Synthesis of azecino[5,4-*b*]indoles and indolo[3,2-*e*][2]benzazonines *via* tandem transformation of hydrogenated indoloquinolizines and indolizines

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The reactions of partially hydrogenated indole-fused quinolizines and indolizines with activated alkynes in methanol, acetonitrile, and dichloromethane were studied. The reactions were shown to be accompanied by the cleavage of the bridging C—N bond. Azecino[5,4-*b*]-indole and indolo[3,2-*e*][2]benzazonine derivatives were synthesized.

Key words: azecino[5,4-*b*]indoles, indolo[3,2-*e*][2]benzazonines, domino reactions, alkynes, hydrogenated indolizines and quinolizines, eburnamenine.

Medium-sized nitrogen-containing heterocyclic compounds are contained in some alkaloids exhibiting high and diverse biological activity. Some of these alkaloids are used in the medical practice. In the first place, let us mention the alkaloids Vincamine and Vinblastine used in the cancer treatment. Although medium-sized heterocycles are of considerable interest to pharmacologists, these compounds are poorly studied. This is primarily associated with the fact that their synthesis from acyclic precursors is, in most cases, a difficult problem. An approach involving transformations of nitrogen-bridged bicyclic systems is tempting and interesting. This approach is based on the quaternization of the nitrogen atom in this class of compounds followed by the cleavage of quaternary salts with bases. Sodium amide in liquid ammonia is very often used for this purpose. Relatively drastic conditions of the cleavage limit the synthetic potential of these reactions. Previously, we have discovered[1] the tandem transformations of (hetero)annulated tetrahydropyridines by the action of electron-deficient alkynes. This is an example of anionic domino reactions involving the Michaelis addition as the first step.[2] In recent years, domino reactions grew in popularity primarily because they do not necessitate the isolation of intermediates that are formed in multistep reactions accompanied by the formation of new chemical bonds.

The tandem transformations of tetrahydropyridines and tetrahydroazepines fused to an aromatic or heteroaromatic moiety, which we performed by the action of activated alkynes, is an efficient and fairly versatile method for the construction of fused azocines bearing the enamine moiety in the azocine ring.[3] The reaction of tetrahydro-β-carbolines substituted at position 1 with ethyl propiolate in acetonitrile resulted in the formation of azocino[5,4-*b*]indoles *via* the tetrahydropyridine ring expansion. In methanol, the reaction affords not only azocinoindoles but also products of the tetrahydropyridine ring cleavage, *viz.*, 2-methoxyalkyl-3-(ethoxycarbonylvinyl-R-amino)ethylindoles.[4] The reactions of alkynes with hexahydroazepino[4,3-*b*]- and hexahydroazepino-[3,4-*b*]indoles both in methanol and acetonitrile produce hexahydroazonino[5,6-*b*]indoles isomeric with respect to the position of the enamine moiety in high yields.[5] Nitrogen-bridged heterocyclic systems, such as fused quinolizines and indolizines, have been not studied in tandem transformation reactions. Heterocycles of this type are contained in a series of alkaloids.[6,7] Hydrogenated quinolizines and indolizines are used to synthesize azonines and azecines fused to aromatic and heteroaromatic rings.[8—10] For this purpose, quinolizines and indolizines are transformed into quaternary ammonium salts followed by the reductive cleavage of the bridging C—N bond by the action of sodium in liquid ammonia to form medium-sized nine- and ten-membered azaheterocycles.

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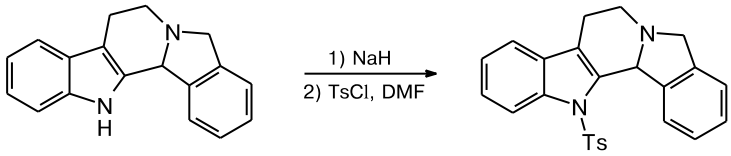
In the present work, we report the results of the study of the reaction of alkynes with tetrahydrobenzo[1,2]-indolizino[8,7-*b*]indole **1** and its *N*-tosyl derivative **2**, as well as with alkaloids 14-hydroxy-14,15-dihydroeburnamenine (Vincamine) **3** and eburnamenine (Vinpocetine) **4** and their derivatives **5** and **6**, respectively. Thus, tandem transformations of tetrahydropyridines by the action of alkynes start with the quaternization of the sp^3-hybridized nitrogen atom, whereas the reactions of compounds **1**—**5** *a priori* would be expected to result in the tetrahydropyridine ring expansion to form the azocine moiety and the cleavage of the bridging C—N bond to give fused azonines and azecines.[9]

Fused indolizine **1** was synthesized according to a known procedure[9] starting from tryptamine and 2-formylbenzoic acid. Compound **1** was transformed into *N*-tosyl derivative **2** by the successive action of sodium hydride and tosyl chloride (Scheme 1).

Alkaloids **3** and **4** are commercial products. The reduction of the ester group in eburnamenine **4** afforded hydroxymethyl derivative **5**, and its acetylation gave acetate **6** (Scheme 2).

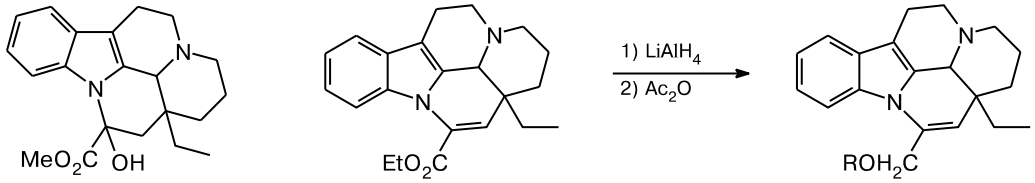
Indolizinoindole **1** reacts with methyl propiolate in acetonitrile to form a multicomponent mixture, from which Stevens rearrangement product **7** was isolated by column chromatography in ~4% yield (Scheme 3).

Scheme 1



1 **2**

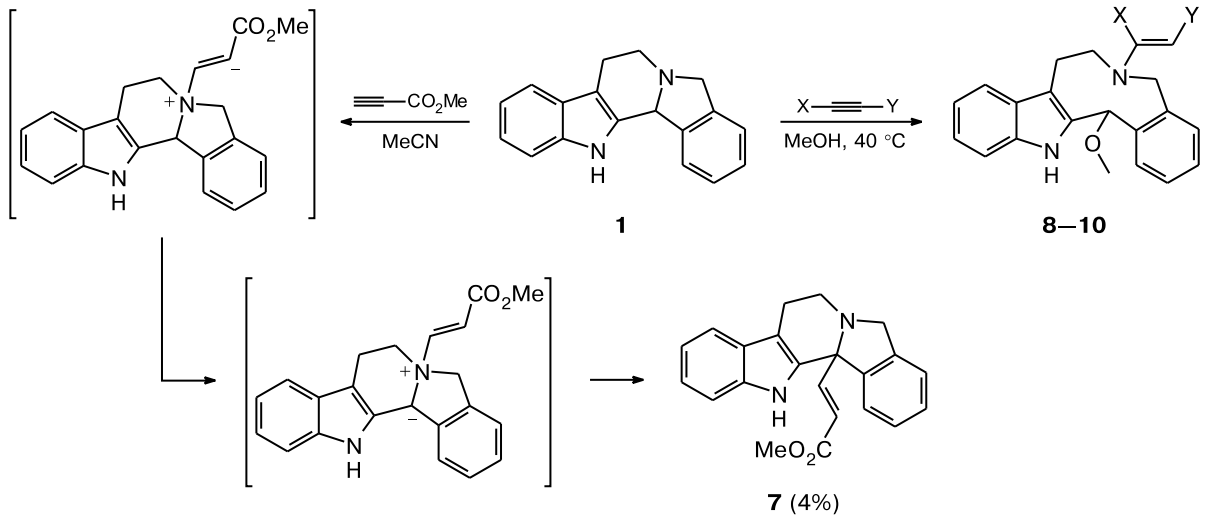
Scheme 2



3 **4** **5**, **6**

R = H (**5**), Ac (**6**)

Scheme 3

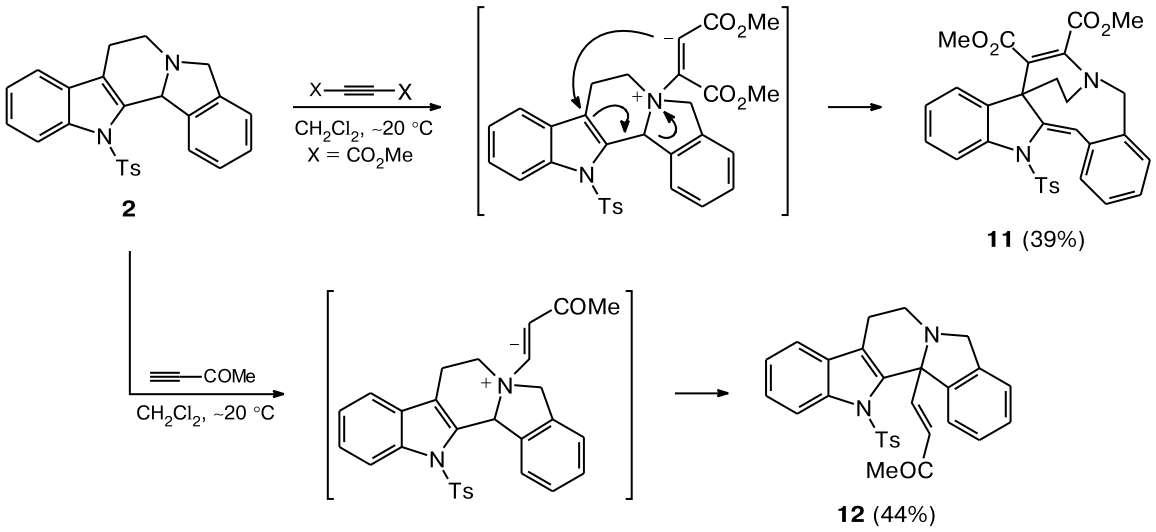


1 **8**—**10**

7 (4%)

X = H, Y = CO_2Me (**8**, 50%); X = H, Y = COMe (**9**, 28%); X = Y = CO_2Me (**10**, 24%)

Scheme 4



The reaction of compound **1** with dimethyl acetylenedicarboxylate (DMAD), methyl propiolate, and acetylacetylene in methanol easily and rapidly (for not longer than 1 h) proceeds at 40 °C to give indolobenzazonines **8**—**10** in moderate yields (see Scheme 3).

