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Thebaine Adducts with Maleimides. Synthesis and Transformations

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Abstract—Diels–Alder reaction of thebaine with maleimides is structurally specific and yields [7,8,3',4']-succinimido-*endo*-ethenotetrahydrothebaines containing *N*'-alkyl, cycloalkyl, aralkyl or aryl substituents. *N*'-[1(S)-hydroxymethyl-2-methylpropyl]-succinimido-6,14-*endo*-ethenotetrahydrothebaine formed in reaction of *S*-valinol with (7α,8α)-anhydrido-6,14-*endo*-ethenotetrahydrothebaine. The reduction of the adducts by $LiAlH_4$ afforded N'-substituted 7,8-pyrrolidino-*endo*-ethenotetrahydrothebaines. The reduction of fused succinimides by $NaBH_4$ resulted in the corresponding 2'α-hydroxylactam derivatives. O-Demethylation of the tetrahydrothebaine pyrrolidine derivatives effected by BBr_3 afforded compounds of the tetrahydrooripavine series. The O-demethylation of tetrahydrothebaine succinimide derivatives gave rise to the corresponding 6-demethyl-*endo*-ethenotetrahydrooripavines. Alkylation conditions were found for *N*'-(4-hydroxyphenethyl)-substituted tetrahydrothebaine succinimide derivatives.

The nature of a substituent in positions *7,8* of morphinane alkaloids in among the most important factors affecting their biological activity [1]. For instance, the opioid analgesic buprenorphine possesses a pharmacological profile interesting for development of antinarcotics [2]. A series of studies treats the influence of a lipophilic substituent at the C^{20} atom of the buprenorphine on the pharmacological activity [3–6]. We previously reported on thebaine cycloaddition to cyclic dienophiles providing 7α,8α-fused derivatives of 6,14-*endo*-ethenotetrahydrothebaine [7–10]. Among these thebaine derivatives promising active analgesics were found [11]. Here we report on thebaine (**I**) cycloaddition to various maleimides: 4-bromophenyl-substituted (**IIa**), 4- and 2-methoxybenzyl-substituted (**IIb** and **IIc**), arylethyl-substituted (**IId–IIg**), cyclohexenylethyl- (**IIh**), and dimethylaminoethyl-substituted (**IIi**) maleimides. At short boiling of reagents mixture in ethanol N'-substituted 7α,8α-succinimido-6,14-*endo*-ethenotetrahydrothebaines **III–IX** were obtained as sole reaction products in a 82–96% yield (Scheme 1).

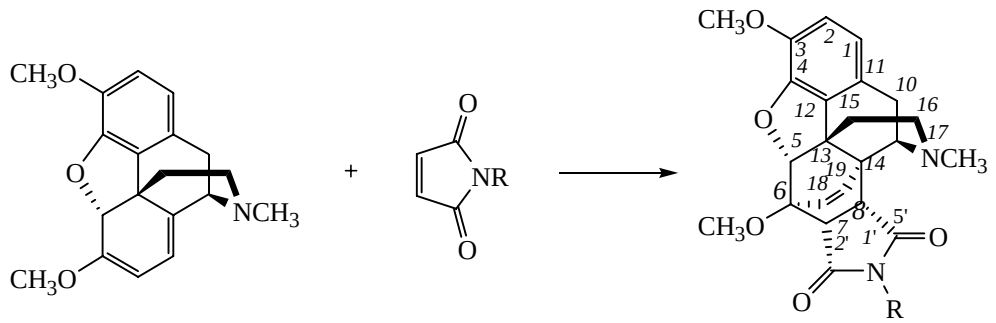
It should be mentioned that in [12] thebaine adducts were obtained with *N*-phenyl- and *N*-benzylmaleimides. Annelation of *N*-arylsuccinimide fragments at the $C^{7,8}$ atoms of thebaine was recently shown to afford a group of selective μ-opioid agonists [13].

The other way to succinimide derivatives of *endo*-ethenotetrahydrothebaine is a reaction of a thebaine adduct with maleic anhydride **XII** [14, 15] and amines. The heating of a mixture of compound **XII** with *S*-valinol (**XIII**) in toluene in the presence of triethylamine and molecular sieves (3A) afforded compound **XIV**. At the use of excess amine **XIII** a considerable amount of diamide **XV** was additionally isolated.

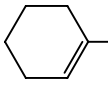
We investigated some transformations of the fused thebaine derivatives synthesized. The additional lipophilic groups were introduced into the molecule of 7,8-*endo*-ethenotetrahydrothebaine (**VII**) by O-alkylation under the conditions of a phase-transfer catalysis using 1,4-dibromobutane to obtain in 82% yield N'-bromobutoxyphenethyl derivative **XVI**. The reaction of compound **XVI** with aminoethanol in acetone in the presence of K_2CO_3 afforded a mixture of products of O- and N-alkylation **XVII** and **XVIII** in 29 and 37% yield respectively (Scheme 3).

The reduction of adducts **III**, **VII**, and **XVI** with excess $LiAlH_4$ in THF resulted in formation of the corresponding 7α,8α-pyrrolidino-6,14-*endo*-ethenotetrahydrothebaines

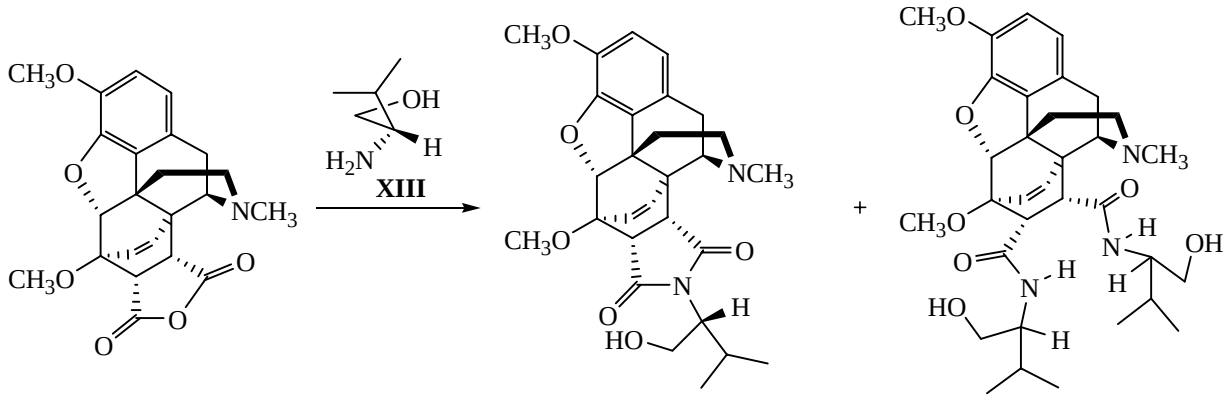
Scheme 1.



I **IIa–IIi** **III–XI**

R = C_6H_4Br (**IIa, III**), 4-$MeOC_6H_4CH_2$ (**IIb, IV**), 2-$MeOC_6H_4CH_2$ (**IIc, V**), $C_6H_5(CH_2)_2$ (**IId, VI**), 4-$HOC_6H_4(CH_2)_2$ (**IIe, VII**), 4-$FC_6H_4(CH_2)_2$ (**IIf, VIII**), 2-$FC_6H_4(CH_2)_2$ (**IIg, IX**),  $(CH_2)_2$ (**IIh, X**), $(CH_2)_2N(CH_3)_2$ (**IIi, XI**).

Scheme 2.

