ISSN 1070-4280, Russian Journal of Organic Chemistry, 2011, Vol. 47, No. 4, pp. 581–588. © Pleiades Publishing, Ltd., 2011.
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Alkaloids of Siberia and Altai Flora: XVIII.* Alkyl 2-Acetylamino-5-[2-(pyridin-3-yl)vinyl]benzoates in the Synthesis of Indolizines Containing an Anthranilic Acid Ester Moiety

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Received June 1, 2010

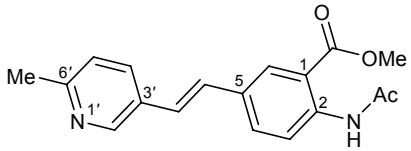
Abstract—Methyl 2-acetylamino-5-[2-(6-methylpyridin-3-yl)vinyl]benzoate reacted with phenacyl bromide to produce quaternary 1-(2-aryl-2-oxoethyl)-2-methyl-5-(4-acetylamino-3-methoxycarbonyl)pyridinium bromides. 1,3-Dipolar cycloaddition of the latter to methyl propynoate and dimethyl but-2-ynedioate gave the corresponding indolizine derivatives containing an anthranilic acid ester moiety. Reactions of acetylenes with *N*-phenacylpyridinium salts obtained from a diterpene alkaloid derivative, 2-(pyridin-3-yl)vinyl-substituted lappaconitine afforded analogous compounds in which the indolizine fragment is conjugated to the aromatic ring of the alkaloid. 1,3-Dipolar cycloaddition of 1-(2-aryl-2-oxoethyl)-2-methyl-5-(4-acetylamino-3-methoxycarbonyl)pyridinium bromides with methyl propynoate was regioselective.

DOI: 10.1134/S1070428011040191

Heterocyclic indolizine system is a structural fragment of a number of alkaloids exhibiting valuable biological activity [2]. In the recent years, synthetic approaches to substituted indolizines possessing a significant therapeutic potential have been extensively developed. 1-α-Ethoxycarbonyl-3-benzoylindolizines were found to act as efficient cardiovascular [3] and antiviral agents [4]. 1-Carbamoylmethylindolizines and 1-oxamoylindolizines were reported to inhibit secretory phospholipase A2 [5]. Functionalized indolizine derivatives are inhibitors of *MPtpA/MPtpB* phosphatases [6], testosterone 5α-reductase [7], and 15-lipoxygenase [8], and they possess antioxidant [9] and antibacterial activity [10]. Taking into account the above stated, we believed that development of methods for the synthesis of compounds possessing indolizine fragments and exhibiting selective biological activity is an important problem.

We were interested in synthesizing indolizines containing a 2-(4-amino-3-R-oxycarbonylphenyl)vinyl substituent (i.e., anthranilic acid ester residue), for heterocyclic derivatives of anthranilic acid are promising as niacin receptor agonists which can be used as therapeutic agents for the treatment of cardiovascular disorders [11]. Among natural anthranilic acid derivatives, some diterpene alkaloids have found application as efficient medical agents [12].

The goal of the present work was to synthesize pyridinium salts having a 2-(4-amino-3-R-oxycarbonyl-



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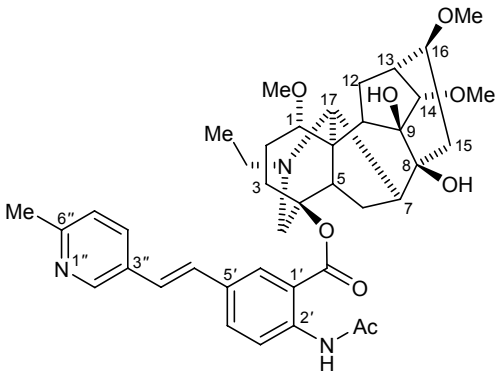
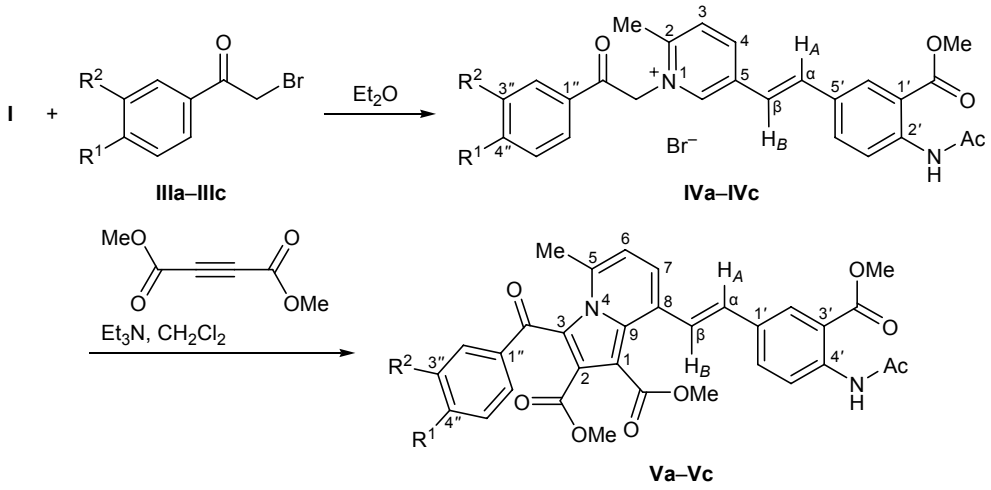


II

* For communication XVII, see [1].

Scheme 1.



$R^1 = R^2 = H$ (**a**); $R^1 = MeO$, $R^2 = H$ (**b**); $R^1 = R^2 = Cl$ (**c**).

phenyl)vinyl substituent and examine their behavior in reactions with carbonyl compounds of the acetylene series. As starting compounds we used methyl 2-acetylamino-5-[(6-methylpyridin-3-yl)vinyl]benzoate (**I**) and its structural analog containing a diterpene moiety in the ester fragment, lappaconitine derivative **II**. Compounds **I** and **II** were synthesized according to Heck from the corresponding iodo-substituted anthranilic acid esters and 5-vinyl-2-methylpyridine, following the procedure described in [13]. The antiarrhythmic activity of compounds **I** and **II** was reported previously [14].

