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Synthetic Transformations of Isoquinoline Alkaloids. Synthesis of *N'*-Substituted 1-Alkynyl-7α,8α-(2,5-dioxopyrrolidino)-[3,4-*h*]-6,14-*endo*-ethenotetrahydrothebaines and Their Transformations

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Abstract—The iodination of *N*'-substituted (2,5-dioxopyrrolidino)[3,4-*h*]-6,14-*endo*-ethenotetrahydrothebaines with *N*-iodosuccinimide in trifluoroacetic acid afforded depending on the excess of the reagent either 1-iodo- or 1,2-diiodo-*endo*-ethenotetrahydrothebaines. The Sonogashira reaction of 1-iodo-6,14-*endo*-ethenotetrahydrothebaines with trimethylsilylacetylene led to the formation of *N*'-substituted 1-(trimethylsilylethynyl)-(2,5-dioxopyrrolidino)-[3,4-*h*]-6,14-*endo*-ethenotetrahydrothebaines whose desilylation cleanly furnished the corresponding 1-ethynyl-*endo*-ethenotetrahydrothebaines. The Mannich reaction of the acetylene derivatives of tetrahydrothebaine with amines and formaldehyde catalyzed by compounds of Cu(I) provided 1-[3-(morpholin-4-yl)propynyl]-, 1-[3-(4-methylpiperazin-1-yl)propynyl]-, and 1-[3-(4-*tert*-butoxycarbonylpiperazin-1-yl)propynyl]-(2,5-dioxopyrrolidino)[3,4-*h*]-6,14-*endo*-ethenotetrahydrothebaines.

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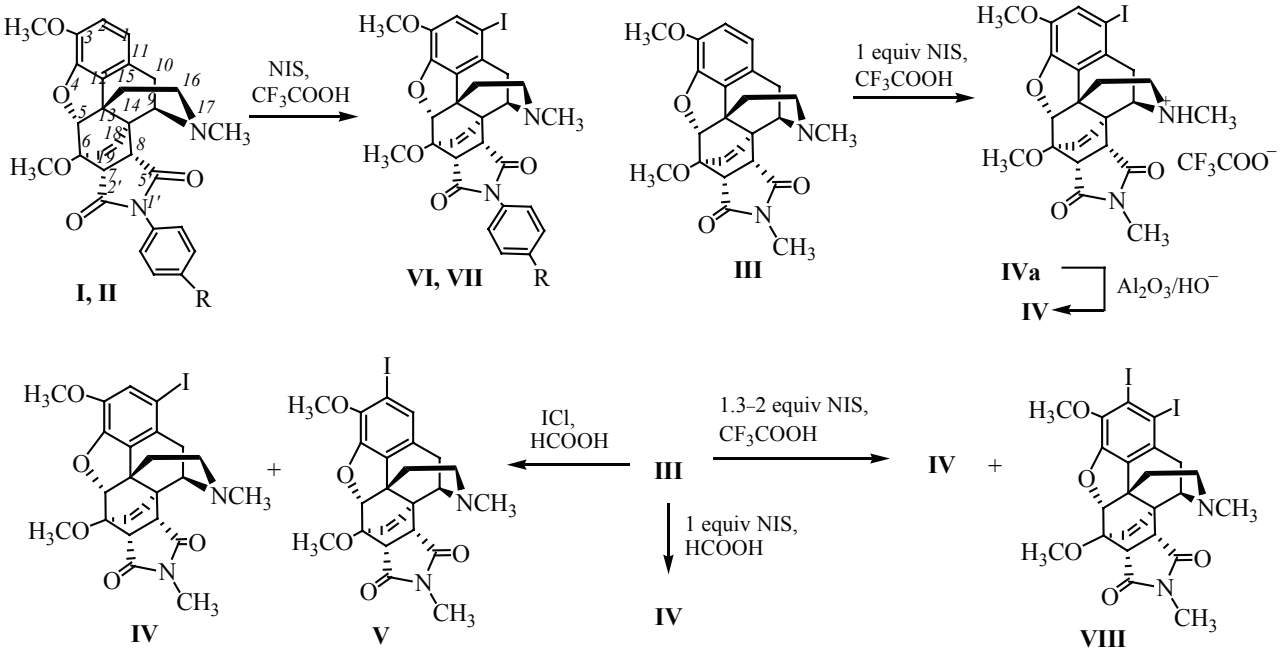
Valuable pharmacological properties of 6,14-*endo*-ethenotetrahydrothebaine derivatives, ethorfine and buprenorfine, used in the clinical practice, attract an interest to the structural modification of thebaine by the introduction of additional cyclic fragments in cycle C [1–5]. The study of the properties of 6,14-*endo*-ethenotetrahydrothebaines (oripavines) fused in the positions $C^{7,8}$ to the *N*-substituted pyrrolidine or succinimide fragments made it possible to find selective agonists of μ-opiate receptors [6] and promising analgesic agents [7]. Our attention was attracted by the possibility to modify the *N'*-substituted (2,5-dioxopyrrolidino)[3,4-*h*]fused 6,14-*endo*-ethenotetrahydrothebaine derivatives by introducing diverse alkynyl substituents in the aromatic ring A aiming at establishing the effect of the acetylene substituents on the basic analgesic activity.

The most convenient procedure of introducing alkynyl fragments is Sonogashira reaction between the appropriate iodo- and bromoarenes and terminal acetylenes. It was shown previously that the iodination of (*N*-aryl-2,5-dioxopyrrolidino)[3,4-*h*]-6,14-*endo*-ethenotetrahydrothebaines **I, II** with iodine monochloride proceeded slowly and resulted in the formation of a complex mixture of substances [8]. The iodination of 7α,8α-(*N*-methyl-2,5-dioxopyrrolidino)-[3,4-*h*]-6,14-*endo*-ethenotetrahydrothebaine (**III**) with iodine monochloride, 1 : 1.5, in formic acid at heating at 45–50°C gave 1-iodo(2,5-dioxo-*N*-methyl-pyrrolidino)-[3,4-*h*]*endo*-ethenotetrahydrothebaine (**IV**) and 2-iodo(2,5-dioxo-*N*-methylpyrrolidino)[3,4-*h*]-*endo*-ethenotetrahydrothebaine (**V**) in the ratio 10:2 and in an overall yield 90% (Scheme 1). The presence in the reaction mixture of compound **V** is indicated by the ^{1}H NMR spectrum of the mixture where two singlet signals of protons H^2 [δ 7.02 ppm (**IV**)] and H^1 [δ 6.66 ppm (**V**)] and also two pairs of proton signals at the atoms $C^{5,10}$ [2.97 d (1H, H^{10}, *J* 18.9 Hz), 4.63 d (H^5, *J* 1.2 Hz) (**IV**); 3.11 d (1H, H^{10}, *J* 19.0 Hz), 4.66 d (H^5, *J* 1.4 Hz) (**V**)] are observed; the signals of the other protons of the morphinan skeleton $H^{7,8,9,15,16,17,18}$ coincide. We failed to isolate compound **V** in the pure state.

Scheme 1.



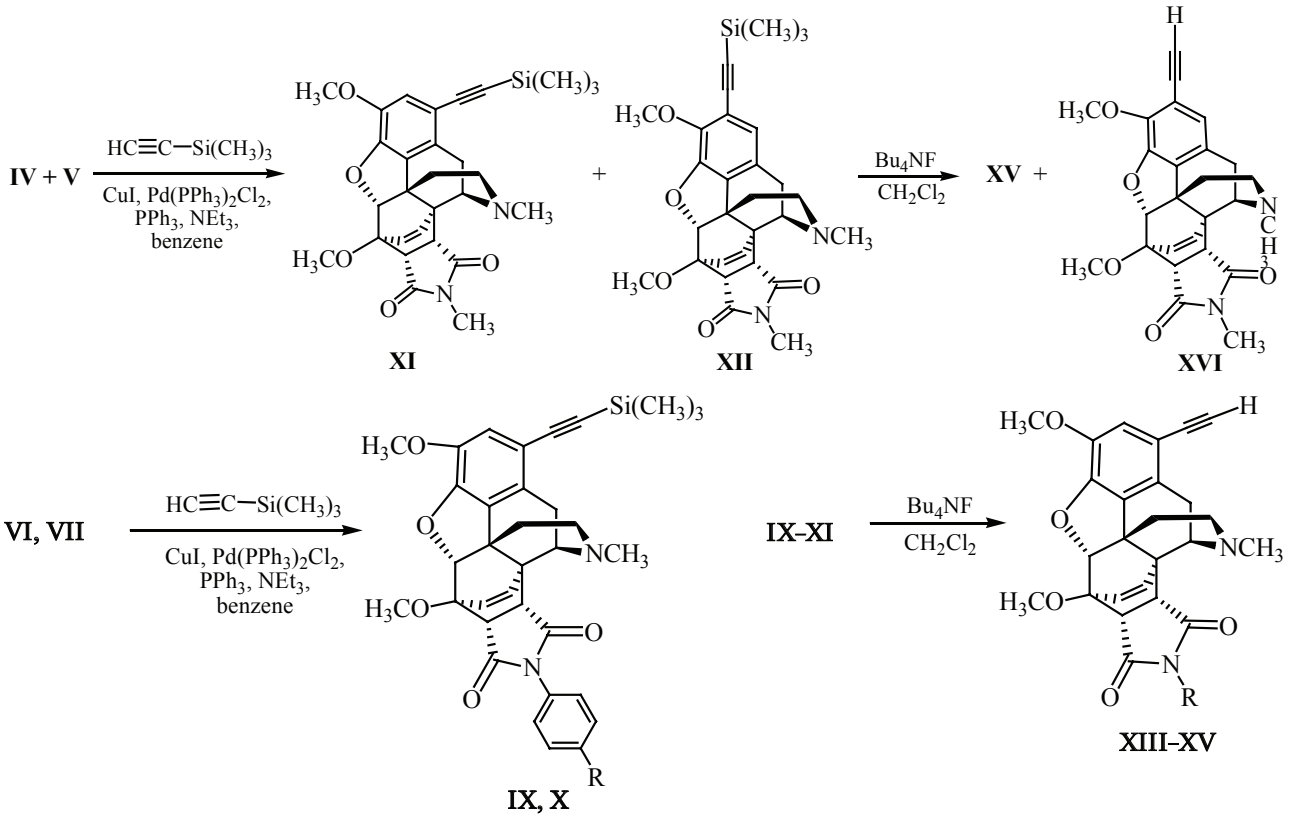
R = H (**I, VII**), Br (**II, VI**).

