyl substituent a derivative of 2,3-dihydroindolizine is formed. In the case of a 1,4-dihydropyridyl substituent cycloaddition does not occur, and a Michael addition product (an acyclic betaine) is formed. The latter can be transformed into a derivative of indolizine only under the conditions of decarboxylation.

The ability of quaternized pyridinium salts to form pyridinium ylides, capable of entering into cycloaddition reactions at the multiple bonds, during the action of bases is widely used in organic synthesis [1-5]. The initial product of the cycloaddition of the pyridinium ylide at the activated carbon—carbon double bond is a derivative of tetrahydroindolizine [1, 4]. This is often oxidized during isolation to the corresponding derivatives of dihydroindolizine [3] and indolizine [1]. As a rule tetrahydroindolizines are unstable compounds. However, a series of derivatives of tetrahydroindolizine, synthesized from ethoxycarbonylmethylpyridinium, carbamoylmethylpyridinium, and cyanomethylpyridinium salts and also from the corresponding quinolinium salts by treatment with bases in the presence of various chalcones, were described in [4]. Among the substituted pyridines α-, β-, and γ-picolinium salts were tested. Derivatives of tetrahydroindolizine were only isolated in the reactions with unsubstituted pyridine and α-picoline.

In the present work we investigated the effect of the 1,4-dihydropyridyl (1,4-DHP) substituent (as a weak electron donor) and the pyridyl substituent (as an electron acceptor) on the above-mentioned reactions.

Scheme 1



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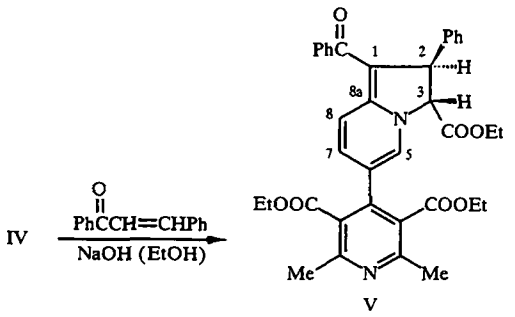
Compounds (IIIa-d, IV) were synthesized from 4-(3-pyridyl)-1,4-dihydropyridines (Ia-d) and the bipyridyl (II) in quaternization with ethyl α-bromoacetate (Scheme 1).

The reactions presented above were observed when equimolar amounts of the initial compounds were boiled in acetone solution. In both cases only the 3-monosubstituted pyridine ring was quaternized. Compound (II) reacted more slowly than (Ia-d). This can be explained by the different electronic effects of the substituents. The 2,6-dimethyl-3,5-dialkoxycarbonyl-1,4-dihydro-4-pyridyl substituent has a small electron-donating effect ($\sigma_I = -0.18$, $\sigma_R = -0.08$) [6], whereas the 2,6-dimethyl-3,5-dialkoxycarbonyl-4-pyridyl substituent is an electron acceptor and reduces the nucleophilicity of the 3-pyridine ring, thereby reducing the activity of the compound in quaternization.

The reaction between (II) and benzylideneacetophenone (Scheme 2) was conducted in ethanol solution in the presence of sodium hydroxide [4]. However, the 2,3-dihydroindolizine derivative (V) was isolated instead of the expected tetrahydroindolizine derivative, which is clearly the initial reaction product.

Scheme 2

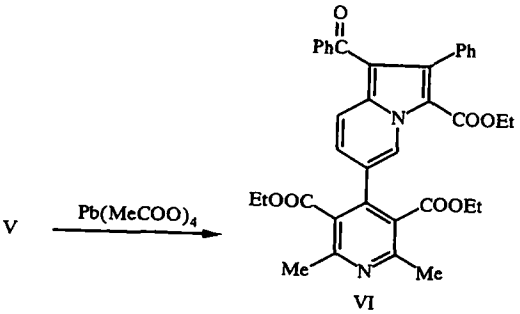


V

In the PMR spectrum of compound (V) there is a pair of doublets for the 2-H and 3-H protons characteristic of the 2,3-dihydroindolizine structure in the region of 4.5-4.7 ppm. The spin—spin coupling constant amounts to 3 Hz, which makes it possible to conclude that the 2- and 3-protons are in the *trans* position. These data agree well with the data presented in [3]. The structures of 1,8a-dihydro- and 3,8a-dihydroindolizines are excluded, since in both cases the 8a proton would have additional splitting from coupling with proton 8, and in the case of 3,8a-dihydroindolizine the signal of proton 3 would be a singlet.