In the reaction with DMAD in dichloromethane, tosyl-substituted benzoindolizinoindole **2** is transformed into pentacyclic derivative **11**, whereas the reaction of compound **2** with acetylacetylene gives Stevens rearrangement product **12** (Scheme 4).

Our results are in good agreement with the data[11] on the reactions of 2-vinyltetrahydro-β-carboline and vinyl-substituted indolizinoindole with activated alkynes.

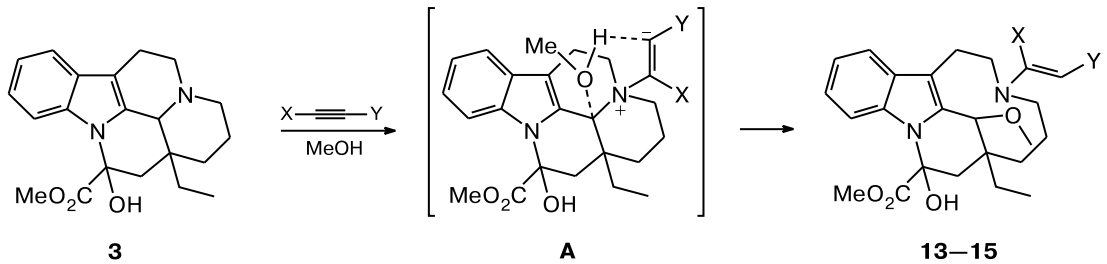
Since 14-hydroxy-14,15-dihydroeburnamenine **3** is poorly soluble in methanol, it reacts much more slowly with activated alkynes compared to indolizinoindole **1**. In this case, the reactions produce azecines **13**—**15** in high yields *via* the cleavage of the bridging C—N bond (Scheme 5). These compounds are high-melting-point colorless crystalline substances. Apparently, the transformation of compound **3** into products **13**—**15** proceeds through the transition state **A**.

Eburnamenine (Vinpocetine) **4** and its derivatives **5** and **6** react with alkynes much more actively than dihydroeburnamenine, which is apparently associated with the stabilization of the transition state **B** (Scheme 6) through the conjugation in the enamine moiety (of the indole group with the double bond of the cyclohexene group).

The methanol-mediated cleavage of the bridging C—N bond of the quinolizine moiety in the transition state **B** affords azecinoindoles **16**—**21**. Acetoxymethyl-substituted compound **6** reacts with methyl propiolate as easily as hydroxymethyl derivative **5**. However, the chromatographic separation on alumina results in the acetyl deprotection and the formation of azecine **19** in 43% yield.

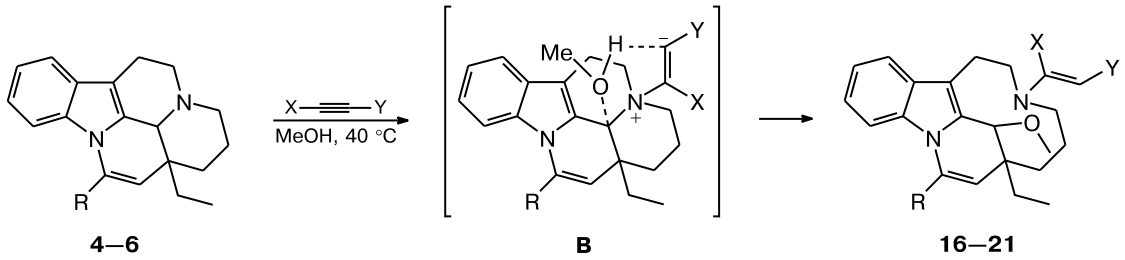
The structures of all the synthesized compounds were confirmed by spectroscopic data. The structure of azonine **10** was studied by X-ray diffraction. Compound **10** is polycyclic and contains four (one five-membered (pyrrole), two six-membered (benzene), and one nine-membered (azonine)) fused rings (Fig. 1). The central nine-membered ring adopts a distorted chair conformation; the N(1),

Scheme 5



X = H, Y = CO_2Me (**13**, 78%); X = H, Y = COMe (**14**, 63%); X = Y = CO_2Me (**15**, 73%)

Scheme 6



R = CO_2Et, X = H, Y = CO_2Me (**16**, 82%), X = H, Y = COMe (**17**, 45%), X = Y = CO_2Me (**18**, 42%),
R = CH_2OH, X = H, Y = CO_2Me (**19**, 57%), X = H, Y = COMe (**20**, 29%), X = Y = CO_2Me (**21**, 41%)

C(5), and C(6) atoms deviate from the mean plane passing through the other atoms of the ring by –0.802, 1.104, and 1.252 Å, respectively. The angle between the planes of the indole and benzene (C(2), C(3), C(9), C(10), C(11), C(12)) groups is 83.2°. The nitrogen atom N(1) has a flattened configuration (the sum of the valence angles at the nitrogen atom N(1) is 358.4°) due to the conjugation in the N(1)—C(20)=C(23)—C(24)=O(4) chain. The orientation of the methoxycarbonyl group at the carbon atom C(20) is determined by both the steric factors and the strong intermolecular N(2)—H(2)...O(2) hydrogen bond [x, $-1 + y$, z] (N...O, 2.935(2) Å; H...O, 2.11 Å; N—H...O, 160°). Molecules **10** are linked by these intermolecular hydrogen bonds to form hydrogen-bonded chains along the b axis. Compound **10** is chiral and has one asymmetric center at the carbon atom C(4). The crystal of compound **10** is a racemate.

Compound **11** is polycyclic and contains five (one five-membered (pyrrole), three six-membered (two benzene and one tetrahydropyridine), and one nine-membered (azonine)) fused rings (Fig. 2). The central azonine ring formed by the atoms C(4A), C(5), N(6), C(16), C(15), C(8A), C(13A), C(14), and C(14A) adopts a chair conformation; the C(4A), C(14A), C(15), and C(16) atoms deviate from the mean plane passing through the other atoms of the ring by 0.983, 1.084, –1.044, and 1.248 Å, respectively. The planes of the benzene rings of the indole and benzazonine moieties are nearly perpendicular to each other (the angle between the corresponding planes is 80.7°). Despite the fact that there is the conjugation between the nitrogen atom N(6) and the C(7)=C(8) double bond in compound **11**, as evidenced by the N(6)—C(7) bond length (1.382(2) Å), the nitrogen atom N(6) has a pyramidalized configuration (the sum of the valence angles at the nitrogen atom N(6) is 351.8°) due apparently to the strained structure of the central bicyclic ring system. The nitrogen atom N(13) is also pyramidalized (the sum of the valence angles at the nitrogen atom N(13) is 353.3°), which may be attributed to steric factors (the presence of the bulky tosyl substituent) and, as a consequence, to the absence of the conjugation between the nitrogen atom N(13) and the C(13A)=C(14) double bond, as evidenced by the N(13)—C(13A) bond length (1.462(2) Å). The mutual arrangement of two methoxycarbonyl substituents in molecule **11** is also determined by steric factors. Compound **11** is chiral and has one asymmetric center at the carbon atom C(8A). The crystal of compound **11** is a racemate.

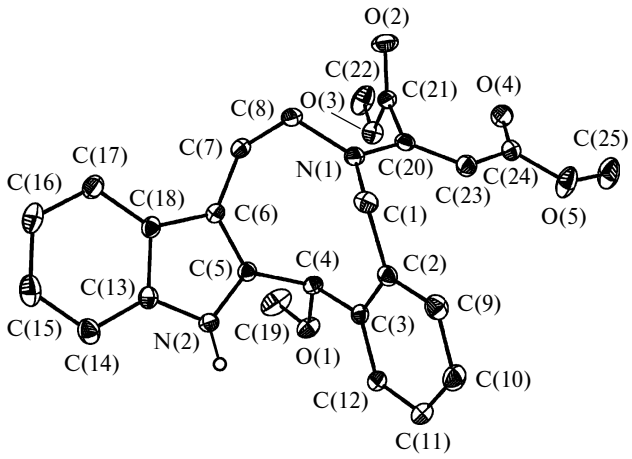


Fig. 1. Molecular structure of compound **10**.

The structures of azecines **13**—**21** were confirmed by spectroscopic data reported in the Experimental section and by X-ray diffraction (for compound **16**, Fig. 3).

In the crystal structure of compound **16**, there are two independent molecules per asymmetric unit, which differ only by the conformations of the ethoxycarbonyl (the C(22)—O(4)—C(23)—C(24) and C(22A)—O(4A)—C(23A)—C(24A) torsion angles are –83.6 and 88.8°, respectively) and propenoate (the C(1)—N(1)—C(18)—C(19) and C(1A)—N(1A)—C(18A)—C(19A) torsion angles are –9.1 and 170.2°, respectively) substituents. Hence, only one of two independent molecules **16** is discussed below.