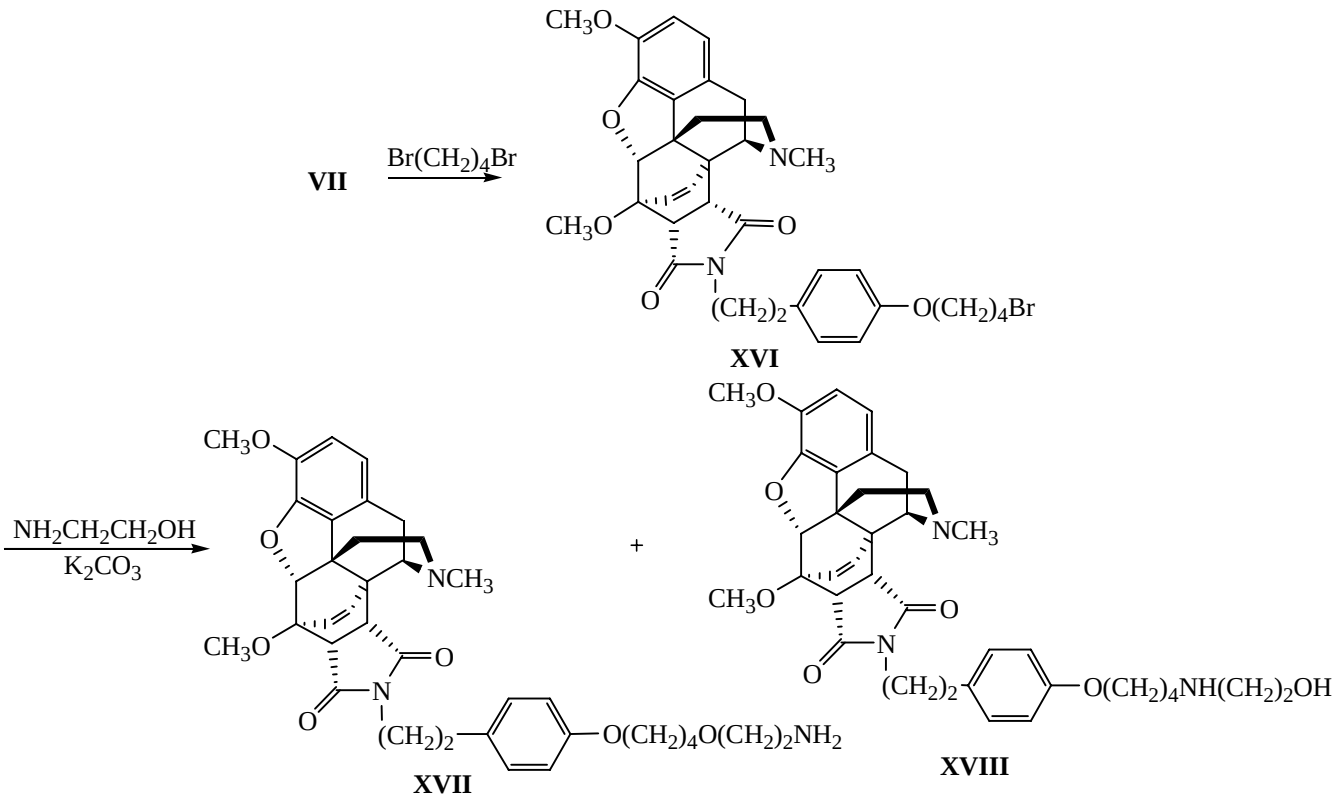


XII **XIII** **XIV** **XV**

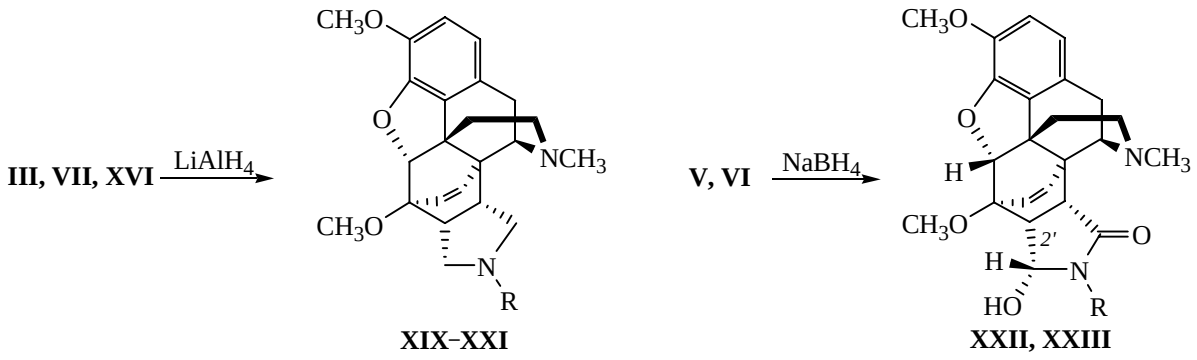
XIX–XXI. The partial reduction of the cyclic imides with various reagents [$NaBH_4$, $(i\text{-Bu})_2AlH$, $NaAlH_2(OCH_2CH_2OEt)_2$] was considered in detail in review [16]. As a rule a problem of regio- and stereoselectivity arises for the unsymmetrically substituted imides. We found that the reduction of compounds **V** and **VI** with sodium borohydride in THF in the presence of ethanol solution of HCl made it possible to isolate 2'α-hydroxylactams of *endo*-ethenotetrahydrothebaine **XXII** and **XXIII** in a 73–78% yield. The reaction is characterized by the regio- and stereospecificity and is apparently governed by the methoxy group attached to C^6 atom of the morphinane skeleton (Scheme 4).

An interesting result was obtained while investigating the O-demethylation of adducts. Pyrrolidinooripavines **XXIV** and **XXV** were cleanly formed at treating compounds **XIX** and **XX** with excess BBr_3 in chloroform [17]. 3-O-Demethylation of adducts **III** and **IV** under similar conditions is accompanied with 6-O-demethylation and results in diols **XXVI** and **XXVII** (yield 79–96%). As seen, here the O-demethylation of the aryl methyl ether in position *3* involves also O-demethylation of the alkyl methyl ether in position *6* of the morphinane skeleton It is presumable that this reaction direction is governed by the carbonyl group of the succinimide moiety. This assumption we confirmed by an example of reaction of compound **XIV** containing a hydroxyethyl substituent at the nitrogen of the succinimide fragment. Under the standard reaction conditions a mixture was obtained of 6-demethyltetrahydrothebaine (**XXVIII**) and 6-demethyloripavine (**XXIX**) in a ratio 1:2, i.e., the demethylation of the alkyl methyl ether is twice faster than the demethylation of the aryl methyl ether. We succeeded in isolating compound **XXIX** in 73% yield when the reaction mixture was kept for a longer time at room temperature. When tetrahydrothebaine **XXIII** containing a 2'-hydroxylactam fragment was brought into reaction 6-demethyltetra-

Scheme 3.



Scheme 4.

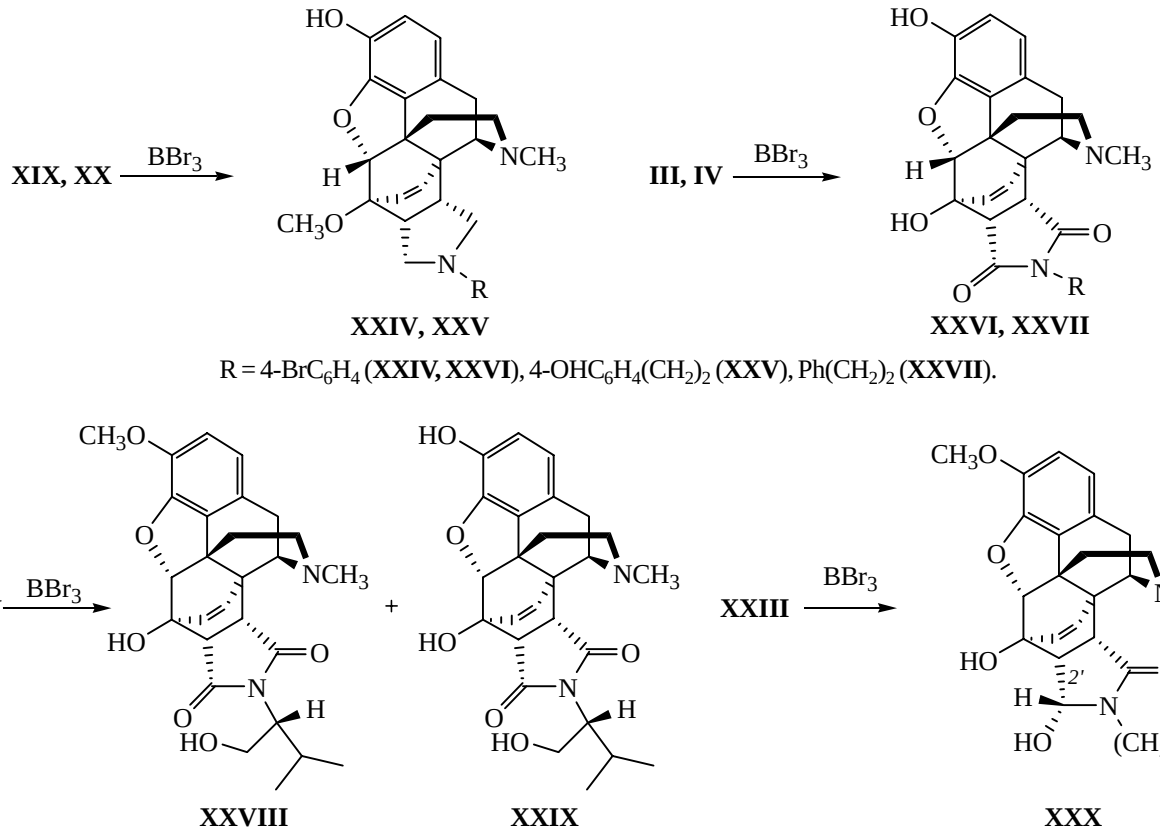


R = 4-BrC_6H_4 (**XIX**), 4-$OHC_6H_4(CH_2)_2$ (**XX**), $(CH_2)_2C_6H_4O(CH_2)_4Br$ (**XXI**), 2-$MeOC_6H_4CH_2$ (**XXII**), $Ph(CH_2)_2$ (**XXIII**).

hydrothebaine **XXX** was obtained in 69% yield. Thus the substituent in the succinimide fragment significantly affects the result of the O-demethylation reaction. This influence is apparently due to the stabilization of the reagent complex with the ether oxygen atom through formation of a six-membered organoboron cyclic intermediate with the oxygen-containing substituent of the succinimide fragment. The selective demethylation of the alkyl methyl ether in the presence of aryl methyl ether was also observed in demethylation by $LiAlH_4$–THF in the presence of CCl_4 of traces of thevinols containing C^{20}-hydroxy or C^{20}-amino substituents [18] (Scheme 5).

The structure of the synthesized *endo*-ethenotetrahydrothebaines and oripavines was established by analysis of spectral data (Tables 1–3). In the IR spectra of adducts **III–XI** and compounds **XIV**, **XVI–XVIII**, and **XXVI–XXIX** appear characteristic bands of stretching vibrations in the regions 1270–1251(C–N), 1696–1706, and 1762–

Scheme 5.



XXIV, XXV **XXVI, XXVII**

R = 4-BrC_6H_4 (**XXIV, XXVI**), 4-$OHC_6H_4(CH_2)_2$ (**XXV**), $Ph(CH_2)_2$ (**XXVII**).

XXVIII **XXIX** **XXX**

1775 (C=O) cm^{-1}. In the IR spectrum of diamide **XV** the absorption bands of amide groups are clearly seen at 1654 cm^{-1}. The amide band in 2'-hydroxy-*endo*-ethenotetrahydrothebaines **XXII**, **XXIII**, and **XXX** is shifted to lower frequencies. In pyrrolidino-*endo*-ethenotetrahydrothebaines and oripavines **XIX–XXI**, **XXIV**, and **XXV** these absorption bands of amide groups disappear, in the spectra of N-aryl-substituted derivatived **XIX** and XXIV a strong band of stretching vibrations at 1595–1605 cm^{-1} is observed (N–Ar). A special feature of the IR spectra of the O-demethylation products **XXVI**, **XXVII**, and **XXIX** is the presence of absorption bands of hydroxy groups at 3240, 3380 or 3440 cm^{-1}. The difference in the absorption of hydroxy groups for compounds **XXVIII** and **XXIX** is revealed in the spectrum of 3-hydroxy derivative **XXIX** by appearance of an additional absorption band at 3450 cm^{-1}. The stretching vibrations of hydroxy group in position *2*' give rise in the spectra of compounds **XXII**, **XXIII**, and **XXX** to narrow bands in the region 3398–3415 cm^{-1}.