During the oxidation of compound (V) with lead tetraacetate (Scheme 3) aromatization of the bicyclic system occurs, and the indolizine derivative (VI) is formed.

Scheme 3



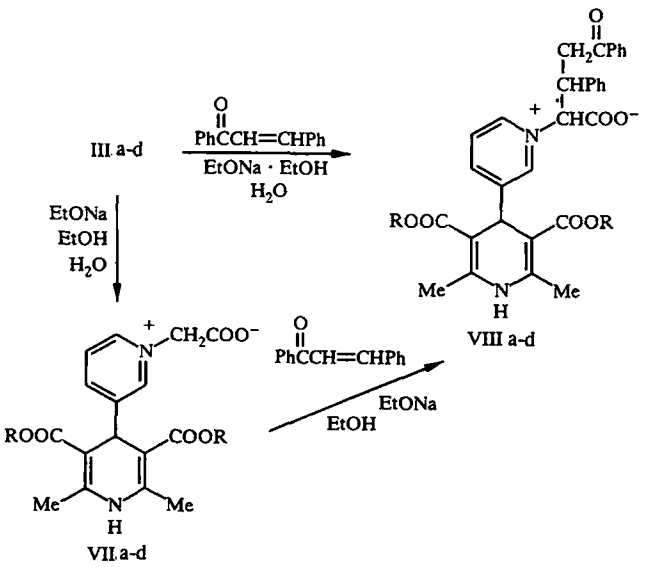
VI

When the reactions between the 1,4-dihydropyridine derivatives (IIIa-d) and benzylideneacetophenone were conducted under analogous conditions (scheme 4), the acyclic betaines (VIIIa-d) were isolated instead of the cycloaddition products. They can be regarded as the products from Michael addition.

TABLE 1. 1-Ethoxycarbonylmethyl-3-(2',6'-dimethyl-3',5'-dialkoxycarbonyl-1',4'-dihydro-4'-pyridyl)pyridinium Bromides (IIIa-d)

Compound	R	Molecular formula	Found %/ Calculated %			mp, °C	Yield, %
			C	H	N		
IIIa	C_2H_5	$C_{22}H_{29}N_2O_6Br$	53.4 53,12	5.9 5,87	5.1 5,63	217...223 (decomp.)	88
IIIb	$(CH_2)_3CH_3$	$C_{26}H_{37}N_2O_6Br$	56.2 56,69	6.6 6,74	5.1 5,06	148...151	96
IIIc	$CH(CH_3)CH_2CH_3$	$C_{26}H_{37}N_2O_6Br$	56.7 56,69	6.7 6,74	4.9 5,06	183...185	50
IIId	$(CH_2)_2O(CH_2)_2CH_3$	$C_{28}H_{41}N_2O_8Br$	54.7 54,81	6.7 6,74	4.6 4,57	144...146	91

Scheme 4



a R = Et, b R = Bu, c R = CH(Me)Et, d R = C_2H_4OPr

The intermediate products of this reaction are probably the betaines (VIIa-d), since they were isolated during the treatment of compounds (IIIa-d) with bases. The treatment of the betaine (VIIa) in turn by a base in the presence of a chalcone gave the product (VIIIa). With perchloric acid both betaines (VIIa, VIIIa) form the corresponding perchlorates (IX) and (X).

In the PMR spectra of compounds (VIIIa-d) a long-range position of the signals for the protons of pyridinium is observed (in the region of 7.3-8.96 ppm). This corresponds to the presence of a positive charge at the nitrogen atom. In addition, nonequivalence in the protons of the CH_2 group attached to the benzoyl group and strong geminal coupling of these protons with a constant of 16 Hz are observed. Only one of them couples with the —CHPh proton with a constant of 9 Hz, while the second must be at an angle of 90° to the adjacent proton, and coupling between them is not therefore observed. The vicinal coupling constant between the $-CHCOO^-$ and the —CHPh protons also amounts to 9 Hz. In addition, in compounds (VIIIa-d) the chemical shifts of the protons of the 2-CH_3 groups differ from those of 6-CH_3; the protons of the 3- and 5-ester groups also have different chemical shifts. This fact indicates that the 1,4-dihydropyridine molecule is unsymmetrical, which may arise as a result of the anisotropic effect of the carbonyl group of the benzoyl substituent on the fragments of the 1,4-dihydropyridine ring, which usually exists in the boat conformation.