Compound **16** is polycyclic and contains four (one five-membered (pyrrole), two six-membered (one benzene and one tetrahydropyridine), and one ten-membered (azecine)) fused rings (see Fig. 3). The ten-membered azecine ring adopts a chair—chair conformation, and the six-mem-

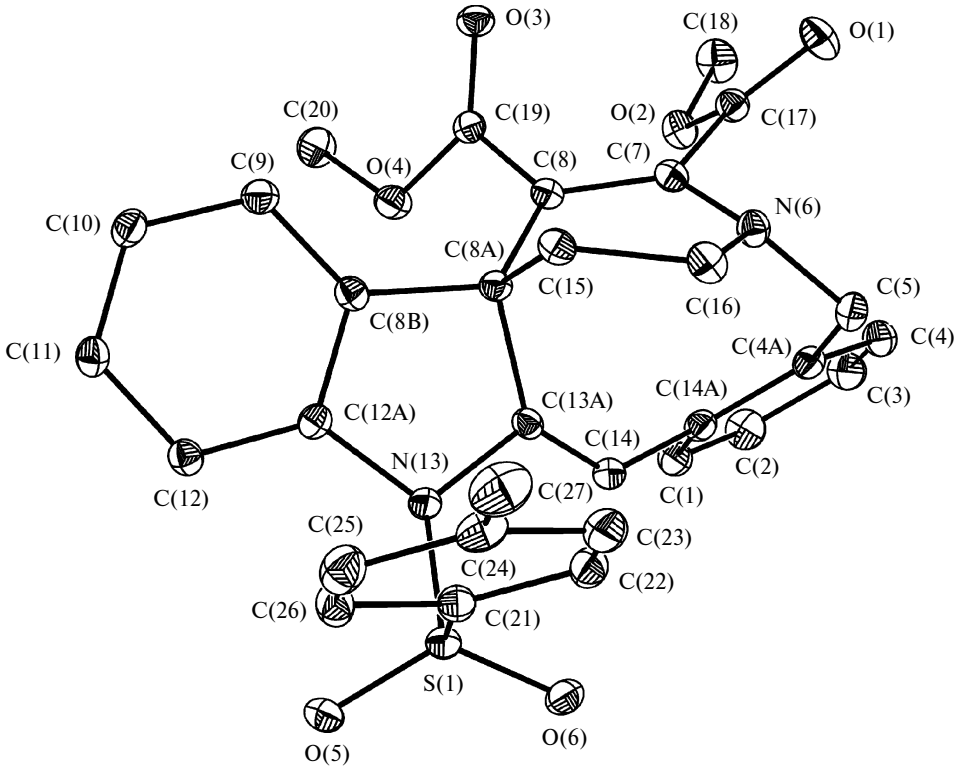


Fig. 2. Molecular structure of compound **11**.

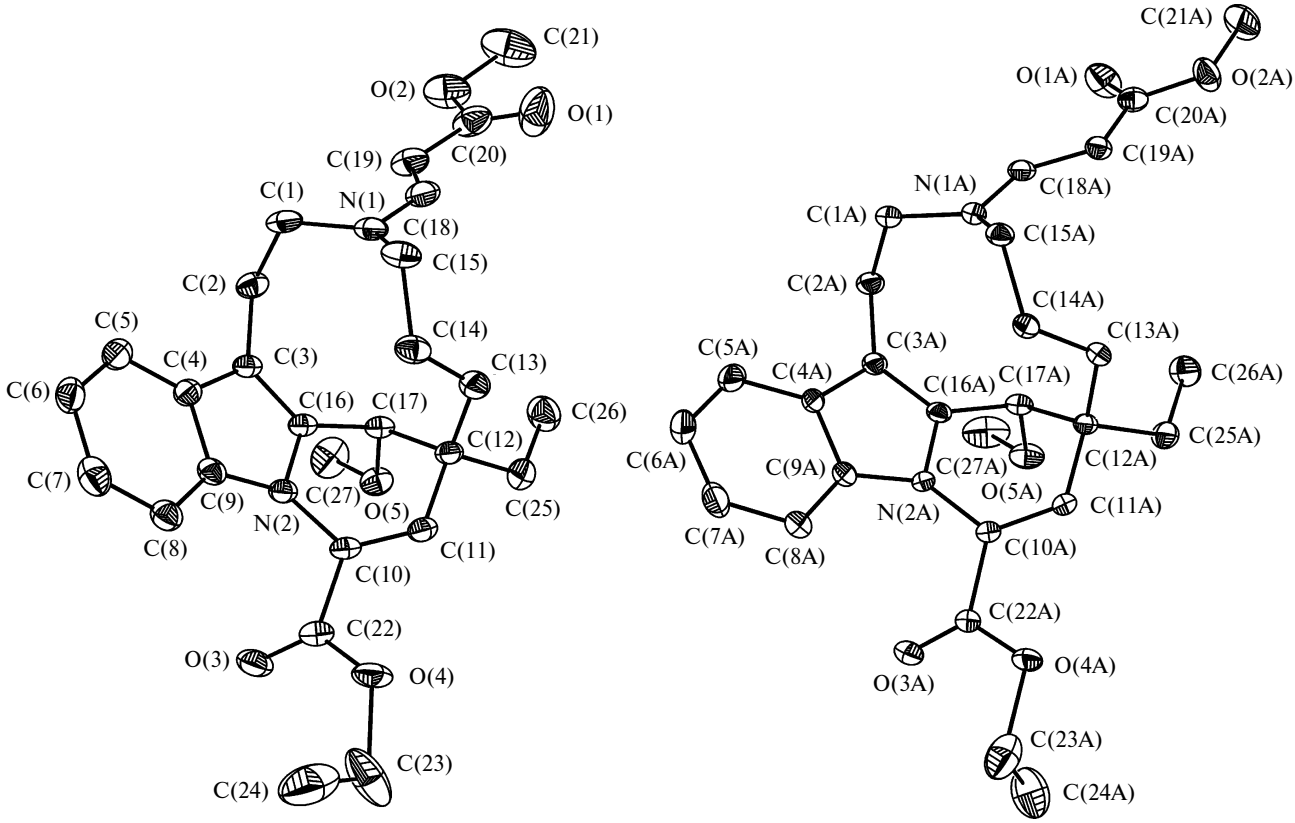


Fig. 3. Molecular structure of azecine **16** (two crystallographically independent molecules are shown).

bered tetrahydropyridine ring has a sofa conformation. The propenoate substituent has an *E* configuration with respect to the C(18)=C(19) double bond. Despite the presence of the conjugation between the nitrogen atom N(1) and the C(18)=C(19) double bond in compound **16**, as evidenced by the N(1)—C(18) bond length (1.360(4) Å), the nitrogen atom N(1) has a pyramidalized configuration (the sum of the valence angles at the nitrogen atom N(1) is 357.9°) due apparently to the strained structure of the polycyclic ring system. The nitrogen atom N(2) is also pyramidalized (the sum of the valence angles at the nitrogen atom N(2) is 354.0°). This may be attributed to steric factors (the presence of the bulky ethoxycarbonyl substituent) and, as a consequence, to the absence of the conjugation between the nitrogen atom N(2) and the C(10)=C(11) double bond, which is confirmed by the N(2)—C10 bond length (1.435(4) Å).

Compound **16** is chiral and has two asymmetric centers at the carbon atoms C(12) and C(17). The crystal of compound **16** is a racemate and consists of enantiomeric pairs with the relative configuration *rac*-12*S**,17*R**.

The tandem transformations of fused indolizines and quinolizines by the action of alkynes can be considered as a new efficient method for the synthesis of fused azonines and azecines.

In the N. N. Blokhin Russian Cancer Research Center of the Russian Academy of Medical Sciences, the cytotoxic activity of azonine **8** and azecines **16** and **17** at a concentration of 10 μmol L^{-1} was studied *in vitro*. The results of the study are given below.

Compound	Survival rate (%)
8	8.6
16	8.2
17	6.2

The assays were performed with the use of LS174T human rectal carcinoma cells. The cell culture was grown in the RPMI1640 medium supplemented with 10% fetal calf serum.

Compounds **8**, **16**, and **17** exhibit high cytotoxic activity in the LS174T cell line. Hence, these compounds can be recommended for the further *in vivo* study of cytotoxic activity.

Therefore, alkaloids of the eburnamenine series (Vincamine, Vinpocetine, and the hydroxymethyl analog of the latter) readily react with alkynes in methanol to form fused octahydro-7,9-ethano(etheno)azecino[5,4-*b*]indoles in moderate to high yields as products of the cleavage of the bridging bond in the hexahydroquinolizine moiety.

In methanol, the hexahydroindolizine moiety in benzoindolizinoindoles is cleaved by the action of alkynes to give azonines fused to the corresponding aromatic rings. In dichloromethane, the pathway of the transformation of *N*-tosyl-substituted hexahydrobenzoindolizinoindole depends on the nature of alkyne. In the reaction with acetylacetylene, the indolizine moiety is retained and the Stevens rearrangement product is generated, whereas in the reaction with DMAD this ring is cleaved to form a polycyclic system containing the spiro[indoline-3,4′-tetrahydropyridine] moiety.

Experimental

The IR spectra were recorded on an Infralyum FT-801 Fourier-transform infrared spectrometer as KBr pellets or in films (for liquid samples). The elemental analysis was performed on a Carlo Erba 1106 instrument. The ^{1}H and ^{13}C NMR spectra were measured on Bruker-300, Bruker-400, and JEOL JNM-ECA600 instruments (for ^{1}H, operating at 300, 400, and 600 MHz) in $CDCl_3$, DMSO-d_6, and CD_3OD using residual signals of the solvent or $SiMe_4$ as the internal standard. Mass spectra were recorded on a Finnigan MAT 95 XL gas chromatography/mass spectrometer (EI, 70 eV). The LCMS spectra were obtained using a system composed of an Agilent 1100 Series liquid chromatograph, an Agilent Technologies LC/MSD VL mass spectrometer (electrospray ionization, APCI), and an ELSD Sedex 75 detector. Thin-layer chromatography was performed on Silufol UV-254 and Alufol plates (visualization using iodine vapor). Column chromatography was carried out on neutral alumina (Fluka, II activity grade, 60 mesh).

