ISSN 1070-4280, Russian Journal of Organic Chemistry, 2009, Vol. 45, No. 10, pp. 1546–1554. © Pleiades Publishing, Ltd., 2009.
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Diels–Alder Reactions with Cyclic Sulfones: X.* Synthesis of 4-Carbamoyl- and 4-Hydrazido-Substituted Hexahydro-1-benzothiophene *S*,*S*-Dioxides

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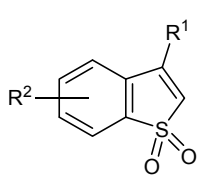
Received December 8, 2008

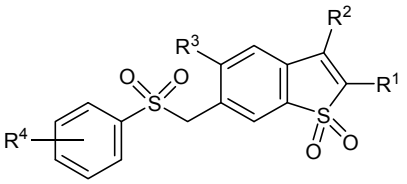
Abstract—Reactions of spiro[1-benzothiophene-4,5′-[1,3]dioxane]-4′,6′-diones with various amines led to the formation of 4-carbamoylhexahydrobenzo[*b*]thiophene-4-carboxylic acid 1,1-dioxides or their decarboxylation products, depending on the conditions. Hydrazinolysis of the spiro adducts in DMF gave the corresponding monohydrazides. The structure of 4-carbamoyl-7-methyl-5-phenyl-2,3,3a,4,5,6-hexahydro-1-benzothiophene-4-carboxylic acid 1,1-dioxide was proved by X-ray analysis.

DOI: 10.1134/S1070428009100224

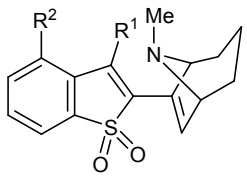
Functionally substituted 1-benzothiophene 1,1-dioxides exhibit a broad spectrum of biological activity; in particular, compounds **I** are promising as medicinal agents for the treatment or prophylactics of various inflammatory processes, including blood poisoning, sepsis, myeloma, leukemia, diabetes, hepatitis, etc. [2]. In the recent years, 1-benzothiophene 1,1-dioxides **II** and **III** have been extensively studied as potential antitumor agents [3–6]. Due to their high lipophilicity, compounds **II** and **III** exhibit cytolytic activity against human tumor cells, such as leukemia, HT29, HTB54, and H562. Compounds like **IV** having an 8-azabicyclooctene fragment attract interest as cholinergic receptor modulators [7]. Procedures for the synthesis of compounds **V** as medicinal agents for the treatment of hypercholesteremia, hyperlipemia, atherosclerosis, and



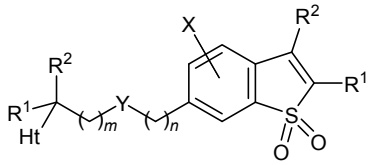
I, **II**



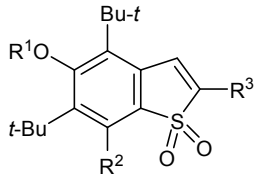
III



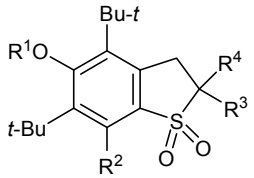
IV



V



VI

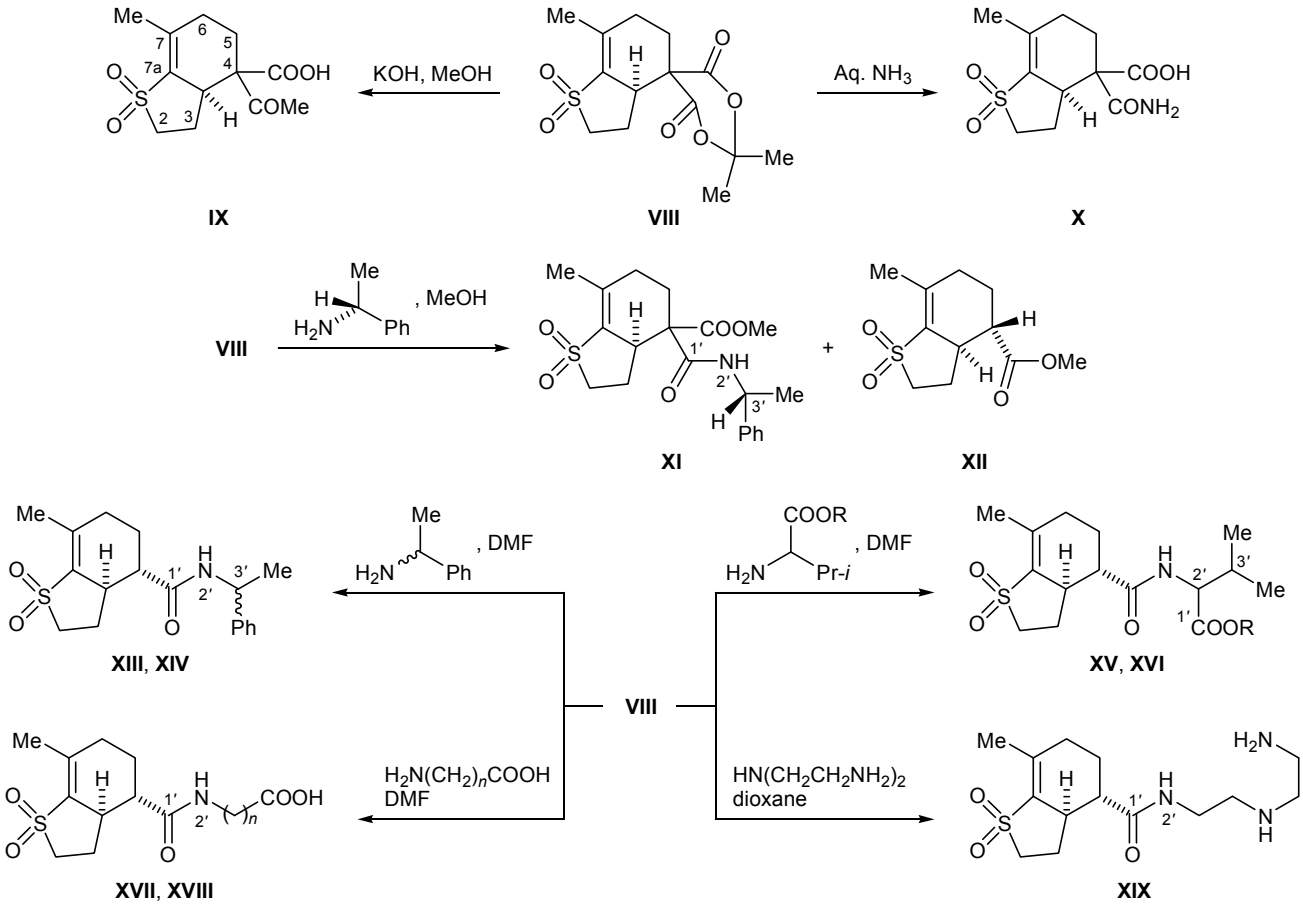


VII

I, R^1 = H, Alk; R^2 = Alk, NO_2; **II**, R^1 = H, Me; R^2 = SO_2NH_2, SO_2Me, SO_2Ph, SO_2CH_2Ar; **III**, R^1–R^4 = H, Me; **IV**, R^1 = H, Me; R^2 = H, Me, *t*-Bu; **V**, R^1, R^2 = H, Alk; Ht = N-heterocycle; Y = O, NR_2, CH_2; X = Hlg; *m*, *n* = 0–7; **VI**, **VII**, R^1 = H, Alk, Ac; R^2, R^4 = H, Alk; R^3 = Alk.