One of the reasons for the impossibility of obtaining derivatives of tetrahydroindolizine may be the electron-donating effect of the 1,4-dihydropyridyl substituent. The latter reduces the positive charge in the pyridine ring and, consequently, on the one hand reduces the electrophilicity of the carbon adjacent to the nitrogen atom, thereby reducing the reactivity of the pyridine ring in the cycloaddition reaction. On the other hand it probably accelerates the hydrolysis of the ester group. As a

TABLE 2. Derivatives of 1-Carboxylatomethyl-3-(2′,6′-dimethyl-3′,5′-dialkoxycarbonyl-1′,4′-dihydro-4′-pyridyl)pyridinium (VIIa-d)

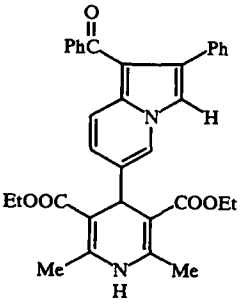
Compound	R	Molecular formula	Found %/ Calculated %			mp, °C	Yield, %
			C	H	N		
VIIa	C_2H_5	$C_{20}H_{24}N_2O_6 \cdot 2H_2O$	56.4 56,69	6.6 6,65	6.3 6,60	128...130	84
VIIb	$(CH_2)_3CH_3$	$C_{24}H_{32}N_2O_6 \cdot 1,5H_2O$	61.6 61,13	6.9 7,47	6.1 5,94	163...165	73
VIIc	$CH(CH_3)CH_2CH_3$	$C_{24}H_{32}N_2O_6 \cdot 1,5H_2O$	59.7 61.13	7.3 7,47	5.7 5,94	Room	61
VIId	$(CH_2)_2O(CH_2)_2CH_3$	$C_{26}H_{36}N_2O_8$	61.9 61,89	7.2 7,19	5.6 5,55	150	63

TABLE 3. Derivatives of 1-(1-Carboxylato-2-phenyl-3-benzoylpropyl)-3-(2′,6′-dimethyl-3′,5′-dialkoxycarbonyl-1′,4′-dihydro-4′-pyridyl)pyridinium (VIIIa-d)

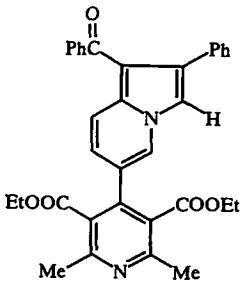
Compound	R	Molecular formula	Found %/ Calculated %			mp, °C	Yield, %
			C	H	N		
VIIIa	C_2H_5	$C_{35}H_{36}N_2O_7$	69.8 70,45	6.0 6,08	4.5 4,69	138...143	86
VIIIb	$(CH_2)_3CH_3$	$C_{39}H_{44}N_2O_7$	71.3 71,76	6.7 6,79	4.2 4,29	133...135	68
VIIIc	$CH(CH_3)CH_2CH_3$	$C_{39}H_{44}N_2O_7$	71.2 71,76	6.7 6,79	4.1 4,29	125...127	61
VIIId	$(CH_2)_2O(CH_2)_2CH_3$	$C_{41}H_{48}N_2O_9$	68.9 69,08	6.7 6,79	4.0 3,93	120...121	89

result during treatment of the initial pyridinium salt (III) with the base the betaine (VII) is formed more quickly than the expected cycloaddition of the pyridinium ylide to the double bond of benzylideneacetophenone would occur. Further reaction of the betaine (VII) in the presence of the base is restricted only to Michael addition to the electrophilic carbon atom of the multiple bond, and cycloaddition does not occur. The reaction leading to the formation of tetrahydroindolizine, known from the literature, only applies to unsubstituted pyridines and to α-picoline [4]. In the same paper it was indicated that the reaction products could not be isolated for β- and γ-picolines.

During the oxidation of (VIIIa) with tetrachloroquinone or benzoquinone (boiling in benzene) compound (XI) was isolated. This is the product of three reactions (decarboxylation, oxidation, and cycloaddition).



XI



XII

The action of tetrachloroquinone on (VIIIa) gives the products (XI) and (XII). In addition, when a benzene solution of (VIIIa) is boiled with three moles of chloranil, a gradual decrease in the amount of the product (XI) and the accumulation of the product (XII) are observed, i.e., the 1,4-dihydropyridine ring is oxidized with some difficulty by chloranil. In the reaction with a milder oxidizing agent (benzoquinone) only one of the two products (XI) was obtained, since the 1,4-dihydropyridine ring in this case is not oxidized by benzoquinone. In both reactions the product yields are low, and compounds (XI) and (XII) are contaminated with side products.