The compounds were assigned to the *endo*-series basing on the NMR spectra. In the ^1H NMR spectra of adducts **III–XI** and all derivatives thereof (Table 1) the *endo*-orientation of the bridge was confirmed by the considerable difference in the chemical shifts of H^{18} and H^{19} protons, and also by existence of coupling between the protons H^5 and H^{19} (^4J 1.2–1.5 Hz) (*W*-shaped position of the bonds) (Table 1). The comparison of ^1H NMR spectra of adducts **III–XI**, and **XIV** reveals the effect of the substituent on the nitrogen atom of the succinimide fragment on some spectral parameters, namely on the chemical shifts of the skeleton protons $H^{7,8,18,19}$. For instance, in the spectrum of N'-*p*-bromophenyl-substituted adduct **III** these protons are shifted downfield with respect to the corresponding protons in the spectra of compounds with aralkyl ($\Delta\delta$ 0.11–0.24 for $H^{7,8}$ and 0.18–0.24 for $H^{18,19}$) and alkyl ($\Delta\delta$ 0.07–0.13 for $H^{7,8}$ and 0.09–0.11 for $H^{18,19}$) substituents at the nitrogen of the succinimide moiety. It should be emphasized that protons $H^{7,8,18,19}$ in the succinimide thebaine derivatives are located downfield from the corresponding protons in adduct **XII**. The reduction of the succinimide fragment into a pyrrole one results in an upfield shift of the resonances from protons $H^{7\beta,8\beta,9\alpha}$, and also in increased difference between the chemical shifts of protons $H^{10,15,16}$ of the piperidine ring.

The characteristic features of the ^1H NMR spectrum of diamide **XV** consist in the downfield shift of the protons

from the olefin double bond in the bridge and in the upfield shift of the proton signal from $H^{9\alpha}$ ($\Delta\delta$ 0.17 ppm) caused by the substituent in the *cis*-position at the atom C^{8}. The value of the vicinal coupling constant for protons $H^{7,8}$ (J 11.6 Hz) corresponds to the cisoid location of the substituents [19].

The position of the hydroxy group at the $C^{2'}$ atom and its α-orientation in compounds **XXII** and **XXIII** was proved by NOESY experiment. At suppressing the signals of the protons from the methoxy group attached to C^{6} atom the NOE-effect was observed for protons H^{5}, H^{7} and $H^{2'}$; suppression of the signal from the hydroxy group results in the NOE-effect on the protons from the bridging double bond $H^{18,19}$. In the spectra of compounds **XXII** and **XXIII** a downfield shift of the olefin protons $H^{18,19}$ and proton signal from H^{8} should also be mentioned. Even stronger downfield displacement of the mentioned signals is characteristic of the ^{1}H NMR spectrum of the 6-O-demethylation product hydroxylactam **XXX** (Table 1).

In Table 2 are presented the ^{13}C NMR spectra of new *endo*-ethenotetrahydrothebaines **III–XI** and also that of adduct **XII** for the sake of comparison. The formation of the O- and N-alkylation products **XVII** and **XVIII** is derived from the presence of the signals from carbon atoms $\underline{C}H_2O$ (δ 66.72, 64.14), $\underline{C}H_2NH_2$ (δ 44.67) for amine **XVII** and $\underline{C}H_2NH$ (δ 51.92, 51.86), $\underline{C}H_2OH$ (δ 67.44 ppm) for alcohol **XVIII**.

We should call attention to the downfield shift of the resonance from C^{5} atom in the products of complete (**XIX–XXI**) and partial (**XXII** and **XXIII**) reduction of the succinimide fragment (Table 3). A similar downfield shift was observed for atom C^{5} in the spectrum of oripavine **XXV**. Besides the spectra of 6-demethyloripavines **XXVI, XXVII, XXIX**, and **XXX** are characterized by a downfield shift of the signal from C^{2} atom and an upfield shift of the peaks from C^{3} and C^{6} (Table 3).

Mass spectra of adducts **III–V**, **IX**, **XI**, and **XIV** and of their derivatives **XVI, XVIII, XXII**, and **XXIII** contain molecular ion peaks (Table 1), and also a peak of a fragment ion with *m/z* 310 (thebaine-1) (of abundance 100, 65.91, 65.88, 60.63, 60.92, 100, 100, 100, 87.12, 98.08% respectively) corresponding to the ion generated by retrodiene cleavage of the compounds. This fragment ion of the retrodiene reaction (with *m/z* 282 and 296, abundance 100%) appears in the mass spectra of 6-demethyloripavines **XXVI, XXVII**, and **XXIX**, and 6-demethyltetrahydrothebaine **XXVIII** respectively. The main fragment ion for the fused pyrrolidino-*endo*-ethenotetrahydrothebaines **XX** and **XXI** is a peak of *m/z* 393 (100%) corresponding to the cleavage with formation of *N*-methylenepyrrolidino[6,14,3',4']ethenotetrahydrothebainium ion. For compound **XXV** the most abundant peak has *m/z* 379 (100%).

Thus the Diels–Alder reaction of thebaine with N-substituted maleimides occurs stereoselectively affording the products of the β-attack of the dienophile: 7α,8α-succinimido-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebainesβ (6α,14α-ethenoisomorphinanes). The reduction of adducts provided 7α,8α-fused pyrrolidino- or 2'α-hydroxy-5'-oxopyrrolidinotetrahydrothebaines. Depending on the nature of the substituent in the fused fragment the O-demethylation effected by BBr_3 yielded C^{6}- (demethylation of alkyl methyl ether) and (or) C^{3}- (demethylation of aryl methyl ether) hydroxy derivatives of isomorphinanes.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were registered on spectrometers Bruker AC-200 [operating frequencies 200.13 (^{1}H) and 50.32 (^{13}C) MHz] and Bruker DRX-500 [operating frequencies 500.13 (^{1}H) and 125.76 (^{13}C) MHz] from 5% solutions in $CDCl_3$, CD_3OD, or CCl_4. The assignment of signals in the NMR spectra were done with the use of various proton-proton and carbon-proton procedures of correlation spectroscopy (COSY, COLOC, CORRD), ^{1}H 2D-NMR spectroscopy, spectra with Overhauser effect NOESY, and also the data from [7, 8]. ^{19}F NMR spectra of 10% solutions of adducts **VIII** and **IX** were registered on spectrometer Bruker WP-200-SY, internal reference C_6F_6. IR spectra were recorded on Vector-22 instrument from samples pelletized with KBr. UV absorption spectra were taken on spectrometer HP 8453 UV Vis in ethanol (C 10^{-4} M). For recording mass spectra, molecular weight estimation, and elemental analysis we used high resolution mass spectrometer Finnigan MAT-8200 (ionizing electrons energy 70 eV, vaporizer temperature 270–300°C). Reaction progress was monitored by TLC on Silufol UV-254 plates. The reaction products were isolated by column chromatography on silica gel (eluent chloroform) or on neutral or alkaline aluminum oxide (eluents chloroform, chloroform–ethanol, 200:1–10:1).

The elemental analyses of compounds synthesized are consistent with the calculated values.

S-Valinol (**XIII**), mp 31–32°C, bp. 75°C (6 mm Hg.), $[\alpha]_{578}^{20}$ +17° (C 11, EtOH) was obtained by procedure from [20].

Table 1. Yields, melting points, data of mass, IR, and ^{1}H NMR spectra of N'-substituted 7α,8α-succinimido-6α,14α-*endo*-etheno-6,7,8,14-tetrahydrothebaines **III, XIV, XVI–XVIII**, 7α,8α-pyrrolidino-6α,14α-*endo*-etheno-6,7,8,14-tetrahydrothebaines **XX–XXII**, corresponding oripavines **XXV, XXVII, XXIX**, and 6-demethyltetrahydrothebaines **XXVIII, XXX** [a]