* For communication IX, see [1].

Scheme 1.



XV, R = Me; **XVI**, R = *t*-Bu; **XVII**, *n* = 3; **XVIII**, *n* = 10.

various vascular diseases were covered by patents [8]. *tert*-Butyl-substituted benzothiophene *S*,*S*-dioxide and dihydrobenzothiophene *S*,*S*-dioxide derivatives **VI** and **VII** inhibit oxidative degradation of low-density lipoprotein (LDL) and are promising for the treatment of atherosclerosis and such heart diseases as infarct and arrhythmia [9].

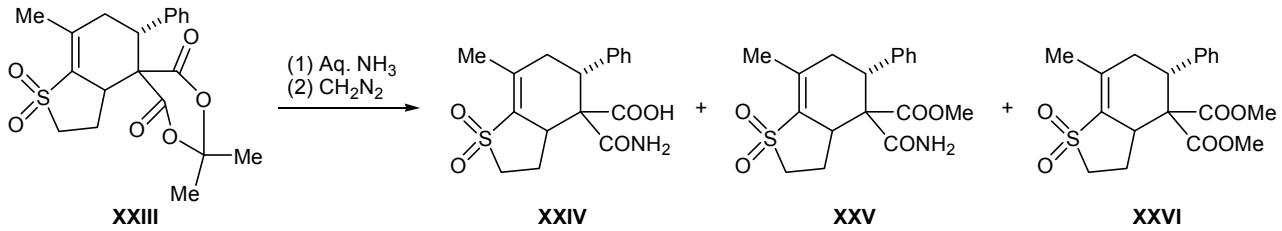
We were interested in the synthesis of hexahydro-1-benzothiophene *S*,*S*-dioxide derivatives from the corresponding hexahydrospiro[1-benzothiophene-4,5′-[1,3]-dioxane]-4′,6′-dione 1,1-dioxides [10] via opening of the 1,3-dioxane ring [11, 12]. We previously showed that the 1,3-dioxane ring in spiro adduct **VIII** is readily cleaved by the action of ammonia in dioxane or potassium hydroxide in methanol. As a result, derivatives of methyl ester **IX** or amic acid **X** are obtained [10]. In the present communication we describe the transformations of compound **VIII** in reactions with various amines, amino acids, and hydrazines. Depending on the conditions, the reaction of spiro-fused sulfone **VIII** with (*R*)-(+)- or (*S*)-(–)-1-phenylethanamine gave different compounds **XI**–**XIV** (Scheme 1). The major product of the reaction of **VIII** with (*R*)-(+)-1-phenylethanamine contained no amide functionality; it was identified as methyl 1-benzothiophene-4-carboxylate 1,1-dioxide (**XII**) (yield 52%). In addition, we isolated methyl 4-[(*R*)-1-phenylethylcarbamoyl]-7-methyl-2,3,3a,4,5,6-hexahydro-1-benzothiophene-4-carboxylate 1,1-dioxide (**XI**) (yield 26%). More severe conditions (heating in DMF to 110°C, 7 h) promoted formation of decarboxylation products, (*R*)-(+)- and (*S*)-(–)-1-benzothiophene-4-carboxamide 1,1-dioxides **XIII** and **XIV**, respectively (yield 59–68%). Interestingly, compounds **XI**, **XIII**, and **XIV** were formed as individual diastereoisomers. Opening of the dioxane ring in **VIII** by the action of ω-amino acids and α-amino acid esters required prolonged heating in dimethylformamide (up to 25 h), and the yields of the corresponding N-substituted 7-methyl-2,3,3a,4,5,6-hexahydro-1-benzothiophene-4-carboxamide 1,1-dioxides **XV**–**XVIII** ranged from 58 to 72%. The reaction of **VIII** with *N*-(2-aminoethyl)ethane-1,2-diamine on

Scheme 2.

XX **XXI**, **XXII**

XXI, X = 4-BrC_6H_4; **XXII**, X = pyridin-4-yl.

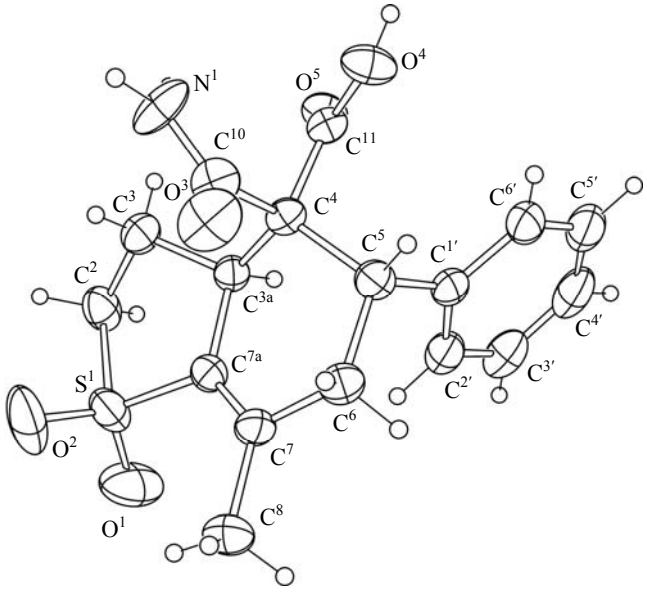
Scheme 3.



XXIII **XXIV** **XXV** **XXVI**

heating in DMF was accompanied by strong tarring and was not selective (a mixture of products was obtained). We succeeded in isolating *N*-[2-(2-aminoethylamino)ethyl]-7-methyl-2,3,3a,4,5,6-hexahydro-1-benzothiophene-4-carboxamide 1,1-dioxide (**XIX**) in 38% yield by heating for a long time a dilute solution of compound **VIII** and an equimolar amount of *N*-(2-aminoethyl)ethane-1,2-diamine.