TABLE 4. PMR Spectra of Compounds (IIIa-d) in Deuterochloroform

Compound	Chemical shifts, δ (ppm), and spin-spin coupling constants, J (Hz)										
	4-Py				N-H, bs	4-H, s	$N-CH_2COOC_2H_5$			2,6-CH_3, s	R
	6-H, d, $J_{6,5}$ = 6	2-H, s	4-H, d, $J_{4,5}$ = 8	5-H, dd, $J_{5,4}$ = 8, $J_{5,6}$ = 6			N—CH_2, s	OCH_2, q, J = 7	CH_3, t, J = 7		
IIIa	8,89	8,45	7,84	7,62	8,98	5,12	6,05	4,26	1,30	3,46	4,06 (4H, q, J = 7); 1,2 (6H, t, J = 7)
IIIb	9,25	8,81	8,48	7,89	8,25	5,15	6,06	4,30	1,32	2,50	4,1 (4H,m); 1,6 (4H,m); 1,3 (4H, m)
IIIc	9,15	8,78	8,40	7,83	8,02	5,10	6,00	4,24	1,30	2,44	4,9...4,6 (2H, m); 1,7...0,85 (16H, m)
IIId	9,32	8,65	8,40	7,80	8,65	5,12	5,91	4,37	1,30	2,52	4,06 (4H,m); 3,59 (4H,m); 3,29 (4H, t, J = 7); 1,58 (4H,m); 0,89 (6H, t)

TABLE 5. PMR Spectra of Compounds (VIIa-d) in Deuterochloroform

Compound	Chemical shifts, δ (ppm), and spin—spin coupling constants, J (Hz)								
	Py				N—H, bs	N—CH_2, s	4-H, s	2,6-CH_3, s	R
	2-H, s	6-H, d, $J_{6,5}$ = 6	4-H, d, $J_{4,5}$ = 8	5-H, dd, $J_{5,4}$ = 8, $J_{5,6}$ = 6					
VIIa	8,73	8,33	8,23	7,62	9,20	5,15	5,01	2,26	4,04 (4H, q, J = 7); 1,20 (6H, t, J = 7)
VIIb	8,75	8,57	8,30	7,69	9,40	5,20	5,10	2,32	4,05 (4H,m); 1,62...1,30 (8H, m); 0,95 (6H, t)
VIIc	8,70	8,12	8,29	7,69	9,00	5,22	5,10	2,37	4,79 (2H,m); 1,65...1,44 (4H, m); 1,20 and 1,10 (6H,two d); 0,9 and 0,77 (6H, two t)
VIId	8,71	8,38	8,27	7,60	9,67	5,08	5,05	2,28	4,13 (4H,m); 3,35 (4H, t, J = 7); 1,75...1,35 (4H,m); 0,89 (6H, t, J = 7)

TABLE 6. PMR Spectra of Compounds (VIIIa-d) in Deuterochloroform

Compound	Chemical shifts, δ, ppm, and spin-spin coupling constants J, Hz													
	N'—H, s	6-H, d, $J_{6,5}$ = 6	2-H, s	4-H, d, $J_{4,5}$ = 8	5-H, m	C(=O)Ph, two m	Ph, two m	N—CH, d, $J_{1,2}$ = 9	4'-H, s	CHPh, t, $J_{2,1}$ = 9, $J_{2,3A}$ = 9	CH_BCOPh, d, $J_{A,B}$ = 16	CH_ACOPh, two d $J_{B,A}$ = 16, $J_{A,2}$ = 9	2',6'-CH_3, two s	R
VIIIa	9,24	8,75	8,70	8,00	7,60	7,91 and 7,48	7,10 and 6,94	5,44	4,89	4,15	4,05	3,65	2,32 and 2,30	4,08...3,95 (4H,m); 1,12 (3H, t, J = 7)
VIIIb	9,25	8,89	8,74	8,04	7,45	7,88 and 7,31	7,15 and 6,98	5,87	4,86	4,25	4,18	3,72	2,42 and 2,10	4,05...3,90 (4H,m); 1,6...1,45 (4H,m); 1,37...1,27 (4H,m); 0,91 (6H, t, J = 7)
VIIIc	9,07	8,67	8,71	7,94	7,40	7,75 and 7,20	7,15 and 6,90	5,83	4,80	4,25	4,20	3,71	2,51 and 2,14	4,80...4,54 (2H,m); 1,57...0,57 (16H,m)
VIIId	9,12	8,96	8,67	8,00	7,31	7,75 and 7,20	7,15 and 6,88	6,15	4,71	4,32	4,20	3,70	2,51 and 1,72	4,20...3,85 (4H,m); 3,68...3,16 (8H, m); 1,63...1,38 (4H,m); 0,88 (6H, t, J = 7)

The PMR spectra of compounds (XI) and (XII) are given in the experimental section. Compound (XII) differs from compound (VI) only in the absence of the ethoxycarbonyl substituent at position 3. Here the chemical shift of the 5-H proton of the indolizine ring in the PMR spectrum amounts to 7.85 ppm in contrast to compound (VI), in which the signal of the 5-H proton is at 9.5 ppm. It is known [7] that if there is an electron-withdrawing substituent at position 3 the signal of proton 5 is shifted downfield. In both compounds (VII) and (XII) the 5-H proton is a singlet. This indicates closure of the indolizine ring at position 6 and not position 2.