The unit cell parameters and intensities of reflections were measured on an Enraf Nonius CAD-4 automated diffractometer (λ(Mo-Kα) radiation, β filter, ω/2θ-scanning technique) for compound **10**, a Bruker SMART 1K CCD automated diffractometer (λ(Mo-Kα) radiation, graphite monochromator, φ- and ω-scanning technique) for compound **11**, and a Bruker SMART APEX II CCD automated diffractometer (λ(Mo-Kα) radiation, graphite monochromator, φ- and ω-scanning technique) for compound **16**. Principal crystallographic data are given in Table 1. The structures of all compounds were solved by direct methods and refined by the full-matrix least-squares method with anisotropic displacement parameters for nonhydrogen atoms. The hydrogen atom of the amino group in molecule **10** was located in difference Fourier maps and refined with fixed positional and thermal parameters. The other hydrogen atoms were positioned geometrically and refined isotropically with fixed positional (a riding model) and thermal ($U_{iso}(H) = 1.5U_{eq}(C)$ for Me groups and $U_{iso}(H) = 1.2U_{eq}(C)$ for all other groups) parameters. All calculations were carried out with the use of the SHELXTL program package.[12]

13-[(4-Methylphenyl)sulfonyl]-7,8,13,13*b*-tetrahydro-5*H*-benzo[1,2]indolizino[8,7-*b*]indole (2). Sodium hydride (0.30 g, 60%; 6.9 mmol) was added portionwise with stirring to a solution of benzoindolizinoindole **1** (1.2 g, 4.6 mmol) in anhydrous DMF (20 mL) under argon atmosphere at 5 °C. After 45 min, tosyl chloride (1.06 g, 5.5 mmol) was added. After the completion of the reaction (monitoring by TLC, Sorbfil, ethyl acetate), water (20 mL) was added to the reaction mixture, and the mixture was extracted with dichloromethane (3×50 mL). The extract was dried with $MgSO_4$, the solvent was evaporated *in vacuo*, and the residue was recrystallized from an ethyl acetate—hexane mixture. *N*-Tosylbenzoindolizinoindole **2** was obtained in a yield of 0.44 g (23%), yellow crystals, m.p. 159—162 °C (ethyl acetate—hexane). Found (%): C, 72.17; H, 5.27; N, 6.69. $C_{25}H_{22}N_2O_2S$. Calculated (%): C, 72.44; H, 5.35; N, 6.76. IR,

Table 1. Principal crystallographic characteristics and the structure refinement statistics for **10**, **11**, and **16**

Parameter	**10**	**11**	**16**
Molecular formula	$C_{25}H_{26}N_2O_5$	$C_{31}H_{28}N_2O_6S$	$C_{27}H_{34}N_2O_5$
Molecular weight	434.48	556.61	466.56
T/K	293	120	296
Crystal system	Triclinic	Monoclinic	Monoclinic
Space group	$P\bar{1}$	$P2_1/c$	$P2_1$
a/Å	8.763(2)	12.2439(6)	8.5296(7)
b/Å	9.278(2)	8.4320(4)	22.2119(19)
c/Å	14.675(3)	26.2594(13)	13.5706(11)
α/deg	80.03(3)	90	90
β/deg	86.77(3)	95.993(1)	97.210(1)
γ/deg	71.81(3)	90	90
V/Å^3	1116.4(4)	2696.2(2)	2550.7(4)
Z	2	4	4
d_{calc}/g cm^{-3}	1.293	1.371	1.215
F(000)	460	1168	1000
μ/mm^{-1}	0.091	0.169	0.084
$2\theta_{max}$/deg	51	58	59
Number of measured reflections	4322	28931	19133
Number of unique reflections	4148	7168	12582
Number of reflections with $I > 2\sigma(I)$	2984	5372	6078
Number of parameters in refinement	290	364	613
R_1 ($I > 2\sigma(I)$)	0.033	0.058	0.060
wR_2 (based on all data)	0.102	0.149	0.146
GOF	1.084	1.000	0.999

ν/cm^{-1}: 1365 (SO); 1169 (SO). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 2.28 (s, 3 H, ArC$\underline{H}_3$); 2.62 (dddd, 1 H, CH_2, J = 16.3 Hz, J = 7.0 Hz, J = 5.3 Hz, J = 1.9 Hz); 2.78 (td, 1 H, CH_2, J = 10.1 Hz, J = 5.3 Hz); 2.91—3.04 (m, 2 H, CH_2); 4.05 (d, 1 H, H(5), J = 13.9 Hz); 4.37 (d, 1 H, H(5), J = 13.9 Hz); 5.98 (s, 1 H, C(13b)H); 7.09 (d, 2 H, Ar, J = 8.3 Hz); 7.18—7.30 (m, 6 H, Ar); 7.55 (d, 2 H, Ar, J = 8.3 Hz); 7.97 (d, 1 H, Ar, J = 7.5 Hz); 8.14 (d, 1 H, Ar, J = 7.5 Hz). MS, m/z (I_{rel} (%)): 414 [M]$^+$ (5), 270 (3), 260 (7), 259 (44), 258 (100), 257 (61), 256 (18), 255 (12), 243 (4), 242 (4), 241 (3), 231 (6), 230 (23), 229 (5), 228 (5), 217 (3), 130 (5), 91 (16), 89 (3), 65 (4).

Methyl 14-hydroxy-14,15-dihydroeburnamenine-14-carboxylate (3). Methyl 14-hydroxy-14,15-dihydroeburnamenine-14-carboxylate (periwinkle alkaloid) was isolated from the drug Vincamine. Vincamine pellets (6 g) were ground to powder, alkalified with a 25% ammonia aqueous solution, and extracted with a 1 : 1 diethyl ether—ethyl acetate mixture. The extract was dried with $MgSO_4$. The solvents were evaporated *in vacuo*. Compound **3** was obtained in a yield of 4.8 g (79%), colorless crystals, m.p. 232—233 °C (ethyl acetate—hexane) (*cf.* lit. data[13]: m.p. 225—227 °C (CH_2Cl_2)). Found (%): C, 70.98; H, 7.23; N, 7.76. $C_{21}H_{26}N_2O_3$. Calculated (%): C, 71.16; H, 7.39; N, 7.90. IR, ν/cm^{-1}: 1748 (CO). ^{1}H NMR (600 MHz, $CDCl_3$), δ: 0.90 (t, 3 H, $CH_2C\underline{H}_3$, J = 7.6 Hz); 1.36—1.39 (m, 1 H, CH_2); 1.43—1.50 (m, 2 H, CH_2); 1.65—1.77 (m, 2 H, CH_2, $C\underline{H}_2CH_3$); 2.12 (d, 1 H, C(15)H, J = 14.2 Hz); 2.21—2.27 (m, 2 H, C(15)H, $C\underline{H}_2CH_3$); 2.48—2.56 (m, 2 H, CH_2); 2.58—2.62 (m, 1 H, CH_2); 2.95—3.01 (m, 1 H, CH_2); 3.25—3.35 (m, 2 H, CH_2); 3.81 (s, 3 H, CO_2CH_3); 3.91 (s, 1 H, OH); 4.61 (s, 1 H, C(3)H); 7.08—7.14 (m, 3 H, Ar); 7.47—7.49 (m, 1 H, Ar). MS, m/z (I_{rel} (%)): 354 [M]$^+$ (56), 353 (20), 307 (8), 295 (24), 267 (41), 266 (19), 252 (75), 251 (25), 237 (30), 224 (47), 223 (16), 209 (19), 197 (16), 196 (16), 180 (30), 169 (18), 168 (41), 167 (40), 144 (15), 115 (16), 70 (18), 67 (19), 59 (27), 55 (23), 43 (61), 42 (100), 41 (71).

Ethyl eburnamenine 14-carboxylate (4) was isolated from the drug Vinpocetine. Vinpocetine pellets (6 g) were ground to powder, alkalified with a 20% sodium carbonate aqueous solution, and extracted with diethyl ether. The extract was dried with $MgSO_4$. Ethyl ether was evaporated *in vacuo*. Compound **4** was obtained in a yield of 3 g (50%), colorless crystals, m.p. 146—148 °C (ethyl acetate) (*cf.* lit. data[14]: m.p. 144 °C (anhydrous ethanol)). Found (%): C, 75.26; H, 7.37; N, 7.91. $C_{22}H_{26}N_2O_2$. Calculated (%): C, 75.40; H, 7.48; N, 7.99. IR, ν/cm^{-1}: 1717 (CO). ^{1}H NMR (400 MHz, $CDCl_3$). δ: 0.94—1.06 (m, 1 H, CH_2); 1.01 (t, 3 H, $CH_2C\underline{H}_3$, J = 7.4 Hz); 1.35—1.43 (m, 1 H, CH_2); 1.39 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.1 Hz); 1.46—1.55 (m, 1 H, CH_2); 1.63—1.80 (m, 1 H, $C\underline{H}_2CH_3$); 1.82—1.99 (m, 2 H, CH_2, $C\underline{H}_2CH_3$); 2.50 (dd, 1 H, CH_2, J = 16.2 Hz, J = 2.6 Hz); 2.58—2.64 (m, 2 H, CH_2); 2.95—3.09 (m, 1 H, CH_2); 3.18—3.40 (m, 2 H, CH_2); 4.14 (s, 1 H, C(3)H); 4.37—4.47 (m, 2 H, $OC\underline{H}_2CH_3$); 6.11 (s, 1 H, C(15)H); 7.08—7.19 (m, 2 H, Ar); 7.21—7.26 (m, 1 H, Ar); 7.44—7.49 (m, 1 H, Ar). MS, m/z (I_{rel} (%)): 350 [M]$^+$ (33), 322 (21), 321 (100), 220 (17), 293 (10), 292 (11), 281 (17), 280 (100), 252 (38), 250 (14), 249 (13), 248 (12), 247 (11), 237 (14), 220 (13), 219 (11), 218 (10), 206 (23), 204 (10), 193 (20), 192 (14), 191 (13), 42 (26), 41 (15).

Eburnamenine-14-ylmethanol (5). Compound **4** (2.4 g, 6.86 mmol) was added portionwise with stirring to a suspension of $LiAlH_4$ (0.78 g, 20.6 mmol) in anhydrous THF (50 mL). The reaction mixture was refluxed. After the completion of the reaction (monitoring by TLC, Sorbfil, ethyl acetate) ethyl acetate (10 mL) and water (50 mL) were added, and the mixture was

extracted with ethyl acetate (3×50 mL). The extracts were dried with $MgSO_4$. The solvent was distilled off *in vacuo*. The residue was recrystallized from a hexane—ethyl acetate mixture. Compound **5** was obtained in a yield of 1.67 g (79%), colorless crystals, m.p. 149—152 °C (ethyl acetate—hexane) (*cf.* lit. data[15]: foamed oil). Found (%): C, 77.72; H, 7.73; N, 8.94. $C_{20}H_{24}N_2O$. Calculated (%): C, 77.89; H, 7.84; N, 9.08. The ^{1}H NMR spectrum corresponds to the published data.[15] MS, *m*/*z* (I_{rel} (%)): 308 $[M]^+$ (67), 307 (38), 280 (21), 279 (100), 252 (18), 251 (25), 250 (35), 249 (21), 236 (16), 222 (18), 208 (38), 206 (20), 193 (31), 180 (21), 167 (12), 154 (13), 125 (16), 42 (24), 41 (25).

