# SUBSTITUTED 1-(2-THIENYL)CYCLOHEXYLAMINES AND RELATED COMPOUNDS AS POTENTIAL NMDA ANTAGONISTS

Karel SINDELAR, Karel DOBROVSKY, Ivan KREJCI and Zdenek POLIVKA

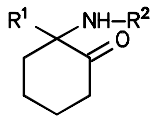
*Research Institute for Pharmacy and Biochemistry,*
*130 60 Prague 3, The Czech Republic*

Received January 18, 1995
Accepted February 16, 1995

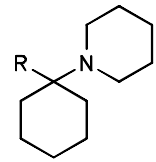
Reactions of bisulfite addition compounds prepared in situ from cyclohexanone or 3,4,5,6-tetrahydro-2*H*-thiopyran-3-one with potassium cyanide and corresponding amines resulted with high yields in amino nitriles type of *V* and *VI*. These compounds were subjected to reactions with 2-thienylmagnesium bromide and in the case of the amino nitriles *Vc* and *Vf* with 5-bromo-2-thienylmagnesium bromide. Only in the case of compound *Vf*, a by-product *X* was isolated in addition to the desired 1-[1-(5-bromo-2-thienyl)-1-cyclohexyl]piperidine (*VIIf*). Compound *VIIf* was used for the synthesis of the carboxylic acid *XI*. The compounds prepared were tested by some methods of biochemical and behavioural pharmacology.

Searching for excitatory amino acid antagonists belongs presently to the first line of our endeavour. For noncompetitive antagonists of the NMDA-receptor complex, anticonvulsant and antipsychotic effects and further favourable influence on learning and memory processes are to be expected. Some compounds with this mechanism of action were synthesized in the 50th already.

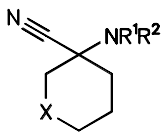
Tiletamine (*I*, Telazol) is a structural analog of ketamine (*II*) and phencyclidine (*III*, PCP). The last named compound was originally synthesized in 1957 by Parke Davis Pharmaceutical Company and was supposed to be a dissociate anesthetic[1]. In clinical trials however, PCP was really found to be a valuable anesthetic, but its action was accompanied by producing post-anesthetic hallucinations[2,3] which was the reason of discontinuation of its administration to humans. Later, PCP was approved for use as a veterinary anesthetic; the mentioned tiletamine (*I*) is being used in the same indication. For humans, PCP is the drug of abuse ("angel dust"). In central nervous system, PCP interacts with various receptors including the σ- and μ-opioid, muscarinic and serotonergic[4–6], but it predominantly binds with high affinity to its own PCP binding site, which has been shown to be associated with the ion channel linked to the NMDA subtype of excitatory amino acid receptor[7–9]. There, PCP and its analog including tiletamine (*I*) and tenocyclidine[10,11] (*IV*, TCP) act as noncompetitive NMDA antagonists, so called "open-channel blockers".



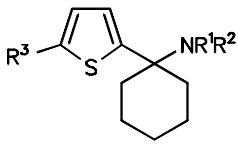
*I*, $R^1$ = 2-thienyl; $R^2$ = $C_2H_5$
*II*, $R^1$ = 3-$ClC_6H_4$; $R^2$ = $CH_3$



*III*, R = $C_6H_5$
*IV*, R = 2 thienyl

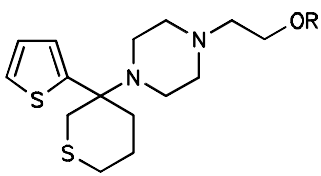


*V*, X = $CH_2$
*VIa*, X = S; $R^1R^2$ = $(CH_2)_5$
*VIb*, X = S; $R^1R^2$ = $CH_2CH_2N(CH_2CH_2OH)CH_2CH_2$

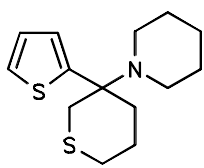


*VII*
In formula *VII*:
*a*, *c*, *d*, *e*, $R^3$ = H;
*b*, *f*, $R^3$ = Br

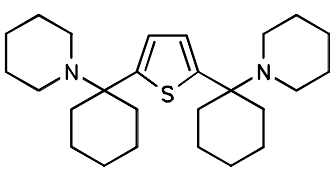
In formulae *V* and *VII*:
*a*, $R^1$ = H; $R^2$ = $CH_2CH_2N(C_2H_5)_2$; *b*, $R^1$ = $CH_3$; $R^2$ = $CH_2C_6H_5$
*c*, $R^1$ = $CH_3$; $R^2$ = $CH_2CH_2C_6H_5$; *d*, $R^1$ = $CH_3$; $R^2$ = $CH_2CH_2CH_2C_6H_5$
*e*, $R^1$ = $CH_3$; $R^2$ = $CH_2CH_2$-3,4-$(CH_3O)C_6H_3$; *f*, $R^1R^2$ = $(CH_2)_5$



