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Dedicated to Full Member of the Russian Academy of Sciences I. P. Beletskaya on occasion of her anniversary

Thebaine Cyclopropanation

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Abstract—[1+2]Cycloaddition to thebaine alcaloid under catalysis by copper triflate of carbene generated from CH_2N_2 occurred stereoselectively affording 6β,7β-methylene-6,7-dihydrothebaine. The simultaneously proceeding 8β,14β-cyclopropanation and nitrogen quaternization furnished *N*,*N*-dimethyl-*N*-nor-8β,14β-methylene-8,14-dihydrothebaine triflate whose structure was established by X-ray diffraction analysis. The possibility of preparation of 14β-hydroxy-6β,7β-methylene-8α-substituted dihydrocodeine derivatives was demonstrated.

We formerly showed that thebaine (**I**) reacted with diazomethane in the presence of copper(II) triflate affording a product of carbene addition across the $\Delta^{6,7}$ bond; the structure of the product was not strictly proved [1]. Here we report on refined data on this reaction. In the reaction of diene **I** with diazomethane in dichloromethane in the presence of 0.02–0.04 mol of $Cu(CF_3SO_3)_2$ alongside the principal product, 6β,7β-methylene-6,7-dihydrothebaine (**II**) (yield 80–95%), formed a product of diazomethane addition across the $\Delta^{8,14}$ bond in **III** in 2–5% yield. Compound **III** is *N*,*N*-dimethyl-*N*-nor-8β,14β-methylene-8,14-dihydrothebaine trifluoromethanesulfonate (**III**), and its structure is proved by spectral data and X-ray diffraction analysis.

The availability of compound **II** gives an opportunity to synthesize therefrom morphinane derivatives with new pharmacologic qualities, in particular, 8β-derivatives of 14β-hydroxy-6β,7β-methylenedihydrocodeine. The oxidation of adduct **II** with excess *m*-chloroperbenzoic acid in dichloromethane furnished N-oxide of 8β,14β-epoxy-6β,7β-methylene-6,7,8,14-tetrahydrothebaine (**IV**). The reaction is kinetically controlled. When the reaction was carried out at low temperature in the presence of 0.8 equiv. of *m*-$ClC_6H_4CO_3H$ we succeeded in isolating N-oxide **V**. The ring opening in epoxide **IV** by treating with sodium azide in aqueous dioxane afforded 8α-azido derivative of 6β,7β-methylene-7,8-dihydrocodein-14β-ol (**VI**).

The structure of compounds obtained was derived from spectral data. The β-configuration of the cyclopropane substituent in compound **II** follows from the results of NOESY experiment since a NOE is observed between H^5 and $H^{6a\beta}$ protons (3.7%) and it is lacking with the H^7 proton. At decoupling from the signal of the methoxy group attached to the C^6 a significant NOE is observed on the H^8 proton (18%), and it is lacking on the protons H^7 and $H^{6a(\alpha,\beta)}$. The latter fact confirms the α-orientation of the methoxy group. The most informative for determining the *endo*- or *exo*-orientation of the cyclopropane fragment turned out to be the ^{13}C NMR spectra. Comparison with the carbon chemical shifts in the ^{13}C NMR spectrum of thebaine [2] showed that the introduction into the molecule of an *exo*-cyclopropane fragment results in a downfield shift of signals from the atoms C^{14} and C^9 (Δδ 10.3 and 3.4 ppm) and in an upfield shift of those from the atoms C^{10} and C^{13} (Δδ 6.8 and 3.9 ppm). Besides the signal of C^5 atom shifts upfield (Δδ 3.6 ppm) at formation of an *exo*-cyclopropane substituent both at $\Delta^{6,7}$ and $\Delta^{8,14}$ bonds compared to its position in the spectra of thebeine (δ 88.8 ppm) and 7,8-dihydrocodeine (δ 90 ppm) [2]. An additional proof was obtained from the NOESY spectrum of the epoxide. No interaction was observed between protons H^5 and $H^{7,8}$ at decoupling from H^5 signal evidencing the *syn*, *cis*-position of the protons. Consequently, both cyclopropane and oxirane rings in compound **IV** have β,β-orientation. Epoxidation of

