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REACTION OF 1-SUBSTITUTED TETRAHYDRO-β-CARBOLINES WITH ACTIVATED ALKYNES – A NEW ORIGINAL APPROACH TO THE SYNTHESIS OF TETRAHYDROAZOCINO[5,4-*b*]INDOLES

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The transformations of 1-substituted tetrahydro-β-carbolines by the action of activated alkynes were studied. The action of dimethyl acetylenedicarboxylate in methanol gives products of the opening of the tetrahydropyridine fragment, namely, 2-methoxyalkylindoles. The action of ethyl propiolate in ethanol and of tosylacetylene in methanol gives mixtures of azocino[5,4-b]indoles and 2-alkoxyindoles. The action of ethyl propiolate in acetonitrile gives azocinoindoles.

Keywords: azocino[5,4-*b*]indoles, 2-alkoxyalkylindoles, activated alkynes, tetrahydro-β-carbolines, ring expansion.

Azocinoindoles with different fusion of the azocine and indole systems are a structural fragment in many alkaloids displaying a broad range of biological activity. The major efforts of synthetic organic chemists have been directed toward the development of methods to synthesize analogs of natural products. There have been only a few reports on methods for the synthesis of azocinoindoles. These methods involve multiple steps and, as a rule, give a low yield of the desired products.

We have recently described a new method for the synthesis of tetrahydroazocino[4,5-*b*]indoles employing tandem transformations of tetrahydro-γ-carbolines by the action of dimethyl acetylenedicarboxylate and ethyl propiolate in methanol and ethanol [1]. This two-step method involving the formation of 3-alkoxyalkyl-2-[N-alkyl-N-dimethoxycarbonyl(ethoxycarbonyl)vinyl]aminoethylindoles and their cyclization to azocinoindoles by the action of aluminum chloride in a *one-pot* procedure provides tetrahydroazocinoindoles at room temperature in 40-75% yield. Preliminary screening of tetrahydroazocino[4,5-*b*]indoles has revealed their strong tendency to inhibit acetyl- and butyrylcholinesterases [2].

We thus found both theoretical and practical interest in the study of the transformations of 1-substituted tetrahydro-β-carbolines by the action of activated alkynes in order to develop a general approach toward the synthesis of isomeric azocinoindoles from tetrahydrocarbolines, determine the effect of the position of the nitrogen atom in the tetrahydropyridine fragment of the tetrahydrocarbolines on the direction of the tandem transformations by the action of activated alkynes and the effects of solvent and substituents at $C_{(1)}$, and provide methods for the preparation of tetrahydroazocino[5,4-*b*]indoles, which hold promise for biological screening.

1-Substituted tetrahydro-β-carbolines were obtained by N-ethylation (**1-5**) and N-methylation (**6**) of the corresponding 1-substituted NH-β-carbolines obtained in the Pictet–Spengler reaction [3].

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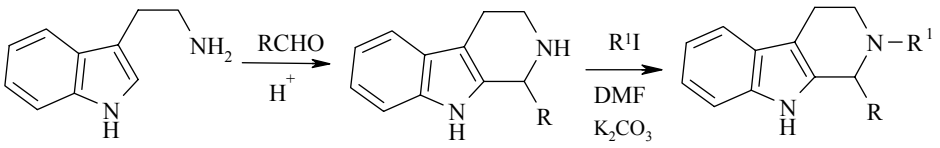
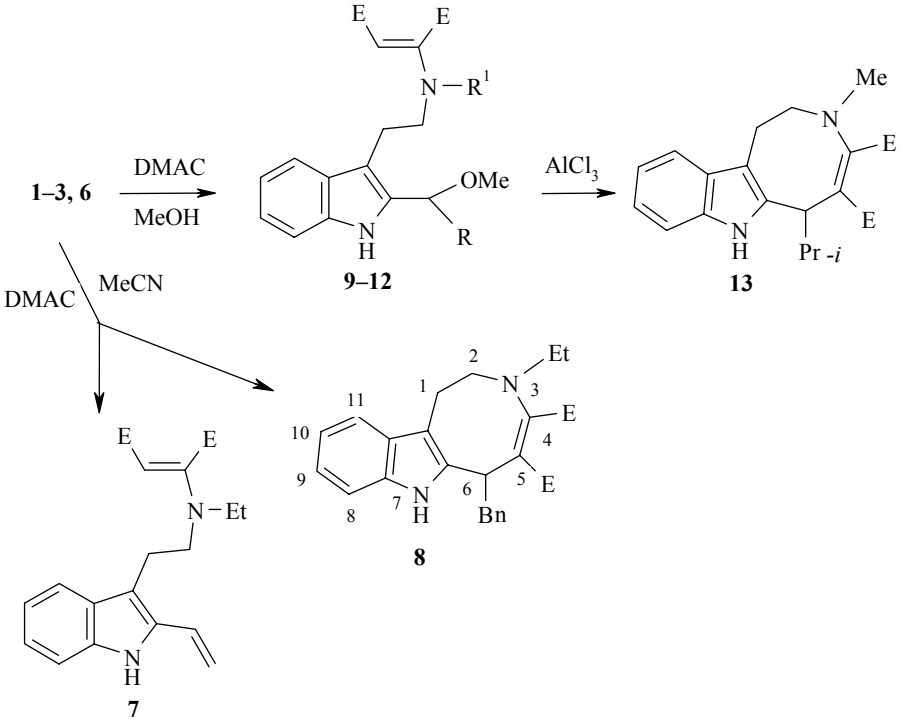
The activated alkynes studied were dimethyl acetylenedicarboxylate (DMAC), ethyl propiolate, tosylacetylene, and acetylacetylene. Acetonitrile, methanol, and ethanol served as the solvents. All the transformations were carried out at room temperature.