Compound **VIII** reacted with phenylhydrazine and isonicotinic and 4-bromobenzoic acid hydrazides on heating in DMF to give the corresponding 1-benzothiophene-4-carbohydrazide 1,1-dioxides **XX**–**XXII** in 52–68% yield (Scheme 2). By treatment of 2′,2′,7-trimethyl-5-phenyl-3,3a,5,6-tetrahydro-2*H*-spiro[1-benzothiophene-4,5′-[1,3]dioxane]-4′,6′-dione 1,1-dioxide (**XXIII**) with ammonia in dioxane (reaction time 8 h; the conditions were the same as in the transformation of compound **VIII** into amido acid **X**) we obtained 4-carbamoylhexahydro-1-benzothiophene-4-carboxylic acid 1,1-dioxide **XXIV** in 28% yield. Increase of the reaction time to 16 h and subsequent methylation with diazomethane resulted in the formation of a mixture of compounds **XXIV** and **XXV** (37 and 42%, respectively). In addition, 16% of diester **XXVI** was isolated (Scheme 3).

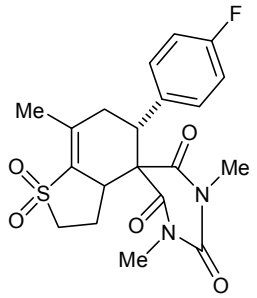


Structure of the molecule of (3a*S*,5*R*)-4-carbamoyl-7-methyl-5-phenyl-2,3,3a,4,5,6-hexahydro-1-benzothiophene-4-carboxylic acid 1,1-dioxide (**XXIV**) according to the X-ray diffraction data.

The structure of the isolated compounds was determined on the basis of their spectral parameters. The 3a-H and 4-H protons in molecules **XII**–**XXII** were assigned *trans* orientation taking into account the corresponding vicinal coupling constant ($J_{3a,4}$ = 10.5–11.2 Hz) in the ^{1}H NMR spectra.

Figure shows the structure of the (4*S*)-isomer of compound **XXIV** according to the X-ray diffraction data. The molecular geometry, conformations of the rings, and intermolecular interactions were analyzed using PLATON program [13]. The bond lengths in molecule **XXIV** approach the corresponding standard values [14], and geometric parameters of the bicyclic benzothiophene fragment coincide within 3σ with those found for 4-carbamoyl-7-methyl-2,3,3a,4,5,6-hexahydro-1-benzothiophene-4-carboxylic acid 1,1-dioxide (**X**) [10] which may be regarded as the closest structural analog of compound **XXIV**. The C^4–C^5 bond in **XXIV** is extended to 1.570(3) Å against 1.545(3) Å

in **X**; obviously, this is due to the presence of bulky substituents in positions *4* and *5* of the benzothiophene ring in **XXIV** (there is no substituent on C^5 in molecule **X**). Analogous extension of the C^4–C^5 bond to 1.589(5) Å was observed in the molecule of 5-substituted compound **XXVII** having an aromatic ring on C^5 and a spiro-fused perhydropyrimidine fragment on C^4 [15]. The six-membered ring in molecule **XXIV** has a distorted *sofa* conformation [16] in which the C^{3a}, C^{7a}, C^7, C^6, and C^5 atoms lie in one plane (the mean-square deviation from that plane is 0.033 Å) while the C^4 atom deviates from that plane by 0.640(3) Å. The five-membered (sulfolane) ring adopts an *envelope* conformation with the C^3 atom deviating by 0.635(4) Å from the plane formed by the four other atoms (mean-square deviation 0.017 Å). The benzene ring plane (mean-square deviation 0.008 Å) is almost orthogonal to the plane formed by five atoms of the cyclohexene fragment: the corresponding dihedral angle is 81.79(8)°. The planar carboxy and carbamoyl groups are turned through a dihedral angle of 73.2(1)° with respect to each other (the corresponding angle in structure **XXVII** is 79.4°] [15].



XXVII

Supramolecular architecture of compound **XXIV** in crystal (as solvate with DMSO) is determined by intermolecular hydrogen bonds N–H···O and O–H···O that link molecule **XXIV** to two nearest DMSO molecules, giving rise to trimers. One DMSO molecule is not disordered; it is involved in the O^4–$H^1OH\cdots O^1R$ hydrogen bond with the following parameters: H···O 1.71(4), N···O 2.560(3) Å, ∠167(4)°; the second DMSO molecule is disordered by two positions with the hydrogen bonds N^1–$H^{1a}\cdots O^2R_2$ [H···O 1.70, N···O 2.517(7) Å, ∠NHO 135°] and N^1–$H^{1a}\cdots O^1R_2$ [H···O 1.84, N···O 2.652(7) Å, ∠NHO 160°]. The trimers form infinite two-dimensional networks via weaker intermolecular contacts C–H···O between the neighboring molecules (2D supramolecular motif); these interactions are characterized by non-valence H···O distances ranging from 2.34 to 2.55 Å (the sum of the corresponding van der Waals radii is equal to 2.68 Å [17]).

Thus opening of the dioxane ring in 2′,2′,7-trimethyl-3,3a,5,6-tetrahydro-2*H*-spiro[1-benzothiophene-4,5′-[1,3]dioxane]-4′,6′-dione 1,1-dioxides by the action of amines, amino acids, and hydrazides provides a convenient synthetic approach to various 4-substituted derivatives of 7-methyl-2,3,3a,4,5,6-hexahydro-1-benzothiophene 1,1-dioxide.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on Bruker AV-300 (300.13 and 75.47 MHz, respectively), AM-400 (400.13 and 100.78 MHz), and Bruker DRX-500 spectrometers (500.13 and 125.76 MHz). Signals were assigned using various proton–proton and carbon–proton shift correlation techniques (COSY, COLOC). The mass spectra (electron impact, 70 eV) were obtained on a Finnigan MAT-8200 high-resolution mass spectrometer (vaporizer temperature 270–300°C); the molecular weights and elemental compositions were determined from the high-resolution mass spectra. The IR spectra were measured on a Bruker Vector-22 instrument from samples prepared as KBr pellets. The optical rotations were determined on a Polar 3005 polarimeter at room temperature (20–23°C). The X-ray diffraction data for compound **XXIV** were acquired on a Bruker P4 diffractometer (MoK_α irradiation, graphite monochromator, 2θ/θ scanning in the range 2θ < 52°).

The progress of reactions was monitored, and the purity of products was checked, by thin-layer chromatography on Silufol UV-254 plates; development with iodine vapor. The products were isolated by column chromatography on silica gel (0.035–0.070 mm, Acros Organics) using chloroform–ethanol as eluent.

Spiro compounds **VIII** and **XXIII** were synthesized as described in [10]. (*R*)-(+)- and (*S*)-(–)-1-Phenylethanamines (Aldrich) and amino acid esters (Reanal, Hungary) were commercial products.