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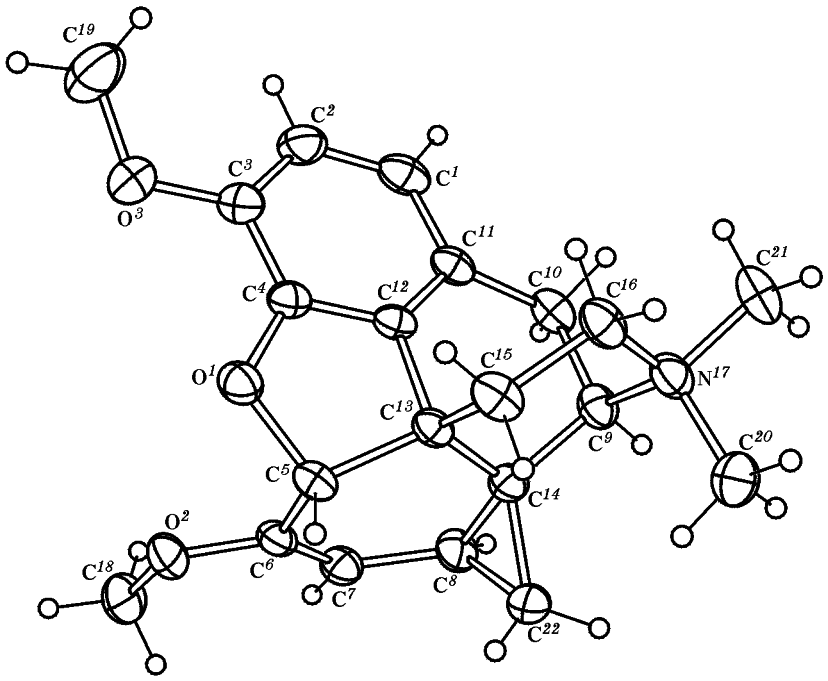
Values of bond angles (deg) of compound **III** according to X-ray diffraction analysis

Angle	Value	Angle	Value
$C^{11}C^{1}C^{2}$	120.6(5)	$C^{12}C^{13}C^{5}$	98.4(3)
$C^{3}C^{2}C^{1}$	122.9(5)	$C^{15}C^{13}C^{5}$	111.3(4)
$C^{2}C^{3}O^{3}$	126.5(5)	$C^{13}C^{14}C^{22}$	122.2(5)
$C^{2}C^{3}C^{4}$	115.7(5)	$C^{13}C^{14}C^{8}$	116.5(4)
$O^{3}C^{3}C^{4}$	117.8(5)	$C^{22}C^{14}C^{8}$	60.6(3)
$C^{12}C^{4}C^{3}$	120.5(5)	$C^{13}C^{14}C^{9}$	109.9(4)
$C^{12}C^{4}O^{1}$	112.7(4)	$C^{22}C^{14}C^{9}$	120.0(5)
$C^{3}C^{4}O^{1}$	126.8(4)	$C^{8}C^{14}C^{9}$	120.0(4)
$O^{1}C^{5}C^{6}$	108.4(4)	$C^{16}C^{15}C^{13}$	110.0(4)
$O^{1}C^{5}C^{13}$	104.2(3)	$N^{17}C^{16}C^{15}$	113.8(4)
$C^{6}C^{5}C^{13}$	111.6(4)	$C^{21}N^{17}C^{20}$	105.8(5)
$C^{7}C^{6}O^{2}$	126.7(4)	$C^{21}N^{17}C^{16}$	108.2(4)
$C^{7}C^{6}C^{5}$	123.6(4)	$C^{20}N^{17}C^{16}$	110.2(5)
$O^{2}C^{6}C^{5}$	109.6(4)	$C^{21}N^{17}C^{9}$	111.5(4)
$C^{6}C^{7}C^{8}$	123.9(4)	$C^{20}N^{17}C^{9}$	109.6(4)
$C^{7}C^{8}C^{14}$	117.5(4)	$C^{16}N^{17}C^{9}$	111.4(4)
$C^{7}C^{8}C^{22}$	119.4(5)	$C^{14}C^{22}C^{8}$	59.9(3)
$C^{14}C^{8}C^{22}$	59.5(3)	$C^{4}O^{1}C^{5}$	104.9(3)
$C^{14}C^{9}C^{10}$	111.9(4)	$C^{6}O^{2}C^{18}$	116.8(4)
$C^{14}C^{9}N^{17}$	108.3(4)	$C^{3}O^{3}C^{19}$	116.0(6)
$C^{10}C^{9}N^{17}$	113.0(4)	$O^{2A}S^{1A}O^{1A}$	123.7(5)
$C^{11}C^{10}C^{9}$	114.1(4)	$O^{2A}S^{1A}O^{3A}$	112.1(5)
$C^{12}C^{11}C^{1}$	114.3(5)	$O^{1A}S^{1A}O^{3A}$	111.4(5)
$C^{12}C^{11}C^{10}$	118.9(4)	$O^{2A}S^{1A}C^{1A}$	106.1(4)
$C^{1}C^{11}C^{10}$	126.6(5)	$O^{1A}S^{1A}C^{1A}$	106.7(4)
$C^{4}C^{12}C^{11}$	125.8(4)	$O^{3A}S^{1A}C^{1A}$	91.3(6)
$C^{4}C^{12}C^{13}$	108.4(4)	$F^{1A}C^{1A}F^{2A}$	110.4(7)
$C^{11}C^{12}C^{13}$	125.8(4)	$F^{1A}C^{1A}F^{3A}$	102.7(9)
$C^{14}C^{13}C^{12}$	108.0(4)	$F^{2A}C^{1A}F^{3A}$	101.5(8)
$C^{14}C^{13}C^{15}$	110.2(4)	$F^{1A}C^{1A}S^{1A}$	118.0(7)
$C^{12}C^{13}C^{15}$	108.3(4)	$F^{2A}C^{1A}S^{1A}$	114.8(7)
$C^{14}C^{13}C^{5}$	119.5(4)	$F^{3A}C^{1A}S^{1A}$	107.3(6)