Eburnamenine-14-ylmethyl acetate (6). Acetic anhydride (0.28 g, 2.76 mmol) was added to a solution of eburnamenine-14-ylmethanol **5** (0.85 g, 2.76 mmol) in triethylamine (0.334 g, 3.31 mmol). The reaction mixture was refluxed for 1.5 h (monitoring by TLC, Sorbfil, 7 : 1 ethyl acetate—ethanol). Then the reaction mixture was cooled, poured into cold water (50 mL), and extracted with diethyl ether (3×40 mL). The extract was dried over $MgSO_4$. The solvent and excess triethylamine were removed. After the distillation, the yellow oil was purified on alumina. Compound **6** was obtained in a yield of 0.78 g (81%), yellow oil. Found (%): C, 75.19; H, 7.30; N, 7.85. $C_{22}H_{26}N_2O_2$. Calculated (%): C, 75.40; H, 7.48; N, 7.99. IR, ν/cm^{-1}: 1738 (CO). ^{1}H NMR (600 MHz, $CDCl_3$), δ: 0.98 (t, 3 H, C$\underline{H}_3$CH$_2$, *J* = 7.5 Hz); 1.11 (td, 1 H, CH$_2$, *J* = 13.7 Hz, *J* = 3.9 Hz); 1.39—1.46 (m, 2 H, CH$_2$); 1.67—1.78 (m, 2 H, CH$_2$, MeC$\underline{H}_2$); 1.90—1.94 (m, 1 H, MeC$\underline{H}_2$); 2.07 (s, 3 H, MeCO); 2.50 (ddd, 1 H, CH$_2$, *J* = 15.9 Hz, *J* = 5.0 Hz, *J* = 1.7 Hz); 2.63—2.66 (m, 1 H, CH$_2$); 2.69—2.73 (m, 1 H, CH$_2$); 2.99—3.06 (m, 1 H, CH$_2$); 3.22—3.27 (m, 1 H, CH$_2$); 3.36 (dd, 1 H, CH$_2$, *J* = 13.7 Hz, *J* = 5.5 Hz); 4.20 (s, 1 H, C(3)H); 4.92 (d, 1 H, C$\underline{H}_2$OAc, *J* = 13.2 Hz); 5.17 (s, 1 H, C(15)H); 5.33 (d, 1 H, C$\underline{H}_2$OAc, *J* = 13.2 Hz); 7.09—7.12 (m, 1 H, Ar); 7.14—7.17 (m, 1 H, Ar); 7.36 (d, 1 H, Ar, *J* = 8.3 Hz); 7.47 (d, 1 H, Ar, *J* = 7.5 Hz). MS, *m*/*z* (I_{rel} (%)): 350 $[M]^+$ (11), 321 (26), 280 (26), 261 (8), 248 (3), 233 (3), 221 (5), 220 (5), 219 (5), 206 (5), 205 (6), 204 (6), 193 (4), 191 (4), 43 (100), 42 (48), 41 (15).

Methyl (2*E*)-3-{8,13-dihydro-5*H*-benzo[1,2]indolizino[8,7-*b*]-indole-13*b*(7*H*)-yl}acrylate (7). A solution of benzoindolizinoindole **1** (0.28 g, 1.06 mmol) and methyl propiolate (0.36 g, 4.23 mmol) in acetonitrile (15 mL) was refluxed until the reaction was completed (monitoring by TLC, Sorbfil, ethyl acetate). The solvent was distilled off *in vacuo*, and the residue was chromatographed on alumina using a 1 : 10 ethyl acetate—hexane mixture as the eluent. Compound **7** was obtained in a yield of 15 mg (4%), yellow crystals, m.p. 168—170 °C (ethyl acetate—hexane). Found (%): C, 76.50; H, 5.72; N, 8.00. $C_{22}H_{20}N_2O_2$. Calculated (%): C, 76.72; H, 5.85; N, 8.13. IR, ν/cm^{-1}: 1724 (CO). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 2.63 (dd, 1 H, CH$_2$, *J* = 3.7 Hz, *J* = 15.8 Hz); 3.11—3.22 (m, 1 H, CH$_2$); 3.28—3.45 (m, 2 H, CH$_2$); 3.74 (s, 3 H, OMe); 4.18—4.27 (m, 2 H, C(5)H); 4.22 (d, 1 H, CH=C$\underline{H}$CO$_2$Me, *J* = 15.7 Hz); 7.08—7.37 (m, 8 H, Ar, C$\underline{H}$=CHCO$_2$Me); 7.51 (d, 1 H, Ar, *J* = 7.4 Hz); 7.74 (s, 1 H, NH). MS, *m*/*z* (I_{rel} (%)): 344 $[M]^+$ (19), 285 (6), 260 (18), 259 (100), 258 (7), 257 (14), 256 (11), 255 (6), 254 (7), 129 (10), 128 (9).

Reactions of benzoindolizinoindole 1 with methyl propiolate, acetylacetylene, and DMAD (general procedure). A solution of benzoindolizinoindole **1** (2 mmol) and methyl propiolate, acetylacetylene, or DMAD (3 mmol) in methanol (20 mL) was kept at 40 °C until the reaction was completed (TLC monitoring, Sorbfil, ethyl acetate). After distillation of methanol, the crystallization (in the case of **8**) or chromatography on alumina using a 1 : 3 ethyl acetate—hexane mixture as the eluent (in the case of **9** and **10**) was performed.

Methyl (2*E*)-3-{14-methoxy-7,8,13,14-tetrahydroindolo-[3,2-*e*][2]benzazonin-6(5*H*)-yl}acrylate (8). Yield 0.38 g (50%), beige crystals, m.p. 215—217 °C (ethyl acetate—hexane). Found (%): C, 73.22; H, 6.38; N, 7.30. $C_{23}H_{24}N_2O_3$. Calculated (%): C, 73.38; H, 6.43; N, 7.44. IR, ν/cm^{-1}: 1681 (CO). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 2.96—3.05 (m, 1 H, CH$_2$); 3.10—3.25 (m, 2 H, CH$_2$); 3.36 (s, 3 H, OMe); 3.60 (s, 3 H, CO$_2$Me); 3.63—3.75 (m, 2 H, CH$_2$, C(5)H); 4.31 (d, 1 H, C(5)H, *J* = 15.8 Hz); 4.74 (br.s, 1 H, CH=C$\underline{H}$CO$_2$Me); 5.54 (br.s, 1 H, C(14)H); 7.11—7.30 (m, 5 H, Ar); 7.36 (d, 1 H, C$\underline{H}$=CHCO$_2$Me, *J* = 13.1 Hz); 7.44 (t, 1 H, Ar, *J* = 7.9 Hz); 7.57 (d, 1 H, Ar, *J* = 7.9 Hz); 7.89 (s, 1 H, NH); 7.96 (d, 1 H, Ar, *J* = 7.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 21.4, 50.5, 56.3, 57.3, 58.9, 73.6, 86.4, 96.0, 111.1, 118.2, 119.5, 122.6, 125.5, 126.3, 127.7, 128.7, 130.4, 132.4, 133.6, 136.1, 138.7, 150.0, 169.7. MS, *m*/*z* (I_{rel} (%)): 376 $[M]^+$ (35), 345 (43), 344 (16), 249 (18), 248 (100), 246 (15), 232 (21), 231 (32), 230 (79), 218 (25), 217 (48), 216 (33), 202 (14), 159 (35), 144 (22), 143 (54), 134 (21), 130 (16), 119 (21), 115 (24).

(3*E*)-4-{14-Methoxy-7,8,13,14-tetrahydroindolo[3,2-*e*]-[2]benzazonin-6(5*H*)-yl}but-3-en-2-one (9). Yield 0.20 g (28%), yellow crystals, m.p. 177—179 °C (ethyl acetate—hexane). Found (%): C, 76.41; H, 6.58; N, 7.64. $C_{23}H_{24}N_2O_2$. Calculated (%): C, 76.64; H, 6.71; N, 7.77. IR, ν/cm^{-1}: 1652 (CO). ^{1}H NMR (400 MHz, CD_3OD), δ: 1.70 (br.s, 3 H, COMe); 2.99—3.03 (m, 1 H, CH$_2$); 3.13—3.33 (m, 2 H, CH$_2$); 3.35 (s, 3 H, OMe); 3.63—3.67 (m, 1 H, CH$_2$); 3.92 (d, 1 H, C(5)H, *J* = 14.9 Hz); 4.53 (d, 1 H, C(5)H, *J* = 14.9 Hz); 4.99 (d, 1 H, CH=C$\underline{H}$COMe, *J* = 13.7 Hz); 5.59 (br.s, 1 H, C(14)H); 7.00—7.08 (m, 2 H, Ar); 7.21—7.33 (m, 4 H, Ar, C$\underline{H}$=CHCOMe); 7.44—7.56 (m, 2 H, Ar); 7.84—7.97 (m, 2 H, NH, Ar). MS, *m*/*z* (I_{rel} (%)): 360 $[M]^+$ (65), 345 (54), 329 (32), 328 (16), 260 (17), 249 (19), 248 (100), 246 (16), 244 (21), 232 (25), 231 (34), 230 (100), 218 (24), 217 (55), 216 (39), 159 (21), 144 (20), 143 (35), 119 (18), 115 (20).