Methyl (3a*S*)-7-methyl-4-[(*R*)-1-phenylethylcarbamoyl]-2,3,3a,4,5,6-hexahydro-1-benzothiophene-4-carboxylate 1,1-dioxide (XI). A solution of 0.56 g (4.7 mmol) of (*R*)-(+)-1-phenylethylamine was added dropwise under stirring to a solution of 0.94 g (3 mmol) of compound **VIII** in 15 ml of methanol. The mixture was stirred for 8 h at room temperature and heated for 10 h under reflux, the precipitate (0.12 g) was filtered off, the filtrate was evaporated, and the

residue was subjected to chromatography on silica gel to isolate (in order of elution) 0.38 g (52%) of compound **XII** and 0.32 g (26%) of amide **XI**.

Compound **XI**. mp 105–108°C (from ethyl acetate), $[\alpha]_D^{20}$ = +21.2° (*c* = 1.62, EtOH). ^{1}H NMR spectrum (CD_3OD), δ, ppm: 1.64 d (3H, CH_3, *J* = 7.0 Hz), 1.62–1.88 m (2H, 3-H, 5-H), 2.06 d (3H, CH_3, *J* = 2.0 Hz), 2.10 m (2H, 5-H, 6-H), 2.35 m (1H, 6-H), 2.32 m (1H, 3-H), 2.90 m (1H, 3a-H), 3.00 m (1H, 2-H), 3.18 m (1H, 2-H), 3.73 s (3H, CH_3), 4.42 d.d (1H, 3′-H, *J* = 7.0, 2.8 Hz), 7.27–7.50 (5H, Ph), 8.32 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 18.26 q (CH_3), 21.05 q (CH_3), 22.26 t (C^3), 29.96 t (C^5), 32.21 t (C^6), 41.06 d (C^{3a}), 46.18 d ($C^{3'}$), 50.65 t (C^2), 54.81 s (C^4), 55.82 q (OCH_3), 125.98 d ($C^{2'}$, $C^{6'}$), 126.34 d ($C^{4'}$), 129.34 d ($C^{3'}$, $C^{5'}$), 132.18 s (C^{7a}), 140.81 s ($C^{1''}$), 142.12 s (C^7), 171.79 s (C=O), 173.02 s (C=O). Found, %: C 61.52; H 7.09; N 3.88; S 7.86. $C_{20}H_{25}NO_5S$. Calculated, %: C 61.36; H 6.44; N 3.58; S 8.19.

Methyl 7-methyl-2,3,3a,4,5,6-hexahydro-1-benzothiophene-4-carboxylate 1,1-dioxide (XII). mp 94–96°C (from Et_2O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.57–1.78 m (2H, 3-H, 5-H), 2.05 d (3H, CH_3, *J* = 2.0 Hz), 2.09 m (1H, 5-H), 2.19 d.d (1H, 4-H, *J* = 10.8, 8.2 Hz), 2.28 m (2H, 6-H), 2.40 m (1H, 3-H), 2.78 m (1H, 3a-H), 2.93 m (1H, 2-H), 3.14 m (1H, 2-H), 3.70 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 18.06 q (CH_3), 25.07 t (C^5), 25.76 t (C^3), 31.91 t (C^6), 39.28 d (C^{3a}), 45.03 d (C^4), 50.24 t (C^2), 52.18 q (CH_3), 134.88 s (C^{7a}), 142.96 s (C^7), 173.86 s (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 245 (3), 244 (19), 213 (5), 185 (29), 184 (100), 167 (5), 119 (31), 105 (69), 91 (53). Found, %: C 54.40; H 6.81; S 12.57. $[M]^+$ 244.07660. $C_{11}H_{16}O_4S$. Calculated, %: C 54.08; H 6.60; S 13.12. *M* 244.07692

7-Methyl-*N*-[(*R*)-1-phenylethyl]-2,3,3a,4,5,6-hexahydro-1-benzothiophene-4-carboxamide 1,1-dioxide (XIII). A solution of 0.94 g (3 mmol) of compound **VIII** and 0.47 g (0.5 ml, 3.9 mmol) of (*R*)-(+)-1-phenylethanamine in 15 ml of DMF was heated for 2 h at 110°C, an additional portion, 0.47 g (0.5 ml), of the amine was added, and the mixture was heated for 5 h at 110°C. The mixture was evaporated in a Petri dish, the residue was ground with diethyl ether, and the precipitate was dried and purified by chromatography on silica gel. Yield 0.59 g (59%). mp 180–184°C (from ethyl acetate), $[\alpha]_D^{20}$ = +36.2° (*c* = 1.62, EtOH–DMSO). ^{1}H NMR spectrum (CD_3OD), δ, ppm: 1.35 d (3H, CH_3, *J* = 7.0 Hz), 1.50–1.62 m (2H, 3-H, 5-H), 1.96 d (3H, CH_3, *J* = 2.0 Hz), 1.93 m (1H, 4-H, $J_{3a,4}$ = 10.8 Hz), 2.11 m (1H, 5-H), 2.10–218 m (2H, 6-H), 2.30 m (1H, 3-H), 2.68 m (1H, 3a-H), 3.00 m (1H, 2-H), 3.15 m (1H, 2-H), 4.11 d.d (1H, 3′-H, *J* = 7.0, 2.8 Hz), 7.25 m (1H, 4″-H), 7.35 m (2H, 2″-H, 6″-H), 7.41 m (2H, 3″-H, 5″-H). ^{13}C NMR spectrum, δ_C, ppm: 17.67 q (CH_3), 23.83 q (CH_3), 25.80 t (C^3), 23.98 t (C^5), 31.60 t (C^6), 38.99 d (C^{3a}), 46.28 d (C^4), 50.19 d ($C^{3'}$), 50.71 t (C^2), 126.10 d ($C^{2''}$, $C^{6''}$), 126.98 d ($C^{4''}$), 128.22 d ($C^{3''}$, $C^{5''}$), 135.17 s (C^{7a}), 139.79 s ($C^{1''}$), 144.82 s (C^7), 175.47 s (C=O). Found, %: C 65.12; H 6.84; N 4.48; S 10.05. $C_{18}H_{23}NO_3S$. Calculated, %: C 64.84; H 6.95; N 4.20; S 9.62.