The iodination of compounds **I–III** with *N*-iodosuccinimide (1 equiv) in trifluoroacetic acid proceeded at room temperature and resulted in the selective formation of individual 1-iodo-7α,8α-(2,5-dioxopyrrolidino)[3,4-*h*]-6,14-*endo*-ethenotetrahydrothebaines **IV, VI, VII** (yield 96–98%). Compound **IV** was easily isolated in the form of salt **IVa** which was converted into the base by treating with the alkaline alumina. The reaction of compound **III** with *N*-iodosuccinimide (1 equiv) in formic acid under the mentioned conditions gave 1-iododerivative **V** in 65% yield (conversion 86%). At the reaction of compound **III** with excess *N*-iodosuccinimide (1.3 equiv) in the trifluoroacetic acid we obtained a mixture of 1-iodo- and 1,2-diiodo-substituted 7α,8α-(*N*-methyl-2,5-dioxopyrrolidino)[3,4-*h*]-6,14-*endo*-ethenotetrahydrothebaines (**IV**, **VIII**), 1:1. At the increase of the *N*-iodosuccinimide excess to 2 equiv compound **VIII** prevailed [(**IV**)–(**VIII**), 1:11 according to ^{1}H NMR data].

The obtained findings show that *N*-iodosuccinimide is a convenient reagent fot iodination of the derivatives of *N'*-substituted (2,5-dioxopyrrolidino)[3,4-*h*]-6,14-*endo*-ethenotetrahydrothebaines and it makes it possible to prepare selectively C^1-substituted 6,14-*endo*-ethenotetrahydrothebaines. The direction of the attack of the reagent may be attributed to the effect of the oxygen atom of the dihydrofuran ring. The analogous direction of the substitution into the *meta*-position with respect to the methoxy group was observed at the chlorination, bromination, and iodination of the aromatic ring of a series of the other morphinans [8–11].

1-Iodotetrahydrothebaines **IV, VI, VII** cleanly reacted with trimethylsilylacetylene in benzene solution in the presence of dichloro(bistriphenylphosphine)palladium, copper(I) iodide, and triethylamine as a base. The corresponding 1-(trimethylsilylethynyl)-(*N*-R-2,5-dioxopyrrolidino)[3,4-*h*]-6,14-*endo*-ethenotetrahydrothebaines **IX–XI** formed in 68–80% yield (Scheme 2). The condensation of trimethylsilylacetylene with the mixture of iodides **IV, V**, 10 : 1.2 provided a mixture of 1-(trimethylsilylethynyl)- and 2-(trimethylsilylethynyl)-*endo*-ethenotetrahydrothebaines **XI, XII**, 10:1.2, as showed the integral intensity of the signals of protons H^2 [δ 6.76 ppm (**XI**)] and H^1 [δ 6.84 ppm (**XII**)] in the ^{1}H NMR spectrum. The column chromatography on silica gel furnished individual compound **XI** (yield 68%) and a fraction containing substances **XI** and **XII**. At the repeated chromatographing of the latter on a plate with unfixed silica gel layer we obtained a mixture enriched with compound **XII** [(**XI**)–(**XII**), 0.6 : 1]. The attempt to bring 1,2-diiododerivative of 6,14-*endo*-ethenotetrahydrothebaine **VIII** into the Sonogashira reaction was unsuccessful,

Scheme 2.

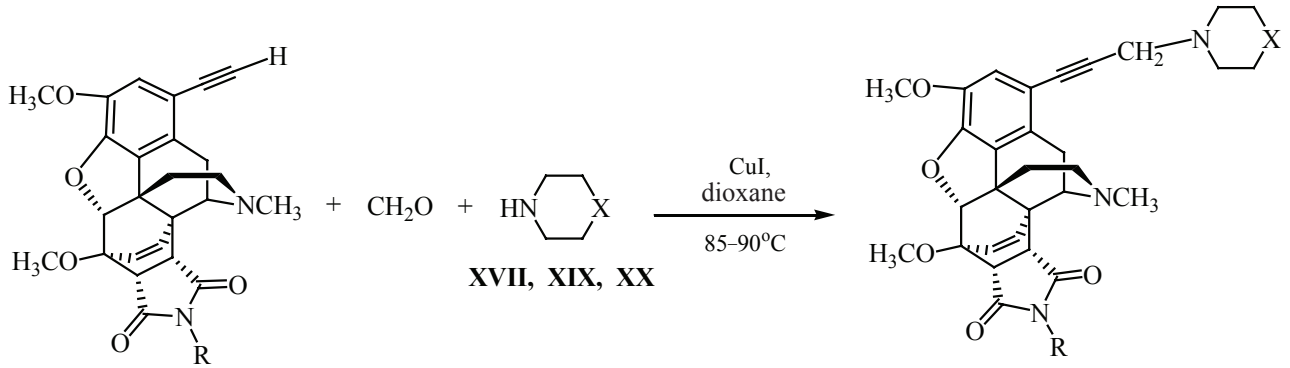


TLC indicated the formation of a mixture of compounds which we failed to obtain in an individual state. By the desilylation of compounds **IX–XII** (Scheme 2) with the use of tetrabutylammonium fluoride in dichloromethane terminal acetylenes, 1-ethynyl(2,5-dioxopyrrolidino) [3,4-*h*]*endo*-ethenotetrahydrothebaines **XIII–XVI**, were obtained in high yields.

Aiming at the extension of the range of the derivatives of 6,14-*endo*-ethenotetrahydrothebaines containing the acetylene substituents we investigated the possibility of the preparation of aminopropargyl-substituted morphinans. An efficient approach to the synthesis of such compounds is the classic Mannich reaction consisting in the interaction between a terminal arylalkyne, formaldehyde (generated *in situ* from paraformaldehyde), and a secondary amine. We examined the possibility to involve the obtained acetylene tetrahydrothebaines **XIII, XV** in the catalytic Mannich reaction [12]. The reaction of compound **XIII** with morpholine (**XVII**) and formaldehyde in dioxane in the presence of catalytic quantity of CuI led to the formation of 1-[3-(morpholin-4-yl)-propynyl]-6,14-*endo*-ethenotetrahydrothebaine (**XVIII**) in 42% yield (Scheme 3). Compound **XV** was more reactive in Mannich reaction. Its reaction with paraformaldehyde and secondary amines [morpholine (**XVII**), *N*-methylpiperazine (**XIX**), or *N*-Boc-piperazine (**XX**)] afforded the corresponding 1-[3-(morpholin-4-yl) propynyl]-, 1-[3-(4-methylpiperazin-1-yl)propynyl]-, or 1-[3-(4-*tert*-butoxycarbonylpiperazin-1-yl)propynyl]-(*N*-R-2,5-dioxopyrrolidino)[3,4-*h*]-6,14-*endo*-ethenotetrahydrothebaines **XXI–XXIII** in the yield 77–88%.

The structure of the synthesized compounds was established combining the elemental analysis data and spectral characteristics. The formation of individual 1-iododerivatives **IV, VI, VII** and 1,2-diiododerivative **VIII** unambiguously follows from the data of ^{1}H NMR spectra with accounting for the increments of iodine substituent [13]. The signal of atom C^1 in compounds **IV, VI, VII** shifts upfield to δ 86.47–86.65 ppm (a singlet in the ^{13}C NMR JMOD spectrum), and the signals of atom C^2 (a doublet in the ^{13}C NMR JMOD spectrum) shift downfield (δ 122.37–122.53 ppm) compared to their position in the spectra of the initial compounds (doublets at δ 119.86 and 113.60 ppm) [8]. Downfield signals are

Scheme 3.



XIII–XV **XVII, XIX, XX** **XVIII, XXI–XXIII**

R = Ph (**XIII, XVIII**), CH_3 (**XV, XXI–XXIII**); X = O (**XVII, XVIII, XXI**), NCH_3 (**XIX, XXII**), N-Boc (**XX, XXIII**).

also characteristic of the atoms C^{10} and C^{11}. The singlets of the atoms C^1 and C^2 in the spectrum of compound **VIII** are observed at 104.03 and 107.55 ppm respectively, and the signals of atoms C^{10}, C^{11} and C^{12} are even more shifted downfield. ^1H and ^{13}C NMR spectra of acetylene derivatives of 6,14-*endo*-ethenotetrahydrothebaines **IX–XI, XIII–XV**, **XVIII, XXI–XXIII** are totally consistent with their structure and contain a single set of the characteristic signals of the morphinan skeleton and the corresponding substituent. The presence of the alkynyl substituent is also confirmed by the IR spectra (strong absorption bands at 2146 cm^{-1} in the spectra of compounds **X, XI** with a trimethylsilylethynyl substituent; 2096 cm^{-1} in the spectra of compounds **XIV, XV** with a terminal acetylene substituent; 2208–2214 cm^{-1} in the spectra of compounds **XXI–XXIII** where the acetylene linker binds the morphinan skeletone and the heterocyclic fragment).

The previously performed investigations showed that the variation of the substituents in the A ring essentially affects the pharmacological properties of the morphinan alkaloids [14–16]. The obtained new derivatives of 6,14-*endo*-ethenotetrahydrothebaine with acetylene fragments in the position *1* provide wide opportunities for the selective modification in the aromatic fragment.