Treatment of compound **I** with phenacyl bromides **IIIa**–**IIIc** in diethyl ether gave the corresponding pyridinium salts **IVa**–**IVc** in 68–71% yield (Scheme 1). 1-Phenacylpyridinium bromides thus obtained were brought into 1,3-dipolar cycloaddition reaction with dimethyl acetylenedicarboxylate in methylene chloride in the presence of triethylamine. As a result, we isolated 51–54% of substituted indolizines **Va**–**Vc** (Scheme 1). By varying conditions (reaction time after mixing the reactants from 10 min to 3 h and order of mixing of the reactants) of the reaction of pyridinium salt **IVa** with dimethyl acetylenedicarboxylate we found that the best results were obtained when a solution of triethylamine and dipolarophile in methylene chloride was gradually added to a solution of pyridinium salt **IVa** in the same solvent at room temperature, followed by keeping the reaction mixture for 1 h.

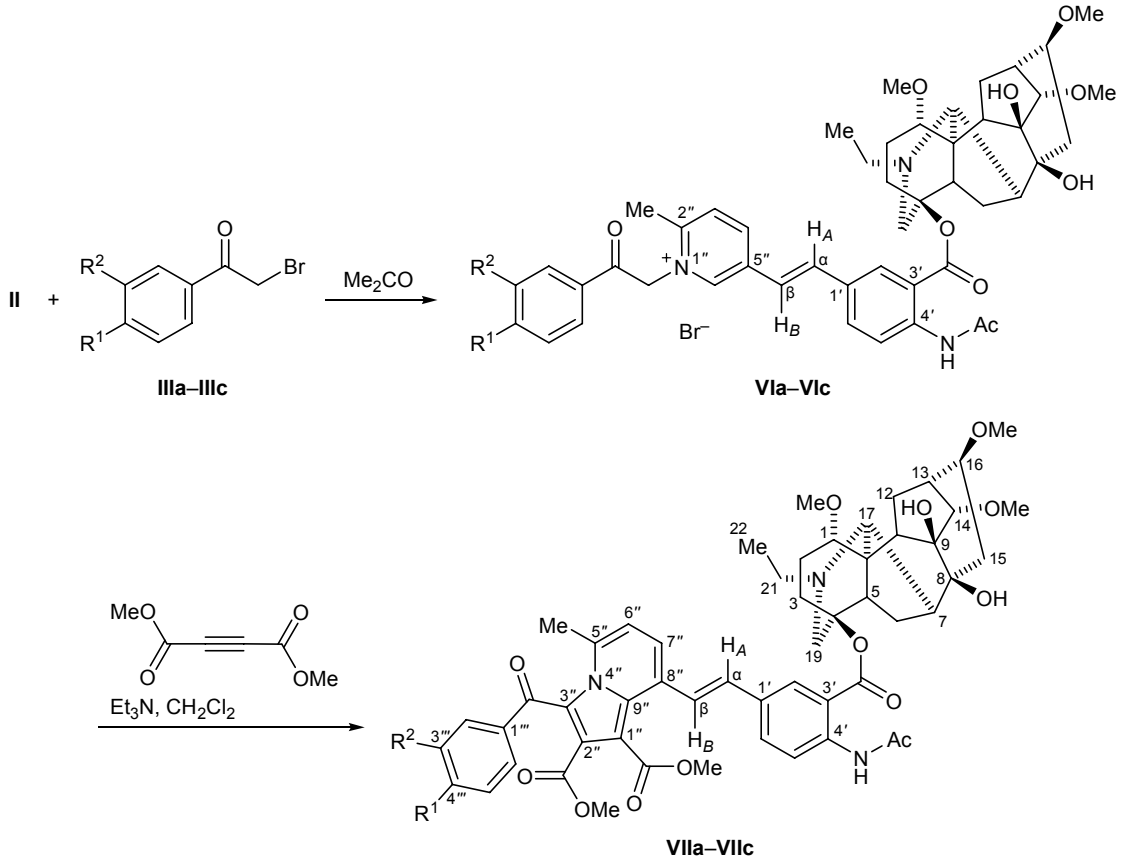
Compounds containing lappaconitine and indolizine fragments were synthesized by 1,3-dipolar cycloaddition of dimethyl acetylenedicarboxylate to pyridinium salts **VIa**–**VIc** which were obtained by alkylation of diterpene derivative **II** with phenacyl bromides **IIIa**–**IIIc** in acetone (yield 70–73%; Scheme 2). Pyridinium bromides **VIa**–**VIc** reacted with dimethyl acetylenedicarboxylate in the presence of triethylamine to produce indolizines **VIIa**–**VIIc** in 50–55% yield.

We found that 1,3-dipolar cycloaddition of unsymmetrical dipolarophile, methyl propynoate, to pyridinium salts **IVc** and **VIb** is regioselective. The reactions carried out according to the standard procedure led to the formation of methyl indolizine-1-carboxylates **VIII** and **IX** which were isolated in 54 and 49% yield, respectively (Scheme 3).

We can conclude that 1,3-dipolar cycloaddition of 1-phenacylpyridinium salts to acetylenic compounds may be regarded as a synthetic route to "hybrid" structures containing a diterpene alkaloid and indolizine fragments. Such indolizine–lappaconitine conjugates attract interest from the viewpoint of search for pharmacologically important metabolites of plant and marine origin, whose molecules contain different structural fragments, including alkaloid dimers [15].

The structure of the isolated compounds was determined on the basis of their spectral parameters and elemental compositions. Pyridinium bromides **IVa**–**IVc** and **VIa**–**VIc** were characterized by sharp melting points. In the ^{1}H NMR spectra of **IVa**–**IVc** and **VIa**–**VIc**, the 6-H proton in the pyridine ring appeared in a weaker field relative to that of initial compound **I** (δ 8.84 ppm for **IVb** against δ 8.53 ppm for **I** [13]), and protons in the phenacyl methylene group resonated as two doublets at δ 6.17 and 6.22 ppm (**IVb**). Indolizines **Va**–**Vc** and **VIIa**–**VIIc** displayed specific UV spectra.

Scheme 2.