Compd. no.	Yield, %	mp, °C, (solvent)	Formula, *m/z* calc/*m/z* exp (I_{rel} %)	IR spectrum, cm^{-1}	^{1}H NMR spectrum, δ, ppm (*J*, Hz)
III	91	245–246 (ethanol)	$C_{29}H_{27}N_2O_5Br$, 562.11037/562.10925, 562 (66), 389 (33), 346 (22), 311 (45), 310 (100), 355 (52), 229 (34), 216 (25), 188 (30)	710, 796, 810, 886, 954, 1012, 1051, 1069, 1110, 1220, 1250, 1500, 1598, 1628, 1706, 1775, 3068, 3454	1.93 m (2H, H^{15}), 2.41 s (3H, CH_3N), 2.43 d.d (1H, H^{10}, *J* 18.7, 6.6), 2.48 d.d.d (1H, H^{16}, *J* 12.4, 4.0, 2.2), 2.55 d.d.d (1H, H^{16}, J_{gem} 12.6, J_{vic} 12.1 and 1.5), 3.15 d (1H, H^7, *J* 8.1), 3.23 d (1H, $H^{10\beta}$, J_{gem} 18.7), 3.68 s (3H, CH_3OC^6), 3.79 s (3H, CH_3OC^3), 3.98 d (1H, $H^{9\alpha}$, *J* 6.6), 4.36 d (1H, H^8, *J* 8.1), 4.66 d (1H, $H^{5\beta}$, *J* 1.5), 5.42 d (1H, H^{19}, *J* 8.7), 5.82 d.d (1H, H^{18}, *J* 8.7 and 1.4), 6.55 d (1H, H^1, *J* 8.1), 6.63 d (1H, H^2, *J* 8.1), 7.04 d (2H, $H^{2',6'}$), 7.49 d (1H, $H^{3',5'}$)
XIV	72	266–267 (ethyl acetate)	$C_{28}H_{34}N_2O_6$, 494.24167/494.24265, 494 (100), 479 (21), 319 (64), 311 (27), 310 (71), 276 (68), 255 (34), 229 (31), 162 (28), 44 (33)	718, 748, 771, 818, 948, 984, 1013, 1047, 1083, 1145, 1228, 1252, 1268, 1500, 1599, 1630, 1694, 1764, 3060, 3445, 3489	0.70 d (3H, CH_3, *J* 7.0), 0.94 d (3H, CH_3, *J* 7.0), 1.90 d.d.d (1H, H^{15}, *J* 13.2, 5.4 and 1.4), 1.98 m (1H, H^{15}, J_{gem} 13.2, *J* 12.2, 6.0), 2.26 m (1H, H-*i*-Pr), 2.46 s (3H, CH_3N), 2.44 m (2H, $H^{10,16}$), 2.61 d.d.d (1H, H^{16}, J_{gem} 12.6, J_{vic} 12.2 and 1.4), 3.15 d (1H, H^7, *J* 8.3), 3.23 d (1H, $H^{10\beta}$, J_{gem} 18.6), 3.62 m and 3.72 m (2H, CH_2), 3.69 C (3H, CH_3OC^6), 3.79 s (3H, CH_3OC^3), 3.94 d.d (1H, CH, *J* 7.0 and 5.6), 3.99 d (1H, $H^{9\alpha}$, *J* 6.4), 4.23 d (1H, H^8, *J* 8.3), 4.67 d (1H, $H^{5\beta}$, *J* 1.4), 5.38 d (1H, H^{19}, *J* 8.7), 5.75 d.d (1H, H^{18}, *J* 8.7 and 1.4), 6.54 d (1H, H^1, *J* 8.2), 6.62 d (1H, H^2, *J* 8.2)
XVI	82	180–182 (ethyl acetate)	$C_{35}H_{39}N_2O_6Br$, 662.15 621 (17), 527 (39), 512 (25), 311 (34), 310 (100), 294 (23), 255 (39), 229 (28), 216 (21), 162 (34), 55(37), 28 (96)	747, 820, 922, 944, 999, 1017, 1051, 1110, 1159, 1213, 1250, 1501, 1511, 1612, 1632, 1699, 1769, 3453	1.80 m (2H, CH_2), 1.85 m (1H, H^{15}), 1.90 m (2H, CH_2 and 1H, H^{15}), 2.47 s (3H, CH_3N), 2.45 m (2H, $H^{10,16}$), 2.57 d.d.d (1H, H^{16}, J_{gem} 12.4, J_{vic} 12.1 and 1.5), 2.67 d.t (2H, CH_2), 3.01 d (1H, H^7, *J* 8.0), 3.26 d (1H, H^{10}, *J* 18.7), 3.43 m (2H, CH_2Br), 3.55 m (2H, CH_2), 3.57 s (3H, CH_3OC^6), 3.78 s (3H, H_3OC^3), 3.90 t (2H, CH_2O), 3.93 d (1H, H^9, *J* 6.7), 4.20 d (1H, H^8, *J* 8.0), 4.62 d (1H, $H^{5\beta}$, *J* 1.6), 5.23 d (1H, H^{19}, *J* 8.7), 5.60 d.d (1H, H^{18}, *J* 8.7 and 1.6), 6.54 d (1H, H^1, *J* 8.2), 6.61 d (1H, H^2, *J* 8.2), 6.74 d (2H, $H^{2',6'}$, *J* 8.7), 7.04 d (2H, $H^{3',5'}$, *J* 8.6)
XVII	29	162–164 (ethanol)	$C_{37}H_{45}N_3O_7$, 643.32	722, 820, 921, 944, 998, 1059, 1009, 1160, 1250, 1511, 1610, 1627, 1700, 1760, 3445	1.83 m (4H, $2CH_2$), 1.88 m (1H, H^{15}), 1.95 m (1H, H^{15}), 2.43 m (1H, H^{16}), 2.43 s (3H, CH_3N), 2.48 m (1H, H^{10}), 2.54 d.d.d (1H, H^{16}, J_{gem} 12.4, J_{vic} 12.1 and 1.8), 2.68 m (2H, CH_2NH_2), 3.01 d (1H, H^7, *J* 7.9), 3.22 d (1H, H^{10}, *J* 18.6), 3.58 m (2H, CH_2O), 3.64 m (2H, CH_2), 3.67 s (3H, CH_3OC^6), 3.79 s (3H, CH_3OC^3), 3.86 m (2H, CH_2), 3.90 t (2H, CH_2O), 3.95 d (1H, H^9, *J* 6.7), 4.16 d (1H, H^8, *J* 7.9), 4.62 d (1H, $H^{5\beta}$, *J* 1.6), 5.26 d (1H, H^{19}, *J* 8.7), 5.48 m (2H, NH_2), 5.60 d.d (1H, H^{18}, *J* 8.7 and 1.6), 6.53 d (1H, H^1, *J* 8.2), 6.61 d (1H, H^2, *J* 8.2), 6.74 d, 6.75 d (2H, $H^{2',6'}$, *J* 8.7), 7.03 d, 7.08 d (2H, $H^{3',5'}$, *J* 8.6)
XVIII	37	142–144 (ethyl acetate)	$C_{37}H_{45}N_3O_7$, 643.32	750, 820, 944, 998, 1052, 1017, 1051, 1110, 1159, 1213, 1250, 1501, 1511, 1612, 1632, 1699, 1769, 3453	1.66 m (2H, CH_2), 1.78 m (2H, CH_2), 190 d.d.d (1H, H^{15}, *J* 13.4, 2.3, 1.8), 1.93 d.d.d (1H, H^{15}, *J* 13.4, 12,1, 3.2), 2.27 m and 2.62 m (2H, CH_2N), 2.41 s (3H, CH_3N), 2.45 m (2H, $H^{10,16}$), 2.54 d.d.d (1H, H^{16}, J_{gem} 12.4, J_{vic} 12.1 and 1.8), 2.67 d.t (2H, CH_2), 2.99 d (1H, H^7, *J* 7.9), 3.22 d (1H, H^{10}, *J* 18.7), 2.48 m and 3.24 m (2H, CH_2N), 3.56 m (2H, CH_2), 3.66 s (3H, CH_3OC^6), 3.79 s (3H, CH_3OC^3), 3.82 and 3.88 m (2H, CH_2), 3.91 t (2H, CH_2O), 3.95 d (1H, H^9, *J* 6.7), 4.15 d (1H, H^8, *J* 7.9), 4.60 d (1H, $H^{5\beta}$, *J* 1.6), 5.25 d (1H, H^{19}, *J* 8.7), 5.61 d.d (1H, H^{18}, *J* 8.7 and 1.6), 6.53 d (1H, H^1, *J* 8.2), 6.61 d (1H, H^2, *J* 8.2), 6.748 d, 6.752 d (2H, $H^{2',6'}$, *J* 8.7), 7.05 d (2H, $H^{3',5'}$, *J* 8.6)

Table 1. (Contd.)