EXPERIMENTAL[1]

^1H and ^{13}C NMR spectra were registered from solutions of compounds in $CDCl_3$ on spectrometers Bruker AV-300 [operating frequencies 300.13 (^1H) and 75.47 MHz (^{13}C)], Bruker AV-400 [operating frequencies 400.13 (^1H) and 100.78 MHz (^{13}C)], and AV-600 [operating frequencies 600.30 (^1H) and 150.96 MHz (^{13}C)] with the solvent signals serving as internal references (δ_H 7.24, δ_C 77.0 ppm). The multiplicity of signals in the ^{13}C NMR spectra were determined by standard procedures in the JMOD mode. The assignment of signals in the NMR spectra was carried out with the help of various types of proton-proton and carbon-proton correlation spectroscopy (COSY, COLOC, COXH, HMCC). The numeration of atoms of the morphinan skeleton used in the description of ^1H and ^{13}C NMR spectra is presented in the structure **I**.

The recording of mass spectra, measuring of the molecular mass and of the elemental compositions was performed using high resolution mass spectrometers DFS Thermo Scientific and Finnigan MAT-8200 with the ionizing voltage 70V (evaporator temperature 270–300°C).

IR spectra were registered on a spectrophotometer Vector-22 from pellets with KBr. The melting points were measured on a Koeffler heating block.

The reaction progress was monitored by TLC on Silufol UV-254 plates using as eluents: chloroform, chloroform–ethanol, 10:1. Spots were visualized in the iodine chamber or under UV irradiation.

The reaction products were isolated by column chromatography on silica gel Acros (0.035–0.070 mm, eluent chloroform–ethanol) and when necessary by preparative TLC on an unfixed silica gel layer on plates of the size 20 × 20 cm with the sorbent layer 1 mm thick (eluents chloroform and chloroform–ethanol–ethyl acetate, 10 : 0.2 : 5).

Solvents (benzene, dichloromethane, chloroform, dioxane), and also Et_3N were purified by standard proce-

[1] Analytical and spectral studies were carried out in the Chemical Service Center of the common use of the Siberian Division of the Russian Academy of Sciences.

dures and were distilled in an argon flow just before use in experiments. *N*-Iodosuccinimide, trimethylsilylacetylene, tetrabutylammonium fluoride, morpholine, *N*-methylpiperazine, and *N*-Boc-piperazine were purchased from Alfa Aesar. Iodine monochloride was obtained as described in [17], $Pd(PPh_3)_2Cl_2$, as described in [18].

Synthesis and physicochemical properties of compounds **I–III** were described in [19–21].

1-Iodo-7α,8α-(*N*-methyl-2,5-dioxopyrrolidino)[3,4-*h*]-6,14-*endo*-etheno-6,7,8,14-tetra-hydrothebaine (IV). *a*. Iodination with iodine monochloride. To a solution of 1 g (2.37 mmol) of compound **III** in 3.6 ml of formic acid was added dropwise at stirring a solution of 0.578 g (4.74 mmol) of ICl in 1 ml of formic acid. The reaction mixture was stirred for 10 h at 45–50°C (TLC monitoring), then it was poured into a Petri dish and evaporated. The solid residue was treated with 10 ml of saturated sodium carbonate solution, the reaction product was extracted into chloroform (4 × 30 ml). The combined extracts were washed with brine, dried with $MgSO_4$, evaporated in a vacuum, and the residue was triturated with ether. We obtained 1.112 g (90%) of a mixture of compound **IV** and **2-iodo-7α,8α-(*N*-methyl-2,5-dioxopyrrolidino)[3,4-*h*]-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (V),** 10:2 (according to the ^{1}H NMR data).

Compound **IV**. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.79–1.99 m (2H, H^{15}), 2.26 d.d (1H, H^{10}, *J* 18.3, 6.7), 2.33–2.52 m (1H, H^{16}), 2.46 s (3H, CH_3N^{17}), 2.53–2.63 m (1H, H^{16}), 2.84 s (3H, $CH_3N^{1'}$), 2.97 d (1H, H^{10}, *J* 18.9), 3.04 d (1H, H^8, *J* 7.9), 3.66 s (3H, CH_3OC^6), 3.77 s (3H, CH_3OC^3), 4.02 d (1H, H^9, *J* 6.5), 4.20 d (1H, H^7, *J* 7.9), 4.62 d (1H, H^5, *J* 1.2), 5.33 d (1H, H^{18}, *J* 8.7), 5.74 d.d (1H, H^{19}, *J* 8.7, 1.2), 7.02 C (1H, H^2).

Characteristic signals of compound **V**, δ, ppm (*J*, Hz): 3.11 d (1H, H^{10}, *J* 19), 4.66 d (1H, H^5, *J* 1.4), 6.66 s (1H, H^1). The chemical shifts of the other protons coincide with the signals of protons of compound **IV**. Mass spectrum, *m/z* (I_{rel}, %): 548 $[M]^+$ (100), 533 (23), 436 (41), 381 (15), 355 (26), 247 (69), 204 (59), 176 (13), 44 (14). Found *m/z* $[M]^+$ 548.0805. $C_{24}H_{25}IN_2O_5$. Calculated m 548.0803.

b. Iodination with *N*-iodosuccinimide in trifluoroacetic acid. To a solution of 0.5 g (1.2 mmol) of compound **III** in 10 ml of trifluoroacetic acid was added at stirring 0.266 g (1.2 mmol) of *N*-iodosuccinimide. The solution was stirred at room temperature for 2 h (TLC monitoring), then it was poured into 150 ml of cold water, and a concn. ammonia solution was added to pH 10–11. The separated colorless precipitate was filtered off to obtain 0.640 g of **1-iodo-7α,8α-(*N*-methyl-2,5-dioxopyrrolidino)-[3,4-*h*]-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine trifluoroacetate (IVa).** The water layer was extracted with chloroform (4 × 15 ml). The extract was dried with $MgSO_4$, evaporated in a vacuum, the residue was triturated in ether. We obtained additionally 0.141 g of salt **IVa**. Overall yield 99%, mp 247°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.07 d.d.d (1H, H^{15}, *J* 14.9, 2.6, 0.8), 2.59 t.d (1H, H^{15}, *J* 14.0, 3.8), 2.77 d.d (1H, H^{10}, *J* 19.5, 7.0), 2.88 s (3H, $CH_3N^{1'}$), 2.89–2.93 m (1H, H^{16}), 3.06 s (3H, CH_3N^{17}), 3.06–3.10 m (1H, H^{10}), 3.25 d (1H, H^8, *J* 7.6), 3.55–3.59 m (1H, H^{16}), 3.68 s (3H, CH_3OC^6), 3.82 s (3H, CH_3OC^3), 4.65–4.70 m (2H, H^{7,9}), 4.76 d (1H, H^5, *J* 1.0), 5.33 d (1H, H^{18}, *J* 8.8), 5.84–5.87 m (1H, H^{19}), 7.08 s (1H, H^2). ^{13}C NMR spectrum, δ, ppm: 24.80 ($CH_3N^{1'}$), 30.06 (C^{15}), 30.45 (C^{10}), 40.90 (C^7), 40.99 (C^8), 42.50 (CH_3N^{17}), 43.83 (C^{14}), 46.05 (C^{16}), 46.78 (C^{13}), 51.44 (CH_3OC^6), 56.52 (CH_3OC^3), 59.71 (C^9), 79.77 (C^6), 86.04 (C^1), 89.26 (C^5), 123.56 (C^2), 126.08 (C^{11}), 130.39 (C^{18}), 131.03 (C^{19}), 131.65 (C^{12}), 144.19 (C^3), 148.46 (C^4), 172.62 (C$^{5'}$), 176.17 (C$^{2'}$). Found, %: C 43.71; H 3.55; F 8.74; I 18.80; N 4.50. $C_{26}H_{26}F_3IN_2O_7$. Calculated, %: C 47.13; H 3.93; F 8.61; I 19.18; N 4.20.

A solution of 0.8 g of the obtained salt in a minimum amount of chloroform was charged into a column of 15 mm diameter packed with 3 g of alkaline alumina, elution with chloroform, the eluate was evaporated, the residue was treated with ether to obtain 0.583 g (90%) of compound **IV**, mp 276°C (from ether). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.83–1.99 m (2H, H^{15}), 2.26 d.d (1H, H^{10}, *J* 18.3, 6.7), 2.36–2.46 m (1H, H^{16}), 2.46 s (3H, CH_3N^{17}), 2.53–2.61 m (1H, H^{16}), 2.86 s (3H, $CH_3N^{1'}$), 2.97 d (1H, H^{10}, *J* 18.9), 3.04 d (1H, H^8, *J* 8.0), 3.68 s (3H, CH_3OC^6), 3.78 s (3H, CH_3OC^3), 4.02 d (1H, H^9, *J* 6.4), 4.20 d (1H, H^7, *J* 8.0), 4.63 d (1H, H^5, *J* 1.2), 5.35 d (1H, H^{18}, *J* 8.8), 5.75 d.d (1H, H^{19}, *J* 8.8, 1.2), 7.02 s (1H, H^2). ^{13}C NMR spectrum, δ, ppm: 24.58 ($CH_3N^{1'}$), 28.52 (C^{10}), 33.40 (C^{15}), 41.40 (C^7), 42.07 (C^8), 43.16 (CH_3N^{17}), 44.78 (C^{14}), 44.81 (C^{16}), 48.17 (C^{13}), 51.65 ($\underline{C}H_3OC^6$), 56.43 ($\underline{C}H_3OC^3$), 57.39 (C^9), 80.37 (C^6), 86.47 (C^1), 91.10 (C^5), 122.37 (C^2), 129.18 (C^{19}), 130.53 (C^{11}), 133.33 (C^{18}), 133.37 (C^{12}), 143.14 (C^3), 148.24 (C^4), 173.85 (C$^{5'}$), 177.05 (C$^{2'}$). Mass spectrum, *m/z* (I_{rel}, %): 548 $[M]^+$ (99), 533 (17), 436 (30), 381 (12), 355 (18), 263 (18), 262 (100), 247 (54), 234 (48), 204 (42), 105 (19), 57 (25), 43 (22). Found *m/z* 548.0800 $[M]^+$. $C_{24}H_{25}IN_2O_5$. Calculated m 548.0803.

c. Iodination with *N*-iodosuccinimide in formic acid. To a solution of 0.125 g (0.30 mmol) of compound **III** in 4 ml of formic acid was added at stirring 0.066 g (0.30 mmol) of *N*-iodosuccinimide. The reaction mixture was stirred at room temperature for 2 h, then it was poured into a Petri dish and evaporated. The solid residue was treated with 10 ml of saturated sodium carbonate solution, the reaction product was extracted into chloroform (4 × 20 ml). The combined extracts were washed with brine, dried with $MgSO_4$, evaporated in a vacuum. We obtained 0.145 g of a mixture of compounds **IV, III**, 10 : 1.3. By the chromatography on a column packed with silica gel we isolated 0.092 g (65%) of compound **IV**.