1–6

1 R = Me, **2, 6** R = *i*-Pr, **3** R = Bn, **4** R = C_6H_4F-*o*, **5** R = C_6H_4F-*p;*
1–5 R^1 = Et, **6** R^1 = Me

In contrast to tetrahydro-γ-carbolines, which give polymeric products by the action of DMAC in acetonitrile, tetrahydro-β-carbolines **1-3** and **6** are cleaved under these conditions to give 2-vinylindole **7** in the case of carboline **1** and azocino[5,4-*b*]indole **8** in the case of carboline **3**.

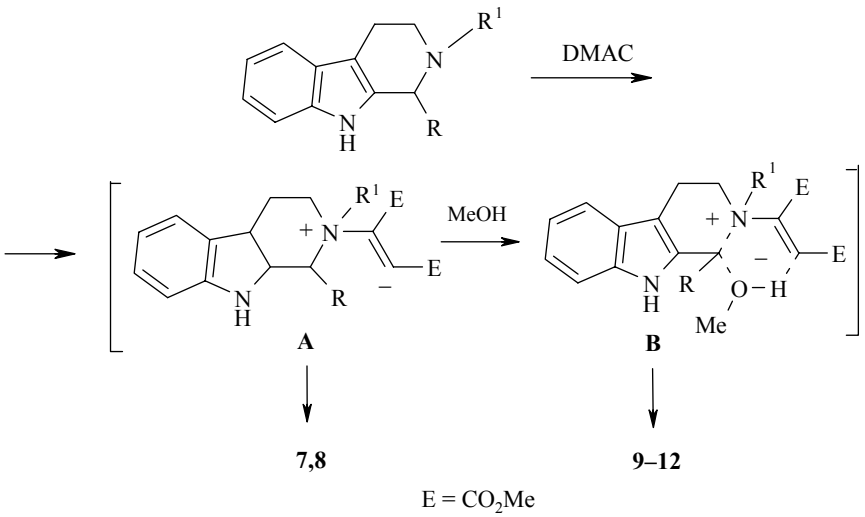


E = CO_2Me; **9** R = Me, **10, 12** R = *i*-Pr, **11** R = Bn; **9–11** R^1 = Et, **12** R^1 = Me

1-Isopropylcarbinols **2** and **6** form multicomponent reaction mixtures, which could not be separated into pure products. However, the finding of singlets in the ^{1}H NMR spectra of these mixtures at 4.68 and 4.72 ppm due to the terminal protons of the $C(CO_2Me)=C(CO_2Me)H$ group [4] suggest that opening of the tetrahydropyridine fragment also occurs in these cases.

Dimethyl acetylenedicarboxylate in methanol cleaves the tetrahydropyridine fragment of β-carbolines to give 2-methoxyalkyl-3-(N-alkyl-N-dimethoxycarbonylvinyl)aminoethylindoles **9-12**. Indole **12** was converted by the action of $AlCl_3$ in acetonitrile to azocinoindole **13**.

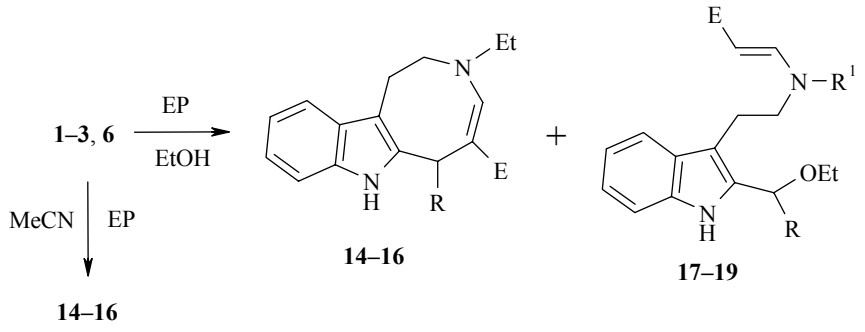
We assume that the reaction of tetrahydro-β-carbolines with alkynes, as in the case of tetrahydro-γ-carbolines, starts with nucleophilic attack of the amine nitrogen atom on the triple bond of the alkynes, leading to zwitter-ion **A**.



E = CO_2Me

Nucleophilic attack in acetonitrile on the substituent at $C_{(1)}$ (Hoffman cleavage) or at $C_{(1)}$ in the ring (ring expansion) leads to **7** or **8**, respectively. An increase in the electron-donor properties of substituent R should presumably facilitate cleavage of the $C_{(1)}$–N^+ bond. Even formation of a carbocation and the corresponding transformations are possible. The formation of multicomponent mixtures in the reactions of carbolines **2** and **6** (R = *i*-Pr) is probably related to the abovementioned processes. Cleavage of the $C_{(1)}$–N^+ bond in methanol is facilitated by the cooperative action of the alcohol and proceeds through six-membered transition state **B**.