7-Methyl-*N*-[(*S*)-1-phenylethyl]-2,3,3a,4,5,6-hexahydro-1-benzothiophene-4-carboxamide 1,1-dioxide (XIV). A solution of 0.94 g (3 mmol) of compound **VIII** and 0.47 g (0.5 ml, 3.9 mmol) of (*S*)-(–)-1-phenylethanamine in 15 ml of DMF was heated for 3 h at 110°C, an additional portion, 0.28 g (0.3 ml), of the amine was added, and the mixture was heated for 7 h at 110°C. The mixture was evaporated in a Petri dish, the residue was ground with diethyl ether, and the precipitate was dried and purified by chromatography on silica gel. Yield 0.68 g (68%), mp 203–206°C (from ethyl acetate), $[\alpha]_D^{20}$ = –28.8° (*c* = 0.82, EtOH–DMSO). ^{1}H NMR spectrum (CD_3OD), δ, ppm: 1.42 d (3H, CH_3, *J* = 7.0 Hz), 1.48–1.56 m (2H, 3-H, 5-H), 1.98 d (3H, CH_3, *J* = 2.0 Hz), 1.89 m (1H, 4-H, $J_{3a,4}$ = 11.0 Hz), 2.05 m (1H, 5-H), 218 m (2H, 6-H), 2.38 m (1H, 3-H), 2.64 m (1H, 3a-H), 2.96 m (1H, 2-H), 3.12 m (1H, 2-H), 4.18 d.d (1H, 3′-H, *J* = 7.0, 3.8 Hz), 7.30–7.42 m (5H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 17.70 q (CH_3), 22.96 q (CH_3), 26.05 t and 26.08 t (C^3, C^5), 31.78 t (C^6), 36.69 d (C^{3a}), 47.06 d (C^4), 50.00 d ($C^{3'}$), 50.81 t (C^2), 125.89 d and 126.28 d ($C^{2''}$, $C^{6''}$), 127.27 d ($C^{4''}$), 128.23 d and 128.29 d ($C^{3''}$, $C^{5''}$), 135.44 s (C^{7a}), 139.65 s ($C^{1''}$), 143.41 s (C^7), 176.08 s (C=O). Found, %: C 64.92; H 6.65; N 3.88; S 9.95. $C_{18}H_{23}NO_3S$. Calculated, %: C 64.84; H 6.95; N 4.20; S 9.62.

7-Methyl-*N*-(3-methyl-1-methoxy-1-oxobutan-2-yl)-2,3,3a,4,5,6-hexahydro-1-benzothiophene-4-carboxamide 1,1-dioxide (XV). A solution of 1.26 g (4 mmol) of compound **VIII** and 0.55 g (4.2 mmol) of L-valine methyl ester in 15 ml of DMF was heated for 25 h at 110°C. The mixture was evaporated in a Petri dish, and the residue was subjected to chromatography on silica gel. Yield 0.99 g (72%), mp 78–80°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 722, 847, 1620 (C=C), 1042 (C–O–C), 1127, 1130, 1290, 1350 (S=O), 1618, 3056, 3192, 3410 (NH), 1662, 1718 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.90 d and 0.96 d (3H each, CH_3, *J* = 6.8 Hz), 1.62–1.88 m (3H,

3-H, 5-H), 1.95 d.d.d (1H, 4-H, J = 10.5, 8.2, 2.0 Hz), 2.14 d (3H, CH_3, J = 2.0 Hz), 2,20 m (2H, 5-H, 6-H), 2.35 m (1H, 6-H), 2.32 m (1H, CH), 2.90 m (2H, 2-H, 3a-H), 3.22 m (1H, 2-H), 3.62 s (3H, OCH_3), 4.29 d (1H, 2′-H, J = 8.5 Hz), 7.82 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 17.64 q (CH_3), 18.35 q (CH_3), 18.96 q (CH_3), 23.12 t (C^3), 25.84 t (C^5), 30.28 d ($C^{3'}$), 31.26 t (C^6), 38.88 d (C^{3a}), 46.18 d (C^4), 49.88 t (C^2), 54.12 d ($C^{2'}$), 55.60 q (OCH_3), 133.12 s (C^{7a}), 141.28 s (C^7), 167.75 s (C=O), 168.07 s (C=O). Mass spectrum, m/z (I_{rel}, %): 343 (1), 257 (13), 184 (25), 161 (36), 156 (100), 127 (82), 113 (92), 99 (34), 85 (69), 72 (100). Found: $[M]^+$ 343.14425. $C_{16}H_{25}NO_5S$. Calculated: M 343.14553.

***N*-(1-*tert*-Butoxy-3-methyl-1-oxobutan-2-yl)-7-methyl-2,3,3a,4,5,6-hexahydro-1-benzothiophene-4-carboxamide 1,1-dioxide (XVI).** A solution of 0.63 g (2 mmol) of compound **VIII** and 0.39 g (2.3 mmol) of L-valine *tert*-butyl ester in 10 ml of DMF was heated for 25 h at 110°C. The mixture was evaporated in a Petri dish, and the residue was subjected to chromatography on silica gel to isolate a fraction containing compound **XVI**. Repeated chromatography gave 0.48 g (62%) of **XVI**, mp 218–222°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 728, 846, 1630 (C=C), 1128, 1162, 1291, 1350 (S=O), 1620, 3056, 3345, 3552 (NH), 1672, 1731 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.88 d and 0.92 d (3H each, CH_3, J = 6.8 Hz), 1.39 s (9H, *t*-Bu), 1.68–1.98 m (3H, 3-H, 5-H), 2.08 d (3H, CH_3, J = 2.0 Hz), 2.15 d.d.d (1H, 4-H, J = 10.8. 8.6, 1.8 Hz), 2.20 m (1H, CH), 2.28 m (1H, 3-H), 2.38 m (2H, 6-H), 2.80 m (1H, 2-H), 3.10 m (1H, 3a-H), 3.20 m (1H, 2-H), 4.39 d.d (1H, 2′-H, J = 8.5, 2.8 Hz), 6.52 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 17.61 q and 17.65 q (CH_3), 18.80 q (CH_3), 23.33 t (C^3), 25.67 t (C^5), 27.61 q [C(**C**H_3)$_3$], 30.09 t (C^6), 31.30 d ($C^{3'}$), 39.68 d (C^{3a}), 44.86 d (C^4), 50.56 t (C^2), 56.89 d ($C^{2'}$), 80.92 s [**C**(CH_3)$_3$], 134.42 s (C^{7a}), 142.96 s (C^7), 169.12 s (C=O), 173.92 s (C=O). Found, %: C 59.62; H 8.32; N 3.81; S 8.62. $C_{19}H_{31}NO_5S$. Calculated, %: C 59.19; H 8.10; N 3.63; S 8.32.

4-(7-Methyl-1,1-dioxido-2,3,3a,4,5,6-hexahydro-1-benzothiophen-4-ylcarbonylamino)butanoic acid (XVII). A solution of 0.63 g (2 mmol) of compound **VIII** and 0.42 g (4 mmol) of γ-aminobutyric acid in 8 ml of DMF was heated for 25 h at 110°C. The mixture was evaporated in a Petri dish, and the residue was purified by chromatography on silica gel. Yield 0.50 g (58%), colorless oily substance. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.62–1.70 m (3H, 4′-H, 3-H), 1.98–2.10 m (2H, 3-H, 5-H), 2.04 d (3H, CH_3, J = 1.8 Hz), 218 d.d.d (1H, 4-H, J = 10.8. 8.8, 1.8 Hz), 2.22–2.38 m (3H, 5-H, 6-H), 2.45–2.54 m (2H, 5′-H), 2.65 m (1H, 3a-H), 2.85 m (1H, 2-H), 3.10 m (1H, 2-H), 3.28 m and 3.43 m (2H, 3′-H), 5.98 br.s (1H, NH), 11.8 br.s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 18.09 q (CH_3), 25.48 t ($C^{4'}$), 24.85 t (C^3), 25.54 t (C^5), 29.46 t ($C^{5'}$), 31.85 t (C^6), 39.25 d (C^{3a}), 40.48 t ($C^{3'}$), 45.32 d (C^4), 50.85 t (C^2), 133.97 s (C^{7a}), 141.46 s (C^7), 173.42 s (CONH), 177.25 s (COOH). Found, %: C 53.06; H 6.43; N 4.02; S 10.42. $C_{14}H_{21}NO_5S$. Calculated, %: C 53.32; H 6.71; N 4.44; S 10.17.