Compd. no.	Yield, %	mp, °C, (solvent)	Formula, *m/z* calc/*m/z* exp (I_{rel} %)	IR spectrum, cm^{-1}	^1H NMR spectrum, , ppm (*J*, Hz)
XX	92	162–164 (ethanol)	$C_{31}H_{36}N_2O_4$, 500.26749/ 500.26812, 500 (1.6), 394 (28), 393 (100), 152 (37)	774, 829, 880, 932, 948, 981, 1018, 1053, 1109, 1144, 1252, 1276, 1345, 1500, 1515, 1598, 1615, 1631, 2799, 2934, 3036, 3431	1.77 d.d.d (1H, H^{15}, *J* 13.2, 4.0, 1.5), 1.96 m (1H, $H^{3'}$, *J* 9.2), 2.10 t.d (1H, H^{15}, *J* 13.2, 12.5, 5.6), 2.15 d.d (1H, $H^{2'}$, *J* 9.8, 9.2), 2.33 s (3H, CH_3N), 2.32 m (1H, H^{10}), 2.40 m (1H, H^{16}), 2.48 d.d.d (1H, H^{16}, J_{gem} 12.6, J_{vic} 12.5 and 1.5), 2.59 m (2H, CH_2), 2.65 m (2H, CH_2), 2.73 m (1H, H^7, *J* 9.2, 7.3, 8.1), 3.09 d (1H, H^9, *J* 6.4), 3.12 t.d (1H, $H^{3'}$, *J* 8.1, 8.1), 3.16 t.d (1H, $H^{2'}$, *J* 9.8 and 7.3), 3.20 d (1H, $H^{10\beta}$, J_{gem} 19.4), 3.49 C (3H, H_3OC^6), 3.66 d.d.d (1H, H^8, *J* 9.2), 3.79 s (3H, CH_3OC^3), 4.58 d (1H, $H^{5\beta}$, *J* 1.3), 5.31 d (1H, H^{19}, *J* 8.8, 1.2), 5.75 d.d (1H, H^{18}, *J* 8.8, 1.5 and 1.3), 6.50 d (1H, H^1, *J* 8.1), 6.60 d (1H, H^2, *J* 8.1), 6.64 d (2H, $H^{2',6'}$, *J* 8.4), 6.94 d (2H, $H^{3',5'}$, *J* 8.5)
XXI	85	188–190 (ethanol)	$C_{35}H_{43}N_2O_4Br$, 634.82, 394 (29), 393 (100), 152 (36), 107 (12), 42 (14), 31 (11)	723, 773, 833, 980, 1013, 1034, 1054, 1105, 1247, 1512, 1596, 1615, 1630, 2936, 3010, 3425	0.93 t (2H, CH_2), 1.44 m (2H, CH_2), 1.71 m (2H, CH_2), 1.80 d.d.d (1H, H^{15}, *J* 13.6, 5.2, 1.8), 2.10 d.t (1H, H^{15}, *J* 13.6, 12.0, 5.6), 2.30 s (3H, CH_3N), 2.35 m (1H, H^{10}, J_{gem} 18.7), 2.49 m (1H, H^{16}), 2.50 d.d.d (1H, H^{16}, J_{gem} 12.2, J_{vic} 12.0 and 1.8), 3.03 m (1H, H^7), 3.06 d (1H, H^9, *J* 5.6), 3.07 m (4H, $2CH_2$), 3.20 d (1H, $H^{10\beta}$, J_{gem} 18.7), 3.49 s (3H, CH_3OC^6), 3.35 m (2H, CH_2), 3.79 s (3H, CH_3OC^3), 3.88 t (2H, CH_2, *J* 7.2), 4.00 m (1H, H^8, *J* 9.5, 6.8, 2.2), 4.59 d (1H, $H^{5\beta}$, *J* 1.4), 5.41 d (1H, H^{19}, *J* 8.7), 5.85 d.d (1H, H^{18}, *J* 8.7 and 1.4), 6.52 d (1H, H^1, *J* 8.2), 6.61 d (1H, H^2, *J* 8.2), 6.79 d (2H, $H^{2',6'}$, *J* 8.5), 7.08 d (2H, $H^{3',5'}$, *J* 8.6)
XXII	73	249–250 (ethanol)	$C_{31}H_{34}N_2O_6$, 530.24167/530.24180, 530 (38), 311 (45), 310 (87), 174 (41), 121(100), 91 (35)	795, 880, 905, 935, 961, 1026, 1050, 1086, 1108, 1600, 1628, 1685, 3024, 3082, 3416	1.85 d.d.d (1H, H^{15}, *J* 13.2, 5.9 and 1.7), 1.96 d.d.d (1H, H^{15}, *J* 13.2, 12.3, 3.8), 2.44 s (3H, CH_3N), 2.43 m (1H, H^{10}), 2.46 d.d.d (1H, H^{16}, *J* 12.6, 5.9, 3.8), 2.55 d.d.d (1H, H^{16}, J_{gem} 12.6, J_{vic} 12.3 and 1.7), 2.70 m (1H, H^7, *J* 9.6, 7.3, 1.1), 3.21 d (1H, $H^{10\beta}$, J_{gem} 18.7, *J* 1.0), 3.66 s (3H, CH_3OC^6), 3.79 s, 3.80 s (6H, $CH_3OC^{3,2'}$), 4.01 d (1H, H^8, *J* 9.6), 4.18 d (1H, $H^{9\alpha}$, *J* 6.6), 4.28 d, 4.61 d (2H, CH_2, *J* 15.2), 4.51 d (1H, $H^{5\beta}$, *J* 1.5), 4.86 d (1H, OH, *J* 2.5), 5.25 d.d (1H, $H^{2'}$, *J* 7.3, 2.5), 5.48 d.d (1H, H^{19}, *J* 8.9, 1.2), 5.96 d.d (1H, H^{18}, *J* 8.9, 1.3 and 1.5), 6.55 d (1H, H^1, *J* 8.2), 6.63 d (1H, H^2, *J* 8.2), 6.81 dd (1H, $H^{3'}$, *J* 7.2, 1.4), 6.85 d.t (1H, $H^{5'}$, *J* 7.2, 7.0 and 1.4), 7.16 d.d (1H, $H^{6'}$, *J* 7.2, 1.5), 7.19 d.t (1H, $H^{4'}$, *J* 7.2, 7.0 and 1.5)
XXV	92	228–230 (ethanol)	$C_{30}H_{34}N_2O_4$, 486.25184/ 486.25117, 486 (1.4), 380 (29), 379 (100), 152 (58), 104 (17)	701, 727, 771, 800, 833, 883, 937, 945, 980, 1031, 1050, 1102, 1125, 1217, 1233, 1250, 1321, 1613, 1636, 3032, 3230, 3428	1.85 d.d.d. (1H, H^{15}, *J* 12.9, 6.2, 2.8), 2.04 m (1H, H^{15}), 2.14 m (2H, CH_2), 2.42 m (2H, $H^{10,16}$), 2.35 s (3H, CH_3N), 2.54 d.d.d (1H, H^{16}, J_{gem} 12.8, J_{vic} 12.2 and 2.8), 2.81 d.t (2H, CH_2, *J* 7.1 and 2.1), 3.06 d (1H, H^7, *J* 5.1), 3.12 m (2H, $H^{3',2'}$), 3.28 d (1H, $H^{10\beta}$, J_{gem} 18.2), 3.35 d (1H, $H^{9\alpha}$, *J* 6.8), 3.46 m (2H, $H^{2',3'}$), 3.48 s (3H, OCH_3), 3.70 d.d.d (1H, H^8, *J* 6.8, 3.4, 2.6), 4.61 d (1H, $H^{5\beta}$, *J* 1.4), 5.30 d (1H, H^{19}, *J* 7.2), 5.71 d.d (1H, H^{18}, *J* 7.2 and 1.4), 6.47 d (1H, H^1, *J* 6.8), 6.64 d (1H, H^2, *J* 6.8), 6.70 d (2H, $H^{2'',6''}$, *J* 7.4), 6.99 d (2H, $H^{3'',5''}$)
XXVII	92	161–164 (ethyl acetate)	$C_{29}H_{28}N_2O_5$, 484.19981/ 484.19795, 484 (36), 308 (30), 283 (40), 282 (100), 227 (30), 44 (26)	750, 794, 819, 934, 973, 1037, 1075, 1105, 1153, 1228, 1250, 1501, 1610, 1632, 1650, 1693, 1766, 3050, 3080, 3439	1.91 d.d.d (1H, H^{15}, *J* 13.6, 5.4, 1.8), 2.04 d.d.d (1H, H^{15} , *J* 13.6, 12.6, 5.4), 2.46 m (1H, H^{10}), 2.51 m (1H, H^{16}), 2.52 s (3H, CH_3N), 2.63 d.d.d (1H, H^{16}, J_{gem} 12.7, J_{vic} 12.6 and 1.8), 2.81 t.d (2H, CH_2, *J* 7.7 and 3.2), 2.86 d (1H, H^7, *J* 8.1), 3.28 d (1H, $H^{10\beta}$, J_{gem} 18.8), 3.70 d.t (2H, CH_2, *J* 7.8 and 0.9), 3.95 d (1H, $H^{9\alpha}$, *J* 6.7), 4.26 d (1H, H^8, *J* 8.1), 4.49 d (1H, $H^{5\beta}$, *J* 1.5), 5.21 d (1H, H^{19}, *J* 8.8), 5.59 d.d (1H, H^{18}, *J* 8.8 and 1.5), 6.53 d (1H, H^1, *J* 8.1), 6.68 d (1H, H^2, *J* 8.1), 7.20 m (3H, Ph), 7.27 m (2H, Ph)

Table 1. (Contd.)

Compd. no.	Yield, %	mp, °C, (solvent)	Formula, *m/z* calc/*m/z* exp (I_{rel} %)	IR spectrum, cm^{-1}	^1H NMR spectrum, ?, ppm (*J*, Hz)
XXVIII	28	181–183 (ethyl acetate)	$C_{27}H_{32}N_2O_6$, 480.22602/ 480.23060, 480 (33), 395 (10), 297 (26), 296 (100), 241 (29), 162 (18), 42 (40)	708, 727, 750, 775, 797, 818, 983, 1011, 1015, 1048, 1079, 1109, 1143, 1499, 1596, 1621, 1690, 1761, 3240, 3331	0.71 d (3H, CH_3, *J* 7.0), 0.95 d (3H, CH_3, *J* 7.0), 1.91 d.d.d (1H, H^{15}, *J* 13.4, 4.1 and 1.4), 1.98 d.d (1H, H^{15}, *J* 13.4, 11.8, 2.4), 2.26 m (1H, H-*i*-Pr), 2.44 s (3H, CH_3N), 2.45 m (2H, $H^{10,16}$), 2.57 d.d.d (1H, H^{16}, J_{gem} 12.5, J_{vic} 11.8 and 1.4), 2.86 d (1H, H^7, *J* 8.2), 3.24 d (1H, $H^{10\beta}$, J_{gem} 18.6), 3.62 d.d and 3.94 d.d (2H, CH_2, *J* 10.6, 6.8, 4.5), 3.72 d.d (1H, CH, *J* 6.8 and 4.5), 3.79 s (3H, CH_3OC^3), 3.89 d (1H, $H^{9\alpha}$, *J* 6.4), 4.24 d (1H, H^8, *J* 8.2), 4.43 d (1H, $H^{5\beta}$, *J* 1.4), 5.34 d (1H, H^{19}, *J* 8.7), 5.77 d.d (1H, H^{18}, *J* 8.7 and 1.4), 6.53 d (1H, H^1, *J* 8.2), 6.62 d (1H, H^2, *J* 8.2)
XXIX	56 (73)	228–230 (ethanol)	$C_{26}H_{30}N_2O_6$, 466.21037/ 466.21500, 466 (28), 381 (18), 283 (42), 282 (100), 227 (31), 148 (41), 44 (79)	724, 751, 788, 820, 857, 933, 952, 1016, 1031, 1077, 1105, 1503, 1622, 1635, 1690, 1764, 3441	0.69 d (3H, CH_3, *J* 7.0), 0.91 d (3H, CH_3, *J* 7.0), 1.84 d.d.d (1H, H^{15}, *J* 13.3, 3.6 and 1.6), 1.99 m (1H, H^{15}, *J* 13.3, 12.6, 2.1), 2.21 m (1H, H-*i*-Pr), 2.38 m (1H, H^{10}), 2.41 s (3H, CH_3N), 2.42 m (1H, H^{16}), 2.53 d.d.d (1H, H^{16}, J_{gem} 12.7, J_{vic} 12.6 and 1.6), 2.98 d (1H, H^7, *J* 8.2), 3.19 d (1H, $H^{10\beta}$, J_{gem} 18.4), 3.74 d.d and 3.99 d.d (2H, CH_2), 3.72 m (1H, CH, *J* 7.0 and 5.6), 3.89 d (1H, $H^{9\alpha}$, *J* 6.6), 4.22 d (1H, H^8, *J* 8.2), 4.46 d (1H, $H^{5\beta}$, *J* 1.4), 5.29 d (1H, H^{19}, *J* 8.7), 5.70 d.d (1H, H^{18}, *J* 8.7 and 1.4), 6.45 d (1H, H^1, *J* 8.2), 6.58 d (1H, H^2, *J* 8.2)
XXX	69	238–241 (ethanol)	$C_{30}H_{32}N_2O_5$, 500.12	722, 751, 802, 815, 891, 930, 960, 1000, 1030, 1050, 1085, 1106, 1160, 1304, 1330, 1500, 1596, 1610, 1667, 1678, 1767, 3048, 3300, 3422	1.90 d.d.d (1H, H^{15}, *J* 13.5, 4.0, 1.6), 2.08 m (1H, H^{15}, *J* 13.5, 12.0, 5.0), 2.46 s (3H, CH_3N), 2.48 m (1H, H^{10}), 2.49 m (1H, H^{16}), 2.63 d.d.d (1H, H^{16}, J_{gem} 12.5, J_{vic} 12.0 and 1.6), 2.86 m (2H, CH_2), 2.90 d.d.t (1H, H^7, *J* 9.0, 6.0, 1.4), 3.19 d (1H, $H^{10\beta}$, J_{gem} 18.7), 3.40 m, 3.60 m (2H, CH_2), 3.84 s (3H, CH_3OC^3), 4.10 d (1H, H^8, *J* 9.0), 4.20 d (1H, $H^{9\alpha}$, *J* 6.5), 4.50 d (1H, $H^{5\beta}$, *J* 1.5), 5.06 m (1H, OH), 4.87 d (1H, $H^{2'}$, *J* 6.0), 5.57 d (1H, H^{19}, *J* 8.9), 6.05 d.d (1H, H^{18}, *J* 8.9 1.5 and 1.4), 6.52 d (1H, H^1, *J* 8.2), 6.62 d (1H, H^2, *J* 8.2), 7.23 m (3H, Ph), 7.30 m (2H, Ph)