Ethyl propiolate reacts with carbolines **1-3** and **6** much more rapidly, probably due to less delocalization of the negative charge in intermediate zwitter-ion **A**. Mixtures of azocino[5,4-*b*]indoles and 2-ethoxyalkyl-3-(N-alkyl-N-ethoxycarbonylvinyl)aminoethylindoles of varying composition are formed in absolute ethanol. We separated azocine **14** from carboline **1**, azocines **15** and **16** and the corresponding indoles **17** and **18** from carbolines **2** and **3**, but only indole **19** from carboline **6**. The action of ethyl propiolate in acetonitrile on tetrahydrocarbolines **1-3** gave only the corresponding azocino[5,4-*b*]indoles **14-16** in 30-75% yield.



14 R = Me, **15, 17, 19** R = *i*-Pr, **16, 18** R = Bn; **17, 18** R^1 = Et, **19** R^1 = Me;
E = CO_2Et; EP – ethyl propiolate

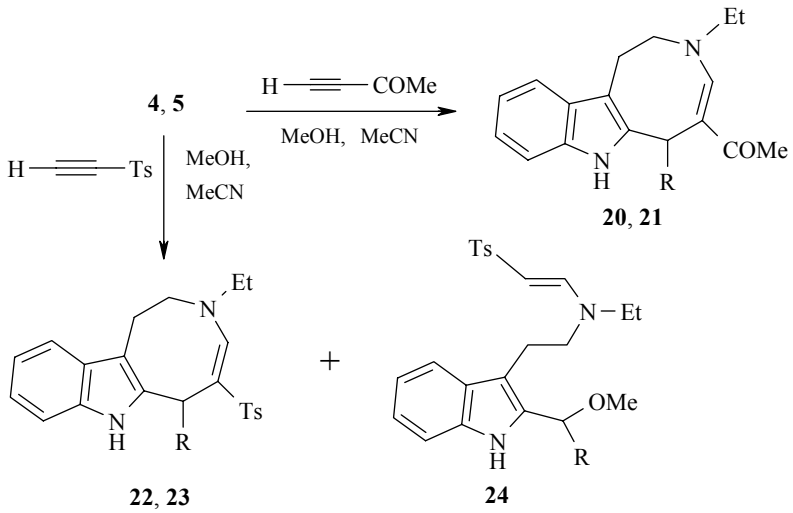
TABLE 1. Characteristics of the Products Synthesized

Compound	Empirical formula	Found, % / Calculated, %			$[M]^{+\bullet}$	mp, °C*	R_f Alufol*[2]	Yield, %
		C	H	N				
1	$C_{14}H_{18}N_2$	78.56 / 78.46	8.56 / 8.47	13.19 / 13.07	214	Oil	0.60	65
2	$C_{16}H_{22}N_2$	79.34 / 79.29	9.30 / 9.15	11.63 / 11.56	242	Oil	0.55	67
3	$C_{20}H_{22}N_2$	82.87 / 82.72	7.85 / 7.64	9.35 / 9.65	290	Oil	0.55	60
4	$C_{19}H_{19}FN_2$	77.30 / 77.52	6.35 / 6.51	9.40 / 9.52	294	95-97	—	73
5	$C_{19}H_{19}FN_2$	77.68 / 77.52	6.71 / 6.51	9.45 / 9.52	294	96-98	—	76
6	$C_{15}H_{20}N_2$	79.15 / 78.90	8.70 / 8.83	12.20 / 12.27	228	Oil	0.55	64
7	$C_{20}H_{24}N_2O_4$	67.54 / 67.40	6.70 / 6.71	7.78 / 7.87	356	Oil	0.60	35
8	$C_{26}H_{28}N_2O_4$	72.03 / 72.22	6.75 / 6.48	6.25 / 6.48	432	148-150	0.50	48
9	$C_{21}H_{28}N_2O_5$	64.67 / 64.93	6.95 / 7.27	7.50 / 7.27	388	136–138	0.55	75
10	$C_{23}H_{32}N_2O_5$	66.02 / 66.32	7.90 / 7.74	6.82 / 6.73	416	148-150	0.45	89
11	$C_{27}H_{32}N_2O_5$	69.93 / 69.81	7.12 / 6.94	5.95 / 6.03	464	144-146	0.60	73
12	$C_{22}H_{30}N_2O_5$	65.53 / 65.65	7.75 / 7.51	7.15 / 6.96	402	112-116	0.48	78
13	$C_{21}H_{26}N_2O_4$	67.90 / 68.09	7.20 / 7.07	7.49 / 7.56	370	175-177	0.55	27
14	$C_{19}H_{24}N_2O_2$	73.20 / 73.05	7.50 / 7.69	8.85 / 8.97	312	188-190	0.55	75
15	$C_{21}H_{28}N_2O_2$	73.93 / 74.08	8.63 / 8.29	8.01 / 8.23	340	222-224	0.50	70
16	$C_{25}H_{28}N_2O_2$	77.05 / 77.29	7.50 / 7.26	7.12 / 7.21	388	246-248	0.53	71
17	$C_{23}H_{34}N_2O_3$	71.57 / 71.47	8.94 / 8.87	7.31 / 7.25	386	88-90	0.55	45
18	$C_{27}H_{34}N_2O_3$	74.55 / 74.62	7.95 / 7.89	6.30 / 6.45	434	Oil	0.60	46
19	$C_{22}H_{32}N_2O_3$	70.87 / 70.94	8.73 / 8.66	7.46 / 7.52	372	79-81	0.60	63
20	$C_{23}H_{23}FN_2O$	75.93 / 76.22	6.58 / 6.40	7.90 / 7.73	362	271-273	—	67
21	$C_{23}H_{23}FN_2O$	76.45 / 76.22	6.70 / 6.40	7.52 / 7.73	362	268-270	—	35
22	$C_{28}H_{27}FN_2O_2S$	70.35 / 70.16	5.40 / 5.73	6.03 / 5.90	474	266-268	—	62
23	$C_{28}H_{27}FN_2O_2S$	69.93 / 70.16	5.87 / 5.73	5.75 / 5.90	474	263-265	—	34
24	$C_{29}H_{31}FN_2O_3S$	68.53 / 68.75	6.30 / 6.17	5.35 / 5.53	507	115-117	—	58
25a	$C_{25}H_{30}N_2O_2$	76.95 / 76.89	7.84 / 7.74	7.11 / 7.17	390	Oil	0.60	27
25b	$C_{25}H_{30}N_2O_2$	76.98 / 76.89	7.57 / 7.74	7.32 / 7.17	390	Oil	0.40	28