Thus, the direction of the reaction of the derivatives of N-ethoxycarbonylmethylpyridinium bromide with chalcone in the presence of bases depends on the substituent at position 3 of the pyridine ring; if there is a pyridyl substituent at position 3, a stable 2,3-dihydroindolizine derivative is formed; if there is a 1,4-dihydropyridine substituent at position 3, the product from Michael addition, i.e., the acyclic betaine, is formed.

EXPERIMENTAL

The ^1H NMR spectra were recorded on a Brucker WH-90/DS instrument at 90 MHz in deuterochloroform or DMFA-d_6 with TMS as internal standard. The UV spectra were obtained on a Hitachi 557 instrument in ethanol. The IR spectra were obtained on a Perkin-Elmer 580 B instrument in Nujol.

Derivatives of 2,6-Dimethyl-3,5-dialkoxycarbonyl-4-(3-pyridyl)-1,4-dihydropyridine (Ia-d). The compounds were obtained from the respective acetoacetic esters, 3-pyridinecarbaldehyde, and ammonia according to published data [8].

2,6-Dimethyl-3,5-dialkoxycarbonyl-4-(3-pyridyl)pyridine (II). The compound was obtained during the oxidation of (Ia) by nitric acid according to [8].

1-Ethoxycarbonylmethyl-3-(2′,6′-dimethyl-3′,5′-dialkoxycarbonyl-1′,4′-dihydro-4′-pyridyl)pyridinium Bromides (IIIa-d). We dissolved the respective 2,6-dimethyl-4-(3-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylic ester (Ia-d) by heating in 10-20 ml of acetone or a 1:1 mixture of acetone and chloroform and added 0.32 ml (0.5 g, 0.003 mole) of ethyl bromoacetate. the mixture was boiled for 2-3 h. After cooling the precipitate was filtered off and recrystallized from acetone. UV spectrum of compound (IIIa) (ethanol), λ_{max} (log ε): 232 (4.42), 270 (3.93), 348 nm (3.68). Compounds (IIIb-d) had similar UV spectra. The other characteristics are given in Tables 1 and 4.

1-Ethoxycarbonylmethyl-3-(2′,6′-dimethyl-3′,5′-diethoxycarbonyl-4′-pyridyl)pyridinium Bromide (IV). We dissolved 3.3 g (0.01 mole) of 2,6-dimethyl-3,5-diethoxycarbonyl-4-(3-pyridyl)pyridine (II) by heating in 30 ml of acetone. To the solution we added 1.68 g (1.11 ml, 0.01 mole) of ethyl bromoacetate. The reaction mixture was boiled for 12 h. After cooling the crystalline precipitate was filtered off and recrystallized from a 1:1 mixture of ethanol and hexane. We obtained 1.9 g (38%) of a light-yellow crystalline substance melting at 160°C (decomp.). PMR spectrum (deuterochloroform): 1.10 (6H, t, J = 7 Hz, 3′,5′-CH_3); 1.30 (3H, t, J = 7 Hz, CH_3); 2.60 (6H, s, 2′,6′-CH_3); 4.11 (4H, q, J = 7 Hz, 3′,5′-CH_2); 4.25 (2H, q, J = 7 Hz, CH_2); 6.35 (2H, s, N—$COOCH_2$); 8.05-8.33 (2H, m, 4+5-H Py); 8.67 (1H, s, 2-H Py); 10.04 (1H, m, 6-H Py). Found, %: C 53.3; H 5.4; N 5.6. $C_{22}H_{27}N_2O_6Br$. Calculated %: 53.34; H 5.49; N 5.66.