compound **II** is accompanied by formation of chromatographically individual N-oxide. The characteristic feature of ^{1}H and ^{13}C NMR spectra of N-oxides **IV–VI** consists in the downfield shift of protons $H^{9,15,16}$ and also of the proton signal from methyl group attached to nitrogen and of carbon atoms C^{16} and $N\underline{C}H_3$ as compared to the corresponding location of these signals in the spectrum of compound **II**. Besides the signal from carbon atom C^{10} in the spectra of compounds **IV, VI** is also shifted downfield. It should be noted that in the ^{1}H NMR spectra of 8,14-epoxy and 14β-hydroxy derivatives an increased magnetic nonequivalence is observed of protons H^{10}, and the signal of $H^{10\alpha}$ proton is shifted upfield. The signal of the C^{15} carbon in the spectra of quaternized compounds **III, IV, VI** is shifted upfield.

The configuration of the nitrogen atom was established on the following grounds. It is known that the different orientations of the methyl group in the N-oxides of 14β-hydroxycodeinone and thebaine results in the difference in the chemical shifts of the singlet from NMe (δ 3.25 and 3.74 ppm respectively) and of signals from the proton at the C^{9} carbon (for 14β-hydroxycodeinone δ 3.72, for thebaine δ 4.12) [3]. In our case the signals from the methyl group of the N-oxides appear at 3.25 (**IV**) and 3.32 (**V**) ppm, from the proton H^{9} at 3.69 (**IV**) and 3.48 (**V**) ppm. We assume that these data correspond to an equatorial position of the methyl group. Note also a considerable downfield shift of proton signals from $N\underline{C}H_3$ and H^{9} in the spectrum of azide (**VI**).

The formation of 8,14-epoxy derivative causes significant changes in the chemical shifts of the carbon signals from the cyclopropane fragment ($C^{6,6a,7}$): the resonances are shifted upfield by Δδ 1.70, 4.45 and 1.64 ppm respectively. The opening



Molecular structure of cation III.