1-Iodo-7α,8α-[*N*-(4-bromophenyl)-2,5-dioxopyrrolidino][3,4-*h*]-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (VI). To a solution of 0.2 g (0.35 mmol) of compound **II** in 4 ml of trifluoroacetic acid was added at stirring 0.079 g (0.35 mmol) of *N*-iodosuccinimide. The solution was stirred at room temperature for 2 h (TLC monitoring), then it was poured into 50 ml of cold water, and a concn. ammonia solution was added to pH 10–11. The separated precipitate was filtered off. Yield 0.240 g (98%), mp 224–226°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.93 d.d.d (1H, H^{15}, *J* 13.7, 2.9, 1.0), 2.03 t.d (1H, H^{15}, *J* 12.6, 5.3), 2.33 d.d (1H, H^{10}, *J* 19.0, 6.4), 2.44–2.51 m (1H, H^{16}), 2.53 s (3H, CH_3N^{17}), 2.67–2.75 m (1H, H^{16}), 3.02 d (1H, H^{10}, *J* 19.0), 3.21 d (1H, H^{8}, *J* 8.0), 3.70 s (3H, CH_3OC^{6}), 3.81 s (3H, CH_3OC^{3}), 4.11 d (1H, H^{7}, *J* 8.0), 4.44 d (1H, H^{9}, *J* 6.4), 4.70 d (1H, H^{5}, *J* 1.3), 5.44 d (1H, H^{18}, *J* 8.8), 5.89 m (1H, H^{19}), 7.03–7.08 m (2H, H$^{2'',6''}$), 7.05 s (1H, H^{2}), 7.49–7.55 m (2H, H$^{3'',5''}$). ^{13}C NMR spectrum, δ, ppm: 28.89 (C^{10}), 33.23 (C^{15}), 41.34 (C^{7}), 42.01 (C^{8}), 43.23 (CH_3N^{17}), 45.06 (C^{14}), 45.12 (C^{16}), 48.22 (C^{13}), 51.70 ($\underline{C}H_3OC^{6}$), 56.53 ($\underline{C}H_3OC^{3}$), 57.71 (C^{9}), 80.57 (C^{6}), 86.65 (C^{1}), 90.67 (C^{5}), 122.39 (C$^{4''}$), 122.53 (C^{2}), 127.80 (C$^{2'',6''}$), 129.68 (C^{19}), 130.01 (C$^{1''}$), 130.54 (C^{11}), 132.16 (C$^{3'',5''}$), 133.04 (C^{12}), 133.36 (C^{18}), 143.39 (C^{3}), 148.36 (C^{4}), 172.38 (C$^{5'}$), 175.74 (C$^{2'}$). Mass spectrum, *m/z* (I_{rel}, %): 688 [*M*]$^+$ (97), 673 (19), 436 (78), 389 (41), 387 (42), 355 (41), 344 (34), 316 (27), 218 (15), 44 (20). Found *m/z* 688.0058 [*M*]$^+$. $C_{29}H_{26}BrIN_2O_5$. Calculated m 688.0064.

1-Iodo-7α,8α-(2,5-dioxo-*N*-phenylpyrrolidino)-[3,4-*h*]-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (VII). To a solution of 0.2 g (0.4 mmol) of compound **I** in 4 ml of trifluoroacetic acid was added at stirring 0.093 g (0.4 mmol) of *N*-iodosuccinimide, 2 h later (TLC monitoring) the mixture was poured into 50 ml of cold water, and a concn. ammonia solution was added to pH 10–11. The separated precipitate was filtered off to obtain 0.208 g (83%) of compound **VII**. From the mother liquor compound **VII** was extracted into chloroform (4 × 15 ml), the extract was dried with $MgSO_4$, evaporated in a vacuum, the residue was chromatographed on silica gel (eluent chloroform). We obtained additionally 0.037 g of compound **VII**. Overall yield 0.245 g (98%). The analyses and spectral characteristics of compound **VII** are in agreement with those published in [8].

1,2-Diiodo-7α,8α-(*N*-methyl-2,5-dioxopyrrolidino)-[3,4-*h*]-6,14-*endo*-etheno-6,7,8,14-tetra-hydrothebaine (VIII). To a solution of 0.2 g (0.47 mmol) of compound **III** in 4 ml of trifluoroacetic acid was added at stirring 0.211 g (0.94 mmol) of *N*-iodosuccinimide. The mixture was stirred at room temperature for 2 h (TLC monitoring), the mixture was poured into 50 ml of cold water, and a concn. ammonia solution was added to pH 10–11. The separated yellow precipitate containing 0.241 g of a mixture of iodides **VIII, IV**, 10:1, was filtered off. From the water layer the reaction products were extracted into chloroform (4 × 15 ml), the combined extracts were dried with $MgSO_4$, evaporated in a vacuum, and the residue was triturated with ether. We obtained additionally 0.087 g of a mixture of compounds **VIII, IV**, 12:1. The chromatographic separation provided 0.165 g (53%) of 1,2-diiodotetrahydrothebaine **VIII**, mp 278°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.86 d.d.d (1H, H^{15}, *J* 13.6, 2.0, 1.3), 1.93 t.d (1H, H^{15}, *J* 12.5, 5.2), 2.33–2.40 m (2H, H^{10,16}), 2.47 s (3H, $CH_3N^{1'}$), 2.56–2.60 m (1H, H^{16}), 2.87 s (3H, CH_3N^{17}), 2.97 d (1H, H^{10}, *J* 18.8), 3.02 d (1H, H^{8}, *J* 8.0), 3.68 s (3H, CH_3OC^{6}), 3.88 s (3H, CH_3OC^{3}), 3.98 d (1H, H^{9}, *J* 6.4), 4.18 d (1H, H^{7}, *J* 8.0), 4.63 d (1H, H^{5}, *J* 1.4), 5.37 d (1H, H^{18}, *J* 8,8), 5.78 m (1H, H^{19}). ^{13}C NMR spectrum, δ, ppm: 27.02 ($CH_3N^{1'}$), 35.27 (C^{10}), 35.58 (C^{15}), 44.19 (C^{7}), 44.30 (C^{8}), 45.55 (CH_3N^{17}), 47.12 (C^{16}), 50.43 (C^{14,13}), 54.48 ($\underline{C}H_3OC^{6}$), 60.31 (C^{9}), 62.54 ($\underline{C}H_3OC^{3}$), 82.72 (C^{6}), 94.52 (C^{5}), 104.03 (C^{1}), 107.55 (C^{2}), 131.23 (C^{19}), 136.03 (C^{18}), 136.94 (C^{11}), 137.67 (C^{12}), 145.02 (C^{3}), 151.61 (C^{4}), 176.11 (C$^{5'}$), 179.27 (C$^{2'}$). Mass spectrum, *m/z* (I_{rel}, %): 674 [*M*]$^+$ (100), 659 (20), 562 (37), 548 (15), 354 (20), 247 (51), 204 (36), 44 (11). Found *m/z* 673.9767 [*M*]$^+$. $C_{24}H_{24}I_2N_2O_5$. Calculated m 673.9769.

1-(2-Trimethylsilylethynyl)-7α,8α-(2,5-dioxo-*N*-phenylpyrrolidino)[3,4-*h*]-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (IX). A two-neck flask equipped with a magnetic stirrer was thrice evacuated and filled

with argon. In an argon flow the flask was charged in succession with 0.714 g (1.4 mmol) of compound **VII**, 0.006 g (0.03 mmol, 2.1 mol%) of CuI, 0.006 g (0.009 mmol, 0.6 mol%) of $Pd(PPh_3)_2Cl_2$, 0.011 g (0.023 mmol, 1.6 mol%) of PPh_3, 7.5 ml of benzene. The mixture was evacuated, and 0.61 ml (4 mmol) of NEt_3 and 0.257 ml (1.8 mmol) of trimethylsilylacetylene were added in an argon flow. After 6 h 0.257 ml (1.8 mmol) of trimethylsilylacetylene and 1 ml of benzene were added again. The mixture was stirred at heating to 60°C in an argon flow for 12 h and was poured into a Petri dish for a free evaporation. The solid residue was treated with chloroform and water, the layers were separated, and the product was extracted from the water layer into chloroform. The combined extracts were washed with water, dried with $MgSO_4$, evaporated in a vacuum, the residue was dissolved in a minimum volume of chloroform and chromatographed on a column packed with silica gel (eluent chloroform–ethanol), the fraction containing the reaction product was triturated with ether, crystals were filtered off. Yield 0.461 g (68%), mp 234–236°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.24 s [9H, $(CH_3)_3Si$)], 1.83–2.04 m (2H, H*15*), 2.40–2.64 m (3H, H*10,16,16*), 2.45 s (3H, CH_3N*17*), 3.18 m (2H, H*8,10*), 3.68 s (3H, CH_3OC*6*), 3.78 s (3H, CH_3OC*3*), 4.06 d (1H, H*9*, *J* 5.8), 4.37 d (1H, H*7*, *J* 7.5), 4.70 m (1H, H*5*), 5.47 d (1H, H*18*, *J* 9.2), 5.83 m (1H, H*19*), 6.78 s (1H, H*2*), 7.09–7.17 m (2H, H*2″,6″*), 7.28–7.43 m (3H, H*3″,4″,5″*). ^{13}C NMR spectrum, δ, ppm: 0.01 [$(CH_3)_3Si$], 22.14 (C*10*), 33.37 (C*15*), 41.16 (C*8*), 42.09 (C*7*), 43.12 (CH_3N*17*), 44.48 (C*13*), 44.99 (C*16*), 47.81 (C*14*), 51.48 ($\underline{C}H_3OC$*6*), 56.07 ($\underline{C}H_3OC$*3*), 56.69 (C*9*), 80.55 (C*6*), 90.98 (C*5*), 97.17 (C*1b*), 102.85 (C*1a*), 114.11 (C*1*), 116.57 (C*2*), 126.19 (C*2″,6″*), 128.40 (C*4″*), 128.83 (C*3″,5″*), 128.94 (C*19*), 130.58 (C*11*), 131.57 (C*1″*), 132.48 (C*12*), 133.64 (C*18*), 141.92 (C*3*), 148.61 (C*4*), 172.78 (C*5′*), 176.11 (C*4′*). Mass spectrum, *m/z* (I_{rel}, %): 580 $[M]^+$ (100), 406 (16), 326 (19), 325 (52), 266 (23), 203 (8), 174 (9), 121 (9), 73 (45), 44 (18), 28 (27). Found *m/z* 580.23789 $[M]^+$. $C_{34}H_{36}N_2O_5Si$. Calculated m 580.23933.