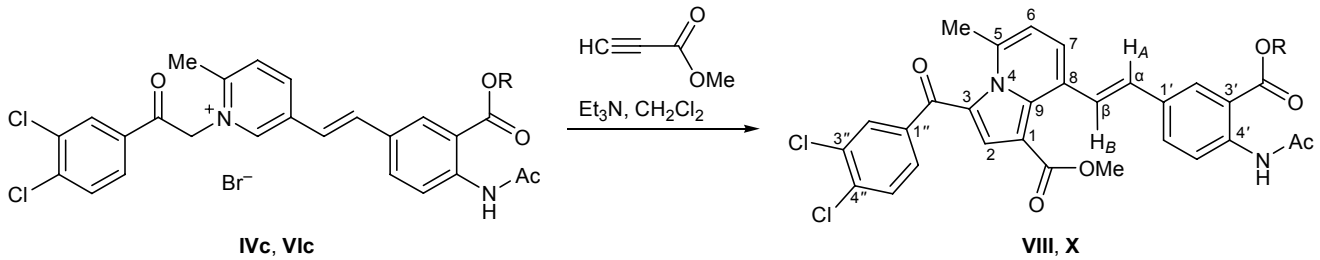


$R^1 = R^2 = H$ (**a**); $R^1 = MeO$, $R^2 = H$ (**b**); $R^1 = R^2 = Cl$ (**c**).

For example, the electronic absorption spectrum of **VIIb** contained strong absorption bands with their maxima at λ 228 (log ε 4.52), 262 (4.49), 302 (4.25), and 382 nm (4.03). The ^{1}H and ^{13}C NMR spectra of **V** and **VII** were fully consistent with their structure: we observed only one set of signals from the indolizine fragment and the corresponding substituents. In the ^{1}H NMR spectra of **VIIa**–**VIIc**, the 6-H and 7-H protons in the indolizine fragment resonated as doublets at δ 6.64–6.97 (6-H) and 7.21–7.67 ppm (7-H) with a coupling constant J of 8.0–8.2 Hz, which is typical of 1,3-dienes. The *E* configuration of the ethylene bridge in pyridinium salts **IVa**–**IVc** and **VIa**–**VIc**, as well as in indolizines **Va**–**Vc** and **VIIa**–**VIIc**, unambiguously followed from the ^{1}H NMR data. Protons at the double bond (H_A and H_B) gave rise to doublets with a coupling constant ^3J of 16.0–16.8 Hz, which indicated their *trans* orientation with respect to each other.

The structure of compounds **VIII** and **IX** was determined by analysis of their ^{1}H and ^{13}C NMR spectra, including two-dimensional 2D COSY and ^{1}H–^{13}C correlation spectra (COSY, COLOC). The 2-H and 2″-H

Scheme 3.



IVc, **VIII**, R = Me; **VIc**, **IX**, R = diterpene residue.

protons in the ^{1}H NMR spectra of **VIII** and **IX** resonated at δ 7.76–7.78 ppm. The ^{13}C NMR spectra of **VIII** and **IX** contained a singlet from C^1 (δ_C 107.51 and 107.37 ppm, respectively) and a doublet from C^2 (δ_C 131.81 and 131.93 ppm, respectively). The presence of three cross-peaks belonging to 2-H in the ^{1}H–^{13}C COLOC spectrum of **VIII** indicated its interaction with C^9 (δ_C 137.97 ppm) and two carbonyl carbon atoms: 1-C=O (δ_C 163.88 ppm) and 3-C=O (δ_C 185.35 ppm). These correlations correspond to the position of the methoxycarbonyl group on C^1. Analogous interactions were observed for the 2″-H proton in the ^{1}H–^{13}C COLOC spectrum of **IX**. The position of the ester group on C^1 also follows from the downfield shift of the doublet signal of H_B in the ^{1}H NMR spectra of **VIII** and **IX** as compared to 1,2-bis(methoxycarbonyl)-substituted indolizines **V** and **VII** and initial pyridine derivatives **I** and **II**. The H_B signal in the ^{1}H NMR spectra of pyridinium salts **IVa**–**IVc** is located at δ 7.24–7.46 ppm, in the spectra of **Va**–**Vc**, at δ 7.53–7.57 ppm, and in the spectra of **VIII** and **IX**, at δ 8.35–8.36 ppm.

The structure of compounds **VIII** and **IX** is consistent with the reaction mechanism shown in Scheme 4. Deprotonation of pyridinium salt **IVc** or **VIc** by the action of triethylamine gives resonance-stabilized pyridinium ylide **A** which reacts with methyl propynoate (as dipolar canonical structure **B**), and oxidative aromatization of cycloaddition product **C** yields final compound **VIII** or **IX**.

EXPERIMENTAL

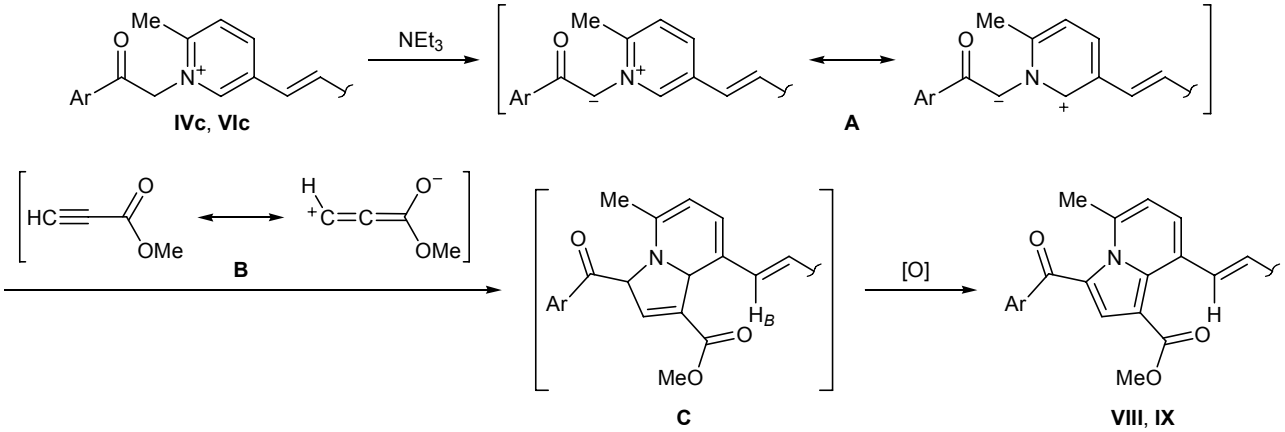
The NMR spectra were recorded on a Bruker AV-300 spectrometer at 300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C. The multiplicities of signals in the ^{13}C NMR spectra were determined using standard *J*-modulation technique (JMOD). The two-dimensional ^{1}H–^{1}H (COSY) and ^{13}C–^{1}H (COSY 125 Hz, COLOC 7 Hz) NMR spectra were obtained on a Bruker DRX-600 instrument (600.30 MHz for ^{1}H and 150.96 MHz for ^{13}C) using standard Bruker procedures. The IR spectra were measured in KBr on a Vector-22 spectrometer. The UV spectra were recorded from solutions in ethanol or chloroform on an HP 8453 UV-Vis spectrophotometer. The melting points were determined on a Kofler hot stage. The elemental compositions were determined on a Carlo Erba 1106 CHN analyzer.