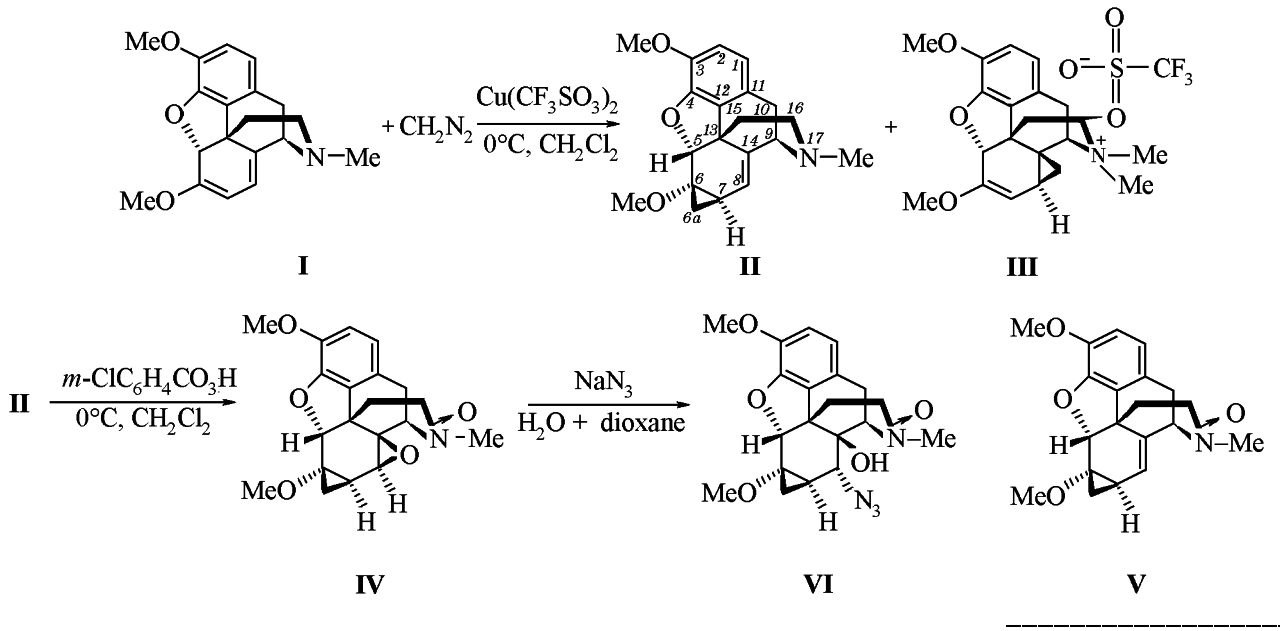
of the epoxy ring and introduction of an azide group to C^{8} carbon is confirmed by the IR spectrum (appearance of a band at 2120 cm^{-1}). It results in a still larger downfield shift of the signal from C^{7} ($\Delta\delta$ 4.68 ppm) and an upfield shift of the signals from carbons $C^{6,6a}$ ($\Delta\delta$ 3.80, 3.03 ppm). The opening of the epoxy ring also causes an upfield shift of signal from proton H^{5} ($\Delta\delta$ 0.6 ppm) apparently due to the influence of the anisotropic azide group.

The structure of the molecule of cation **III** is presented on the figure, and the values of bond angles are given in the table.

Among over 50 isomorphinanes described in Cambridge Structural Database [4] only two compounds have similar skeleton (the same configuration of the asymmetric centers and a double bond in the C ring). The *cis*-fused to the C ring six-membered ring B in the molecule **III** is in a *sofa* conformation, and the atom C^{14} deviates by – 0.664(6) from a plane $C^{9}\cdots C^{13}$ that is accurate within 0.047 Å. The piperidine ring *trans*-fused to the C ring is in a *chair* conformation. The dihydrofuran ring is fused to the C ring in the *cis*-position and is in an *envelope* conformation where the C^{5} atom deviates from the plane of the other four atoms by –0.513(6) Å (the mean square deviation from the plane of the other atoms is 0.021 Å). The C ring has a *sofa* conformation; therewith the atom C^{13} deviates from the plane accurate within 0.046 Å $C^{5}C^{6}C^{7}C^{8}C^{13}$ by –0.358(6) Å. The methoxy group attached to C^{6} (O^{2}–C^{18}) is in eclipsed position with respect to the $\Delta^{6,7}$ bond. The dihedral angle between the C ring and the cyclopropane fragment equals to 77.2°. The geometrical parameters of the alcaloid moiety including the atoms of all substituents are quite common for codeine derivatives [4] and within 3σ coincide with analogous parameters of 8β-bis(methoxycarbonyl)methyldeoxypseudocodeine [5]. Only the bond C^{13}–C^{14} is an exclusion being shortened to 1.493(7) Å in the molecule **III** due to the neighboring cyclopropane ring against 1.535(3) Å in the 8β-bis(methoxycarbonyl)methyldeoxypseudocodeine. The geometrical parameters of the anion molecules are also close to the published data [4]. The great scatter in the C–F bond lengths (from 1.265 to 1.426 Å) should be mentioned as caused by large thermal vibrations of the fluorine atom. The presence of weak contacts C–H···O is also worthy of notice: $C^{10}\cdots O^{1}$ (–1 + *x*, *y*, *z*) 3.222(6), $H^{10B}\cdots O^{1}$ 2.38 Å, C^{10}–$H^{10B}\cdots O^{1}$ 144.5°, $C^{10A}\cdots O^{3}$ (1 – *x*, 5 + *y*, 5 – *z*) 3.343(9), $H^{10A}\cdots O^{3}$ 2.46 Å, C^{10}–$H^{10A}\cdots O^{1}$ 151.3°.