Dimethyl (2*E*)-2-{14-methoxy-7,8,13,14-tetrahydroindolo[3,2-*e*][2]benzazonin-6(5*H*)-yl}but-2-enedioate (10). Yield 0.21 g (24%), colorless crystals, m.p. 210—212 °C (ethyl acetate—hexane). Found (%): C, 68.92; H, 5.89; N, 6.31. $C_{25}H_{26}N_2O_5$. Calculated (%): C, 69.11; H, 6.03; N, 6.45. IR, ν/cm^{-1}: 1737 (CO), 1692 (CO). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.02 (d, 1 H, C(5)H, *J* = 15.8 Hz); 3.09—3.29 (m, 2 H, CH$_2$); 3.42 (s, 3 H, MeO); 3.56 (s, 3 H, CO$_2$Me); 3.68 (br.s, 3 H, CO$_2$Me); 3.74—3.82 (m, 2 H, CH$_2$); 4.43 (d, 1 H, C(5)H, *J* = 15.8 Hz); 4.68 (s, 1 H, =C$\underline{H}$CO$_2$Me); 5.92 (s, 1 H, C(14)H); 7.07—7.25 (m, 5 H, Ar); 7.41 (t, 1 H, Ar, *J* = 7.9 Hz); 7.55 (d, 1 H, Ar, *J* = 7.9 Hz); 7.81 (s, 1 H, NH); 7.97 (d, 1 H, Ar, *J* = 7.9 Hz). ^{13}C NMR (150 MHz, $CDCl_3$). δ: 23.5, 51.0, 52.8, 54.0, 56.5, 58.7, 73.0, 100.0, 111.2, 111.3, 118.3, 119.5, 122.7, 124.9, 126.3, 127.6, 128.5, 130.1, 132.8, 133.1, 136.3, 139.4, 153.9, 166.1, 167.9. MS, *m*/*z* (I_{rel} (%)): 434 $[M]^+$ (5), 403 (5), 375 (4), 343 (5), 276 (4), 260 (10), 250 (5), 249 (15), 248 (100), 246 (6), 244 (6), 233 (5), 232 (12), 231 (13), 230 (40), 218 (13), 217 (34), 216 (21), 202 (4), 159 (4), 144 (4), 143 (9), 134 (7), 119 (9), 115 (9).

Dimethyl 13-[(4-methylphenyl)sulfonyl]-5,13-dihydro-6,8a-ethanoindolo[3,2-*e*][2]benzazonine-7,8-dicarboxylate (11). A solution of benzoindolizinoindole **2** (0.20 g, 0.48 mmol) and DMAD (0.14 g, 0.96 mmol) in dichloromethane (12 mL) was

stirred at 20 °C until the reaction was completed (TLC monitoring, Sorbfil, ethyl acetate). Dichloromethane was distilled off *in vacuo*, and the residue was crystallized from an ethyl acetate—hexane mixture. Benzazonine **11** was obtained in a yield of 0.11 g (39%), yellow crystals, m.p. 198—200 °C (ethyl acetate—hexane). Found (%): C, 66.76; H, 4.99; N, 4.96. $C_{31}H_{28}N_2O_6S$. Calculated (%): C, 66.89; H, 5.07; N, 5.03. IR, ν/cm^{-1}: 1725 (CO), 1708 (CO), 1354 (SO), 1169 (SO). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.40 (t, 2 H, CH_2, J = 7.8 Hz); 2.41 (s, 3 H, ArMe); 2.94—3.02 (m, 1 H, CH_2); 3.06—3.13 (m, 1 H, CH_2); 3.31 (s, 3 H, CO_2Me); 3.40 (s, 3 H, CO_2Me); 4.13 (d, 1 H, C(5)H, J = 11.8 Hz); 4.32 (d, 1 H, C(5)H, J = 11.8 Hz); 6.87 (d, 1 H, Ar, J = 7.4 Hz); 7.03 (t, 1 H, Ar, J = 7.4 Hz); 7.07—7.11 (m, 2 H, Ar, C(14)H); 7.20—7.30 (m, 6 H, Ar); 7.70 (d, 2 H, Ar, J = 8.2); 7.86 (d, 1 H, Ar, J = 8.2 Hz). ^{13}C NMR (150 MHz, $CDCl_3$), δ: 21.8, 41.1, 49.1, 50.8, 51.8, 52.3, 57.5, 117.4, 122.0, 122.1, 125.5, 126.8, 127.6 (2 C), 128.3, 128.4, 129.7 (2 C), 130.6, 130.8, 132.5, 132.8, 135.4, 135.6, 136.3, 139.6, 142.2, 145.0, 145.8, 164.0, 166.8. MS, m/z (I_{rel} (%)): 557 (0.1), 556 [M]$^+$ (0.3), 526 (0.2), 525 (0.5), 497 (0.3), 492 (0.2), 442 (0.2), 402 (20.3), 401 (80.5), 374 (22.8), 373 (100.0), 341 (10.2), 327 (8.4), 326 (35.6), 314 (8.0), 283 (14.8), 282 (18.8), 281 (14.5), 256 (19.3), 255 (49.2), 254 (42.0), 253 (13.4), 241 (7.8), 230 (12.4), 228 (8.5), 115 (13.5), 91 (38.2).

(3*E*)-4-{13-[(4-Methylphenyl)sulfonyl]-8,13-dihydro-5*H*-benzo[1,2]indolizino[8,7-*b*]indol-13*b*(7*H*)-yl}but-3-en-2-one (12). A solution of benzoindolizinoindole **2** (0.19 g, 0.46 mmol) and acetylacetylene (0.11 g, 1.61 mmol) in dichloromethane (12 mL) was stirred at 20 °C until the reaction was completed (TLC monitoring, Sorbfil, ethyl acetate). The solvent was distilled off *in vacuo*. The residue was chromatographed on SiO_2. Compound **12** was eluted with a 1 : 1 ethyl acetate—hexane mixture; the yield was 0.10 g (44%), orange oil. Found (%): C, 71.94; H, 5.31; N, 5.68. $C_{29}H_{26}N_2O_3S$. Calculated (%): C, 72.17; H, 5.43; N, 5.80. IR, ν/cm^{-1}: 1668 (CO), 1362 (SO), 1169 (SO). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 2.28 (s, 3 H, ArMe); 2.36 (s, 3 H, COMe); 2.58 (dd, 1 H, CH_2, J = 17.6 Hz, J = 5.1 Hz); 2.78 (ddd, 1 H, CH_2, J = 17.6 Hz, J = 11.8 Hz, J = 6.1 Hz); 2.58 (dd, 1 H, CH_2, J = 14.5 Hz, J = 6.1 Hz); 2.78 (ddd, 1 H, CH_2, J = 14.5 Hz, J = 11.8 Hz, J = 5.1 Hz); 4.00 (d, 1 H, C(5)H, J = 12.4 Hz); 4.05 (d, 1 H, C(5)H, J = 12.4 Hz); 6.33 (d, 1 H, CH=C<u>H</u>COMe, J = 16.1 Hz); 7.05 (d, 2 H, Ar, J = 8.5 Hz); 7.10—7.14 (m, 1 H, Ar); 7.18—7.23 (m, 3 H, Ar); 7.32 (d, 2 H, Ar, J = 8.5 Hz); 7.35—7.37 (m, 1 H, Ar); 7.46—7.53 (m, 1 H, Ar); 7.65 (d, 1 H, CH=CHCOMe, J = 16.1 Hz); 7.82—7.84 (m, 1 H, Ar); 8.28—8.30 (m, 1 H, Ar). MS, m/z (I_{rel} (%)): 483 [M + H]$^+$ (100).

Reactions of eburnamenine derivative 3 with methyl propiolate, acetylacetylene, and DMAD (general procedure). A solution of eburnamenine **3** (1 mmol) and methyl propiolate, acetylacetylene, or DMAD (1.5 mmol) in methanol (60 mL) was refluxed until the reaction was completed (TLC monitoring, Sorbfil, ethyl acetate). Methanol was distilled off *in vacuo*, and the residue was crystallized from ethyl acetate.

Methyl 7-ethyl-14-hydroxy-8-methoxy-3-[(1*E*)-3-methoxy-3-oxoprop-1-en-1-yl]-1,2,3,4,5,6,7,8-octahydro-7,9-ethanoazecino[5,4-*b*]indole-14-carboxylate (13). Yield 0.37 g (78%), colorless crystals, m.p. 205—206 °C (ethyl acetate). Found (%): C, 66.15; H, 7.12; N, 5.80. $C_{26}H_{34}N_2O_6$. Calculated (%): C, 66.36; H, 7.28; N, 5.95. IR, ν/cm^{-1}: 1742 (CO), 1668(CO). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.86 (t, 3 H, $CH_2C\underline{H}_3$, J = 7.5 Hz); 1.23—1.30 (m, 1 H, CH_2); 1.50—1.64 (m, 2 H, CH_2); 1.72—1.91 (m, 4 H, CH_2, C<u>H</u>$_2$Me, C(15)H); 2.31 (dd, 1 H, CH_2, J = 9.3 Hz, J = 13.8 Hz); 2.75 (d, 1 H, C(15)H, J = 13.4 Hz); 2.84—2.99 (m, 2 H, CH_2); 3.19—3.26 (m, 1 H, CH_2); 3.22 (s, 3 H, OMe); 3.54—3.58 (m, 1 H, CH_2); 3.70—3.73 (m, 1 H, CH_2); 3.72 (s, 3 H, CO_2Me); 3.83 (s, 3 H, CO_2Me); 4.20 (s, 1 H, OH); 4.60 (s, 1 H, C(8)H); 4.83 (d, 1 H, CH=C<u>H</u>CO_2Me, J = 13.1 Hz); 7.14—7.22 (m, 3 H, Ar); 7.53 (d, 1 H, Ar, J = 6.9 Hz); 7.60 (d, 1 H, C<u>H</u>=CHCO_2Me, J = 13.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 8.0, 20.3, 22.5, 26.9, 33.1, 40.3, 40.8, 50.9, 54.4, 55.5, 56.3, 60.6, 75.4, 82.9, 86.5, 112.1, 113.5, 118.5, 120.5, 123.0, 128.0, 133.2, 135.3, 150.4, 169.8, 174.9. MS, m/z (I_{rel} (%)): 471 (22), 470 [M]$^+$ (79), 456 (26), 455 (100), 452 (32), 439 (44), 438 (15), 437 (20), 423 (49), 421 (19), 405 (32), 380 (22), 379 (83), 186 (49), 174 (17), 168 (17), 167 (16), 158 (17), 156 (20), 82 (29).