1-Benzoyl-2-phenyl-3-ethoxycarbonyl-6-(2′,6′-dimethyl-3′,5′-diethoxycarbonyl-4′-pyridyl)-2,3-dihydroindolizine (V). We dissolved 1.3 g (0.0026 mole) of 1-ethoxycarbonylmethyl-3-(2′,6′-dimethyl-3′,5′-diethoxycarbonyl-4′-pyridyl)-pyridinium bromide (IV) by heating to 50°C in 20 ml of ethanol. We added 0.55 g (0.0026 mole) of benzylideneacetophenone and gradually added in small portions a solution of 0.11 g (0.0026 mole) of sodium hydroxide in 3 ml of water. The mixture was stirred for 2 h, and the solvent was evaporated. The residue (an orange oil) was treated with water, decanted, and dissolved in 150 ml of chloroform. The obtained solution was washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated, and the residue was mixed with a 1:1 mixture of hexane and ethyl acetate. The precipitate was filtered off and recrystallized from ethanol. We obtained 0.7 g (42%) of a bright-yellow crystalline substance, melting at 140°C (decomp.). PMR spectrum (deuterochloroform): 1.22 (6H, t, J = 7 Hz, 3′,5′-CH_3); 1.34 (3H, t, J = 7 Hz, 3-CH_3); 2.55 (6H, s, 2′,6′-CH_3); 4.23 (6H, q, J = 7 Hz, 3′,5′- and 3-CH_2); 4.54, (1H, d, J = 3 Hz, 2-H); 4.70 (1H, d, J = 3 Hz, 3-H); 6.87-7.29 (13H, m, 5,7,8-H + C_6H_5). UV spectrum (ethanol), λ_{max} (log ε): 204 (4.70), 260 (3.96) sh, 370 (4.26), 428 nm (4.09) sh. Found, %: C 71.2; H 5.8; N 4.4. $C_{37}H_{36}N_2O_7$. Calculated %: C 71.60; H 5.85; N 4.51.

1-Benzoyl-2-phenyl-3-ethoxycarbonyl-6-(2′,6′-dimethyl-3′,5′-diethoxycarbonyl-4′-pyridyl)indolizine (VI). In 25 ml of benzene we dissolved 0.1 g (0.16 mmole) of 1-benzoyl-2-phenyl-3-ethoxycarbonyl-6-(2′,6′-dimethyl-3′,5′-diethoxy-carbonyl-4′-pyridyl)-2,3-dihydroindolizine (V). We added 0.08 g (0.16 mmole) of lead tetraacetate. The mixture was stirred at room temperature for 24 h. The precipitate was filtered off, and the filtrate was purified on a column of silica gel. Benzene

was used as eluant. After distilling the benzene we obtained 0.6 g (60%) of a colorless crystalline substance, melting at 130-132°C. PMR spectrum (deuterochloroform): 0.93 (3H, t, J = 7 Hz, 3-CH_3); 1.11 (6H, t, J = 7 Hz, 3′,5′-CH_3); 2.61 (6H, s, 2′,6′-CH_3); 4.05 (2H, q, J = 7 Hz, 3-CH_2); 4.13 (4H, q, J = 7 Hz, 3′,5′-CH_2); 6.98-7.44 [11H, m, 7-H + $(C_6H_5)_2$]; 7.92 (1H, d, J = 9 Hz, 8-H); 9.57 (1H, s, 5-H). UV spectrum (ethanol), λ_{max} (log ε): 202 (4.56), 255 (4.55), 340 (4.16) nm. Found, %: C 71.6; H 5.9; N 4.2. $C_{37}H_{34}N_2O_7$. Calculated %: C 71.83; H 5.54; N 4.53.

Derivatives of 1-Carboxylatomethyl-3-(2′,6′-dimethyl-3′,5′-dialkoxycarbonyl-1′,4′-dihydro-4′-pyridyl)pyridinium (VIIa-d). A. We dissolved 0.005 mole of the respective 1-ethoxycarbonylmethyl-3-(2′,6′-dimethyl-3′,5′-dialkoxycarbonyl-1′,4′-dihydro-4′-pyridyl)pyridinium bromide (IIIa-d) by heating to 50°C in 30 ml of absolute ethanol. We then added a solution of 0.11 g (0.005 mole) of metallic sodium in 2.5 ml of absolute ethanol. The reaction mixture was stirred for 2 h, and the solvent was distilled. The residue was mixed with 5 ml of water, and the crystalline product was filtered off and recrystallized from water. The yields were 80%. UV spectrum of (VIIa) (ethanol), λ_{max} (log ε): 236 (4.43), 272 (3.93), 362 nm (3.68). Compounds (VIIb-d) have similar UV spectra. The other characteristics are given in Tables 2 and 5.