11-(7-Methyl-1,1-dioxido-2,3,3a,4,5,6-hexahydro-1-benzothiophen-4-ylcarbonylamino)undecanoic acid (XVIII). A solution of 1.26 g (4 mmol) of compound **VIII** and 0.84 g (4.2 mmol) of 11-aminoundecanoic acid in 8 ml of DMF was heated for 25 h at 110°C. The mixture was evaporated in a Petri dish, the residue was ground with ethyl acetate, and the precipitate, 0.83 g (50%) of compound **XVIII**, was filtered off. The filtrate was subjected to chromatography on silica gel to isolate an additional portion, 0.18 g, of **XVIII**. Overall yield 61%, mp 78–80°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 721, 1471, 1541 (C=C), 1094, 1122, 1296 (S=O), 1618, 3331, 3371 (NH), 1669, 1718 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.23 m (12H, CH_2), 1.48 m (2H, CH_2), 1.60 m (3H, 3-H, 5-H), 1.85 m (2H, CH_2), 1.92 d.d.d (1H, 4-H, J = 11.0, 8.8, 2.0 Hz), 2.05 d (3H, CH_3, J = 2.0 Hz), 2,20 m (2H, 6-H), 2.35 m (3H, 5-H, CH_2), 2.90 m (2H, 2-H, 3a-H), 3.10 m (1H, 2-H), 3.20 m (2H, CH_2), 5.90 br.s (1H, NH), 11.8 br.s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 18.15 q (CH_3), 24.50 t (CH_2), 25.55 t (C^3), 26.18 t (C^5), 26.60 t (CH_2), 28.76 t (CH_2), 29.91 t (CH_2), 28.92 t (CH_2), 29.02 t (CH_2), 29.12 t (CH_2), 29.36 t (CH_2), 31.93 t (C^6), 33.83 t (CH_2), 39.47 t (CH_2), 39.52 d (C^{3a}), 47.39 d (C^4), 50.90 t (C^2), 134.48 s (C^{7a}), 141.04 s (C^7), 172.91 s (CONH), 178.59 s (COOH). Mass spectrum, m/z (I_{rel}, %): 413 (4), 395 (39), 367 (43), 185 (63), 184 (100), 183 (62), 155 (33), 119 (32), 105 (43), 93 (31), 91 (32), 41 (36), 28 (36). Found: $[M]^+$ 413.22135. $C_{21}H_{35}NO_5S$. Calculated: M 413.22358.

***N*-[2-(2-Aminoethylamino)ethyl]-7-methyl-2,3,3a,4,5,6-hexahydro-1-benzothiophene-4-carboxamide 1,1-dioxide (XIX).** A solution of 1.26 g (4 mmol) of compound **VIII** and 0.46 g (4.5 mmol) of *N*-(2-aminoethyl)ethane-1,2-diamine in 50 ml of dioxane was heated for 35 h under reflux. The mixture was evaporated, the residue was ground in ethyl acetate, the undissolved material (0.13 g) was filtered off, and the residue was subjected to double chromato-

graphic purification on silica gel. Yield 0.48 g (38%), mp 112–115°C (from Et_2O). IR spectrum, ν, cm^{-1}: 725, 1530, 1618 (C=C), 1005, 1035 (C–O–C), 1115, 1120, 1291 (S=O), 1643, 3306, 3416, 3502 (NH), 1680 (C=O). ^1H NMR spectrum (CD_3OD), δ, ppm: 1.63 m (1H, 3-H), 1.77 m (2H, 3-H, 5-H), 2.09 d (3H, CH_3, J = 2.0 Hz), 2.22 d.d.d (1H, 4-H, J = 11.0, 8.8, 1.8 Hz), 2,28 m (2H, 5-H, 6-H), 2.35 m (2H, CH_2), 2.40 m (1H, 6-H), 2.52 m (2H, CH_2), 2.88 m (1H, 3a-H), 3.00 m (1H, 2-H), 3.10 m (2H, CH_2), 3.22 m (1H, 2-H), 3.42 m (2H, CH_2), 6.60 br.s, 7.90 br.s, and 8.68 br.s (4H, NH, NH_2). ^{13}C NMR spectrum, δ_C, ppm: 18.42 q (CH_3), 25.22 t (C^3), 27.17 t (C^5), 28.07 t (CH_2), 29.07 t (CH_2), 30.08 t (C^6), 32.65 t (CH_2), 40.26 t (CH_2), 41.15 d (C^{3a}), 46.18 d (C^4), 50.58 t (C^2), 134.87 s (C^{7a}), 142.72 s (C^7), 168.80 s (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 315 (4), 285 (52) $[M - CH_2NH_2]^+$, 256 (43), 185 (6), 176 (3), 119 (14), 105 (19), 98 (32), 73 (86), 44 (100). Found, %: C 53.68; H 7.69; N 8.12; S 10.48. $C_{14}H_{25}N_3O_3S$. Calculated, %: C 53.31; H 7.99; N 13.32; S 10.17.

7-Methyl-*N*′-phenyl-2,3,3a,4,5,6-hexahydro-1-benzothiophene-4-carbohydrazide 1,1-dioxide (XX). Phenylhydrazine, 0.32 ml, was added to a solution of 0.94 g (3 mmol) of compound **VIII** in 10 ml of DMF, and the mixture was heated for 30 h at 130°C. The mixture was evaporated in a Petri dish, and the residue was recrystallized from ethanol. Yield 0.65 g (68%), mp 201–204°C (from EtOH). ^1H NMR spectrum (CD_3OD), δ, ppm: 1.66 m (1H, 3-H), 1.89 m (1H, 5-H), 1.88 m (1H, 3-H), 2.10 d (3H, CH_3, J = 2.0 Hz), 2.20 d.d.d (1H, 4-H, $J_{3a,4}$ = 10.8, J = 10.2, 2 Hz), 2.40 m (3H, 5-H, 6-H), 2.50 m (1H, 5-H), 2.89 m (1H, 3a-H), 3.08 m (1H, 2-H), 3.22 m (1H, 2-H), 6.85 m (3H, Ph), 7.22 m (2H, Ph), 7.90 br.s (2H, NH). ^{13}C NMR spectrum, δ_C, ppm: 18.43 q (CH_3), 26.83 t (C^3), 27.40 t (C^5), 32.92 t (C^6), 40.77 d (C^{3a}), 46.31 d (C^4), 52.05 t (C^2), 113.98 d, 114.03 d ($C^{2'}$, $C^{6'}$), 121.03 s ($C^{4'}$), 130.10 d and 130.36 d ($C^{3'}$, $C^{5'}$), 135.99 s (C^{7a}), 142.38 s (C^7), 150.13 s ($C^{1'}$), 175.48 s (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 320 (12), 256 (2), 209 (83), 118 (46), 93 (100), 77 (53), 65 (66). Found: $[M]^+$ 320.11860. $C_{16}H_{20}BrN_2O_3S$. Calculated: M 320.11945.