Methyl 7-ethyl-14-hydroxy-8-methoxy-3-[(1*E*)-3-oxobut-1-en-1-yl]-1,2,3,4,5,6,7,8-octahydro-7,9-ethanoazecino[5,4-*b*]indole-14-carboxylate (14). Yield 0.29 g (63%), colorless crystals, m.p. 221—222 °C (ethyl acetate). Found (%): C, 68.47; H, 7.39; N, 6.02. $C_{26}H_{34}N_2O_5$. Calculated (%): C, 68.70; H, 7.54; N, 6.16. IR, ν/cm^{-1}: 1745 (CO), 1652(CO). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.86 (t, 3 H, $CH_2C\underline{H}_3$, J = 7.5 Hz); 1.26—1.30 (m, 1 H, CH_2); 1.53—1.62 (m, 2 H, CH_2); 1.69—1.91 (m, 4 H, CH_2, C<u>H</u>$_2$Me, C(15)H); 2.18 (s, 3 H, COMe); 2.36 (dd, 1 H, CH_2, J = 8.7 Hz, J = 13.1 Hz); 2.75 (d, 1 H, C(15)H, J = 13.4 Hz); 2.90—2.99 (m, 2 H, CH_2); 3.19—3.26 (m, 1 H, CH_2); 3.21 (s, 3 H, OMe); 3.56—3.60 (m, 1 H, CH_2); 3.73—3.76 (m, 1 H, CH_2); 3.83 (s, 3 H, CO_2Me); 4.16 (s, 1 H, OH); 4.64 (s, 1 H, C(8)H); 5.33 (br.s, 1 H, CH=C<u>H</u>COMe); 7.14—7.23 (m, 3 H, Ar); 7.53 (d, 1 H, Ar, J = 6.9 Hz); 7.61 (d, 1 H, C<u>H</u>=CHCOMe, J = 13.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 8.0, 20.5, 22.8, 27.0, 28.6, 33.1, 40.3, 40.7, 54.4, 55.2, 56.2, 60.6, 75.4, 82.9, 98.9, 112.2, 113.3, 118.5, 120.5, 123.1, 127.9, 133.3, 135.4, 149.7, 174.8, 195.6. MS, m/z (I_{rel} (%)): 454 [M]$^+$ (24), 439 (54), 436 (25), 422 (27), 421 (79), 238 (25), 224 (46), 194 (29), 186 (100), 182 (26), 180 (44), 174 (26), 168 (62), 167 (73), 158 (53), 156 (35), 154 (23), 144 (34), 143 (26), 140 (38), 43 (31).

Dimethyl (2*E*)-2-[7-ethyl-14-hydroxy-8-methoxy-14-(methoxycarbonyl)-1,4,5,6,7,8-hexahydro-7,9-ethanoazecino[5,4-*b*]indol-3(2*H*)-yl]but-2-enedioate (15). Yield 0.39 g (73%), colorless crystals, m.p. 201—203 °C (ethyl acetate). Found (%): C, 63.37; H, 6.71; N, 5.22. $C_{28}H_{36}N_2O_8$. Calculated (%): C, 63.62; H, 6.86; N, 5.30. IR, ν/cm^{-1}: 1755 (CO), 1739 (CO), 1671 (CO). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.83 (t, 3 H, $CH_2C\underline{H}_3$, J = 7.5 Hz); 1.18—1.22 (m, 1 H, CH_2); 1.53—1.60 (m, 2 H, C<u>H</u>$_2$Me, CH_2); 1.62—1.70 (m, 1 H, CH_2); 1.78—1.88 (m, 3 H, CH_2, C<u>H</u>$_2$Me, C(15)H); 2.27 (ddd, 1 H, CH_2, J = 14.3 Hz, J = 6.9 Hz, J = 1.9 Hz); 2.73 (d, 1 H, C(15)H, J = 13.7 Hz); 2.83—2.89 (m, 1 H, CH_2); 2.98 (dd, 1 H, CH_2, J = 14.9 Hz, J = 4.4 Hz); 3.21 (ddd, 1 H, CH_2, J = 14.3 Hz, J = 11.8 Hz, J = 1.9 Hz); 3.32 (s, 3 H, OMe); 3.59 (dd, 1 H, CH_2, J = 14.4 Hz, J = 8.3 Hz); 3.68 (s, 3 H, CO_2Me); 3.77—3.82 (m, 1 H, CH_2); 3.82 (s, 3 H, CO_2Me); 3.97 (s, 3 H, CO_2Me); 4.48 (s, 1 H, OH); 4.57 (s, 1 H, C(8)H); 4.69 (s, 1 H, CH=); 7.13—7.21 (m, 3 H, Ar); 7.48 (d, 1 H, Ar, J = 8.1 Hz). ^{13}C NMR (150 MHz, $CDCl_3$), δ: 8.1, 20.1, 22.7, 24.6, 26.3, 33.0, 39.0, 41.0, 51.1, 53.0, 54.5, 56.2, 58.1, 74.5, 82.9, 88.8, 112.2, 112.6, 118.5, 120.5, 123.1, 127.8, 133.2, 135.4, 154.4, 166.6, 167.9, 174.9. MS, m/z (I_{rel} (%)): 528 [M]$^+$ (72), 514 (29), 513 (100), 510 (20), 497 (30), 496 (17), 495 (35), 469 (47), 437 (26), 356 (19), 266 (16),

224 (19), 186 (35), 180 (17), 168 (18), 167 (18), 158 (20), 156 (17), 144 (18).

Reactions of eburnamenine derivatives 4 and 5 with methyl propiolate, acetylacetylene, and DMAD (general procedure). A solution of compound **4** or **5** (1 mmol) and methyl propiolate, acetylacetylene, or DMAD (2 mmol) in methanol (20 mL) was kept at 40 °C until the reaction was completed (monitoring by TLC, Sorbfil, ethyl acetate). Methanol was distilled off *in vacuo*. The residue was chromatographed on alumina using a 1 : 5 ethyl acetate—hexane mixture as the eluent for compounds **16**—**18** and ethyl acetate as the eluent for compounds **19**—**21**.

Ethyl 7-ethyl-8-methoxy-3-[(1*E*)-3-methoxy-3-oxoprop-1-en-1-yl]-1,2,3,4,5,6,7,8-octahydro-7,9-ethenoazecino[5,4-*b*]-indole-14-carboxylate (16). Yield 0.38 g (82%), colorless crystals, m.p. 157—159 °C (ethyl acetate—hexane). Found (%): C, 69.25; H, 7.22; N, 5.88. $C_{27}H_{34}N_2O_5$. Calculated (%): C, 69.50; H, 7.35; N, 6.00. IR, ν/cm^{-1}: 1721 (CO), 1693 (CO). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.86—1.02 (m, 1 H, CH_2); 0.97 (t, 3 H, $CH_2C\underline{H}_3$, J = 7.4 Hz); 1.34—1.47 (m, 1 H, CH_2); 1.39 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.2 Hz); 1.56—1.88 (m, 4 H, CH_2, $C\underline{H}_2Me$); 2.48 (dd, 1 H, CH_2, J = 14.1 Hz, J = 4.9 Hz); 2.92—3.00 (m, 2 H, CH_2); 3.19—3.38 (m, 2 H, CH_2); 3.22 (s, 3 H, OMe); 3.71 (s, 3 H, CO_2Me); 3.73—3.82 (m, 1 H, CH_2); 4.08 (s, 1 H, C(8)H); 4.42 (q, 2 H, $OC\underline{H}_2Me$, J = 7.2 Hz); 4.79 (d, 1 H, CH=C$\underline{H}CO_2Me$, J = 13.1 Hz); 6.22 (s, 1 H, C(15)H); 7.16—7.24 (m, 2 H, Ar); 7.31—7.34 (m, 1 H, Ar); 7.51—7.57 (m, 2 H, Ar, $C\underline{H}$=$CHCO_2Me$). MS, m/z (I_{rel} (%)): 466 $[M]^+$ (27), 437 (15), 435 (16), 419 (13), 407 (10), 324 (14), 311 (42), 310 (100), 296 (10), 294 (16), 282 (24), 280 (28), 266 (16), 252 (35), 250 (10), 237 (16), 220 (12), 206 (10), 203 (16), 193 (12).

Ethyl 7-ethyl-8-methoxy-3-[(1*E*)-3-oxobut-1-en-1-yl]-1,2,3,4,5,6,7,8-octahydro-7,9-ethenoazecino[5,4-*b*]indole-14-carboxylate (17). Yield 0.19 g (43%), colorless crystals, m.p. 156—158 °C (ethyl acetate—hexane). Found (%): C, 71.69; H, 7.48; N, 6.14. $C_{27}H_{34}N_2O_4$. Calculated (%): C, 71.97; H, 7.61; N, 6.22. IR, ν/cm^{-1}: 1722 (CO), 1662 (CO). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.88—1.02 (m, 1 H, CH_2); 0.97 (t, 3 H, $CH_2C\underline{H}_3$, J = 7.3 Hz); 1.36—1.46 (m, 1 H, CH_2); 1.40 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.1 Hz); 1.60—1.82 (m, 4 H, CH_2, CH_2Me); 2.15 (s, 3 H, COMe); 2.50—2.60 (m, 1 H, CH_2); 2.92—3.10 (m, 2 H, CH_2); 3.17—3.41 (m, 2 H, CH_2); 3.21 (s, 3 H, OMe); 3.76—3.85 (m, 1 H, CH_2); 4.04 (s, 1 H, C(8)H); 4.42 (q, 2 H, OCH_2Me, J = 7.1 Hz); 5.29 (br.s, 1 H, CH=CHCOMe); 6.21 (s, 1 H, C(15)H); 7.17—7.25 (m, 2 H, Ar); 7.31—7.36 (m, 1 H, Ar); 7.50—7.57 (m, 2 H, Ar, CH=CHCOMe). ^{13}C NMR (100 MHz, DMSO-d_6), δ: 7.6, 13.9, 20.8, 20.9, 26.5, 26.9, 30.0, 42.8, 54.1, 55.3, 55.8, 61.5, 73.4, 98.5, 112.4, 115.9, 118.9, 120.6, 123.1, 127.8, 128.9, 129.1, 132.8, 135.2, 152.0, 163.0, 194.8. MS, m/z (I_{rel} (%)): 450 $[M]^+$ (94), 435 (30), 434 (26), 421 (38), 419 (23), 389 (14), 377 (17), 338 (47), 325 (14), 324 (14), 311 (22), 310 (100), 294 (13), 282 (23), 280 (33), 266 (21), 252 (35), 252 (45), 237 (25), 220 (20), 206 (14), 204 (12), 193 (15), 180 (12), 140 (72), 43 (12).