* Solvent: acetone (**4, 5**), ethyl acetate–hexane (**8-12, 17, 24**), ethyl acetate (**13-16, 20-23**), hexane (**19**).

*[2] 1:3 ethyl acetate–hexane (**1, 7, 9-12, 14-19**), 1:1 ethyl acetate–hexane (**2, 3, 6, 8, 13**), 1:2 ethyl acetate–hexane (**25a, 25b**).

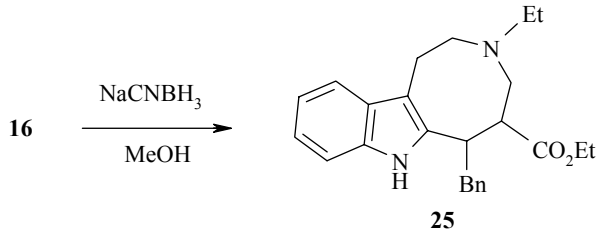
Carbolines **4** and **5** are transformed by the action of acetylacetylene in methanol and acetonitrile and by the action of tosylacetylene in acetonitrile into 5-acetyl-6-fluorophenyl- **20, 21** and 5-tosylazocino-[5,4-*b*]indoles **22, 23**. In methanol, 1-*o*-fluorophenylcarboline **4** and tosylacetylene give a ~1:1 mixture of azocinoindole **22** and 2-(*o*-fluorophenyl)-2-methoxymethylindole **24**.



20, **22**, **24** R = C_6H_4F-*o*, **21**, **23** R = C_6H_4F-*p*

These results are in good accord with the formation of an intermediate zwitter-ion **A** and the electronic effects of the substituents and solvents on the direction of the transformation of this intermediate.

Azocinoindole **16** was reduced by sodium cyanoborohydride to the corresponding hexahydro derivative **25**, which is formed as a ~1:1 mixture of geometric isomers by interchange of the benzyl and ethoxycarbovinyl groups and separated into pure products by column chromatography. Unfortunately, an unequivocal assignment of the NMR signals could not be made due to the complexity of these spectra.



The ^{1}H NMR spectra of indoles **9-12, 17-19,** and **24**, azocinoindoles **13-16** and **20-23** show the signals for all the protons in their structures. The spectra of indoles **9-12** show a singlet for the dimethoxycarbonylvinyl group at 4.50-4.80 ppm, while indoles **17-19** and **24** show two doublets for the protons of the double bond of the N-ethoxycarbonyl and N-tosylvinyl fragments at 4.45 and 7.40 ppm and a coupling constant of 12.7 Hz. The spectra of azocinoindoles **14-16** and **20-23** show a characteristic singlet at 7.35-7.69 ppm due to H-4.

Thus, we have developed an original preparative two-step approach to the synthesis of tetrahydroazocino[5,4-*b*]indoles.

TABLE 2. Parameters of the ^{1}H NMR Spectra of Tetrahydro-β-carbolines **1–4, 6**