Thus the addition of carbene generated from diazomethane to thebaine was characterized by β-selectivity. A similar selectivity was observed with opiate dienes, in particular, with thebaine (**I**), when these compounds were used as a dienophile

component in reaction with 1-cyano-*o*-quinodimethane [6]. Besides in [6] was mentioned the higher dienophilic activity of the $\Delta^{8,14}$ bond of thebaine (**I**) in the Diels–Alder reaction. The results of the double bond $\Delta^{8,14}$ reduction with diimide (NH_2NH_2, H_2O, O_2) [7] are also worth mentioning. In our case the attention should be drawn to the decisive role in of the nitrogen-containing substituent that is able to coordinate with the catalyst in directing carbene addition to a double bond. The exclusive formation of 8β,14β-epoxy derivative of 6β,7β-cyclopropyldihydrothebaine also originates from the orientation produced by coordination of the peracid with substituents. Henbest et al. [8] were the first to observe such substituents effect in oxidation of polyfunctional compounds; this phenomenon is treated in detail in [9].



EXPERIMENTAL

^1H and ^{13}C NMR spectra were registered on spectrometers Bruker AC 200 (operating frequencies 200.13 and 50.32 MHz respectively) and Bruker DRX 500 (operating frequencies 500.13 and 125.76 MHz respectively) from solutions in $CDCl_3$ or CD_2OD. The assignment of signals in the NMR spectra was performed with the use of various proton–proton and carbon–proton correlation spectra (COSY, COLOC, CORRD) and ^1H NMR 2D-spectroscopy of Overhauser effect NOESY. IR spectra were recorded on spectrometer VECTOR-22 from KBr pellets. The mass spectra were measured on a high-resolution instrument Finnigan MAT 8200 (ionizing electrons energy 70 eV, vaporizer temperature 270°C). Molecular weights and elemental composition of compounds were derived from the mass spectra.

X-ray diffraction analysis was performed with the use of a diffractometer Bruker P4 (Mo *K*α-radiation, graphite monochromator, 2θ/θ-scanning in the range $2\theta < 50°$). The reaction progress was monitored by TLC on Sulifol UV-254 plates. The reaction products were isolated by column chromatography on neutral or basic alumina (eluents chloroform; chloroform–ethanol, 100 : 1 or 10 : 1).

6β,7β-Methylene-6,7-dihydrothebaine (II) and *N,N*-dimethyl-*N*-nor-8β,14β-methylene-8,14-dihydrothebaine trifluoromethanesulfonate (III). To a solution of 1.55 g (5 mmol) of thebaine **I** in 30 ml of dichloromethane cooled to 0°C was added 0.038 g (0.1 mmol) of copper(II) trifluoromethanesulfonate, then within 30 min was added dropwise a solution of diazomethane (prepared from 5.0 g of *N*-nitroso-*N*-methylurea) in 80 ml of dichloromethane. The stirring was continued for 30 min at room temperature, the solvent was evaporated, the residue was dissolved in 10 ml of chloroform and passed through a layer of alumina (3 g). By crystallization from ethyl acetate 1.31 g (81%) of compound **II** was isolated. On cooling the mother liquor 0.11 g (4.5%) of compound **III** separated. Compound **II**, mp 160–162°C. IR spectrum, ν, cm^{-1}: 738, 911, 1020, 1050, 1188, 1230, 1278, 1375, 1506, 1610, 1645, 1665, 2965. ^1H NMR spectrum ($CDCl_3$), δ, ppm, (*J*, Hz): 0.38 d.d