The progress of reactions was monitored, and the purity of products was checked, by thin-layer chromatography on Silufol UV-254 plates using chloroform–ethanol (20:1) as eluent; spots were detected under UV light. The products were isolated by preparative thin-layer chromatography on silica gel containing 1% of K-35 luminophore (1-mm unfixed layer, 20×20 cm; chloroform–ethanol, 20:1).

Freshly distilled solvents and commercially available reagents of pure grade were used. 2-Acetylamino-5-[(*E*)-2-(6-methylpyridin-3-yl)vinyl]benzoates **I** and **II** were synthesized by the Heck reaction of methyl 5-iodo-2-(acetylamino)benzoate or 5′-iodolappaconitine with 5-vinyl-2-methylpyridine according to the procedure described in [13]. Compounds **VIa**–**VIc** and **VIIa**–**VIIc** were reported previously [16].

Pyridinium salts IVa–IVc (*general procedure***).** A solution of 310 mg (1 mmol) of compound **I** and 1.1 mmol of the corresponding phenacyl bromide **IIIa**–**IIIc** in 20 ml of anhydrous diethyl ether was stirred for 48 h at room temperature. The precipitate was filtered off, washed with anhydrous diethyl ether, and dried in air until constant weight.

Scheme 4.



(*E*)-5-[4-Acetylamino-3-(methoxycarbonyl)-styryl]-2-methyl-1-(2-oxo-2-phenylethyl)pyridinium bromide (IVa) was synthesized from 310 mg (1 mmol) of compound **I** and 220 mg (1.1 mmol) of ω-bromoacetophenone (**IIIa**). Yield 361 mg (71%), mp 245–247°C (decomp.). IR spectrum, ν, cm^{-1}: 3473, 3256, 3053, 3001, 2954, 1702, 1686, 1679, 1633, 1593, 1526, 1371, 1339, 1319, 1300, 1287, 1231, 1219, 1165, 1089, 1035, 998, 966, 942, 927, 849, 833, 795, 758, 704, 688, 572, 534. ^{1}H NMR spectrum (CD_3OD–$CDCl_3$, 1:1 by volume), δ, ppm: 2.12 s (3H, CH_3CO), 2.62 s (3H, 2-CH_3), 3.93 s (3H, 3′-$COOCH_3$), 6.38 d and 6.52 d (1H each, CH_2N^+, J = 14.2 Hz), 7.18 d (1H, H_A, J = 16.3 Hz), 7.46 d (1H, H_B, J = 16.3 Hz), 7.58–7.64 m (2H, 3″-H, 5″-H), 7.73 m (1H, 4″-H), 7.81 d.d (1H, 6′-H, J = 7.8, 2.0 Hz), 8.01 d (1H, 3-H, J = 8.2 Hz), 8.03–8.08 m (2H, 2″-H, 6″-H), 8.11 d (1H, 2′-H, J = 2.0 Hz), 8.36 d (1H, 5′-H, J = 7.8 Hz), 8.66 d.d (1H, 4-H, J = 8.2, 2.2 Hz), 9.03 d (1H, 6-H, J = 2.2 Hz), 10.75 br.s (1H, NHCO). ^{13}C NMR spectrum (CD_3OD–$CDCl_3$, 1:1 by volume), δ_C, ppm: 19.92 q (2-CH_3), 25.30 q (**C**H_3CO), 53.10 q (OCH_3), 64.33 t (CH_2), 117.34 s ($C^{3'}$), 121.08 d (C_β), 121.56 d ($C^{5'}$), 128.96 d ($C^{2''}$, $C^{6''}$), 129.66 d ($C^{3''}$, $C^{5''}$), 130.31 d ($C^{2'}$), 130.66 s ($C^{1'}$), 132.12 d (C_α), 132.56 d ($C^{6'}$), 133.68 s ($C^{1''}$), 134.02 d ($C^{4''}$), 135.60 d (C^4), 135.84 s (C^5), 141.02 s ($C^{4'}$), 142.59 d (C^3), 144.51 d (C^6), 154.44 s (C^2), 168.06 s (3′-CO), 169.68 s (NHCO), 190.70 s (C=O). Found, %: C 60.88; H 4.72; Br 16.01; N 5.60. $C_{26}H_{25}BrN_2O_4$. Calculated, %: C 61.30; H 4.91; Br 15.72; N 5.50.