***N*′-(4-Bromobenzoyl)-7-methyl-2,3,3a,4,5,6-hexahydro-1-benzothiophene-4-carbohydrazide 1,1-dioxide (XXI).** A solution of 0.94 g (3 mmol) of compound **VIII** and 0.69 g (3.2 mmol) of 4-bromobenzohydrazide in 15 ml of DMF was heated for 18 h at 130°C. The mixture was evaporated in a Petri dish, the residue was ground with ethyl acetate, and the precipitate was recrystallized from ethanol. Yield 1.23 g (66%), mp 181–184°C. ^1H NMR spectrum (CD_3OD–$CDCl_3$), δ, ppm: 1.75 m (1H, 3-H), 1.93 m (2H, 3-H, 5-H), 2.08 d (3H, CH_3, J = 2.2 Hz), 2.26 d.d.d (1H, 4-H, J = 10.6, 9.8, 2.1, Hz), 2.38 m (2H, 6-H), 2.60 m (1H, 5-H), 2.94 m (1H, 3a-H), 3.02 m (1H, 2-H), 3.20 m (1H, 2-H), 7.63 d and 7.76 d (4H, H_{arom}, J = 7.8 Hz), 7.90 br.s (2H, NH). ^{13}C NMR spectrum, δ_C, ppm: 18.22 q (CH_3), 25.91 t (C^3), 26.92 t (C^5), 32.41 t (C^6), 40.36 d (C^{3a}), 45.35 d (C^4), 51.60 t (C^2), 125.34 s ($C^{4'}$), 129.60 d ($C^{2'}$, $C^{6'}$), 131.34 s ($C^{1'}$), 132.26 d ($C^{3'}$, $C^{5'}$), 134.80 s (C^{7a}), 143.18 s (C^7), 166.78 s (C=O), 173.77 s (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 427 (2), 426 (4), 217 (29), 185 (100), 183 (94), 157 (26), 155 (25), 119 (20), 105 (35), 93 (12), 92 (18), 91 (32), 81 (30), 79 (15), 77 (24). Found: $[M]^+$ 426.02522. $C_{17}H_{19}BrN_2O_4S$. Calculated: M 426.02493.

***N*′-(7-Methyl-1,1-dioxido-2,3,3a,4,5,6-hexahydro-1-benzothiophene-4-ylcarbonyl)isonicotinohydrazide (XXII).** A solution of 0.94 g (3 mmol) of compound **VIII** and 0.44 g (3.2 mmol) of isonicotinic acid hydrazide in 15 ml of DMF was heated for 18 h at 130°C. The mixture was evaporated in a Petri dish, the residue was dissolved in ethyl acetate, the undissolved material (0.22 g) was filtered off, and the filtrate was dried by azeotrope distillation with benzene. The oily material was dissolved in diethyl ether, dry gaseous hydrogen chloride was passed through the solution, and the precipitate (0.98 g) was filtered off, dried under reduced pressure, and treated with a 3% solution of ammonia. The product was extracted into methylene chloride, the extract was evaporated, and the residue was recrystallized from ethyl acetate. Yield 0.54 g (52%), mp 132–135°C. ^1H NMR spectrum (CD_3OD), δ, ppm: 1.58–1.92 m (3H, 3-H, 5-H), 2.05 d (3H, CH_3, J = 2.0 Hz), 2.25 d.d.d (1H, 4-H, J = 10.5, 9.8, 2.1 Hz), 2.38 m (2H, 6-H), 2.53–2.64 m (1H, 5-H), 2.92 m (1H, 3a-H), 3.08 m (1H, 2-H), 3.22 m (1H, 2-H), 8.20 d (2H, 2′-H, 6′-H, J = 8.0 Hz), 8.88 d (2H, 3′-H, 5′-H, J = 8.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 16.43 q (CH_3), 24.93 t and 25.19 t (C^3, C^5), 31.01 t (C^6), 39.21 d (C^{3a}), 44.98 d (C^4), 50.38 t (C^2), 123.22 s and 123.67 d ($C^{2'}$, $C^{6'}$), 133.97 s (C^{7a}), 141.05 s ($C^{1'}$), 143.98 s (C^7), 144.79 d and 145.89 d ($C^{3'}$, $C^{5'}$), 163.54 s (C=O), 173.38 s (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 349 (1), 257 (2), 242 (4), 184 (19), 138 (31), 119 (29), 106 (98), 91 (40), 78 (100). Found: $[M]^+$ 349.10895. $C_{16}H_{19}N_3O_4S$. Calculated: M 349.10962.

(3a*S*,5*R*)-4-Carbamoyl-7-methyl-5-phenyl-2,3,3a,4,5,6-hexahydro-1-benzothiophene-4-carboxylic acid 1,1-dioxide (XXIV). Compound **XXIII**,

0.78 g (2 mmol), was dissolved in 15 ml of dioxane, 15 ml of concentrated aqueous ammonia was added dropwise over a period of 10 min, and the mixture was stirred for 15 h at room temperature and evaporated under reduced pressure. The residue was diluted with 5 ml of water and treated with 6 N hydrochloric acid to pH ~2. The precipitate was filtered off and washed with chloroform. Yield 0.26 g (37%), mp 253–256°C (from DMSO). IR spectrum, ν, cm^{-1}: 708, 742, 1496, 1602 (C=C), 1029, 1054 (C–O), 1118, 1128, 1277, 1298 (S=O), 1650, 3253, 3370, 3507 (NH, OH), 1703, 1734 (C=O). ^{1}H NMR spectrum (CD_3OD), δ, ppm: 2.08 m (1H, 3-H), 2.11 d (3H, CH_3, J = 2.0 Hz), 2.47 m (2H, 3-H, 6-H), 2.66 m (1H, 6-H), 2.95 m (1H, 2-H), 3.08 m (1H, 3a-H), 3.28 m (1H, 2-H), 3.73 d (1H, 5-H, J = 6.7 Hz), 6.09 br.s and 7.80 br.s (3H, OH, NH_2), 7.14 m (2H, Ph), 7.38 m (3H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 17.82 q (CH_3), 21.92 t (C^3), 35.45 d (C^{3a}), 37.40 t (C^6), 46.02 d (C^5), 50.68 t (C^2), 58.81 s (C^4), 127.81 d ($C^{2'}$, $C^{6'}$), 127.97 d ($C^{4'}$), 128.59 d ($C^{3'}$, $C^{5'}$), 132.17 s (C^{7a}), 137.48 s ($C^{1'}$), 140.28 s (C^7), 169.92 s (C=O), 173.61 s (C=O). Found, %: C 58.09; H 5.59; N 4.29; S 9.56. $C_{17}H_{19}NO_5S$. Calculated, %: C 58.44; H 5.48; N 4.01; S 9.18.