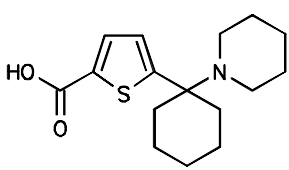
*VIIIa*, R = H
*VIIIb*, R = $COCH_3$
*VIIIc*, R = $CH_2C_6H_5$



*IX*



*X*



*XI*

A number of new compounds, whose structures were derived from those of *I – III*, has recently been prepared. The aim of such investigations is the research for similar substances with antagonistic effect on the NMDA receptor in which the undesired hallucinogenic effect would be suppressed.

Our synthesis of compounds of type *VII* and *VIII* started from the corresponding bisulfite addition compounds prepared in situ from cyclohexanone or 3,4,5,6-tetrahydro-2*H*-thiopyran-3-one. Their reactions with potassium cyanide and the corresponding amine resulted with high yields in the amino nitriles *V* and *VI*. These compounds were subjected to reactions with 2-thienylmagnesium bromide and in the case of the amino nitriles *Vb* and *Vf* with 5-bromo-2-thienylmagnesium bromide. Only in the case of compound *Vf*, a by-product was isolated in addition to the desired 1-[1-(5-bromo-2-thienyl)-1-cyclohexyl]piperidine (*VIIf*). This by-product *X* resulted from reaction of the amino nitrile *Vf* with 2,5-bis(bromomagnesium)thiophene which was formed as a by-product of the preparation of the Grignard reagent mentioned. Compound *VIIf* was used for the synthesis of the carboxylic acid *XI* (preparation of the organometallic reagent by means of butyllithium and reaction with solid carbon dioxide).

The compounds prepared were tested by some methods of biochemical and behavioural pharmacology. Inhibition of binding of 1 nM [$^3$H]MK-801 in rat brain cortex membranes, $IC_{50}$ (μM): *VIIa*, 6.2; *VIIb*, 26; *VIIc*, 5.3; *VIId*, 4.1; *VIIe*, 40.7; *VIIf*, 1.1; *IX*, 0.23; *X*, 100. Compounds *VIIb*, *VIIc*, *VIId* and *VIIf* in concentrations 1 000 nM inhibied the binding of 10 nM [$^3$H] kainate in membranes, isolated from rat brains (subpopulation of the glutamate receptors), to 50% of the original values (this finding is being further studied). Inhibition of binding of 1 nM [$^3$H] glycine to compound in a concentration of 1 000 nM, % of inhibition of the original binding: *VIIb*, 44; *VIIc*, 55; *VIIe*, 89; *VIIf*, 87; *X*, 76. Anticonvulsant effect in the electroshock test in female mice, i.p. dose of 20 mg/kg, number of protected mice in groups by 6 animals: *VIIb*, 5/6; *VIIc*, 5/6; *VIId*, 3/6; *VIIe*, 3/6; *VIIIa*, and *X*, indication of effect. Protection from acute anoxia brought about by potassium cyanide in mice, the i.p. doses of 20 mg/kg used, survival in sec (in the control group survival of 30 – 36 s): *VIIb*, 60; *VIIc*, 61; *VIId*, 48; *VIIe*, 48. More detailed results of the pharmacological testing will be published elsewhere.

## EXPERIMENTAL

The melting points of analytical samples were determined with the Mettler FP-5 melting point recorder and they are not corrected; the samples were dried in vacuo of about 40 Pa at a room temperature or at a suitably elevated temperature. IR spectra were recorded with the Unicam SP 2000 or Perkin–Elmer 298 spectrophotometers, NMR spectra on a Tesla BS 567A ($^1$H at 100 MHz, $^{13}$C at 25.14 MHz) in $CD_3SOCD_3$ unless stated otherwise, chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz; mass spectra (*m*/*z*, %) were measured on a Varian-MAT 44S (GC-MS) spectrometer. The homogeneity of the products and composition of the mixtures were checked by thin-layer chromatography (TLC) on silica gel (Silufol $UV_{254}$). Preparative chromatographic separ-

ations were carried out on columns of silica gel (Fluka 60). The extracts were dried with $K_2CO_3$ and evaporated under reduced pressure on a rotary evaporator.