1-(2-Trimethylsilylethynyl)-7α,8α-[*N*-(4-bromophenyl)-2,5-dioxopyrrolidino][3,4-*h*]-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (X). After the above described preparation the flask was charged in an argon flow in succession with 0.150 g (2.2 mmol) of compound **VI**, 0.002 g (0.01 mmol, 4.2 mol%) of CuI, 0.0019 g (0.003 mmol, 1.2 mol%) of $Pd(PPh_3)_2Cl_2$, 0.0035 g (0.007 mmol, 3.2 mol%) of PPh_3, and 4 ml of benzene. The mixture was evacuated, and 0.09 ml (2.8 mmol) of NEt_3 and 0.08 ml (2.6 mmol) of trimethylsilylacetylene were added in an argon flow. After 10 h 0.08 ml (2.6 mmol) of trimethylsilylacetylene and 0.09 ml (2.8 mmol) of NEt_3 were added again. The mixture was stirred at heating to 60°C in an argon flow for 18 h and was poured into a Petri dish for evaporation in air. The solid residue was treated with chloroform and water, the layers were separated, and the product was extracted from the water layer with chloroform (4 × 15 ml). The combined extracts were washed with water, dried with $MgSO_4$, evaporated in a vacuum, the residue was chromatographed on silica gel (eluent chloroform–ethanol), the fraction containing the reaction product was triturated with ether, the precipitate was filtered off. Yield 0.110 g (80%), mp 182°C. IR spectrum, cm^{-1}: 2146, 1778, 1714, 1618, 1595, 746, 705. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.26 s [9H, $(CH_3)_3Si$], 1.90–2.04 m (2H, H*15*), 2.40–2.64 m (3H, H*10,16,16*), 2.47 s (3H, CH_3N*17*), 3.21 d (1H, H*10*, *J* 19.1), 3.23 d (1H, H*8*, *J* 8.3), 3.70 s (3H, CH_3OC*6*), 3.80 s (3H, CH_3OC*3*), 4.06 d (1H, H*9*, *J* 6.2), 4.40 d (1H, H*7*, *J* 8.3), 4.65 d (1H, H*5*, *J* 1.3), 5.46 d (1H, H*18*, *J* 8.5), 5.82 m (1H, H*19*), 6.80 s (1H, H*2*), 7.03–7.10 m (2H, H*2″,6″*), 7.50–7.56 m (2H, H*3″,5″*). ^{13}C NMR spectrum, δ, ppm: 0.14 [$(CH_3)_3Si$], 22.31 (C*10*), 33.56 (C*15*), 41.37 (C*7*), 42.29 (C*8*), 43.27 (CH_3N*17*), 44.91 (C*14*), 45.18 (C*16*), 47.99 (C*13*), 51.68 ($\underline{C}H_3OC$*6*), 56.25 ($\underline{C}H_3OC$*3*), 56.84 (C*9*), 80.68 (C*6*), 91.09 (C*5*), 97.38 (C*1b*), 102.93 (C*1a*), 114.33 (C*1*), 116.85 (C*2*), 122.33 (C*4″*), 127.84 (C*2″,6″*), 129.07 (C*19*), 130.67 (C*11*), 131.57 (C*1″*), 132.13 (C*3″,5″*), 132.53 (C*12*), 133.92 (C*18*), 142.09 (C*3*), 148.74 (C*4*), 172.55 (C*5′*), 174.16 (C*2′*). Mass spectrum, *m/z* (I_{rel}, %): 658 $[M]^+$ (89), 645 (18), 643 (17), 406 (30), 387 (20), 351 (15), 325 (59), 318 (16), 174 (12), 121 (11), 73 (33), 44 (15). Found *m/z* 658.1491 $[M]^+$. $C_{34}H_{35}BrIN_2O_5$. Calculated m 658.1493.

1-(2-Trimethylsilylethynyl)-7α,8α-(*N*-methyl-2,5-dioxopyrrolidino)[3,4-*h*]-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (XI) was obtained under the above conditions from 0.533 g (1.0 mmol) of compound **IV**, 0.007 g (0.04 mmol, 4.1 mol%) of CuI, 0.008 g (0.012 mmol, 1.2 mol%) of $Pd(PPh_3)_2Cl_2$, 0.015 g (0.031 mmol, 3.2 mol%) of PPh_3, 12 ml of benzene, 0.41 ml (2.8 mmol) of NEt_3 and 0.35 ml (2.6 mmol) of trimethylsilylacetylene. After 6 h 0.35 ml (2.6 mmol) of trimethylsilylacetylene and 1 ml of benzene were added again. The total time of heating at 70–75°C in an argon flow was 19 h. The reaction mixture was poured in a Petri dish and evaporated in air. The solid residue was treated with chloroform and water, the layers were separated, and

the product was extracted from the water layer with chloroform (4 × 20 ml). The combined extracts were washed with water, dried with $MgSO_4$, evaporated in a vacuum, yield 0.8 g of oily substance containing according to ^{1}H NMR spectrum an impurity of trimethylsilylacetylene. The product was subjected to desilylation without additional purification.

1-(2-Trimethylsilylethynyl)-7α,8α-(*N*-methyl-2,5-dioxopyrrolidino)[3,4-*h*]-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (XI) and 2-(2-trimethylsilylethynyl)-7α,8α-(*N*-methyl-2,5-dioxopyrrolidino)[3,4-*h*]-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (XII) were obtained in similar conditions from 0.6 g (1.1 mmol) of a mixture of compounds **IV, V**, 10:1.2, 0.004 g (0.02 mmol, 2.5 mol%) of CuI, 0.0046 g (0.006 mmol, 0.74 mol%) of $Pd(PPh_3)_2Cl_2$, 0.087 g (0.02 mmol, 2.5 mol%) of PPh_3, 6.3 ml of benzene. The mixture was evacuated, and 0.46 ml (3 mmol) of NEt_3 and 0.2 ml (1.4 mmol) of trimethylsilylacetylene were added in an argon flow. After 6 h 0.2 ml (3 mmol) of trimethylsilylacetylene was added again. The mixture was stirred at heating to 60°C in an argon flow for 13 h and was poured into a Petri dish for evaporation in air. The solid residue was treated with chloroform and water, the layers were separated, and the product was extracted from the water layer with chloroform (4 × 20 ml). The combined extracts were washed with water, dried with $MgSO_4$, evaporated in a vacuum to obtain 0.626 g of a mixture of compounds **IV, XI, XII** in a ratio 1 : 10 : 1.2. The mixture was dissolved in a minimum volume of chloroform and was subjected to chromatography on silica gel (eluent chloroform–ethanol) to isolate in succession 0.319 g (68%) of compound **XI**, 0.120 g of the mixture of compounds **XI, XII**, 1:0.2, and 0.116 g of compound **IV**. At a subsequent chromatography of the mixture of compounds **XI, XII** on a plate with unfixed silica gel layer we isolated 33 mg of a mixture enriched with compound **XII** [(**XI**)–(**XII**), 0.6:1].

Compound **XI**, mp 180–183°C (from ether). IR spectrum, cm^{-1}: 2146, 1772, 1699, 1618, 1594, 721, 702. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.23 s [9H, $(CH_3)_3Si$], 1.70–1.99 m (2H, H^{15}), 2.36–2.60 m (3H, H^{10,16,16}), 2.45 s (3H, CH_3N^{17}), 2.84 s (3H, N^1CH_3), 3.03 d (1H, H^8, *J* 8.0), 3.17 d (1H, H^{10}, *J* 19.4), 3.67 s (3H, CH_3OC^6), 3.76 s (3H, CH_3OC^3), 4.01 d (1H, H^9, *J* 6.4), 4.18 d (1H, H^7, *J* 8.0), 4.65 m (1H, H^5), 5.34 d (1H, H^{18}, *J* 9.2), 5.68 m (1H, H^{19}), 6.76 s (1H, H^2). ^{13}C NMR spectrum, δ, ppm: 0.023 [$Si(CH_3)_3$], 22.12 (C^{10}), 24.54 ($CH_3N^{1'}$), 33.35 (C^{15}), 41.35 (C^7), 42.23 (C^8), 43.12 (CH_3N^{17}), 44.70 (C^{16}), 44.79 (C^{13}), 47.77 (C^{14}), 51.60 ($\underline{C}H_3OC^6$), 56.16 ($\underline{C}H_3OC^3$), 56.74 (C^9), 80.41 (C^6), 91.31 (C^5), 97.15 (C^{1b}), 102.91 (C^{1a}), 114.11 (C^1), 116.75 (C^2), 128.75 (C^{19}), 130.66 (C^{11}), 132.67 (C^{12}), 133.58 (C^{18}), 141.94 (C^3), 148.66 (C^4), 173.90 (C$^{5'}$), 177.12 (C$^{2'}$). Mass spectrum, *m/z* (I_{rel}, %): 518 [*M*]$^+$ (100), 502 (30), 405 (18), 324 (57), 276 (84), 246 (31), 203 (30), 198 (16), 76 (19), 72 (35), 73 (35), 44 (21). Found *m/z* 518.22368 [*M*]$^+$. $C_{29}H_{34}N_2O_5Si$. Calculated m 518.22324.