(1H, H^{6aA}, *J* 4.3, 3.8, 0.7), 1.07 d.d (1H, H^{6aB}, *J* 7.8, 4.3), 1.26 d.d.d (1H, H^{7}, *J* 7.8, 5.6, 3.8), 1.77 d.d.d (1H, H^{15}, *J* 12.2, 3.6, 1.8), 2.11 t.d (1H, H^{5}, *J* 12.2, 4.9), 2.38 d.d.d (1H, H^{16}, *J* 13.5, 4.2, 1.4), 2.41 s (3H, $NC\underline{H}_3$), 2.42 d (1H, $H^{9\alpha}$, *J* 6.4), 2.46 d.d.d (1H, H^{10}, *J* 18.5, 10.2, 3.1), 2.64 d.d.d (1H, H^{16}, *J* 12.2, 4.2 and 1.5), 3.10 br.d (1H, $H4^{10\beta}$, *J* 17.6, 0.7), 3.42 s (3H, $C\underline{H}_3OC^{6}$), 3.82 s (3H, $C\underline{H}_3OC^{3}$), 4.56 s (1H, $H^{5\beta}$), 5.06 d (1H, H^{8}, *J* 5.6), 6.62 t (1H, H^{1}, *J* 8.2, 0.7), 6.70 d (1H, H^{2}, *J* 7.8). ^{13}C NMR spectrum, δ, ppm: 15.67 d (C^{7}), 22.42 t (C^{10}), 24.40 t (C^{6a}), 25.72 s (C^{6}), 34.03 t (C^{15}), 41.84 s (C^{13}), 43.09 q ($\underline{C}H_3N$), 47.37 t (C^{16}), 54.47 q ($\underline{C}H_3O$ C^{6}), 56.44 q ($\underline{C}H_3O$ C^{3}), 64.06 d (C^{9}), 84.99 d (C^{5}), 101.51 d (C^{8}), 113.68 d (C^{2}), 118.82 d (C^{1}), 127.33 s (C^{11}), 132.06 s (C^{12}), 142.67 s (C^{14}), 143.54 s (C^{3}), 148.45 s (C^{4}). $C_{20}H_{23}NO_3$.

Compound **III**, mp 141–143°C. IR spectrum, ν, cm^{-1}: 638, 880, 912, 1029, 1188, 1278, 1506, 1551, 1614, 3044, 3444. ^{1}H NMR spectrum (CD_3OD), δ, ppm, (*J* Hz): 0.96 t.d (1H, H^{8aA}, *J* 4.5, 0.9), 1.49 d.d (1H, H^{8aB}, *J* 8.4, 4.5), 1.56 d.d.d (1H, H^{8}, *J* 8.4, 5.6, 4.3), 1.94 m (1H, H^{15}, *J*gem 14.4, *J* 3.6, 1.8), 2.66 d.d.d (1H, H^{15}, *J* 14.4, 13.2, 4.5), 3.18 br.d (1H, H^{10}, *J* 19.7), 3.30 s (3H, $NC\underline{H}_3$), 3.32 m (1H, H^{16}), 3.47 s (3H, $C\underline{H}_3OC^{6}$), 3.46 m (1H, H^{16}), 3.48 d (1H, $H^{9}\alpha$, *J* 6.4), 3.51 s (3H, $NC\underline{H}_3$), 3.64 d (1H, H^{10}, *J* 19.7), 3.87 s (3H, CH_3OC^{3}), 4.79 s (1H, $H^{5\beta}$), 5.22 d (1H, H^{7}, *J* 5.6), 6.81 d.t (1H, H^{1}, *J* 8.2, 1.0), 6.87 d (1H, H^{2}, *J* 8.2). ^{13}C NMR spectrum, δ, ppm: 15.77 d (C^{8}), 22.02 s (C^{14}), 27.72 t (C^{10}), 27.89 t (C^{8a}), 29.74 t (C^{15}), 42.23 s (C^{13}), 52.41 q ($\underline{C}H_3N$), 54.62 q ($\underline{C}H_3N$), 55.32 q ($\underline{C}H_3OC^{6}$), 57.54 q ($\underline{C}H_3OC^{3}$), 59.22 t (C^{16}), 76.36 d (C^{9}), 85.21 d (C^{5}), 101.81 d (C^{7}), 117.30 d (C^{2}), 121.19 d (C^{1}), 124.22 s (C^{11}), 131.99 s (C^{12}), 144.69 s (C^{6}), 145.28 s (C^{3}), 149.95 s (C^{4}). Mass spectrum, *m/z* (T_{rel}, %): 339 [M^+] (0.6), 325 (2.22), 239 (1.29), 217 (4.07), 192 (4.63), 167 (6.9), 149 (22.20), 111 (15.05), 97 (22.69), 43 (100). $C_{22}H_{26}F_3NO_6S$.