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)									
	H-1	2-R[1]	3-CH_2	4-CH_2	H-5	H-6	H-7	H-8	1-R	NH (br. s)
1	3.84 (q, *J* = 6.7)	1.16 (t, *J* = 7.3, CH_3); 2.80 (q, *J* = 7.3, CH_2)	3.18 (td, *J* = 4.75, *J* = 11.3); 2.82–2.85 (m)	2.55-2.79 (m)	7.28 (m)	7.00-7.15 (m)		7.46 (m)	1.40 (d, *J* = 6.7, CH_3)	7.73
2	3.05-3.30 (m)	1.13 (t, *J* = 7.3, CH_3); 2.45–2.55 (m, CH_2)	3.05–3.30 (m)	2.60-2.90 (m)	7.25 (d, *J* = 7.6)	7.10 (t, *J* = 7.6)	7.15 (t, *J* = 7.6)	7.50 (d, *J* = 7.6)	1.05 (d, *J* = 6.8, CH_3); 1.21 (d, *J* = 6.8, CH_3); 2.00 (m, CH)	7.71
3	4.02 (dd, *J* = 5.3, *J* = 9.6)	1.20 (t, *J* = 7.1, CH_3); 2.62 (q, *J* = 7.1, CH_2)	3.10 (ddd, *J* = 2.7, *J* = 5.3, *J* = 13.1); 3.29 (ddd, *J* = 4.6, *J* = 10. 2, *J* = 13.1)	3.10 (ddd, *J* = 2.7, *J* = 4.6, *J* = 15.6); 3.88 (ddd, *J* = 5.3, *J* = 10.2, *J* = 15.6)	7.21-7.49 (m, H-5–H-8, C_6H_5)				2.94 (dd, *J* = 5.3, *J* = 13.1, CH_2); 3.34 (dd, *J* = 5.3, *J* = 13.1, CH_2); 7.21-7.49 (m, C_6H_5)	6.78
4	4.02 (dd, *J* = 6.6)	1.17 (t, *J* = 7.0, CH_3); 2.82 (q, *J* = 7.0, CH_2)	2.82–2.85 (m); 3.14 (td, *J* = 4.8, *J* = 11.5)	2.72-2.83 (m)	7.25-7.50 (m, H-5–H-8, C_6H_4-F-*o*)					7.85
6	3.16 (d, *J* = 6.8)	2.47 (s)	2.60 (ddd, *J* = 2.2, *J* = 5.7, *J* = 15.7); 3.21 (ddd, *J* = 5.5, *J* = 11.5, *J* = 15.7)	2.85-2.90 (m)	7.32 (dd, *J* = 1.2, *J* = 7.9)	7.11–7.16 (m)		7.51 (br. d, *J* = 7.6)	1.00 (d, CH_3, *J* = 6.8, CH_3); 1.15 (d, *J* = 6.8, CH_3); 2.40 (m, *J* = 6.8, CH)	7.52

EXPERIMENTAL

The IR spectra of the products were taken neat (for oils) on a Specord IR-75 spectrometer. The electron impact ionization mass spectra were taken on a Finnigan MAT 95 XL GC/MS with direct sample inlet into the ion source at 70 eV. The ^{1}H NMR spectra were taken on Bruker WP-400 spectrometers at 400 MHz in $CDCl_3$ at 23°C with TMS as the internal standard. Alufol alumina plates were used for the thin-layer chromatography and Fluka-507C (0.05-0.15 mm granularity) alumina was used for the column chromatography. The physicochemical and elemental analysis data are given in Table 1, while the ^{1}H NMR spectral data are given in Tables 2-4.

1-R-2-R^1-2,3,4,9-Tetrahydro-1H-pyrido[3,4-*b*]indoles 1-6 (General Procedure). A solution of tryptamine (0.03 mol) and the corresponding aldehyde (0.03 mol) was heated at reflux in benzene or toluene (100 ml) with a Dean–Stark trap until the theoretically calculated amount of water was removed. The solvent was evaporated. Then, water (100 ml) and 2 N sulfuric acid (16 ml) were added to the residue and heated for 48 h at 50°C with monitoring by thin-layer chromatography. The mixture was cooled and brought to pH 9 by adding 20% aq. NaOH. Crystals of indoles **1-6** were filtered off, dried, and alkylated with methyl or ethyl iodide as follows. A solution of pyridoindole (5 mmol), corresponding alkyl iodide (8 mmol), and potassium carbonate (16 mmol) in absolute DMF (10 ml) was heated for 4 h at 50°C with monitoring by thin-layer chromatography. Then, water (10 ml) was added and the mixture was extracted with ether (3×100 ml). The extract was dried over $MgSO_4$. After distilling off the ether, the residue was subjected to chromatography on an alumina column to give 2-alkyltetrahydropyridoindoles **1-6** as yellow oils.

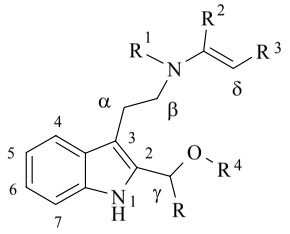
Reaction of Tetrahydro-β-carbolines 1-3 and 6 with Dimethyl Acetylenedicarboxylate (General Procedure). DMAC (1.2 mmol) was added to a solution of carboline **1-3** or **6** (1 mmol) in absolute methanol (10 ml) or in acetonitrile (10 ml) at 20°C. The mixture was monitored for 24 h by thin-layer chromatography and the solvent was evaporated. When the reaction was carried out in methanol, the residue was purified on alumina to give dimethyl (2*E*)-2-[ethyl(2-{2-[methoxy-(R)-methyl]-1H-indol-3-yl]-ethyl}amino]but- 2-enedioates **9-12**. When the reaction was carried out in acetonitrile, the residue was subjected to column chromatography using 1:10 and 1:5 ethyl acetate–hexane as the eluent. Carboline **1** gave dimethyl (2*E*)-2-{ethyl[2-(2-vinyl-1H-indol-3-yl)ethyl]amino}but-2-endioate (**7**), while carboline **3** gave 6-benzyl-3-ethyl-4,5-dimethoxycarbonyl-1,2,3,6-tetrahydroazocino[5,4-*b*]indole (**8**).

Reaction of Tetrahydro-β-carbolines 1-3 and 6 with Ethyl Propiolate and of Tetrahydro-β-carbolines 4 and 5 with Acetylacetylene and Tosylacetylene (General Procedure). Corresponding activated alkyne (1.2 mmol) was added to a solution of tetrahydro-β-carboline (1 mmol) in ethanol, methanol, or acetonitrile (10 ml) at 20°C with monitoring by thin-layer chromatography. The reaction with ethyl propiolate is complete after 3-5 h, while the reactions with tosylacetylene and acetylacetylene were complete after 120 h. The solvent was evaporated off. The residue was either crystallized from ethyl acetate to give azocino[5,4-*b*]indoles **14-16** and **20-23** or subjected to column chromatography, isolating azocino[5,4-*b*]indoles **15, 16,** and **20** and the corresponding 2-aminoalkyl-3-(N-ethyl(methyl)-N-vinyl-aminoethylindoles **17-19** and **24**.