B. We dissolved 0.0025 mole of the respective 1-ethoxycarbonylmethyl-3-(2′,6′-dimethyl-3′,5′-dialkoxycarbonyl-1′,4′-dihydro-4′-pyridyl)pyridinium bromide by heating to 50°C in 20 ml of absolute ethanol. We added a solution of 0.1 g (0.0025 mole) of sodium hydroxide in 2.5 ml of water. The reaction mixture was stirred for 2 h. After distillation of the ethanol the residue was mixed with 5 ml of water. The crystallizing product was filtered off and recrystallized from water. The yields of the products were 55%.

Derivatives of 1-(1-Carboxylato-2-phenyl-3-benzoylpropyl)-3-(2′,6′-dimethyl-3′,5′-dialkoxycarbonyl-1′,4′-dihydro-4′-pyridyl)pyridinium (VIIIa-d). A. We dissolved 0.01 mole of the respective 1-ethoxycarbonylmethyl-3-(2′,6′-dimethyl-3′,5′-dialkoxycarbonyl-1′,4′-dihydro-4′-pyridyl)pyridiniumbromide(IIIa-d)or1-carboxylatomethyl-3-(2′,6′-dimethyl-3′,5′-diethoxycarbonyl-1′,4′-dihydro-4′-pyridyl)pyridinium (VIIa) bromide by heating to 50°C in 55 ml of absolute ethanol. We added 2.08 g (0.01 mole) of benzylideneacetophenone, and we gradually added in small portions 0.23 g (0.01 mole) of metallic sodium in 5 ml of absolute ethanol. The reaction mixture was stirred for 2 h, and the solvent was evaporated. The residue (an orange oil) was treated with water, decanted, and dissolved in 150 ml of chloroform. The obtained solution was washed with water and dried over anhydrous sodium sulfate. We then added 70 ml of hexane. The crystalline substance that separated was filtered off and recrystallized from chloroform. The yield of the products was 85%. UV spectrum of (VIIIa) (ethanol), λ_{max} (log ε): 236 (4.54), 275 (3.99), 341 (3.67), 372 nm (3.57) sh. Compounds (VIIIb-d) have similar UV spectra. The other characteristics of the compounds are given in Tables 3 and 6.

B. We dissolved 0.0025 mole of the respective 1-ethoxycarbonylmethyl-3-(2′,6′-dimethyl-3′,5′-dialkoxycarbonyl-1′,4′-dihydro-4′-pyridyl)pyridinium bromide by heating to 50°C in 20 ml of absolute ethanol. We added 0.53 g (0.0025 mole) of benzylideneacetophenone, and we gradually added in small portions a solution of 0.1 g (0.0025 mole) of sodium hydroxide in 2.5 ml of water. The reaction mixture was stirred for 2 h, and the solvent was evaporated. The residue was treated with water and dissolved in chloroform. The solution was washed with water and dried over anhydrous sodium sulfate. The precipitate that crystallized on cooling was filtered off and recrystallized from chloroform. The yields were 50%.

1-Carboxymethyl-3-(2′,6′-dimethyl-3′,5′-diethoxycarbonyl-1′,4′-dihydro-4′-pyridyl)pyridinium (IX) and 1-(1-Carboxy-2-phenyl-3-benzoylpropyl)-3-(2′,6′-dimethyl-3′,5′-dialkoxycarbonyl-1′,4′-dihydro-4′-pyridyl)pyridinium (X) Perchlorates. To a solution of 0.001 mole of the respective pyridinium betaine [compounds (VIIa, VIIIa) in 10 ml of ethanol while stirring we added 0.12 ml (0.18 g, 0.001 mole) of 57% perchloric acid. The precipitate was filtered off, washed with ethanol, and dried in air. We obtained 38-41% of a light-yellow crystalline substance. Compound (IX): mp 118-120°C. PMR spectrum (deuterochloroform): 1.22 (6H, t, J = 7 Hz, 3′,5′-CH_3); 2.36 (6H, s, 2′,6′-CH_3); 4.10 (4H, q, J = 7 Hz, 3′,5′-CH_2); 5.14 (1H, s, 4′-H); 5.42 (2H, s, NCH_2); 7.09 (1H, bs, N′—H); 7.79 (1H, dd, 5-H Py); 8.41 (1H, d, 4-H Py); 8.50 (1H, d, 6-H Py); 8.53 (1H, s, 2-H Py). Found, %: C 46.3; H 5.4; N 5.3. $C_{20}H_{25}N_2O_{10}Cl{\cdot}2H_2O$. Calculated, %: C 45.8; H 5.6; N 5.3.