Dimethyl (2*E*)-2-{14-(ethoxycarbonyl)-7-ethyl-8-methoxy-1,4,5,6,7,8-hexahydro-7,9-ethenoazecino[5,4-*b*]indol-3(2*H*)-yl}but-2-enedioate (18). Yield 0.22 g (42%), colorless crystals, m.p. 154—156 °C (ethyl acetate—hexane). Found (%): C, 66.21; H, 6.80; N, 5.26. $C_{29}H_{36}N_2O_7$. Calculated (%): C, 66.39; H, 6.92; N, 5.34. IR, ν/cm^{-1}: 1738 (CO), 1725 (CO), 1701 (CO). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.51—0.62 (m, 1 H, CH_2); 0.97 (t, 3 H, $CH_2C\underline{H}_3$, J = 7.4 Hz); 1.10—1.30 (m, 1 H, CH_2); 1.39 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.1 Hz); 1.47—1.69 (m, 2 H, CH_2, $C\underline{H}_2Me$); 1.72—1.84 (m, 1 H, $C\underline{H}_2Me$); 1.86—1.97 (m, 1 H, CH_2); 2.37 (dd, 1 H, CH_2, J = 14.5 Hz, J = 5.1 Hz); 2.93—3.04 (m, 2 H, CH_2); 3.16—3.27 (m, 1 H, CH_2); 3.32 (s, 3 H, OMe); 3.52 (dd, 1 H, CH_2, J = 14.0 Hz, J = 8.6 Hz); 3.68 (s, 3 H, CO_2Me); 3.83—3.92 (m, 1 H, CH_2); 3.93 (s, 3 H, CO_2Me); 4.37 (s, 1 H, C(8)H); 4.41 (q, 2 H, $OC\underline{H}_2Me$, J = 7.1 Hz); 4.64 (s, 1 H, CH=); 6.34 (s, 1 H, C(15)H); 7.14—7.27 (m, 2 H, Ar); 7.31 (d, 1 H, Ar, J = 8.1 Hz); 7.47 (d, 1 H, Ar, J = 7.5 Hz). MS, m/z (I_{rel} (%)): 524 $[M]^+$ (67), 509 (24), 495 (21), 494 (11), 493 (24), 465 (11), 352 (27), 324 (15), 312 (13), 311 (56), 310 (100), 309 (20), 308 (13), 294 (14), 282 (13), 280 (26), 266 (10), 252 (16), 214 (13).

Methyl (2*E*)-3-{7-ethyl-14-(hydroxymethyl)-8-methoxy-1,4,5,6,7,8-hexahydro-7,9-ethenoazecino[5,4-*b*]indol-3(2*H*)-yl}acrylate (19). Yield 0.24 g (57%), colorless crystals, m.p. 136—138 °C (ethyl acetate). Found (%): C, 70.49; H, 7.44; N, 6.48. $C_{25}H_{32}N_2O_4$. Calculated (%): C, 70.73; H, 7.60; N, 6.60. IR, ν/cm^{-1}: 1696 (CO). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.93 (t, 3 H, $CH_2C\underline{H}_3$, J = 7.4 Hz); 1.23—1.46 (m, 2 H, CH_2); 1.59—1.78 (m, 4 H, CH_2, $C\underline{H}_2Me$); 2.33 (s, 1 H, $CH_2O\underline{H}$); 2.56 (dd, 1 H, CH_2, J = 13.6 Hz, J = 2.0 Hz); 2.86—2.98 (m, 2 H, CH_2); 3.10—3.39 (m, 2 H, CH_2); 3.16 (s, 3 H, OMe); 3.71 (s, 3 H, CO_2Me); 3.75—3.81 (m, 1 H, CH_2); 4.02 (s, 1 H, C(8)H); 4.61 (d, 1 H, $C\underline{H}_2OH$, J = 13.4 Hz); 4.81 (d, 1 H, CH=C$\underline{H}CO_2Me$, J = 13.4 Hz); 4.90 (d, 1 H, $C\underline{H}_2OH$, J = 13.4 Hz); 5.09 (s, 1 H, C(15)H); 7.16—7.21 (m, 1 H, Ar); 7.26—7.31 (m, 1 H, Ar); 7.53 (d, 1 H, Ar, J = 7.8 Hz); 7.57 (d, 1 H, $C\underline{H}$=$CHCO_2Me$, J = 13.4 Hz); 7.78 (d, 1 H, Ar, J = 8.4 Hz). MS, m/z (I_{rel} (%)): 424 $[M]^+$ (44), 409 (11), 395 (20), 393 (30), 377 (17), 363 (23), 282 (13), 269 (30), 268 (100), 252 (20), 239 (10), 238 (40), 236 (16), 223 (13), 222 (12), 208 (16), 206 (10), 193 (11), 180 (10).

(3*E*)-4-{7-Ethyl-14-(hydroxymethyl)-8-methoxy-1,4,5,6,7,8-octahydro-7,9-ethenoazecino[5,4-*b*]indol-3(2*H*)-yl}but-3-en-2-one (20). Yield 0.12 g (28%), colorless crystals, m.p. 139—141 °C (ethyl acetate). Found (%): C, 73.22; H, 7.75; N, 6.77. $C_{25}H_{32}N_2O_3$. Calculated (%): C, 73.50; H, 7.90; N, 6.86. IR, ν/cm^{-1}: 1643 (CO). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.93 (t, 3 H, $CH_2C\underline{H}_3$, J = 7.4 Hz); 1.17—1.37 (m, 1 H, CH_2); 1.57—1.69 (m, 3 H, CH_2, $C\underline{H}_2Me$); 2.13—2.19 (m, 2 H, CH_2); 2.16 (s, 3 H, COMe); 2.38 (t, 1 H, $CH_2O\underline{H}$, J = 6.0 Hz); 2.63 (d, 1 H, CH_2, J = 13.0 Hz); 2.90—3.04 (m, 2 H, CH_2); 3.12—3.38 (m, 2 H, CH_2); 3.14 (s, 3 H, OMe); 3.81 (td, 1 H, CH_2, J = 13.8 Hz, J = 2.8 Hz); 3.98 (s, 1 H, C(8)H); 4.61 (dd, 1 H, $C\underline{H}_2OH$, J = 13.5 Hz, J = 6.0 Hz); 4.90 (dd, 1 H, $C\underline{H}_2OH$, J = 13.5 Hz, J = 6.0 Hz); 5.07 (s, 1 H, C(15)H); 5.31 (br.s, 1 H, CH=C$\underline{H}$COMe); 7.17—7.21 (m, 1 H, Ar); 7.26—7.31 (m, 1 H, Ar); 7.53 (d, 1 H, Ar, J = 7.4 Hz); 7.55 (d, 1 H, $C\underline{H}$=CHCOMe, J = 13.3 Hz); 7.78 (d, 1 H, Ar, J = 8.4 Hz). MS, m/z (I_{rel} (%)): 408 $[M]^+$ (40), 393 (49), 379 (18), 377 (16), 347 (16), 282 (15), 269 (22), 268 (100), 252 (28), 250 (18), 239 (19), 238 (68), 236 (31), 223 (27), 222 (17), 221 (14), 220 (17), 204 (14), 140 (59).

Dimethyl (2*E*)-2-{7-ethyl-14-(hydroxymethyl)-8-methoxy-1,4,5,6,7,8-hexahydro-7,9-ethenoazecino[5,4-*b*]indol-3(2*H*)-yl}but-2-enedioate (21). Yield 0.19 g (40%), colorless crystals, m.p. 133—135 °C (ethyl acetate). Found (%): C, 66.96; H, 6.97; N, 5.74. $C_{27}H_{34}N_2O_6$. Calculated (%): C, 67.20; H, 7.10; N, 5.81. IR, ν/cm^{-1}: 1742 (CO), 1698 (CO). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.77—0.87 (m, 1 H, CH_2); 0.93 (t, 3 H, $CH_2C\underline{H}_3$, J = 7.5 Hz); 1.25—1.33 (m, 1 H, CH_2); 1.45—1.55 (m, 1 H, CH_2); 1.57—1.67 (m, 1 H, CH_2); 1.71—1.86 (m, 2 H, $C\underline{H}_2Me$); 2.31 (t, 1 H, $CH_2O\underline{H}$, J = 6.0 Hz); 2.46 (ddd, 1 H, CH_2, J = 14.6 Hz,

J = 5.8 Hz, J = 2.4 Hz); 2.91—3.02 (m, 2 H, CH_2); 3.19 (ddd, 1 H, CH_2, J = 15.0 Hz, J = 11.8 Hz, J = 1.9 Hz); 3.26 (s, 3 H, OMe); 3.48—3.55 (m, 1 H, CH_2); 3.67 (s, 3 H, CO_2Me); 3.86 (ddd, 1 H, CH_2, J = 14.9 Hz, J = 4.3 Hz, J = 2.2 Hz); 3.91 (s, 3 H, CO_2Me); 4.30 (s, 1 H, C(8)H); 4.61 (dd, 1 H, C$\underline{H}_2$OH, J = 13.5 Hz, J = 6.0 Hz); 4.67 (s, 1 H, CH=); 4.88 (dd, 1 H, C$\underline{H}_2$OH, J = 13.5 Hz, J = 6.0 Hz); 5.22 (s, 1 H, C(15)H); 7.17 (t, 1 H, Ar, J = 7.4 Hz); 7.23—7.31 (m, 1 H, Ar); 7.48 (d, 1 H, Ar, J = 7.8 Hz); 7.77 (d, 1 H, Ar, J = 8.4 Hz). MS, m/z (I_{rel} (%)): 482 $[M]^+$ (74), 467 (57), 453 (38), 451 (35), 435 (18), 423 (25), 422 (27), 421 (100), 310 (21), 282 (17), 269 (26), 268 (61), 252 (21), 250 (18), 238 (29), 222 (24), 208 (32), 193 (25), 180 (23).

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