Characteristic signals of compound **XII**, δ, ppm (*J*, Hz): 0.21 s [9H, $(CH_3)_3Si$], 3.19 d (1H, H^{10}, *J* 19.4), 3.68 s (3H, CH_3OC^6), 3.81 s (3H, CH_3OC^3), 4.67 m (1H, H^5), 6.84 s (1H, H^1). The chemical shifts of the other protons coincide with the signals of protons of compound **XI**.

1-Ethynyl-7α,8α-(2,5-dioxo-*N*-phenylpyrrolidino)[3,4-*h*]-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (XIII). To a solution of 0.6 g (1 mmol) of compound **IX** in 4 ml of dichloromethane was added dropwise at stirring a solution of 0.4 g (1.5 mmol) of Bu_4NF in 2 ml of dichloromethane. The mixture was stirred at room temperature for 15 min, the separated precipitate was filtered off. The organic layer was washed with water, dried with magnesium sulfate, evaporated in a vacuum, the residue was triturated with dichloromethane. Yield 0.367 g (70%), mp 265–270°C. ^{1}H NMR spectrum (DMCO-d_6), δ, ppm (*J*, Hz): 2.10 m (1H, H^{15}), 2.28 m (1H, H^{15}), 2.44–2.60 m (3H, H^{10,16,16}), 2.49 s (3H, CH_3N^{17}), 3.08 d (1H, H^{10}, *J* 18.8), 3.54 s (3H, CH_3OC^6), 3.72 s (3H, CH_3OC^3), 3.98 d (1H, H^9, *J* 6.4), 3.77 d (1H, H^8, *J* 7.5), 4.13 s (1H, H^{1b}), 4.31 d (1H, H^7, *J* 7.5), 4.93 m (1H, H^5), 5.50 d (1H, H^{18}, *J* 8.8), 5.69 m (1H, H^{19}), 6.81 s (1H, H^2), 7.09 m (2H, H$^{2'',6''}$), 7.37 m (1H, H$^{4''}$), 7.44 m (3H, H$^{3'',5''}$). ^{13}C NMR spectrum, δ, ppm: 21.75 (C^{10}), 32.27 (C^{15}), 40.66 (C^8), 42.28 (C^7), 42.96 ($CH_3N^{17'}$), 44.53 (C^{13}), 44.64 (C^{16}), 47.18 (C^{14}), 50.58 ($\underline{C}H_3OC^6$), 56.06 ($\underline{C}H_3OC^3$), 56.49 (C^9), 80.50 (C^6), 80.53 (C^{1b}), 81.85 (C^{1a}), 89.22 (C^5), 112.58 (C^1), 116.93 (C^2), 126.89 (C$^{2'',6''}$), 128.35 (C$^{4''}$), 128.81 (C$^{3'',5''}$), 129.18 (C^{19}), 130.89 (C^{11}), 132.20 (C$^{1''}$), 133.23 (C^{12}), 133.68 (C^{18}), 141.48 (C^3), 148.50 (C^4), 173.18 (C$^{5'}$), 176.27 (C$^{4'}$). Mass spectrum, *m/z* (I_{rel}, %): 508 [*M*]$^+$ (100), 503 (21), 335 (44), 311 (41), 268 (41), 255 (49), 174 (19), 121 (16), 58 (22), 44 (61), 28 (21). Found [*M*]$^+$ 508.18865. $C_{31}H_{28}N_2O_5$. Calculated m 508.19981.

1-Ethynyl-7α,8α-[*N*-(4-bromophenyl)-2,5-dioxopyrrolidino][3,4-*h*]-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (XIV). To a solution of 0.110 g (0.16 mmol) of compound **X** in 3 ml of dichloromethane was added dropwise at stirring a solution of 0.12 g

(0.47 mmol) of Bu_4NF in 1 ml of dichloromethane. The mixture was stirred at room temperature for 15 min, washed with water, the organic layer was dried with magnesium sulfate, evaporated in a vacuum, the residue was triturated with ether. Yield 0.090 g (92%), mp 202°C. IR spectrum, cm^{-1}: 2096, 1776, 1714, 1616, 1595, 744, 705. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.86–2.04 m (2H, H^{15}), 2.40–2.62 m (3H, $H^{10,16,16}$), 2.44 s (3H, CH_3N^{17}), 3.18 d (1H, H^8, *J* 8.0), 3.22 s (1H, H^{1b}), 3.23 d (1H, H^{10}, *J* 19.3), 3.69 s (3H, CH_3OC^6), 3.79 s (3H, CH_3OC^3), 4.03 d (1H, H^9, *J* 6.4), 4.38 d (1H, H^7, *J* 8.0), 4.71 d (1H, H^5, *J* 1.0), 5.47 d (1H, H^{18}, *J* 8.8), 5.83 d.d (1H, H^{19}, *J* 8.8, 1.0), 6.81 s (1H, H^2), 7.02–7.06 m (2H, $H^{2'',6''}$), 7.48–7.53 m (2H, $H^{3'',5''}$). ^{13}C NMR spectrum, δ, ppm: 22.34 (C^{10}), 33.52 (C^{15}), 41.37 (C^7), 42.28 (C^8), 43.25 (CH_3N^{17}), 44.90 (C^{14}), 45.14 (C^{16}), 47.94 (C^{13}), 51.70 ($\underline{C}H_3OC^6$), 56.30 ($\underline{C}H_3OC^3$), 56.81 (C^9), 65.81 (C^{1b}), 80.10 (C^{1a}), 80.66 (C^6), 91.11 (C^5), 113.14 (C^1), 117.24 (C^2), 122.32 ($C^{4''}$), 127.81 ($C^{2'',6''}$), 129.17 (C^{19}), 130.61 (C^{11}), 130.82 ($C^{1''}$), 132.12 ($C^{3'',5''}$), 132.61 (C^{12}), 133.84 (C^{18}), 142.08 (C^3), 148.66 (C^4), 172.52 ($C^{5'}$), 175.86 ($C^{2'}$). Mass spectrum, *m/z* (I_{rel}, %): 586 $[M]^+$ (97), 573 (16), 532 (29), 589 (25), 587 (25), 334 (78), 279 (38), 253 (71), 174 (14), 121 (16), 59 (17). Found *m/z* 568.1096 $[M]^+$. $C_{31}H_{27}BrIN_2O_5$. Calculated m 568.1098.

1-Ethynyl-7α,8α-(*N*-methyl-2,5-dioxopyrrolidino)[3,4-*h*]-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (XV). To a solution of 0.8 g of oily substance containing compound **XI** in 6 ml of dichloromethane was added dropwise at stirring 1.06 ml of 1 M solution of Bu_4NF in THF. The mixture was stirred at room temperature for 15 min, washed with water, the organic layer was dried with magnesium sulfate, evaporated in a vacuum, the residue was dissolved in a minimum volume of chloroform and chromatographed on silica gel (eluent chloroform). Yield 0.337 g (78%) (calculated for two stages of the reaction), mp 286°C. IR spectrum, cm^{-1}: 2096, 1770, 1695, 1622, 1602, 752, 705. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.80–2.05 m (2H, H^{15}), 2.36–2.50 m (1H, H^{16}), 2.46 s (3H, CH_3N^{17}), 2.52–2.63 m (2H, $H^{10,16}$), 2.86 s (3H, $N^{1'}CH_3$), 3.04 d (1H, H^8, *J* 8.3), 3.21 s (1H, H^{1b}), 3.27 d (1H, H^{10}, *J* 19.2), 3.68 s (3H, CH_3OC^6), 3.79 s (3H, CH_3OC^3), 4.03 d (1H, H^9, *J* 6.6), 4.20 d (1H, H^7, *J* 8.3), 4.68 d (1H, H^5, *J* 1.0), 5.36 d (1H, H^{18}, *J* 8.5), 5.73 m (1H, H^{19}), 6.83 s (1H, H^2). ^{13}C NMR spectrum, δ, ppm: 22.31 (C^{10}), 22.50 (C^{15}), 24.60 ($CH_3N^{1'}$), 41.27 (C^7), 42.22 (C^8), 43.20 (CH_3N^{17}), 44.65 (C^{16}), 44.75 (C^{13}), 47.74 (C^{14}), 51.66 ($\underline{C}H_3OC^6$), 56.15 ($\underline{C}H_3OC^3$), 56.71 (C^9), 76.66 (C^{1b}), 80.36 (C^6), 80.50 (C^{1a}), 91.41 (C^5), 112.63 (C^1), 117.34 (C^2), 128.95 (C^{19}), 131.78 (C^{11}), 132.91 (C^{12}), 133.47 (C^{18}), 142.08 (C^3), 149.28 (C^4), 173.86 ($C^{5'}$), 177.07 ($C^{2'}$). Mass spectrum, *m/z* (I_{rel}, %): 446 $[M]^+$ (100), 431 (17), 334 (26), 279 (11), 253 (22), 247 (29), 204 (25), 44 (3). Found *m/z* 446.1837 $[M]^+$. $C_{26}H_{26}N_2O_5$. Calculated m 446.1836.