Compound (X). mp 197-202°C (decomp.). PMR spectrum (DMSO-d_6): 1.10 and 1.13 (6H, tt, J = 7 Hz, 3′,5′-CH_3); 2.32 (6H, s, 2′,6′-CH_3); 3.54-4.43 (7H, m, 3′,5′-CH_2 + CHPh + CH_2COPh); 4:88 (1H, s, 4′-H); 6.15 (1H, d, J = 11 Hz, N—CH—); 6.99-7.14 (5H, m, Ph); 7.50-7.95 (6H, m, 5-H Py + COC_6H_5); 8.18 (1H, d, J = 8 Hz, 4-Py); 8.67 (1H, s, 2-H, Py); 8.90 (1H, d, J = 6 Hz, 6-H Py); 9.11 (1H, s, N′—H). Found, %: C 60.0; H 5.3; N 4.0. $C_{35}H_{37}N_2O_{11}Cl$. Calculated, %: C 60.30; H 5.35; N 4.02.

1-Benzoyl-2-phenyl-6-(2′,6′-dimethyl-3′,5′-diethoxycarbonyl-1′,4′-dihydro-4′-pyridyl)indolizine (XI). We dissolved 0.3 g (0.0005 mole) of 1-(1-carboxylato-2-phenyl-3-benzoylpropyl)-3-(2′,6′-dimethyl-3′,5′-diethoxycarbonyl-1′,4′-dihydro-4′-pyridyl)pyridinium [compound (VIIIa)] by heating in 75 ml of benzene, and we added 0.11 g (0.001 mole) of

benzoquinone.The reaction mixture was boiled for 3 h. After cooling the precipitate was filtered off. The filtrate was washed three times with a 5% solution of sodium hydroxide and six times with water and dried over anhydrous sodium sulfate. The benzene was distilled, and the residue was applied to a column of silica gel. The product was eluted with a 1:1 mixture of hexane and ethyl acetate. We obtained 0.07 g (26% of the theoretical) of a greenish crystalline substance melting at 98-101°C (decomp.). PMR spectrum (deuterochloroform): 1.21 (6H, t, H = 7 Hz, 3',5'-CH_3); 2.29 (6H, s, 2',6'-CH_3); 4.05 (4H, q, J = 7 Hz, 3',5'-CH_2); 4.93 (1H, s, 4'-H); 6.57 (1H, bs, N'—H); 6.94-7.07 [10H, m, C_6H_5 + (β+γ)-H COC_6H_5 + 3-H + 7-H]; 7.43 (2H, dist. d, α-H COC_6H_5); 7.85 (1H, s, 5-H); 7.92 (1H, d, J = 7 Hz, 8-H). UV spectrum (ethanol), λ_{max} (log ε): 244 (4.65), 368 (4.26), 380 nm (4.24) sh. Found, %: C 72.2; H 6.0; N 4.2. $C_{34}H_{32}N_2O_5 \cdot H_2O$. Calculated, %: C 72.07; H 6.05; N 4.94.

1-Benzoyl-2-phenyl-6-(2',6'-dimethyl-3',5'-diethoxycarbonyl-4'-pyridyl)indolizine (XII). We dissolved 0.6 g (0.001 mole) of 1-(1-carboxylato-2-phenyl-3-benzoylpropyl)-3-(2',6'-dimethyl-3',5'-diethoxycarbonyl-1',4'-dihydro-4'-pyridyl)-pyridinium [compound (VIIIa)] by heating in 150 ml of benzene, and we added 0.86 g (0.0035 mole) of tetrachloroquinone. The reaction mixture was boiled for 6 h. After cooling the precipitate was filtered off. The filtrate was washed three times with 5% sodium hydroxide solution and six times with water and dried over anhydrous sodium sulfate. The benzene was distilled, and the residue was applied to a column of silica gel. The product was eluted with a 1:1 mixture of hexane and ethyl acetate. We obtained 0.1 g (18% of the theoretical) of a greyish crystalline substance melting at 153-155°C. PMR spectrum (deuterochloroform): 1.04 (6H, t, J = 7 Hz, 3',5'-CH_3); 2.60 (6H, s, 2',6'-CH_3); 4.08 (4H, q, J = 7 Hz, 3',5'-CH_2); 6.80-7.50 [12H, m, $(C_6H_5)_2$ + 3-H + 7-H]; 7.85 (1H, s, 5-H); 7.9 (1H, d, J = 8 Hz, 8-H). UV spectrum (ethanol), λ_{max} (log ε): 248 (4.60), 270 (4.34), 370 (4.20), 384 nm (4.13) sh. Found, %: C 74.2; H 5.5; N 5.1. $C_{34}H_{30}N_2O_5$. Calculated, %: C 74.71; H 5.53; N 5.12.

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