(*E*)-5-[4-Acetylamino-3-(methoxycarbonyl)-styryl]-1-[2-(4-methoxyphenyl)-2-oxoethyl]-2-methylpyridinium bromide (IVb) was synthesized from 310 mg (1 mmol) of compound **I** and 252 mg (1.1 mmol) of 2-bromo-1-(4-methoxyphenyl)ethanone (**IIIb**). Yield 367 mg (68%), mp 232–235°C (decomp.). IR spectrum, ν, cm^{-1}: 3435, 3263, 3037, 3000, 2953, 1701, 1679, 1634, 1600, 1524, 1368, 1342, 1284, 1242, 1172, 1120, 1090, 1015, 974, 836, 795, 755, 695, 669, 632, 572, 530. ^{1}H NMR spectrum (CD_3OD–$CDCl_3$, 1:1 by volume), δ, ppm: 2.00 s (3H, CH_3CO), 2.45 s (3H, 2-CH_3), 3.68 s (3H, 3′-$COCH_3$), 3.73 s (3H, 4″-OCH_3), 6.17 d and 6.22 d (1H each, CH_2N^+, J = 14.2 Hz), 6.81 br.d (2H, 3″-H, 5″-H, J = 8.2 Hz), 6.90 d (1H, H_A, J = 16.3 Hz), 7.24 d (1H, H_B, J = 16.3 Hz), 7.53 d.d (1H, 6′-H, J = 8.0, 2.2 Hz), 7.66 d (1H, 3-H, J = 8.4 Hz), 7.87 d (2H, 2″-H, 6″-H, J = 8.2 Hz), 8.00 d (1H, 2′-H, J = 2.2 Hz), 8.32 d.d (1H, 4-H, J = 8.4, 2.0 Hz), 8.39 d (1H, 5′-H, J = 8.0 Hz), 8.84 d (1H, 6-H, J = 2.0 Hz), 10.88 br.s (1H, NHCO). ^{13}C NMR spectrum (CD_3OD–$CDCl_3$, 1:1 by volume), δ_C, ppm: 20.16 q (2-CH_3), 25.30 q (**C**H_3CO), 52.99 q (**C**H_3OCO), 56.07 q (4″-OCH_3), 64.64 t (CH_2), 115.01 d ($C^{3''}$, $C^{5''}$), 116.21 s ($C^{3'}$), 120.50 d (C_β), 121.19 d ($C^{5'}$), 126.58 s ($C^{1'}$), 130.22 d ($C^{2'}$), 130.65 s ($C^{1''}$), 130.75 d (C_α), 131.70 d ($C^{2''}$, $C^{6''}$), 133.22 d ($C^{6'}$), 134.98 d (C^4), 136.74 s (C^5), 141.93 s ($C^{4'}$), 142.32 d (C^3), 144.79 d (C^6), 154.21 s (C^2), 165.89 s ($C^{4''}$), 168.67 s (3′-**C**$OOCH_3$), 170.40 s (NHCO), 188.38 s (C=O). Found, %: C 59.87; H 4.93; Br 15.38; N 6.25. $C_{27}H_{27}BrN_2O_5$. Calculated, %: C 60.11; H 5.01; Br 14.84; N 5.69.

(*E*)-5-[4-Acetylamino-3-(methoxycarbonyl)-styryl]-1-[2-(3,4-dichlorophenyl)-2-oxoethyl]-2-methylpyridinium bromide (IVc) was synthesized from 310 mg (1 mmol) of compound **I** and 294 mg (1.1 mmol) of 2-bromo-1-(3,4-dichlorophenyl)ethanone (**IIIc**). Yield 410 mg (71%), mp 238–240°C (decomp.). IR spectrum, ν, cm^{-1}: 3413, 3267, 3224, 3059, 2997, 2954, 1704, 1639, 1587, 1557, 1520, 1441, 1412, 1379, 1349, 1304, 1283, 1233, 1213, 1155, 1089, 1032, 1009, 993, 968, 882, 848, 821, 795, 781, 747, 697, 675, 605, 575, 536. ^{1}H NMR spectrum (CD_3OD–$CDCl_3$, 1:1 by volume), δ, ppm: 2.03 s (3H, CH_3CO), 2.54 s (3H, 2-CH_3), 3.81 s (3H, 3′-$COOCH_3$), 6.44 d and 6.52 d (1H each, CH_2N^+, J = 14.2 Hz), 7.00 d (1H, H_A, J = 16.2 Hz), 7.30 d (1H, H_B, J = 16.2 Hz), 7.53 d (1H, 5″-H, J = 7.6 Hz), 7.60 d.d (1H, 6′-H, J = 7.8, 1.8 Hz), 7.73 d (1H, 3-H, J = 7.6 Hz), 7.95 d.d (1H, 6″-H, J = 7.6, 2.0 Hz), 8.04 d (1H, 2″-H, J = 2.0 Hz), 8.09 d (1H, 2′-H, J = 1.8 Hz), 8.34 d.d (1H, 4-H, J = 7.6, 2.0 Hz), 8.47 d (1H, 5′-H, J = 7.8 Hz), 9.07 d (1H, 6-H, J = 2.0 Hz), 11.00 br.s (1H, NHCO). ^{13}C NMR spectrum (CD_3OD–$CDCl_3$, 1:1 by volume), δ_C, ppm: 20.32 q (2-CH_3), 25.59 q (**C**H_3CO), 53.01 q (**C**H_3OCO), 64.48 t (CH_2), 116.02 s ($C^{3'}$), 120.26 d (C_β), 121.19 d ($C^{5'}$), 127.58 d ($C^{6''}$), 129.07 s ($C^{1'}$), 129.36 d ($C^{2'}$), 129.65 d (C_α), 129.91 d ($C^{2''}$), 130.94 d ($C^{5''}$), 131.20 s ($C^{1''}$), 132.34 d ($C^{6'}$), 133.82 s ($C^{3''}$), 135.60 d (C^4), 135.84 s (C^5), 138.08 s ($C^{4''}$), 141.02 s ($C^{4'}$), 142.28 d (C^3), 143.89 d (C^6), 154.04 s (C^2), 168.70 s (3′-CO), 170.28 s (NHCO), 188.72 s (C=O). Found, %: Br 13.61; Cl 11.96; N 4.57. $C_{26}H_{23}BrCl_2N_2O_4$. Calculated, %: Br 13.84; Cl 12.28; N 4.84.

Indolizines Va–Vc (*general procedure***).** A solution of 1.1 equiv of dimethyl acetylenedicarboxylate and 1 equiv of triethylamine in 10 ml of anhydrous methylene chloride was added dropwise over a period of 10 min to a solution of pyridinium bromide **IVa–IVc**

in 10 ml of anhydrous methylene chloride. The dark red solution was stirred for 1 h at room temperature, treated with aqueous ammonia to pH ~11, stirred for 10 min, treated with 10% sulfuric acid to pH ≈ 3, stirred for 10 min, and treated again with aqueous ammonia to pH ≈ 11. The organic phase was separated and dried over $MgSO_4$, the solvent was distilled off, and the residue was subjected to chromatography on silica gel using chloroform–ethanol as eluent. A yellow–orange fraction (with bright luminescence under UV light) was separated, and the product was washed off from the sorbent with ethanol. The solvent was distilled off, and the residue (a brown–red powder) was dried under reduced pressure until constant weight.