[a] Compound **IV**, yield 92%, mp 188–190 (from ethyl acetate); compound **V**, yield 80%, mp 210–212 (from ethanol); compound **VI**, yield 96%, mp 239–241 (from ethanol); compound **VII**, yield 92%, mp 278–280 (from ethanol); compound **VIII**, yield 82%, mp 212–214 (from ethyl acetate); compound **IX**, yield 87%, mp 219–220 (from ethyl acetate); compound **X**, yield 85%, mp 192–195 (from ethyl acetate); compound **XI**, yield 85%, mp 188–190 (from ethanol); compound **XIX**, yield 72%, mp 248–250 (from ethyl acetate); compound **XXIII**, yield 78%, mp 185–186 (from mixture ethyl acetate–ether); compound **XXIV**, yield 79%, mp 221–222 (from ethanol); compound **XXVI**, yield 96%, mp 219–220 (from ethyl acetate).

The thebaine adduct with maleic anhydride was prepared as in [15]. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.89 d.d.d (1H, H^{15}, *J* 13.3, 4.1 and 1.4), 1.91 d.d.d (1H, H^{15}, *J* 13.3, 11.2 and 3.1), 2.44 s [3H, (CH_3N)], 2.48 m (1H, H^{16}, *J* 12.3, 10.3 and 1.4), 2.45 d.d (1H, H^{10}, *J* 18.6, 1.2), 2.58 d.d.d (1H, H^{16}, J_{gem} 12.3, J_{vic} 4.2 and 1.5), 3.35 d (1H, $H^{10\beta}$, J_{gem} 18.6), 3.30 d (1H, H^8, *J* 8.6), 3.67 C (3H, CH_3OC^6), 3.80 s (3H, CH_3OC^3), 3.89 d (1H, $H^{9\alpha}$, *J* 6.4), 4.55 d (1H, H^7, *J* 8.6), 4.59 d (1H, $H^{5\beta}$, *J* 1.3), 5.48 d (1H, H^{19}, *J* 8.7), 5.88 d.d (1H, H^{18}, *J* 8.7 and 1.3), 6.57 d (1H, H^1, *J* 8.2), 6.64 d (1H, H^2, *J* 8.2).

Maleimides IIb–IIi. To a solution of 0.02 mol of maleic anhydride in 80 ml of acetic acid was added 0.02 mol of amine. The reaction mixture was boiled for 2–10 h (TLC monitoring). The solvent was removed in a vacuum, water was eliminated from the residue by an azeotropic distillation with benzene, then the residue was dissolved in a minimum amount of chloroform, and the solution was passed through a bed of silica gel. The chloroform was evaporated in a vacuum, the residue was ground with ether to isolate the corresponding maleimide as a solid substance that was recrystallized from an

Table 2. ^{13}C NMR spectra of N'-substituted 7α,8α-succinimido-6α,14α-*endo*-ethenotetrahydrothebaines **III, IV, VI–XI, XIV, XVI–XVIII**, δ, ppm[a]

Atom no.	III	IV	VI	VII	VIII	IX	X	XI	XII	XIV	XVI	XVII	XVIII
1	119.85	119.81	119.49	119.77	119.81	119.68	119.74	119.78	120.13	119.84	119.80	119.72	119.80
2	113.43	113.39	113.17	113.48	113.42	113.34	113.31	113.49	114.17	113.58	114.43	113.53	113.42
3	141.93	142.04	141.61	141.95	142.00	141.85	141.94	142.02	142.17	142.11	142.05	141.92	141.96
4	147.68	147.75	147.38	147.66	147.69	147.59	147.67	147.80	147.71	147.77	147.63	147.66	147.67
5	90.48	90.48	90.37	90.78	90.81	90.68	90.81	90.68	90.55	90.39	90.99	90.79	90.75
6	80.59	80.53	80.16	80.44	80.48	80.34	80.45	80.54	79.93	80.52	80.52	80.43	80.49
7	41.31	41.18	40.88	41.25	41.27	41.13	41.19	41.28	42.71	40.95	39.69	39.85	41.23
8	42.20	42.12	41.76	42.03	42.12	41.98	42.07	42.24	43.43	43.15	41.23	41.24	42.06
9	58.16	56.96	56.53	56.86	56.89	56.71	56.85	56.93	56.59	56.33	56.95	56.82	56.87
10	22.26	22.36	21.93	22.25	22.28	22.15	22.61	22.31	22.50	22.46	22.36	22.22	22.26
11	127.38	128.98	127.18	127.40	127.44	127.40	127.46	127.56	127.19	129.21	127.53	127.44	127.48
12	132.25	132.50	132.26	132.46	132.49	132.46	132.56	132.64	131.99	133.26	131.65	132.50	132.51
13	47.78	47.68	47.36	47.68	47.78	47.61	47.72	47.78	47.95	47.68	47.75	47.66	47.73
14	45.13	44.89	44.53	44.83	44.89	44.73	44.80	44.92	44.97	44.84	45.03	44.83	44.88
15	33.43	33.32	33.99	33.35	33.48	33.31	33.42	33.48	33.50	33.03	33.47	33.37	33.41
16	44.91	45.05	44.67	44.95	44.99	44.87	44.95	45.06	44.87	45.08	44.94	44.92	44.98
17-N$\underline{C}H_3$	43.09	43.13	42.87	43.10	43.19	43.05	43.13	43.21	43.12	41.66	43.15	43.08	43.17
18	133.59	133.09	132.78	133.06	133.16	133.07	133.04	133.21	134.28	133.26	133.15	133.08	133.15
19	128.77	127.94	128.10	128.65	128.75	128.61	128.79	128.88	129.26	129.56	128.68	128.61	128.71
O$\underline{C}H_3C^3$	56.78	56.27	55.95	56.28	56.30	56.19	56.23	56.35	56.45	56.99	56.45	56.28	56.33
O$\underline{C}H_3C^6$	51.52	51.47	51.19	51.56	51.62	51.46	51.54	51.50	51.95	51.41	51.63	51.52	51.57
CH_2N	–	41.67	39.25	39.84	39.65	38.16	37.16	36.19	–	–	39.79	39.85	39.94
CH_2R	–	–	32.99	32.38	32.53	26.88	35.72	55.85	–	61.47	32.38	32.47	32.54
$C^{2'}$	172.56	173.73	173.46	173.88	173.84	173.61	173.81	174.05	167.46	175.06	173.88	173.74	173.84
$C^{2'}$	175.93	176.96	176.77	177.20	177.15	176.92	177.21	177.34	170.91	178.65	176.82	177.09	177.19

[a] Signals of other carbon atoms, δ, ppm: **III**, 122.10 s, 127.69 d, 131.92 d, 132.25 s (Ar); **IV**, 56.95 q, 113.63 d, 113.91 d, 128.98 s, 129.95 d, 158.97 s (Ar); **VI**, 126.14 d, 128.01 d, 128.36 d, 137.27 s (Ar); **VII**, 115.16 d, 129.80 d, 129.50 s, 154.26 s (Ar); **VIII**, 115.07 d, 115.23 d, 130.12 d, 130.18 d, 133.25 s, 162.54 s (Ar); IX, 115.16 d, 123.77 d, 124.53 s, 128.23 d, 130.90 d, 160.13 s (Ar); **X**, 22.04 t, 22.61 t, 25.14 t, 27.46 t, 123.73 d, 133.78 s; **XI**, 45.10 q, 45.03 q (CH_3); **XIV**, 19.81 q, 19.93 q (CH_3), 26.06 d (CH), 60.53 d (CH); **XVI**, 27.64 t, 29.22 t, 33.12 t, 66.57 t (CH_2), 114.22 d ($C^{3',5'}$), 129.56 s ($C^{1'}$), 29.62 d ($C^{2',6'}$), 157.34 c ($C^{4'}$); **XVII**, 25.84 t, 29.56 t, 44.67 t, 64.14 t, 66.72 t, 67.30 t (CH_2), 114.34 d ($C^{3',5'}$), 129.65 d ($C^{2',6'}$), 131.54 s ($C^{1'}$), 155.54 s ($C^{4'}$); **XVIII**, 25.81 t, 26.71 t, 51.92 t, 51.86 t , 61.65 t, 67.44 t (CH_2), 114.31 d ($C^{3',5'}$), 129.54 d ($C^{2',6'}$), 131.13 s ($C^{1'}$), 157.56 s ($C^{4'}$).

appropriate solvent. ***N*-(4-Methoxybenzyl)maleimide (IIb)**. Yield 56%, mp 101–103°C (from ether) (publ.: mp 101.5–103°C [21]). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.70 m, 2.84 m (2H, CH_2), 3.73 s (3H, CH_3O), 6.56 s (2H, $H^{3,4}$), 6.79 m (2H, $H^{2',6'}$), 7.22 m (2H, $H^{3',5'}$).