The mother liquor was evaporated, and the residue (0.65 g) was treated with diazomethane (by stirring with excess diazomethane in diethyl ether for 12 h at 20°C). The solution was evaporated, and the residue was subjected to chromatography on silica gel to isolate (in order of elution) 0.31 g (42%) of compound **XXV** and 0.12 g (16%) of diester **XXVI**.

Methyl (3a*S*,5*R*)-4-carbamoyl-7-methyl-5-phenyl-2,3,3a,4,5,6-hexahydro-1-benzothiophene-4-carboxylate 1,1-dioxide (XXV). mp 203–205°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 708, 726, 1495, 1613 (C=C), 1030, 1050, 1080 (C–O–C), 1119, 1280, 1300 (S=O), 1650, 3280, 3342, 3466 (NH), 1689, 1742 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.11 m (1H, 3-H), 2.14 d (3H, CH_3, J = 2.0 Hz), 2.40–2.47 m (2H, 3-H, 6-H), 2.98 m (1H, 6-H), 2.92 m (1H, 2-H), 3.08 m (1H, 3a-H), 3.22 m (1H, 2-H), 3.73 d (1H, 5-H, J = 6.6 Hz), 3.81 s (3H, OCH_3), 5.59 br.s (1H, NH), 6.88 br.s (1H, NH), 7.16 m (2H, Ph), 7.33 m (3H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 17.74 q (CH_3), 21.97 t (C^3), 35.45 d (C^{3a}), 37.40 t (C^6), 47.11 d (C^5), 50.62 t (C^2), 53.24 q (OCH_3), 61.08 s (C^4), 127.81 d ($C^{2'}$, $C^{6'}$), 127.97 d ($C^{4'}$), 128.59 d ($C^{3'}$, $C^{5'}$), 133.87 s (C^{7a}), 138.64 s ($C^{1'}$), 139.36 s (C^7), 168.29 s (C=O), 172.54 s (C=O). Found, %: C 59.92; H 5.91; N 4.02; S 9.18. $C_{18}H_{21}NO_5S$. Calculated, %: C 59.49; H 5.82; N 3.85; S 8.82.

Dimethyl (3a*S*,5*R*)-7-methyl-5-phenyl-2,3,3a,4,5,6-hexahydro-1-benzothiophene-4,4-dicarboxylate 1,1-dioxide (XXVI). mp 161–163°C (from EtOH). IR spectrum, ν, cm^{-1}: 742, 1496, 1602 (C=C), 1029, 1054 (C–O–C), 1118, 1128, 1277, 1298 (S=O), 1650, 3253, 3370, 3507 (NH), 1703, 1734 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.12 m (1H, 3-H), 2.16 d (3H, CH_3, J = 2.0 Hz), 2.46 d.d (1H, 6-H, J = 16.2, 2.2 Hz), 2.50 m (1H, 3-H), 2.99 m (1H, 2-H), 3.11 m (1H, 2-H), 3.23 m (1H, 3a-H), 3.40 m (1H, 6-H), 3.61 s (3H, OCH_3), 3.77 s (3H, OCH_3), 3.79 d (1H, 5-H, J = 6.5 Hz), 7.02 m (2H, Ph), 7.35 m (3H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 18.14 q (CH_3), 23.31 t (C^3), 36.52 d (C^{3a}), 38.07 t (C^6), 43.42 d (C^5), 50.78 t (C^2), 52.40 q and 52.76 q (OCH_3), 59.94 s (C^4), 127.91 d ($C^{2'}$, $C^{6'}$), 127.93 d ($C^{4'}$), 128.85 d ($C^{3'}$, $C^{5'}$), 131.89 s (C^{7a}), 140.85 s ($C^{1'}$), 142.11 s (C^7), 168.95 s (C=O), 168.98 s (C=O). Mass spectrum, m/z (I_{rel}, %): 378 (55), 318 (97), 314 (54), 287 (48), 271 (30), 254 (24), 239 (23), 221 (30), 207 (27), 195 (100). Found, %: C 60.41; H 6.15; S 9.01. $[M]^+$ 378.11264. $C_{19}H_{22}O_6S$. Calculated, %: C 60.30; H 5.86; S 8.47. M 378.11370.

X-Ray analysis of compound XXIV. A 0.60×0.54×0.16-mm colorless pyramidal single crystal of **XXIV**–DMSO solvate was selected. Monoclinic crystal system; unit cell parameters: a = 10.600(1), b = 14.638(2), c = 16.634(2) Å; β = 103.37(1)°; V = 2511.0(5) $Å^3$; space group $P2_1/c$; Z = 4; $C_{17}H_{19}NO_5S\cdot 2C_2H_6OS$; d_{calc} = 1.332 g/cm^3; μ = 0.335 mm^{-1}. Intensities of 4935 independent reflections were measured. No correction for absorption was introduced. The structure was solved by the direct method using SHELXS-97 software package [18]. The structure was refined by the least-squares procedure in full-matrix anisotropic–isotropic (for hydrogen atom in the hydroxy group) approximation using SHELXL-97 software [18]. The OH hydrogen atom was localized by difference synthesis of electron density. Parameters of the other hydrogen atoms were calculated in each iteration cycle from coordinates of the corresponding carbon atoms (riding model). The final refinement with respect to all F^2 was performed until wR_2 = 0.1572, S = 1.03; 331 parameters were refined (R = 0.0539 for 3532 reflections with $F > 4\sigma$). Independent part of a unit cell contains two DMSO molecules, one of which is disordered by two positions (oxygen and sulfur atoms; S^1R^2, O^1R^2 and S^2R^2, O^2R^2) at a ratio of ~0.60:0.40. The complete set of crystallographic data for **XXIV** was deposited to the Cambridge Crystallographic Data Centre (entry no. CCDC 705004; *http://www.ccdc.cam.ac.uk/data_request/cif deposit*).

This study was performed under financial support by the Russian Foundation for Basic Research (project nos. 09-03-00183, 08-03-00340).

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