6β,7β-Methylene-8β,14β-epoxy-6,7,8,14-tetrahydrothebaine *N*-oxide (IV). A solution of 0.65 g (2 mmol) of compound **II** in 25 ml of dichloromethane was cooled to 0°C, and at stirring thereto was added dropwise a solution of 0.86 g (4.47 mmol) of 90% *m*-chloroperbenzoic acid in 10 ml of dichloromethane. The reaction mixture was stirred for 2 h, then it was diluted with 30 ml of dichloromethane, and washed in succession with 10% solution of sodium sulfite and water. The organic layer was dried on sodium sulfate, the solvent was evaporated in a vacuum to afford 0.68 g of solid substance. By column chromatography on alumina followed by recrystallization from ethanol we isolated 0.55 g (77%) of ethoxy derivative **IV**, mp 126–128°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, (*J* Hz): 1.03 d.d (1H, H^{6aA}, *J*6.2, 4.6), 1.21 d.d.d (1H, H^{7}, *J* 8.3, 4.6, 4.2), 1.72 d.t (1H, H^{10}, *J* 12.8, 2.7), 1.84 d.d (1H, H^{6aB}, *J* 8.3, 6.2), 2.83 d.d.d (1H, H^{10}, *J* 12.8, 1.5, 1.0), 2.87 d (1H, H^{8}, *J* 4.2), 3.01 d.d (1H, H^{15}, *J* 18.9, 5.6, 1.2), 3.13 m (1H, H^{15}, *J* 18.9), 3.20 d.d (1H, H^{16}, *J* 9.1, 2.8), 3.25 s (3H, $NC\underline{H}_3$), 3.28 s (3H, $C\underline{H}_3OC^{6}$), 3.30 m (1H, H^{16}), 3.69 d (1H, $H^{9\alpha}$, *J*2.7), 3.86 s (3H, $C\underline{H}_3OC^{3}$), 4.81 s (1H, $H^{5\beta}$), 6.61 d.t (1H, H^{1}, *J* 8.2, 1.0), 6.74 d (1H, H^{2}, *J* 8.2). ^{13}C NMR spectrum, δ, ppm: 14.03 d (C^{7}), 19.86 t (C^{6a}), 23.94 s (C^{6}), 28.63 t (C^{15}), 29.34 t (C^{10}), 40.38 t (C^{13}), 51.48 q ($C\underline{H}_3OC^{6}$), 56.59 q ($\underline{C}H_3OC^{3}$), 58.69 q ($\underline{C}H_3N$), 61.68 t (C^{16}), 61.18 d (C^{9}), 78.33 d (C^{8}), 82.57 s (C^{14}), 89.24 d (C^{5}), 114.83 d (C^{2}), 119.36 d (C^{1}), 121.38 s (C^{11}), 130.23 s (C^{12}), 142.89 s (C^{3}), 145.12 s (C^{4}). $C_{20}H_{23}NO_5$.

6β,7β-Methylene-8,14-dihydrothebaine N-oxide (V). A solution of 0.325 g (1 mmol) of compound **II** in 20 ml of dichloromethane was cooled to –20°C, and at stirring thereto was added dropwise a solution of 0.15 g (0.78 mmol) of 90% *m*-chloroperbenzoic acid in 3 ml of dichloromethane. The reaction mixture was stirred for 30 h, then it was washed in succession with cooled 10% solution of sodium sulfite and water. The organic layer was dried on sodium sulfate, the solvent was evaporated in a vacuum to afford 0.33 g of sold residue. By column chromatography on alumina were isolated in succession 0.12 g of compound **II** (eluent chloroform) and 0.15 g of N-oxide **V** (eluent chloroform–ethanol, 10 : 1). The latter was a solid amorphous substance. ^{1}H NMR spectrum (CD_3OD), δ, ppm, (*J*Hz): 0.73 d.d (1H, H^{6aA}, *J* 6.2, 4.3), 0.98 d.d (1H, H^{6aB}, *J* 6.2, 4.3, 3.8), 1.26 d.d.d (1H, H^{7}, *J* 5.6, 4.3, 3.8), 2.34 d.d.d (1H, H^{10}, *J* 12.2, 3.6, 1.8), 3.06 t.d (1H, H^{10}, *J* 12.8, 12.2, 4.0), 3.08 d.d.d (1H, H^{15}, *J* 13.5, 4.2, 1.4), 3.28 m (1H, H^{15}), 3.32 s (3H, $NC\underline{H}_3$), 3.34 m (1H, H^{16}), 3.42 s (3H, $C\underline{H}_3OC^{6}$), 3.48 d (1H, $H^{9\alpha}$, *J* 6.4), 3.60 br.d (1H, H^{16}, *J* 18.4, 1.0), 3.87 s (3H, $C\underline{H}_3OC^{3}$), 4.63 s (1H, $H^{5\beta}$), 5.10 d (1H, H^{8}, *J* 5.6), 6.60 d.t (1H, H^{1}, *J* 8.1, 1.0), 6.77 d (1H, H^{2}, *J* 8.1). $C_{20}H_{23}NO_4$.