***N*-(2-Methoxybenzyl)maleimide (IIc)**. Yield 68%, mp 108–110°C (from ethyl acetate). ^1H NMR spectrum (CD_3OD), δ, ppm (*J*, Hz): 3.68 d, 3.75 d (2H, CH_2, *J* 7.6), 3.87 s (3H, CH_3O), 6.60 s (2H, $H^{3,4}$), 6.96 m (2H, $H^{3',5'}$), 7.12 m (2H, $H^{4',6'}$).

***N*-(Phenethyl)maleimide (IId)**. Yield 82%, mp 108–110°C (from ethanol) (publ.: mp 112°C [22]). IR spectrum, Cm^{-1}: 743, 824, 842, 954, 1085, 1138, 1583, 1606, 1705, 1755. UV spectrum, λ_{max}, nm (lg å): 208 (4.48), 248 (3.28), 289 (3.02). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.84 d, 2.89 d (2H, CH_2, *J* 7.8 Hz), 3.68 d, 3.75 d (2H, CH_2, *J* 7.8 Hz), 6.59 s (2H, $H^{3,4}$), 7.19 m (5H, Ph). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 34.27 t ($C\underline{H}_2Ar$), 38.87 t (CH_2N), 126.46 d ($C^{4'}$), 128.34 d, 128.61 d ($C^{3',5',2',6'}$), 137.67 s ($C^{1'}$), 133.81 d ($C^{3,4}$), 170.38 d ($C^{2,5}$).

***N*-(4-Hydroxyphenethyl)maleimide (IIe)**. Yield 62%, mp 174–176°C (from ethanol) (publ.: mp 175–178°C [23]). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.88 m (2H, CH_2), 3.28 m (2H, CH_2), 6.60 s (2H, $H^{3,4}$), 6.88 d (2H, $H^{2',6'}$, *J* 8.5 Hz), 7.08 d (2H, $H^{3'5'}$, *J* 8.5 Hz).

***N*-(4-Fluorophenethyl)maleimide (IIf)**. Yield 68%, mp 148–150°C (from ethyl acetate). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.84 d, 2.89 d (2H, CH_2, *J* 7.6 Hz),

Table 3. ^{13}C NMR spectra of N'-substituted 7α,8α-pyrrolidino- (**XIX–XXI**), 7α,8α-(2'-hydroxy-5-oxo)pyrrolidino- (**XXII, XXIII**) - *endo*-ethenotetrahydrothebaines and 6-demethyltetrahydrothebaines **XXVIII, XXX** and the corresponding oripavines **XXIV–XXVII**, XXIX, δ, ppm[a]

Atom no.	**XIX**	**XX**	**XXI**	**XXII**	**XXIII**	**XXIV**	**XXV**	**XXVI**	**XVII**	**XXVIII**	**XXIX**	**XXX**
1	119.21	119.10	119.53	119.72	119.79	119.80	120.82	120.42	120.36	119.80	120.40	120.02
2	113.28	112.94	113.52	113.34	113.63	116.57	117.85	117.53	117.22	113.93	117.41	116.22
3	141.93	141.84	142.04	141.75	141.79	137.79	139.93	138.01	137.91	142.07	138.03	141.18
4	146.90	147.75	147.54	147.58	147.63	148.41	148.14	146.46	146.32	147.88	146.43	147.28
5	93.81	92.98	91.89	93.34	93.40	93.24	93.98	94.94	95.33	95.31	95.13	97.22
6	81.28	81.63	81.05	81.75	81.88	81.50	82.79	76.08	75.80	75.69	76.04	79.12
7	40.22	41.93	40.72	44.36	41.31	42.58	43.67	45.30	44.99	44.84	45.03	45.05*
8	43.57	40.69	39.34	38.85	38.81	40.33	41.27	41.61	41.26	40.89	41.24	44.52*
9	59.08	58.71	58.58	56.48	56.56	59.12	60.10	56.92	56.92	56.68	56.88	58.06
10	22.14	22.02	22.10	22.15	22.21	22.42	23.15	22.59	22.58	22.36	22.50	22.27
11	127.71	127.69	127.12	128.18	128.17	127.15	127.77	126.42	127.29	127.32	126.54	126.82
12	133.90	134.19	133.22	133.03	133.08	133.79	131.01	132.28	132.36	132.61	132.53	132.03
13	47.98	48.30	48.35	48.06	48.09	48.26	48.36	47.66	47.79	47.54	47.79	48.22
14	45.30	44.46	44.76	45.08*	45.10*	45.42	46.10	44.99	45.02	44.88	45.07	47.25
15	32.96	32.62	32.37	33.42	33.48	32.80	33.72	32.31	33.21	32.68	32.36	33.38
16	49.86*	45.17	44.88	45.01*	45.08*	45.42	46.58	43.10	45.49	45.47	45.50	46.66
17-NCH_3	42.22	43.54	43.48	43.16	44.32	43.50	43.63	45.30	43.14	43.11	43.18	43.10
18	134.49	135.34	134.96	133.10	133.19	134.61	134.99	133.73	133.37	133.62	133.90	133.80
19	129.18	130.04	130.21	127.75	127.30	129.03	131.43	130.22	130.43	131.41	130.52	128.88
OCH_3C^3	56.42	56.30	56.41	56.36	56.46	–	–	–	–	56.45	–	56.19
OCH_3C^6	51.99	51.48	51.83	52.92	53.05	51.60	52.33	–	–		–	55.05
CH_2N	–	56.10*	55.96*	37.99	38.81	–	39.86	–	39.74	–	–	37.41
CH_2R	–	33.94	31.12	–	33.66	–	33.71	–	32.51	61.31	60.51	32.12
$C^{2'}$	49.94*	56.38*	55.82*	82.23	83.12	50.98	–	175.84*	177.01*	178.42*	178.48*	86.12
$C^{5'}$	51.00	58.11	56.22	172.36	172.34	51.53	–	175.92*	177.28*	178.51*	178.40*	177.12

[a] The starred signals should probably be interchanged within the same column. The signals of the other carbon atoms , δ, ppm: **XIX**, 108.15 s ($C^{1'}$), 114.27 d, 112.79 d ($C^{3',5'}$), 128.87 d, 131.47 d ($C^{2',6'}$), 148.12 s (C^4); **XX**, 115.32 d, 129.95 d, 129.38 s, 155.02 s (Ar); **XXI**, 27.86 t, 29.26 t, 33.34 t, 67.35 t (CH_2), 114.86 d ($C^{3',5'}$), 129.77 s ($C^{1'}$), 130.22 d ($C^{2',6'}$), 156.84 s ($C^{4'}$); **XXII**, 55.36 q (CH_3), 110.19 d , 120.24 d, 124.30 s, 128.33 d, 129.64 d, 157.27 s (Ar); (XXIII) – 126.12 d, 128.17 d, 128.28 d, 128.32 d, 128.62 d, 139.02 s (Ph); **XXIV**, 126.49 d, 128.01 d, 128.96 d, 137.48 s (Ar); **XXV**, 115.46 d, 129.18 d, 129.56 s, 155.18 s (Ar); **XXVI**, 137.29 s ($C^{1'}$), 126.35 d, 128.68 d ($C^{2',3',5',6'}$), 128.29 s ($C^{4'}$); **XXVII**, 127.35 d, 128.51 d, 128.88 d, 136.43 s (Ar); **XXVIII**, 19.64 q, 19.85 q (CH_3), 26.00 d (CH), 60.64 d (CH); **XXIX**, 19.88 q, 20.03 q (CH_3), 26.34 d (CH), 60.70 d (CH); **XXX**, 126.24 d, 126.32 d, 128.45 d, 128.70 d, 138.46 s (Ph).

3.71 d, 3.73 d (2H, CH_2, *J* 7.8 Hz), 6.62 s (2H, $H^{3,4}$), 6.93 m (2H, $H^{2',6'}$), 7.12 m (2H, $H^{3',5'}$). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 33.50 t ($C\underline{H}_2Ar$), 38.92 t (CH_2N), 115.15 d, 115.36 d ($C^{3',5'}$), 130.10 d, 130.18 d ($C^{2',6'}$), 133.35 s ($C^{1'}$), 133.91 d ($C^{3,4}$), 160.42 s ($C^{4'}$), 170.38 d ($C^{2,5}$).

***N*-(2-Fluorophenethyl)maleimide (IIg)**. Yield 65%, mp 138–140°C (from ethyl acetate). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.84 m (2H, CH_2), 3.29 m (2H, CH_2), 6.62 s (2H, $H^{3,4}$), 6.90 m (2H, Ph), 7.18 m (2H, Ph).

***N*-[2-(Cyclohex-1-enyl)ethyl]maleimide (IIh)**. Yield 62%, mp 172–175°C (from ether). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.62 m (4H, $H^{4',5'}$), 1.99 m (4H, $H^{3',6'}$), 2.14 m (2H, CH_2), 2.29 m (2H, CH_2), 5.33 m (1H, $H^{2'}$), 6.64 s (2H, $H^{3,4}$).

***N*-[2-(*N*,*N*-Dimethylamino)ethyl]maleimide (IIi)**. Yield 58%, mp 175–178°C (from ethanol). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.22 c (6H, $2CH_3N$), 2.22 m (2H, CH_2), 2.39 m (2H, CH_2), 6.56 s (2H, $H^{3,4}$).

Thebaine adducts with maleimides. To a solution of 5 mmol of thebaine (**I**) in 15 ml of ethanol 5.2 mmol of an appropriate maleimide in 10 ml of ethanol was added. The reaction mixture was heated at reflux for 3–9 h (TLC monitoring). On cooling the precipitated crystals

of adducts **III–XI** were filtered off, the mother liquor was evaporated, and the oily compound obtained was subjected to column chromatography on alkaline aluminum oxide to isolate additionally 15–20% of the adduct. Yields and spectral characteristics of N'-substituted [7α,8α,3',4']succinimido-6,14-*endo*-ethenotetrahydrothebaines **III–XI** are presented in Tables 1, 2. ^{19}F NMR spectrum, δ, ppm: 45.38 m ($F^{4'}$, **VIII**), 43.90 m ($F^{2'}$, **IX**).