6-Isopropyl-3-methyl-4,5-dimethyloxycarbonyl-1,2,3,6-tetrahydroazocino[5,4-*b*]indole (13). $AlCl_3$ (~3 mg) was added to a solution of 2-(1-methoxyisobutyl)indole (**12**) (0.6 mmol) in acetonitrile (10 ml) at 20°C. The mixture was monitored by thin-layer chromatography for 24 h and methanol was then evaporated in vacuum. The residue was subjected to column chromatography. Elution with 1:5 ethyl acetate–hexane gave 60 mg (27%) azocinoindole **13**.

6-Benzyl-5-ethoxycarbonyl-3-ethyl-1,2,3,4,5,6-hexahydroazocino[5,4-*b*]indole (25). Sodium cyano-borohydride (30 mg, 0.5 mmol) was added to a solution of acozinoindole **16** (0.2 g, 0.5 mmol) in methanol (10 ml) and heated at reflux for 2 h with monitoring by thin-layer chromatography. The solvent was

TABLE 3. Parameters of the ^{1}H NMR Spectra of 2-Alkoxyalkyl(2-vinyl)-3-(N-alkyl-N-vinyl)aminoethylindoles **7, 9-12, 17-19, 24**

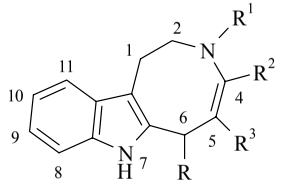


Com-pound	Chemical shifts, δ, ppm. (*J*, Hz)													
	α-CH_2	β-CH_2	γ-CH_2	δ-CH_2	H-4	H-5	H-6	H-7	R	R^1	R^2	R^3	R^4	NH (br. s)
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
7	3.07 (dd, *J* = 6.6, *J* = 8.3)	3.31 (t, *J* = 7.3)	4.81 (dd, *J* = 11.3, *J* = 17.7, CH=)	4.72 (s)	7.20 (d, *J* = 7.5, CH=)	7.11 (d, *J* = 7.5)	7.32 (d, *J* = 7.5)	7.53 (d, *J* = 7.5)	5.31 (d, *J* = 11.3, CH_2=); 5.51 (d, *J* = 17.7, CH_2=)	1.12 (t, *J* = 7.0, CH_3); 4.12 (q, *J* = 7.0, CH_2)	3.92 (s, CH_3)	3.66 (s, CH_3)	—	8.27
9	3.04 (dd, *J* = 4.5, *J* = 11.5)	3.16 (m)	4.65 (q, *J* = 6.5)	4.72 (s)	7.20 (d, *J* = 7.9)	7.14 (d, *J* = 7.9)	7.39 (d, *J* = 7.9)	7.55 (d, *J* = 7.9)	1.54 (d, *J* = 6.5, CH_3)	1.17 (t, *J* = 7.0, CH_3); 3.35 (q, *J* = 7.0, CH_2)	3.91 (s, CH_3)	3.67 (s, CH_3)	3.26 (s, CH_3)	8.35
10	3.05 (m)	3.25 (m)	4.09 (q, *J* = 7.2)	4.72 (s)	7.25 (d, *J* = 7.6)	7.11 (d, *J* = 7.6)	7.25 (d, *J* = 7.6)	7.56 (d, *J* = 7.6)	0.82 (t, *J* = 7.2, CH_3); 3.17 (q, *J* = 7.2, CH_2)	1.19 (t, *J* = 7.2, CH_3); 3.17 (q, *J* = 7.2, CH_2)	3.66 (s, CH_3)	3.35 (s, CH_3)	3.17 (s, CH_3)	8.14
11	3.10 (m)	3.42 (m)	4.18 (m)	4.66 (s)	7.02-7.15 (m)			7.61 (d, *J* = 7.9)	2.70-2.75 (m, CH_2); 7.02-7.17 (m, C_6H_5)	1.17 (t, *J* = 7.0, CH_3); 3.20 (q, *J* = 7.0, CH_2)	3.78 (s, CH_3)	3.65 (s, CH_3)	3.30 (s, CH_3)	8.31