2-Ethynyl-7α,8α-(*N*-methyl-2,5-dioxopyrrolidino)-[3,4-*h*]-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (XVI). To a solution of 0.158 g (0.31 mmol) of a mixture of compounds **XI, XII**, 10:3, in 2.5 ml of dichloromethane was added dropwise at stirring a solution of 0.3 g (1.2 mmol) of Bu_4NF in 1 ml of dichloromethane. The mixture was stirred at room temperature for 15 min, the separated precipitate was filtered off, the organic layer was washed with water, dried with magnesium sulfate, evaporated in a vacuum to obtain 0.2 g of oily substance containing compounds **XV, XVI**, 10:3. The residue was dissolved in a minimum volume of chloroform and chromatographed on silica gel (eluent chloroform–ethanol). We isolated in succession mixtures of compounds **XV, XVI** from 1.7:1 to 4:1, and 0.095 g (70%) of compound **XV**, mp 286°C. By the repeated chromatography of the mixture of compounds **XV, XVI** on silica gel (eluent chloroform–ethanol) we isolated 17 mg of the mixture enriched with compound **XVI** [(**XV**)–(**XVI**), 1.7:1]. Characteristic signals of compound **XVI** (from the ^1H NMR spectrum of the mixture of compounds **XV, XVI**, 1.7:1), δ, ppm (*J*, Hz): 3.12 d (1H, H^{10}, *J* 19.1), 4.22 d (1H, H^8, *J* 7.9), 4.65 d (1H, H^5, *J* 1.3), 5.76 m (1H, H^{19}), 6.66 C (1H, H^1). The chemical shifts of the other protons coincide with the signals of protons of compound **XV**.

1-[(3-Morpholin-4-yl)propynyl]-7α,8α-(2,5-dioxo-*N*-phenylpyrrolidino)[3,4-*h*]-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (XVIII). A two-neck flask in an argon flow was charged at stirring in succession with 0.011 g (0.35 mmol) of paraformaldehyde, 0.027 g (0.35 mmol) of morpholine (**XVII**), 0.0006 g (0.003 mmol) of CuI, 2.2 ml of dioxane, and 0.16 g (0.31 mmol) of compound **XIII**. The mixture was heated at 90–92°C for 6 h, then 0.011 g (0.35 mmol) of paraformaldehyde, 0.027 g (0.35 mmol) of morpholine, and 0.5 ml of dioxane were again added, and the heating was continued for 6 h more. The separated precipitate was filtered off and washed with ether. Yield 0.06 g (32%). The mother liquor was evaporated, the solid residue was treated with chloroform (4 × 10 ml), the extract was washed with water, the organic solutions were dried with $MgSO_4$, evaporated in a vacuum, the residue was

chromatographed on silica gel (eluent chloroform). We isolated additionally 0.02 g of compound **IV** and 0.03 g of compound **XIII**. Overall yield of compound **XVIII** 0.08 g (42% taking into account the conversion of 52%), mp 260–263°C. IR spectrum, cm^{-1}: 2208, 2131, 1775, 1712, 1595, 746, 694. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.90 m (1H, H^{15}), 1.98 m (1H, H^{15}), 2.42–2.56 m (4H, $H^{3''',5'''}$), 2.46 s (3H, CH_3N^{17}), 2.56–2.66 m (3H, $H^{10,16,16}$), 3.18 d (1H, H^8, *J* 8.2), 3.28 d (1H, H^{10}, *J* 19.4), 3.65–3.78 m (4H, $H^{2''', 6'''}$), 3.67 s (3H, H^{1C}), 3.70 s (3H, CH_3OC^6), 3.80 s (3H, CH_3OC^3), 4.08 d (1H, H^9, *J* 6.6), 4.38 d (1H, H^7, *J* 8.2), 4.73 d (1H, H^5, *J* 1.3), 5.47 d (1H, H^{18}, *J* 8.7), 5.87 m (1H, H^{19}), 6.85 s (1H, H^2), 7.12–7.16 m (2H, $H^{2'', 6''}$), 7.32 m (2H, $H^{4''}$), 7.36–7.40 m (2H, $H^{3'', 5''}$). ^{13}C NMR spectrum, δ, ppm: 22.42 (C^{10}), 33.43 (C^{15}), 42.16 (C^7), 41.30 (C^8), 43.20 ($\underline{C}H_3N^{17}$), 45.05 (C^{16}), 44.81 (C^{13}), 47.84 (C^{14}), 51.62 ($\underline{C}H_3OC^6$), 51.90 (2C, $C^{2''', 6'''}$), 56.26 ($\underline{C}H_3OC^3$), 56.74 (C^9), 66.91 (C^{1C}), 66.97 (2C, $C^{3''', 5'''}$), 76.75 (C^{1b}), 80.54 (C^6), 80.54 (C^{1a}), 91.32 (C^5), 112.77 (C^1), 117.62 (C^2), 126.24 (2C, $C^{2'',6''}$), 128.46 ($C^{4''}$), 128.88 (2C, $C^{3'',5''}$), 129.14 (C^{19}), 131.59 ($C^{1''}$), 131.84 (C^{11}), 132.91 (C^{12}), 133.70 (C^{18}), 142.17 (C^3), 149.42 (C^4), 172.69 ($C^{5'}$), 176.04 ($C^{2'}$). Mass spectrum, *m/z* (I_{rel}, %): 607 $[M]^+$ (5), 577 (6), 518 (24), 309 (18), 266 (17), 238 (13), 173 (19), 124 (96), 97 (32), 71 (36), 69 (43), 55 (52), 43 (48), 18 (100). Found *m/z* 607.2674 $[M]^+$. $C_{36}H_{37}N_3O_6$. Calculated m 607.2677.

1-[(3-Morpholin-4-yl)propynyl]-7α,8α-(*N*-methyl-2,5-dioxopyrrolidino)[3,4-*h*]-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (XXI). A flask in an argon flow was charged at stirring in succession with 0.011 g (0.35 mmol) of paraformaldehyde, 0.027 g (0.35 mmol) of morpholine, 0.001 g (0.005 mmol) of CuI, 3.2 ml of dioxane, and 0.1 g (0.2 mmol) of compound **XV**. The mixture was heated at 90–92°C for 6 h, then 0.011 g (0.35 mmol) of paraformaldehyde, 0.027 g (0.35 mmol) of morpholine, 0.001 g (0.005 mmol) of CuI, and 1 ml of dioxane were again added, and the heating was continued for 6 h more.. The reaction mixture was evaporated in a Petri dish, the solid residue was treated with chloroform and water, the layers were separated, and the product was extracted from the water layer with chloroform. The combined extracts were washed with water, dried with $MgSO_4$, evaporated in a vacuum, the residue was crystallized from ether. Yield 0.107 g (88%), mp 226–230°C. IR spectrum, cm^{-1}: 2208, 2131, 1775, 1712, 1595, 746, 694. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.81–2.02 m (2H, H^{15}), 2.37–2.52 m (4H, $H^{3''', 5'''}$), 2.46 s (3H, CH_3N^{17}), 2.52–2.64 m (3H, $H^{10,16,16}$), 2.86 s (3H, $CH_3N^{1'}$), 3.04 d (1H, H^8, *J* 7.9), 3.27 d (1H, H^{10}, *J* 19.3), 3.60–3.75 m (4H, $H^{2''', 6'''}$), 3.65 s (2H, $H^{1\gamma}$), 3.68 s (3H, CH_3OC^6), 3.79 s (3H, CH_3OC^3), 4.03 d (1H, H^9, *J* 6.3), 4.20 d (1H, H^7, *J* 7.9), 4.60 d (1H, H^5, *J* 1.2), 5.36 d (1H, H^{18}, *J* 8.7), 5.73 m (1H, H^{19}), 6.83 s (1H, H^2). ^{13}C NMR spectrum, δ, ppm: 22.33 (C^{10}), 33.31 (C^{15}), 24.62 ($CH_3N^{1'}$), 41.31 (C^7), 42.24 (C^8), 43.21 (CH_3N^{17}), 44.50 (C^{16}), 44.68 (C^{13}), 47.77 (C^{14}), 51.68 ($\underline{C}H_3OC^6$), 51.92 (2C, $C^{2''', 6'''}$), 56.18 ($\underline{C}H_3OC^3$), 56.79 (C^9), 66.90 (C^{1C}), 66.97 (2C, $C^{3''', 5'''}$), 76.68 (C^{1b}), 80.41 (C^6), 80.51 (C^{1a}), 91.46 (C^5), 112.66 (C^1), 117.40 (C^2), 128.99 (C^{19}), 131.81 (C^{11}), 132.94 (C^{12}), 133.49 (C^{18}), 149.31(C^4), 142.10 (C^3), 173.86 ($C^{5'}$), 177.07 ($C^{2'}$).