8α-Azido-14β-hydroxy-6β,7β-methylene-6,7,8,14-tetrahydrothebaine N-oxide (VI). To a solution of 0.36 g (1 mmol) of epoxide **IV** in 15 ml of dioxane was added in one portion 0.33 g (5 mmol) of sodium azide in 5 ml of water. The mixture was heated at 100°C for 6 h, and on cooling the darkened

reaction mixture was poured into 50 ml of ice water, the mixture was stirred for 30 min,then alkalized to pH 9, and the reaction product was extracted into dichloromethane. The organic solutions were combined, washed with water, and dried on magnesium sulfate. The solvent was evaporated, the residue was subjected to column chromatography on basic alumina. On crystallization from THF we obtained 0.25 g (62%) of azide **VI**, mp 125–128°C. IR spectrum, ν, cm^{-1}: 705, 786, 920, 1019, 1042, 1120, 1148, 1185, 1220, 1300, 1320, 1500, 1551, 1620, 2120, 3085, 3248. ^{1}H NMR spectrum (CD_3OD), δ, ppm, (*J*, Hz): 1.33 d.d (1H, H^{7}, *J* 4.2, 3.8), 1.70 d.d (1H, H^{6aA}, *J* 6.3, 4.2), 1.65 d.d.d (1H, H^{10}, *J* 13.2, 3.6, 0.8), 1.84 d.d (1H, H^{6aB}, *J* 6.3, 2.8), 2.78 t.d (1H, H^{10}, *J* 13.2, 0.8), 3.23 m (1H, H^{15}), 3.30 m (1H, H^{15}), 3.35 m (1H, H^{16}), 3.64 s (3H, $C\underline{H}_3OC^{6}$), 3.70 m (1H, H^{16}), 3.74 s (3H, $NC\underline{H}_3$), 3.86 s (3H, $C\underline{H}_3OC^{3}$), 4.12 d.d (1H, H^{9}, *J* 3.6, 0.8), 4.18 d.d (1H, H^{8}, *J*), 4.21 s (1H, $H^{5\beta}$), 6.68 br. d (1H, H^{1}, *J* 8.2, 0.8), 6.77 d (1H, H^{2}, *J* 8.2). ^{13}C NMR spectrum, δ, ppm: 16.93 t (C^{6a}), 18.66 d (C^{7}), 20.92 t (C^{6}), 28.00 t (C^{10}), 30.81 t (C^{15}), 41.90 s (C^{13}), 52.31 q ($\underline{C}H_3O$), 55.75 q ($\underline{C}H_3N$), 56.78 q ($\underline{C}H_3OC^{3}$), 60.29 t (C^{16}), 69.71 d (C^{9}), 77.83 d (C^{8}), 88.78 d (C^{5}), 90.22 s (C^{14}), 115.35 d (C^{2}), 119.99 d (C^{1}), 121.51 s (C^{11}), 129.94 s (C^{12}), 143.13 s (C^{3}), 144.63 s (C^{4}). $C_{20}H_{24}N_4O_5$.

X-ray diffraction study of compound III. For measurement was chosen a crystal of the following habit: 2.00 × 1.80 » 1.60 mm. Rhombic crystals: (a) 7.192(1), *b* 8.971(2), *c* 34.227(7) Å, *V* 2208.1(8) $Å^3$, space group *P* 2_1 2_1 2_1, *Z* 4. $C_{22}H_{26}F_3NO_6S$. d_{calc} 1.472 g cm^{-1}, μ 0.212 mm^{-1}. Intensities of 2260 independent reflections were measured, The absorption was not taken into account. The structure was solved by the direct method with the use of SHELXS-97 software. The refining of structural parameters was carried out by the least-squares procedure in the full-matrix anisotropic approximation applying the program SHELXS-97. The hydrogen atoms were not accounted for in the refinement. The parameters of H atoms were calculated in each cycle from the coordinates of the corresponding carbons. The final refinement of structure was performed by all F^2 till wR_2 = 0.1822, *S* = 0.995, 299 parameters were refined (*R* = 0.0593 for 1815 $F > 4\sigma$).

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