Dimethyl 8-[(*E*)-4-acetylamino-3-(methoxycarbonyl)styryl]-3-benzoyl-5-methylindolizine-1,2-dicarboxylate (Va) was synthesized from 200 mg (0.39 mmol) of pyridinium salt **IVa** and 62 mg (0.43 mmol) of dimethyl acetylenedicarboxylate. Yield 120 mg (54%), mp 143–146°C. IR spectrum, ν, cm^{-1}: 3432, 3316, 3266, 2952, 1705, 1643, 1589, 1519, 1377, 1294, 1233, 1089, 1062, 1001, 957, 915, 836, 790, 751, 728, 693, 645, 584. UV spectrum (chloroform), λ_{max}, nm (log ε): 260 (4.37), 302 (4.19), 380 (3.69). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.22 s (3H, CH_3CO), 2.31 s (3H, 5-CH_3), 3.36 s and 3.83 s (3H each, 1-$COOCH_3$, 2-$COOCH_3$), 3.92 s (3H, 3′-$COOCH_3$), 6.65 d (1H, 6-H, *J* = 8.2 Hz), 6.96 d (1H, H_A, *J* = 16.5 Hz), 7.22 d (1H, 7-H, *J* = 8.2 Hz), 7.42–7.50 m (2H, 3″-H, 5″-H), 7.53 d (1H, H_B, *J* = 16.5 Hz), 7.52–7.58 m (1H, 4″-H), 7.69 d.d (1H, 6′-H, *J* = 7.4, 2.2 Hz), 7.82–7.89 m (2H, 2″-H, 6″-H), 8.15 d (1H, 2′-H, *J* = 2.2 Hz), 8.71 d (1H, 5′-H, *J* = 7.4 Hz), 11.03 br.s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 22.52 q (5-CH_3), 25.35 q (NHCO**C**H_3), 51.81 q (1-COO**C**H_3), 52.30 q (2-COO**C**H_3), 52.40 q (3′-COO**C**H_3), 107.31 s (C^1), 114.90 s ($C^{3'}$), 115.85 d (C^6), 120.51 d ($C^{5'}$), 120.75 d (C^7), 123.46 s (C^2), 123.55 s ($C^{1'}$), 124.07 d (C^β), 128.13 s (C^8), 128.48 d ($C^{3''}$, $C^{5''}$), 128.98 d ($C^{2'}$), 129.38 d ($C^{2''}$, $C^{6''}$), 129.95 d (C^α), 131.32 s ($C^{1''}$), 132.28 d ($C^{6'}$), 133.10 s (C^9), 133.30 d ($C^{4''}$), 135.34 s (C^5), 138.66 s (C^3), 140.97 s ($C^{4'}$), 163.97 s and 166.20 s (1-CO, 2-CO), 168.40 s (3′-CO), 168.83 s (NHCO), 188.01 s (3-C=O). Found, %: C 67.24; H 4.71; N 4.64. $C_{32}H_{28}N_2O_8$. Calculated, %: C 67.60; H 4.96; N 4.93.

Dimethyl 8-[(*E*)-4-acetylamino-3-(methoxycarbonyl)styryl]-3-(4-methoxybenzoyl)-5-methylindolizine-1,2-dicarboxylate (Vb) was synthesized from 190 mg (0.35 mmol) of pyridinium salt **IVb** and 55 mg (0.39 mmol) of dimethyl acetylenedicarboxylate. Yield 107 mg (51%), mp 136–138°C. IR spectrum, ν, cm^{-1}: 3436, 3309, 2953, 2845, 1703, 1597, 1515, 1372, 1293, 1238, 1168, 1089, 1062, 1025, 955, 921, 835, 789, 758, 661, 620, 583. UV spectrum (ethanol), λ_{max}, nm (log ε): 228 (4.52), 262 (4.49), 302 (4.25), 382 (4.03). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.25 s (3H, NHCOC**H**$_3$), 2.35 s (3H, 5-CH_3), 3.48 s and 3.86 s (3H each, 1-$COOCH_3$, 2-$COOCH_3$), 3.89 s (3H, 4″-OCH_3), 3.96 s (3H, 3′-$COOCH_3$), 6.64 d (1H, 6-H, *J* = 8.2 Hz), 6.93 d (2H, 3″-H, 5″-H, *J* = 7.6 Hz), 6.99 d (1H, H_A, *J* = 16.2 Hz), 7.21 d (1H, 7-H, *J* = 8.2 Hz), 7.57 d (1H, H_B, *J* = 16.2 Hz), 7.73 d.d (1H, 6′-H, *J* = 7.5, 2.0 Hz), 7.85 d (2H, 2″-H, 6″-H, *J* = 7.6 Hz), 8.18 d (1H, 2′-H, *J* = 2.0 Hz), 8.74 d (1H, 5′-H, *J* = 7.5 Hz), 11.06 br.s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 22.16 q (5-CH_3), 25.36 q (NHCO**C**H_3), 51.81 q (1-COO**C**H_3), 52.30 q (2-$COOCH_3$), 52.40 q (3′-$COOCH_3$), 55.44 q (4″-OCH_3), 107.23 s (C^1), 113.82 d ($C^{3''}$, $C^{5''}$), 114.95 s ($C^{3'}$), 115.51 d (C^6), 120.30 d (C^7), 120.56 d ($C^{5'}$), 122.38 s (C^2), 124.16 d (C^β), 124.34 s ($C^{1'}$), 128.16 s (C^8), 128.97 d ($C^{2'}$), 129.91 d (C^α), 131.39 s (C^3), 131.92 s (C^9), 131.96 d ($C^{6'}$), 132.32 d ($C^{2''}$, $C^{6''}$), 132.66 s ($C^{1''}$), 135.18 s (C^5), 140.97 s ($C^{4'}$), 163.83 s ($C^{4''}$), 164.02 s and 166.47 s (1-CO, 2-CO), 168.45 s (3′-CO), 168.85 s (NHCO), 187.20 s (3-C=O). Found, %: C 65.88; H 5.15; N 4.46. $C_{33}H_{30}N_2O_9$. Calculated, %: C 66.21; H 5.05; N 4.68.