1-{[3-(4-Methylpiperazin-1-yl)]propynyl}-7α,8α-(*N*-methyl-2,5-dioxopyrrolidino)[3,4-*h*]-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (XXII). A flask in an argon flow was charged at stirring in succession with 0.009 g (0.30 mmol) of paraformaldehyde, 0.033 ml (0.30 mmol) of 4-methylpiperazine (**XIX**), 0.0004 g (0.002 mmol) of CuI, 4 ml of dioxane, and 0.1 g (0.24 mmol) of compound **XV**. The mixture was heated at 90–92°C for 7 h, then 0.001 g (0.30 mmol) of paraformaldehyde, 0.033 ml (0.30 mmol) of 4-methylpiperazine, 0.0004 g (0.002 mmol) of CuI were again added, and the heating was continued for 7.5 h more. The reaction mixture was evaporated in a Petri dish, the solid residue was treated with chloroform and water, the layers were separated, and the product was extracted from the water layer with chloroform. The combined extracts were washed with water, dried with $MgSO_4$, evaporated in a vacuum, and the residue was chromatographed on silica gel (eluent chloroform–ethanol). Yield 0.097 g (77%), mp 134°C. IR spectrum, Cm^{-1}: 2214, 1770, 1699, 1618, 1595, 752, 704. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.80–1.98 m (2H, H^{15}), 2.24–2.75 m (11H, $H^{10,16,16,2''',2''',3''',3''',5''',5''',6'''$ $,6'''$), 2.30 s (3H, $N^{4'''}CH_3$), 2.44 s (3H, CH_3–N^{17}), 2.85 s (3H, $CH_3N^{1'}$), 3.03 d (1H, H^8, *J* 8.0), 3.17 d (1H, H^{10}, *J* 19.0), 3.54 s (2H, H^{1C}), 3.67 s (3H, CH_3OC^6), 3.76 s (3H, CH_3OC^3), 4.00 d (1H, H^9, *J* 6.6), 4.18 d (1H, H^7, *J* 8.0), 4.64 d (1H, H^5, *J* 0.9), 5.34 d (1H, H^{18}, *J* 8.5), 5.71 m (1H, H^{19}), 6.73 s (1H, H^2). ^{13}C NMR spectrum, δ, ppm: 22.40 (C^{10}), 24.66 ($CH_3N^{1'}$), 33.42 (C^{15}), 41.40 (C^7), 42.30 (C^8), 43.24 (CH_3N^{17}), 44.75 (C^{16}), 44.90 (C^{13}), 45.87 ($CH_3N^{4'''}$), 47.79 (C^{14}), 47.86 (2C, $C^{3''', 5'''}$), 51.71 ($\underline{C}H_3OC^6$), 51.88 (2C, $C^{2''', 6'''}$), 54.91 (C^{1C}), 56.22 ($\underline{C}H_3OC^3$), 56.83 (C^9), 80.48 (C^6), 83.14 (C^{1b}), 87.10 (C^{1a}), 91.28 (C^5), 114.14 (C^1), 116.69 (C^2), 128.88 (C^{19}), 130.11 (C^{11}), 132.59 (C^{12}), 133.60 (C^{18}), 141.95 (C^3), 148.24 (C^4), 174.05 ($C^{5'}$), 177.27 ($C^{2'}$). Mass spectrum,

m/z (I_{rel}, %): 558 $[M]^+$ (15), 502 (68), 461 (100), 268 (41), 99 (49), 97 (70), 70 (37), 58 (64), 56 (35), 42 (26). Found *m/z* 558.2841 $[M]^+$. $C_{32}H_{38}N_4O_5$. Calculated m 558.2837.

1-[3-(4-*tert*-Butoxycarbonylpiperazin-1-yl)propynyl]-7α,8α-(*N*'-methyl-2,5-dioxopyrrolidino)-[3,4-*h*]-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (XXIII). A flask in an argon flow was charged at stirring in succession with 0.0085 g (0.27 mmol) of paraformaldehyde, 0.05 g (0.27 mmol) of *N*-Boc-piperazine (**XX**), 0.0004 g (0.002 mmol) of CuI, 4 ml of dioxane, and 0.1 g (0.22 mmol) of compound **XV**. The mixture was heated at 90–95°C for 5 h, then 0.0085 g (0.27 mmol) of paraformaldehyde, 0.05 g (0.27 mmol) of *N*-Boc-piperazine, 0.0004 g (0.002 mmol) of CuI, 1 ml of dioxane were again added, and the heating was continued for 7.5 h more. The reaction mixture was evaporated in a Petri dish, the solid residue was treated with chloroform and water, the layers were separated, and the product was extracted from the water layer with chloroform. The combined extracts were washed with water, dried with $MgSO_4$, evaporated in a vacuum, and the residue was chromatographed on silica gel (eluent chloroform–ethanol). Yield 0.107 g (80%). IR spectrum, cm^{-1}: 2208, 1770, 1701, 1620, 1598, 765, 700. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.44 s [9H, $C(CH_3)_3$], 1.86–2.00 m (2H, H^{15}), 2.35–2.53 m (3H, $H^{10,16,16}$), 2.45 s (3H, CH_3N^{17}), 2.54–2.60 m (4H, $H^{3''',3''',5''',5'''}$), 2.86 s (3H, $CH_3N^{1'}$), 3.03 d (1H, H^8, *J* 8.0), 3.18 d (1H, H^{10}, *J* 19.0), 2.54–2.60 m (4H, $H^{2''',2''',6''',6'''}$), 3.55 s (2H, H^{1C}), 3.68 s (3H, CH_3OC^6), 3.77 s (3H, CH_3OC^3), 4.01 d (1H, H^9, *J* 6.7), 4.19 d (1H, H^7, *J* 8.0), 4.66 d (1H, H^5, *J* 0.9), 5.34 d (1H, H^{18}, *J* 8.5), 5.71 m (1H, H^{19}), 6.74 s (1H, H^2). ^{13}C NMR spectrum, δ, ppm: 22.42 (C^{10}), 24.70 ($CH_3N^{1'}$), 28.40 [$C(\underline{C}H_3)_3$], 33.45 (C^{15}), 41.42 (C^7), 42.33 (C^8), 43.28 (CH_3N^{17}), 44.77 ($C^{13,14}$), 44.92 (C^{16}), 47.86 (C^{1C}), 48.02 (2C, $C^{2''',4'''}$), 51.74 ($\underline{C}H_3OC^6$), 51.88 (2C, $C^{2''',6'''}$), 56.27 ($\underline{C}H_3OC^3$), 56.85 (C^9), 79.72 [$\underline{C}(CH_3)_3$], 80.52 (C^6), 83.33 (C^{1b}), 86.85 (C^{1a}), 91.33 (C^5), 113.99 (C^1), 116.74 (C^2), 128.99 (C^{19}), 130.13 (C^{11}), 132.73 (C^{12}), 133.59 (C^{18}), 142.03 (C^3), 148.38 (C^4), 154.69 (C=O), 174.05 ($C^{5'}$), 177.27 ($C^{2'}$). Mass spectrum, *m/z* (I_{rel}, %): 644 $[M]^+$ (37), 543 (46), 501 (21), 461 (100), 458 (34), 266 (33), 204 (15), 57 (22). Found *m/z* 644.3191 $[M]^+$. $C_{36}H_{44}N_4O_7$. Calculated m 644.3205.

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REFERENCES

1. Coop, A., Grivas, K., Husbands, S., and Lewis, J.W., *Tetrahedron Lett*., 1995, vol. 36, p. 1689.
2. Maat, L., Woudenberg, R.H., Meuzelaar, G.J., and Linders, J.T.M., *Bioorg. Med. Chem*., 1999, vol. 7, p. 529.
3. Kalinin, V.N., Shishkov, I.V., Moiseev, S.K., Shults, E.E., Tolstikov, G.A., Sosnina, N.I., Petrovskii, P.V., Lyssenko, K.A. and Schmidhammer, H., *Helv. Shim. Acta*, 2006, vol. 89, p. 861.
4. Yavuz, S. and Yildirir, Y., *Helv. Chim. Acta,* 2010, vol. 93, p. 2406.
5. Li, W., Tao, Y.-M., Tang, Y., Xu, X.-J., Chen, J., Fu, W., Wang, X.-H., Chao, B., Sheng, W., Xie, Q., Qiu, Z.-B., and Liu, J.-G., *Bioorg. Med. Chem*., 2010, vol. 20, p. 418.
6. Shafiee, A., Amanlou, M., Farsam, H., Dehpour, A.R., Mir-Ershadi, F., and Mani, A.R., *Pharm. Acta Helv*., 1999, vol. 73, p. 251.
7. Shul'ts, E.E., Tolstikova, T.G., Tolstikov, S.E., Daibova, V.T., Shakirov, M.M., Bolkunov, A.V., and Tolstikov, G.A., *Khim.-Farm. Zh*., 2007, no. 2, p. 15.
8. Bauman, V.T., Shul'ts, E.E., Shakirov, M.M., and Tolstikov, G.A., *Zh. Org. Khim.,* 2007, vol. 43, p. 529.
9. Görlitzer, K. and Schumann, R., *Pharmazie*, 1992, vol. 47, p. 893.
10. Nan, Y., Xu, W., Zaw, K., Hughes, K.E., Huang, L.-F., Dunn, III, W.J., Bauer, L., and Bhargava, H.N., *J. Heterocycl. Chem*., 1997, vol. 34, p. 1995.
11. Bauman, V.T., Shul'ts, E.E., Shakirov, M.M., and Tolstikov, G.A., *Izv. Akad. Nauk, Ser. Khim*., 2007, p. 1206.
12. Bieber, L.W. and da Silva, M.F., *Tetrahedron Lett*., 2004, vol. 45, p. 8281.
13. Stothers, J.B., *Carbon-13, NMR Spectroscopy,* New York: Acad. Press, 1972, 251 p.
14. Setea, M., Schüllner, F., Moisa, R.C., Berseteï-Gurske, I.P., Schraml, B., Dörfler, C., Aceto, M.D., Harris, L.S., Coop, A., and Schmidhammer, H., *J. Med. Chem*., 2004, no. 47, p. 3243.
15. Wentland, M.P., Lu, Q., Lou, R., Bu, Y., Knapp, B.I., and Bidlack, J.M., *Bioorg. Med. Chem. Lett*., 2005, vol. 15, 2107.
16. Tolstikova, T.G., Morozova, E.A., Bolkunov, A.V., Dolgikh, M.P., Bauman, V.T., Tolstikov, S.E., and Shul'ts, E.E., *Vopr. Biol. Med. Farm. Khim*, 2007, no. 1, p. 39.
17. *Sintezy organicheskikh preparatov* (Syntheses of Organic Chemicals), Moscow: 1949, p. 199.
18. Erguson, G., McCrindle, R., McAlees, A.J., and Parvez, M.T., *Acta Cryst*., 1982, vol. 38, p. 2679.
19. Pindur, U. and Keilhofer, D., *Lieb. Ann*., 1993, p. 947.
20. Shul'ts, E.E., Shakirov, M.M., Tolstikov, G.A., Kalinin, V.N., and Shmidkhammer, G., *Zh. Org. Khim.,* 2005, vol. 41, p. 1155.
21. Stevens, W.C., Jones, R.M., Subramanian, G., Metzger, T.G., Terguson, D.M., and Portoghese, P.S., *J. Med. Chem*., 2000, vol. 43, p. 2759.