[7α,8α,3',4']{*N*'-[(1*S*)-1-Hydroxymethyl-2-methylpropyl]succinimido}-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (XIV). To a solution of 1.0 g (2.42 mmol) of compound **XII** in 45 ml of freshly distilled toluene was added under argon 0.25 g (2.4 mmol) of *S*-valinol (**XIII**). The reaction mixture was boiled at stirring for 2 h. Into the homogeneous solution obtained 0.48 g (4.8 mmol) of triethylamine and molecular sieves (3 A) were added, and the reaction mixture was boiled for another 17 h. On cooling the reaction mixture was washed with water and dried with $MgSO_4$. The solvent was evaporated, the residue was crystallized from ethanol. We filtered off 0.80 g (65%) of compound **XIV**. The chromatography of the mother liquor on a column charged with aluminum oxide afforded in succession 0.085 g (7.2%) of adduct **XIV** and 0.29 g (20%) of **7α,8α-bis{*N*'-[(1*S*)-1-hydroxymethyl-2-methylpropyl]-aminocarbonyl}-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (XV)**. mp 240–242°C (from ethanol). IR spectrum, cm^{-1}: 755, 797, 923, 986, 1012, 1040, 1055, 1083, 1107, 1146, 1156, 1210, 1252, 1499, 1537, 1568, 1598, 1654, 3075, 3384. UV spectrum, λ_{max}, nm (log ε): 215 (4.26), 245 (3.28), 286 (2.18). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.80 d (3H, CH_3, *J* 7.0), 0.86 d (3H, CH_3, *J* 7.0), 1.01 d (3H, CH_3, *J* 7.0), 1.07 d (3H, CH_3, *J* 7.0), 1.63 m [1H, CH(*i*-Pr)], 1.81 d.d.d (1H, H^{15}, *J* 13.5, 4.2 and 1.4), 1.99 m [1H, CH(*i*-Pr)], 2.06 d.d.d (1H, H^{15}, *J* 13.5, 10.2 and 3.1), 2.32 s [3H, (CH_3N)], 2.41 m (1H, H^{16}, *J* 12.2, 10.3 and 1.4), 2.45 m (1H, H^{10}), 2.51 d.d.d (1H, H^{16}, J_{gem} 12.2, J_{vic} 4.2 and 1.5), 3.03 m (1H, CH), 3.16 d (1H, $H^{10\beta}$, J_{gem} 18.6), 3.28 d (1H, H^7, *J* 11.6), 3.39 d.d (1H, CH, *J* 7.6 and 5.3), 3.56 s (3H, CH_3OC^6), 3.55 m and 3.76 m (2H, CH_2), 3.67 m (1H, CH), 3.79 s (3H, CH_3OC^3), 3.81 d (1H, $H^{9\alpha}$, *J* 6.4), 4.08 d (1H, H^8, *J* 11.6), 4.62 d (1H, $H^{5\beta}$, *J* 1.3), 5.82 d (1H, H^{19}, *J* 8.7), 5.90 d.d (1H, H^{18}, *J* 8.7 and 1.3), 6.10 m (2H, NH), 6.52 d (1H, H^1, *J* 8.2), 6.60 d (1H, H^2, *J* 8.2). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 17.88 q, 18.52 q, 19.01 q, 19.54 q (CH_3), 22.36 t (C^{10}), 28.58 d, 29.73 d [CH(*i*-Pr)], 32.92 t (C^{15}), 43.43 q (CH_3N), 43.88 s (C^{13}), 45.22 t (C^{16}), 47.28 s (C^{14}), 50.30 d (C^8), 51.92 d (C^7), 52.08 q (C^6 O<u>C</u>H$_3$), 56.42 q (C^3<u>C</u>H$_3$O), 57.28 d (C^9), 58.60 d (2<u>C</u>HN), 60.45 t, 63.65 t (CH_2OH), 80.19 s (C^6), 92.93 d (C^5), 113.46 d (C^2), 119.49 d (C^1), 124.00 d (C^{19}), 127.84 C (C^{11}), 133.57 s (C^{12}), 139.64 d (C^{18}), 141.89 C (C^3), 147.67 s (C^4), 172.50 s ($C^{2'}$), 178.15 s ($C^{5''}$). $C_{33}H_{47}N_3O_7$. Mass spectrum, *m/z* (I_{rel}, %): 494 (100), 409 (46), 319 (63), 311 (39), 310 (73), 276 (64), 255 (57), 216 (34), 162 (37), 60 (55) and 42 (96).

[7α,8α,3',4']-*N*'-[4-(Bromobutoxy)phenethyl]-succinimido-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (XVI). To a solution of 0.53 g (1 mmol) of compound **VII** in 20 ml of CH_2Cl_2 was added 8 ml of 24% aqueous NaOH, 0.01 g of tetrabutylammonium bromide, and 0.25 g (1.3 mmol) of 1,4-dibromobutane. The reaction mixture was stirred at room temperature for 24 h, then diluted with 50 ml of water, and the reaction products were extracted into dichloromethane. The organic solution was washed in succession with water and saturated NaCl solution, dried over $MgSO_4$, and the solvent was evaporated in a vacuum. The obtained crude product (0.8 g) was ground into amorphous powder in a mixture acetone –hexane. On recrystallization from ethyl acetate we isolated 0.54 g (82%) of compound **XVI**. UV spectrum, λ_{max}, nm (log å): 220 (4.21), 250 (2.48), 278 (1.88).

[7α,8α,3',4']-*N*'-{4-[4-(2-Aminoethoxy)butoxy]-phenethyl}- and [7α,8α,3',4']-N'-{4-[4-(2-hydroxyethylamino)butoxy]phenethyl}succinimido-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaines (XVII, XVIII). To a solution of 0.65 g (1 mmol) of compound **XVI** in 30 ml 0.82 g of K_2CO_3, and the reaction mixture was heated at reflux for 8th till complete disappearance of the initial compound (TLC monitoring). On cooling the precipitate was filtered off, washed with acetone, the compound acetone solution was evaporated in a vacuum, the residue was subjected to chromatography on aluminum oxide. We isolated 0.18 g (29%) of amine **XVII** and 0.23 g (37%) of compound **XVIII**. UV spectrum, λ_{max}, nm (log å): 215 (4.26), 245 (3.28), 286 (2.18) (**XVII**); 222 (4.32), 245 (2.28), 284 (2.98) (**XVIII**).

Reduction of adducts III, VII, and XVI by $LiAlH_4$. To a solution of 2.5 mmol of adducts **III** or **VII** in 20 ml of anhydrous THF was added by small portions in an argon flow 0.2 g of $LiAlH_4$. The reaction mixture was heated at reflux for 6–8 h (TLC monitoring). On cooling 0.2 ml of water was cautiously added to the reaction mixture, the mixture was stirred for 20 min, the precipitate formed was filtered off, boiled with THF (3×10 ml), the mother liquors were combined, washed with a saturated

NaCl solution, the organic layer was separated, dried with $MgSO_4$, and evaporated in a vacuum. The residue was subjected to column chromatography on aluminum oxide. Thus we isolated N'-substituted **[7α,8α,3'4']pyrrolidino-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaines (XIX–XXI)**.

Reduction of adducts V and VI by $NaBH_4$. In 50 ml of anhydrous THF was dissolved 5.9 mmol of succinimides **V** and **VI**, the solution was cooled to 0°C, and at stirring in an argon flow 2.24 g (59 mmol) of $NaBH_4$ was added. The reaction mixture was stirred at room temperature for 4 h, then 3 ml (5.9 mmol) of 2.2 M solution of HCl in ethanol was added dropwise. The reaction mixture was stirred for 2 h, then poured in 50 ml of saturated $NaHCO_3$ solution. The organic layer was separated, the water layer was extracted with chloroform (3×50 ml). The combined organic solutions were dried over $MgSO_4$ and evaporated in a vacuum. The residue was was subjected to column chromatography on aluminum oxide. Thus we isolated N-substituted **[7α,8α,3'4']-(2'α-hydroxy-5'-oxopyrrolidino)-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaines (XXII, XXIII)**.

O-Demethylation of compounds III, IV, XIV, XIX, XX, and XXIII. To a solution of 2 mmol of compound in 20 ml of chloroform was added at stirring 1 M solution of BBr_3 in 20 ml of chloroform. The reaction mixture was stirred at room temperature for 3 h, then poured into the cooled to 3–5°C diluted (1:1) solution of ammonium hydroxide, and the mixture was stirred at 0°C for 30 min. The organic layer was separated, the water layer was extracted with chloroform (2×15 ml). The combined organic solutions were washed with a saturated NaCl solution, and dried over $MgSO_4$. The magnesium sulfate was filtered off, and the solution was passed through a bed (5.0 g) of alkaline aluminum oxide, evaporated, and the residue was ground with ether. We isolated N-substituted [7α,8α,3',4']pyrrolidino-6,14-*endo*-ethenotetrahydrooripavines **XXIV** and **XXV**, 6-demethyl-N-substituted [7α,8α,3',4']-succinimido-6,14-*endo*-ethenotetrahydrooripavines **XXVI**, **XXVII**, and **XXIX**, [7α,8α,3',4']{*N*'-[(1*S*)-1-hydroxymethyl-2-methylpropyl]-succinimido}-6-demethyl-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (**XXVIII**), and [7α,8α,3',4'](*N*'-phenethyl-2'α-hydroxy-5'-oxo)-pyrrolidino-6,14-*endo*-ethenotetrahydrothebaine (**XXX**). Compounds **XXVIII** and **XXIX** were separated by column chromatography on aluminum oxide. The treating of succinimide **XIV** with BBr_3 under the above conditions and keeping the reaction mixture at room temperature for 12 h resulted in formation of chromatographically individual 6-demethyloripavine **XXIX**. The samples for analysis of all compounds were recrystallized from appropriate solvents (Table 1).

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