(*E*)-Dimethyl 8-[4-acetylamino-3-(methoxycarbonyl)styryl]-3-(3,4-dichloroobenzoyl)-5-methylindolizine-1,2-dicarboxylate (Vc) was synthesized from 230 mg (0.4 mmol) of salt **IVc** and 63 mg (0.44 mmol) of dimethyl acetylenedicarboxylate. Yield 138 mg (54%), mp 151–154°C. IR spectrum, ν, cm^{-1}: 3430, 2953, 1724, 1699, 1590, 937, 956, 999, 1030, 1062, 1095, 1159, 1221, 1261, 1292, 1384, 1523, 832, 788, 767, 681, 587, 553. UV spectrum (chloroform), λ_{max}, nm (log ε): 260 (4.34), 303 (4.09), 380 (3.09). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.26 s (3H, NHCOC**H**$_3$), 2.32 s (3H, 5-CH_3), 3.52 s and 3.86 s (3H each, 1-$COOCH_3$, 2-$COOCH_3$), 3.97 s (3H, 3′-$COOCH_3$), 6.73 d (1H, 6-H, *J* = 8.0 Hz), 6.96 d (1H, H_A, *J* = 16.6 Hz), 7.31 d (1H, 7-H, *J* = 8.0 Hz), 7.53 d (1H, H_B, *J* = 16.6 Hz), 7.56 d (1H, 5″-H, *J* = 7.8 Hz), 7.72 d.d (1H, 6″-H, *J* = 7.8, 2.3 Hz), 7.74 d.d (1H, 6′-H, *J* = 7.5, 2.0 Hz), 8.05 d (1H, 2″-H, *J* = 2.3 Hz), 8.18 d (1H, 2′-H, *J* = 2.0 Hz), 8.73 d (1H, 5′-H, *J* = 7.5 Hz), 11.09 br.s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 22.73 q (5-CH_3), 25.38 q (NHCO**C**H_3), 52.05 q (1-COO**C**H_3), 52.34 q (2-COO**C**H_3), 52.52 q

(3′-COO**C**H$_3$), 107.73 s (C^1), 115.01 s (C$^{3'}$), 116.35 d (C^6), 120.63 d (C$^{5'}$), 121.28 d (C^7), 122.78 s (C^2), 123.88 d (C$^\beta$), 123.90 s (C$^{1'}$), 128.44 s (C^8), 128.62 d (C$^{2'}$), 129.08 d (C$^{6''}$), 130.39 d (C$^\alpha$), 130.65 d (C$^{5''}$), 131.13 d (C$^{2''}$), 131.28 s (C^3), 132.34 d (C$^{6'}$), 133.32 s (C$^{1''}$), 133.57 s (C$^{3''}$), 135.33 s (C^5), 137.97 s (C^9), 138.32 s (C$^{4''}$), 141.11 s (C$^{4'}$), 163.88 s and 166.08 s (1-CO, 2-CO), 168.53 s (3′-CO), 168.94 s (NHCO), 185.35 s (3-CO). Found, %: C 59.85; H 4.20; Cl 10.88; N 3.83. $C_{32}H_{26}Cl_2N_2O_8$. Calculated, %: C 60.29; H 4.11; Cl 11.12; N 4.39.

(*E*)-Methyl 8-[4-acetylamino-3-(methoxycarbonyl)styryl]-3-(3,4-dichlorobenzoyl)-5-methylindolizine-1-carboxylate (VIII). A solution of 62 mg (0.432 mmol) of methyl propynoate and 40 mg (0.393 mmol) of triethylamine in 10 ml of methylene chloride was added dropwise over a period of 10 min to a solution of 509 mg (0.393 mmol) of pyridinium salt **IVc** in 10 ml of methylene chloride. The dark red solution was stirred for 1 h and treated in succession with aqueous ammonia, 10% sulfuric acid, and aqueous ammonia again. The organic phase was separated and dried over magnesium sulfate, and the product was isolated by chromatography. Yield 120 mg (54%), bright yellow powder. An analytical sample was obtained by additional purification by TLC, mp 173–175°C. IR spectrum, ν, cm^{-1}: 3435, 2955, 1727, 1699, 1591, 1530, 1387, 1295, 1260, 1227, 1153, 1091, 1065, 1030, 1013, 958, 937, 835, 790, 761, 689, 583. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.24 s (3H, NHCOC**H**$_3$), 2.55 s (3H, 5-CH$_3$), 3.83 s (3H, 1-COOCH$_3$), 3.95 s (3H, 3′-COOCH$_3$), 6.94 d (1H, H$_A$, *J* = 16.2 Hz), 6.97 d (1H, 6-H, *J* = 8.0 Hz), 7.60 d (1H, 5″-H, *J* = 7.0 Hz), 7.67 d (1H, 7-H, *J* = 8.0 Hz), 7.78 s (1H, 2-H), 7.83 d.d (1H, 6′-H, *J* = 7.5, 2.3 Hz), 7.87 d.d (1H, 6″-H, *J* = 7.0, 2.0 Hz), 8.11 d (1H, 2″-H, *J* = 2.0 Hz), 8.21 d (1H, 2′-H, *J* = 2.3 Hz), 8.35 d (1H, H$_B$, *J* = 16.2 Hz), 8.74 d (1H, 5′-H, *J* = 7.5 Hz), 11.05 br.s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ$_C$, ppm: 23.35 q (5-CH$_3$), 25.44 q (NHCO**C**H$_3$), 51.71 q (1-COO**C**H$_3$), 52.31 q (3′-COO**C**H$_3$), 107.37 s (C^1), 114.86 s (C$^{3'}$), 117.38 d (C^6), 120.60 d (C$^{5'}$), 124.13 s (C$^{1'}$), 125.19 d (C^7), 126.55 d (C$^\beta$), 128.11 s (C^8), 128.84 d (C$^\alpha$), 129.07 d (C$^{6''}$), 129.35 d (C$^{2'}$), 130.47 d (C$^{5''}$), 131.78 d (C$^{2''}$), 131.81 d (C^2), 131.88 s (C$^{3''}$), 132.33 d (C$^{6'}$), 133.01 s (C$^{4''}$), 137.04 s (C$^{1''}$), 138.07 s (C^3), 138.77 s (C^5), 139.49 s (C^9), 140.85 s (C$^{4'}$), 162.27 s (1-CO), 168.59 s (3′-CO), 168.86 s (NHCO), 179.58 s (3-CO). Found, %: C 61.66; H 4.24; Cl 12.25; N 4.44. $C_{30}H_{24}Cl_2N_2O_6$. Calculated, %: C 62.18; H 4.14; Cl 12.24; N 4.84.