TABLE 3. (continued)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
12	3.03 (m)	3.38 (m)	4.08 (d, J = 6.8)	4.65 (s)	7.20 (d, J = 8.0)	7.13 (d, J = 8.0)	7.35 (d, J = 8.0)	7.55 (d, J = 8.0)	0.82 (d, J = 6.8, CH3); 1.09 (d, J = 6.8, CH3); 2.02 (d. q, J = 6.8, J = 13.5, CH2)	2.88 (s, CH3)	3.92 (s, CH3)	3.66 (s, CH3)	3.20 (s, CH3)	8.17
17	3.00 (m)	3.36 (m)	4.14 (d, J = 7.16)	4.70 (d, J = 12.2)	7.34 (d, J = 8.0)	7.11 (d, J = 8.0)	7.15 (d, J = 8.0)	7.53 (d, J = 8.0)	0.82 (d, J = 6.6, CH_3); 1.10 (d, J = 6.6, CH_3); 2.00 (m, CH)	1.15 (t, J = 7.2, CH_3); 3.16 (q, J = 7.2, CH_2)	7.48 (H, d, J = 12.2)	1.27 (t, J = 7.1, CH_3); 3.35 (q, J = 7.1, CH_2)	1.16 (t, J = 7.1, CH_3); 4.14 (q, J = 7.1, CH_2)	8.21
18	2.59-2.68 (m)		4.65 (dd, J = 5.9, J = 8.3)	4.57 (d, J = 12.8)	7.00-7.38 (m)				3.03 (m, CH_2); 7.00-7.38 (m, C_6H_5)	1.05 (t, J = 7.2, CH_3); 3.01-3.99 (m)	7.45 (H, d, J = 12.7)	1.29 (t, J = 7.1, CH_3); 3.34 (q, J = 7.1, CH_2)	1.16 (t, J = 7.0, CH_3); 4.16 (q, J = 7.0, CH_2)	8.21
19	2.97 (dd, J = 6.02, J = 9.2)	3.43 (m)	4.14 (m)	4.58 (d, J = 12.7)	7.35 (d, J = 8.0)	7.19 (dd, J = 8.9, J = 8.0)	7.12 (d J = 8.0)	7.51 (d, J = 8.0)	0.81 (d, J = 6.7, CH_3); 1.08 (d, J = 6.7, CH_3); 2.01 (dq, J = 6.7, J = 13.4, CH_2)	2.84 (s, CH_3)	7.45 (H, d, J = 12.7)	1.27 (t, J = 7.1, CH_3); 3.53 (q, J = 7.1, CH_2)	1.16 (t, J = 7.0, CH_3); 4.15 (q, J = 7.0, CH_2)	8.16
24	3.00-3.25 (m)		3.76 (s)	4.65 (d, J = 12.6)	7.10-7.45 (m)				7.10-7.45 (m)	1.05 (t, J = 7.0, CH_3); 3.18 (q, J = 7.0, CH_2)	7.66 (H, d, J = 12.6)	2.32 (s, CH_3); 7.10-7.75 (m, Ts)	3.40 (s, CH_3)	8.20

TABLE 4. Parameters of the ^{1}H NMR Spectra of Tetrahydroazocino[5,4-*b*]indoles **8, 13-16, 20-23**



Com-pound	Chemicak shifts, δ, ppm (*J*, Hz)											
	1-CH_2	R-CH_2	H-6	H-8	H-9	H-10	H-11	R	R^1	R^2	R^3	NH (br. s)
1	2	3	4	5	6	7	8	9	10	11	12	13
8	2.74 (m)	3.65 (m)	4.53 (dd, *J* = 4.0, *J* = 10.1)	6.93-7.82				7.15 (m, CH_2); 6.93-7.82 (m, C_6H_5)	1.12 (t, *J* = 7.0, CH_3); 3.25 (q, *J* = 7.0, CH_2)	3.78 (s, CH_3)	3.70 (s, CH_3)	8.01
13	2.91 (m)	3.72 (m)	4.74 (m)	7.54 (d, *J* = 7.6)	7.03-7.11 (m)		7.18 (d, *J* = 7.6)	0.92 (d, *J* = 6.9, CH_3); 1.12 (d, *J* = 6.9, CH_3); 1.98 (2H, m, CH_2)	2.96 (s, CH_3)	3.93 (s, CH_3)	3.76 (s, CH_3)	7.95
14	3.29 (m)	3.57 (dt *J* = 3.4, *J* = 14.5); 4.08 (dt *J* = 2.8, *J* = 14.5)	4.69 (q, *J* = 7.3)	7.45 (d, *J* = 7.6)	7.05-7.15 (m)		7.25 (d, *J* = 7.6)	1.59 (d, *J* = 7.3, CH_3)	1.16 (t, *J* = 7.2, CH_3); 3.25 (q, *J* = 7.2, CH_2)	7.61 (s, H)	1.28 (t, *J* = 7.1, CH_3); 4.18 (q, *J* = 7.1, CH_2)	7.95

TABLE 4. (continued)