Methyl 8-{(*E*)-4-acetylamino-3-[(8,9-dihydroxy-1α,14α,16β-trimethoxy-20-ethylaconitan-4β-yl)oxycarbonyl]styryl}-3-(3,4-dichlorobenzoyl)-5-methylindolizine-1-carboxylate (IX). A solution of 20 mg (0.23 mmol) of methyl propynoate and 22 mg (0.21 mmol) of triethylamine in 10 ml of methylene chloride was added dropwise over a period of 10 min to a solution of 200 mg (0.21 mmol) of pyridinium salt **VIc** (prepared as described in [16]) in 10 ml of methylene chloride. The dark red solution was stirred for 1 h and treated in succession with aqueous ammonia, 10% sulfuric acid, and aqueous ammonia again. The organic phase was separated and dried over magnesium sulfate, and the product was purified by chromatography. Yield 98 mg (49%), yellow powder, mp 126–128°C. IR spectrum, ν, cm^{-1}: 3403, 2962, 2819, 1705, 1634, 1587, 1553, 1515, 1368, 1330, 1264, 1212, 1117, 1089, 1032, 967, 915, 792, 765, 752, 676. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.12 t (3H, 22-H, *J* = 7.2 Hz), 1.52 br.s (2H, OH, *w*/2 = 18.0 Hz), 1.62 d.d (1H, 6-H, *J* = 15.0, 8.2 Hz), 1.83 m (1H, 3-H, ^2J = 13.2 Hz), 1.97–2.10 m (2H, 12-H, 15-H), 2.08 d.d (1H, 10-H, *J* = 11.6, 4.2 Hz), 2.13–2.23 m (3H, 2-H, 7-H, 12-H), 2.23 s (3H, NHCOC**H**$_3$), 2.29–2.41 m (2H, 13-H, 15-H), 2.46 d.d (1H, 2-H, *J* = 14.8, 2.6 Hz), 2.48–2.60 m (4H, 5-H, 19-H, 21-H), 2.55 s (3H, 5″-CH$_3$), 2.60 m (1H, 3-H, ^2J = 13.2 Hz), 2.72 d.d (1H, 6-H, *J* = 15.0, 6.2 Hz), 3.00 s (1H, 17-H), 3.18 d.d (1H, 1-H, *J* = 9.9, 6.4 Hz), 3.28 s (3H, 1-OCH$_3$), 3.29 s (3H, 16-OCH$_3$), 3.30 m (1H, 16-H), 3.39 s (3H, 14-OCH$_3$), 3.42 d (1H, 14-H, *J* = 5.0 Hz), 3.60 d (1H, 19-H, *J* = 11.5 Hz), 3.82 s (3H, 1″-COOCH$_3$), 6.94 d (1H, 6″-H, *J* = 8.0 Hz), 6.97 d (1H, H$_A$, *J* = 16.8 Hz), 7.60 d (1H, 5‴-H, *J* = 7.2 Hz), 7.72 d (1H, 7″-H, *J* = 8.0 Hz), 7.76 br.s (1H, 2″-H), 7.86 d.d (1H, 6‴-H, *J* = 7.2, 2.2 Hz), 7.89 d.d (1H, 6′-H, *J* = 8.0, 2.4 Hz), 7.98 (1H, 2‴-H, *J* = 2.2 Hz), 8.12 d (1H, 2′-H, *J* = 2.4 Hz), 8.36 d (1H, H$_B$, *J* = 16.8 Hz), 8.72 (1H, 5-H, *J* = 8.0 Hz), 11.04 br.s (1H, 2′-NH). ^{13}C NMR spectrum ($CDCl_3$), δ$_C$, ppm: 13.48 q (C^{22}), 23.34 q (5″-CH$_3$), 24.10 t (C^6), 25.50 q (NHCO**C**H$_3$), 26.17 t (C^{12}), 26.76 t (C^2), 31.82 t (C^3), 36.29 d (C^{13}), 44.79 t (C^{15}), 47.56 d (C^7), 48.51 d (C^5), 48.89 t (C^{21}), 49.85 d (C^{10}), 50.98 s (C^{11}), 51.82 q (1″-COO**C**H$_3$), 55.48 t (C^{19}), 56.05 q (16-OCH$_3$), 56.44 q (1-OCH$_3$), 57.85 q (14-OCH$_3$), 61.43 d (C^{17}), 75.61 s (C^8), 78.53 s (C^9), 82.83 d (C^{16}), 84.11 s (C^4), 84.83 d (C^1), 90.10 d (C^{14}), 107.51 s (C$^{1''}$), 115.86 s (C$^{3'}$), 117.40 d (C$^{6''}$), 120.70 d (C$^{5'}$), 124.10 s (C$^{1'}$), 125.01 d (C$^{7''}$), 126.43 d (C$^\beta$), 128.26 s (C$^{8''}$), 129.10 d and 129.18 d (C$^{6'''}$, C$^\alpha$), 130.06 d (C$^{2'}$), 130.46 d (C$^{5'''}$), 131.46 d (C$^{6'}$), 131.77 s (C$^{3''}$), 131.86 d (C$^{2'''}$), 131.93 d

($C^{2''}$), 133.88 s ($C^{3'''}$), 136.99 s ($C^{4'''}$), 138.19 s ($C^{1'''}$), 138.74 s ($C^{5''}$), 139.53 s ($C^{9''}$), 141.02 s ($C^{4'}$), 164.26 s ($C^{1''}$-$COOCH_3$), 167.29 s (3′-CO), 168.83 s (NHCO), 179.56 s (3″-C=O). Found, %: C 63.96; H 5.64; Cl 7.36; N 4.04. $C_{52}H_{57}Cl_2N_3O_{11}$. Calculated, %: C 64.32; H 5.88; Cl 7.32; N 4.33.

This study was performed under financial support by the Russian Foundation for Basic Research (project nos. 08-03-00340, 09-03-00183).

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