1	2	3	4	5	6	7	8	9	10	11	12	13
15	2.99 (dt J = 2.8, J = 14.1); 3.23 (m)	3.57 (ddt, J = 1.8, J = 2.6, J = 14.1); 4.09 (dt J = 2.6, J = 14.1)	4.15-4.18 (m)	7.46 (d, J = 7.6)	7.08-7.11 (m)		7.25 (d, J = 7.6)	0.89 (d, J = 6.8, CH_3); 1.06 (d, J = 6.8, CH_3); 2.04 (m, CH_2)	1.16 (t, J = 7.2, CH_3); 3.25 (q, J = 7.2, CH_2)	7.64 (s, H)	1.26 (t, J = 7.1, CH_3); 4.15-4.18 (m, CH_2)	8.07
16	3.11-3.27 (m)		4.64 (dd, J = 4.0, J = 10.2)	7.04-7.47 (m)				3.65 (dd, J = 4.0, J = 14.2, CH_2); 4.21 (dd, J = 10.2, J = 14.2, CH_2); 7.04-7.47 (m, C_6H_5)	1.20 (t, J = 7.2, CH_3); 3.30-3.37 (q, J = 7.2, CH_2)	7.26 (s, H)	1.28 (t, J = 7.1, CH_3); 4.15 (q, J = 7.1, CH_2)	7.67
20	2.57 (m); 3.07 (m)	3.22 (m); 3.76 (m)	6.27 (s)	7.33 (d, J = 7.3)	6.90-7.20 (m)			6.90-7.20 (m)	1.11 (t, J = 7.1, CH_3); 3.27 (q, J = 7.1, CH_2)	7.69 (s, H)	2.24 (s, CH_3)	10.93
21	2.62 (m); 3.07 (m)	3.13 (m); 3.46 (m)	6.17 (s)	7.38 (d, J = 8.1)	6.98-7.08 (m)		7.20 (d, J = 8.1)	6.98-7.08	1.10 (t, J = 7.1, CH_3); 3.30 (q, J = 7.1, CH_2)	7.67 (s, H)	2.27 (s, CH_3)	10.98
22	2.62 (m); 3.07 (m)	3.20 (m); 3.67 (m)	5.56 (s)	7.28 (d, J = 7.3)	6.88-7.19 (m)			6.88-7.19 (m)	1.13 (t, J = 7.1, CH_3); 3.32 (q, J = 7.1, CH_2)	7.66 (s, H)	2.28 (s, CH_3); 7.20 (d, J = 7.2, C_6H_5); 7.65 (d, J = 7.9, C_6H_5)	10.76
23	2.70 (m); 3.10 (m)	3.15 (m); 3.70 (m)	5.42 (s)	7.30 (d, J = 7.8)	6.90-7.10 (m)		7.20 (d, J = 8.9)	6.90-7.10 (m)	1.12 (t, J = 7.1, CH_3); 3.20 (q, J = 7.1, CH_2)	7.61 (s, H)	2.28 (s, CH_3); 7.22 (d, J = 7.2, C_6H_5); 7.70 (d, J = 7.9, C_6H_5)	10.67

evaporated and water (10 ml) was added to the residue. The mixture was extracted with ethyl acetate. The extract was dried over magnesium sulfate. Filtration and evaporation gave 0.13 g (55%) of a light-yellow, oily residue, which was subjected to column chromatography, eluting with from 1:3 to 1:1 ethyl acetate–hexane to give consecutives 0.05 g (27%) isomer with R_f 0.60 [IR spectrum, ν, cm^{-1}: 1658 (CO_2Et). ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.98 (3H, t, *J* = 7.0, N-$CH_2\underline{CH_3}$); 1.23 (3H, t, *J* = 7.0, $OCH_2\underline{CH_3}$); 2.12-2.16 (2H, m); 2.53-2.83 (4H, m); 2.91-3.00 (2H, m); 3.18-3.24 (1H, m); 3.37-3.43 (1H, m); 4.03-4.14 (4H, m); 7.00-7.48 (9H, m); 8.75 (1H, br. s, NH). Mass spectrum, *m/z* (I_{rel}, %): 390 $[M]^+$ (100), 376 (10), 345 (16), 317 (16), 299 (58), 260 (16), 245 (22), 242 (66), 233 (46), 219 (18), 199 (26), 168 (54), 156 (22), 143 (26), 115 (14), 91 (32), 85 (14), 72 (38), 42 (14)] and 0.06 g (28%) of an isomer with R_f 0.40 [IR spectrum, ν, cm^{-1}: 1653 (CO_2Et). ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.96 (3H, t, *J* = 7.0, N-$CH_2\underline{CH_3}$); 1.33 (3H, t, *J* = 7.0, $OCH_2\underline{CH_3}$); 2.29 (1H, dd, *J* = 3.5, *J* = 14.6); 2.51-2.59 (4H, m); 2.79-3.05 (6H, m); 3.27 (1H, dd, *J* = 4.0, *J* = 14.6); 4.15-4.17 (1H, m); 4.22 (2H, dq, *J* = 1.2, *J* = 7.1), $CH_3\underline{CH_2}O$); 7.05-7.22 (7H, m); 7.27 (1H, dd, *J* = 1.2, *J* = 7.0, H-11); 7.47 (1H, d, *J* = 7.4, H-8); 7.85 (1H, br. s, NH). Mass spectrum, m/z (I_{rel}, %): 390 $[M]^+$ (100), 389 (10), 345 (18), 317 (14), 299 (66), 260 (14), 245 (30), 242 (86), 233 (54), 218 (14), 199 (34), 186 (18), 168 (62), 156 (30), 143 (34), 130 (18), 128 (14), 91 (30), 85 (22), 72 (66), 57 (22), 42 (16)].

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REFERENCES

1. I. G. Voskressensky, T. N. Borisova, L. N. Kulikova, A. V. Varlamov, M. Catto, C. Altomare, and A. Carotti, *Eur. J. Org. Chem.*, 3128 (2004).
2. I. G. Voskressensky, T. N. Borisova, T. A. Soklakova, L. N. Kulikova, 4. R. S. Borisov, and A. V. Varlamov, *Lett. Org. Chem.*, **2**, 18 (2005).
3. P. D. Bailey and S. P. Hollinshead, *J. Chem. Soc., Perkin Trans. 1*, 739 (1988).
4. A. V. Varlamov, T. N. Borisova, I. G. Voskressensky, B. Nsabimane, and A. I. Chernyshev, *Heterocycl. Commun.*, **7**, 461 (2001).