[2-(3,4-Dimethoxyphenyl)ethyl]methylamine

*N*-[2-(3,4-Dimethoxyphenyl)ethyl]formamide[12] (35.5 g, 0.17 mol) was dissolved in tetrahydrofuran (340 ml), the solution was treated with $NaBH_4$ (14.1 g, 0.37 mol) and at 20 – 27 °C under stirring dropwise with $BF_3$ etherate (50.7 g, 0.36 mol). The mixture was stirred for 1 h at room temperature and then refluxed for 3 h. After cooling it was made alkaline with 20% NaOH (300 ml), the aqueous layer was separated and extracted with benzene (300 ml). The organic layers were combined, the solvents were evaporated and the residue was distilled in vacuo; 29.7 g (90%), b.p. 115 – 117 °C/50 Pa. The literature[13] gave b.p. 159 °C/1.48 kPa.

The hydrochloride was obtained by neutralization of the base with the solution of HCl in ether, m.p. 134 – 136 °C (ethanol–acetone). $^1$H NMR spectrum: 2.56 s, 3 H ($CH_3N$); 3.00 m, 4 H ($CH_2CH_2$); 3.74 s and 3.76 s, 2 × 3 H (2 × $OCH_3$); 6.77 dd, 1 H, $J$(2′,6′) = 2.5, $J$ (5′,6′) = 9 (H-6′); 6.88 d, 1 H, $J$(2′,6′) = 2.5 (H-2′); 6.96 d, 1 H, $J$(5′,6′) = 9 (H-5′). $^{13}$C NMR spectrum: 30.92 t (Ar-**C**$H_2$); 32.19 q (N–$CH_3$); 49.22 t ($CH_2$N); 2 × 55.50 q (2 × $OCH_3$); 112.04 d (C-5′); 112.58 d (C-2′); 120.56 d (C-6′); 129.60 s (C-1′); 147.67 s (C-4′); 148.87 s (C-3′). For $C_{11}H_{18}ClNO_2$ + 0.5 $H_2O$ (240.7) calculated: 54.88% C, 7.96% H, 14.73% Cl, 5.82% N; found: 55.10% C, 7.99% H, 14.83% Cl, 5.29% N.

General Procedure for Preparation of Aminonitriles *Va – Vf*, *VIa* and *VIb*

A solution of $Na_2S_2O_5$ (10.4 g, 0.1 mol) in water (40 ml) was added to cyclohexanone (11.6 g, 0.1 mol) or 3,4,5,6-tetrahydro-2*H*-thiopyran-3-one[14] (11.6 g, 0.1 mol) and the mixture was stirred for 2 h. It was then treated over 5 min with a solution of KCN (6.6 g, 0.1 mol) in water (15 ml) and with the corresponding amine (0.11 mol) at 20 – 30 °C. After 4 h of stirring, the mixture was extracted with ether, the extract was processed, and the residue was either distilled in vacuo or crystallized.

*N′-(1-Cyano-1-cyclohexyl)-N,N-diethylethylenediamine* (Va): Reaction of cyclohexanone with *N,N*-diethylethylenediamine (12.7 g, 0.11 mol) gave 20.5 g (92%) of *Va*, b.p. 130 °C/0.5 kPa. Literature[15] gave the b.p. of 120 °C/0.5 kPa. Dihydrochloride hemihydrate was obtained by neutralization of the base with HCl in ether and crystallization from ethanol–acetone, m.p. 110 – 113 °C. For $C_{13}H_{27}Cl_2N_3$ + 0.5 $H_2O$ (305.3) calculated: 51.14% C, 9.24% H, 23.23% Cl, 13.76% N; found: 51.17% C, 8.91% H, 23.48% Cl, 14.07% N.

*N-(1-Cyano-1-cyclohexyl)-N-benzylmethylamine* (Vb): Reaction of cyclohexanone with *N*-benzylmethylamine (13.3 g, 0.11 mol) afforded 16.0 g (70%) of *Vb*, b.p. 156 – 158 °C/30 Pa (in agreement with ref.[16]).

*N-(1-Cyano-1-cyclohexyl)-N-(2-phenylethyl)methylamine* (Vc): Reaction of cyclohexanone with *N*-(2-phenylethyl)methylamine (14.9 g, 0.11 mol) resulted in 19.9 g (82%) of *Vc*, b.p. 168 – 172 °C/0.2 kPa. For $C_{16}H_{22}N_2$ (242.4) calculated: 79.29% C, 9.15% H, 11.56% N; found: 79.03% C, 9.05% H, 11.75% N.

*N-(1-Cyano-1-cyclohexyl)-N-(3-phenylpropyl)methylamine* (Vd): Cyclohexanone and *N*-(3-phenylpropyl)methylamine (16.4 g, 0.11 mol) gave by similar procedure 21.6 g (84%) of *Vd*, b.p. 175 – 178 °C/0.2 kPa. For $C_{17}H_{24}N_2$ (256.4) calculated: 79.64% C, 9.44% H, 10.93% N; found: 79.49% C, 9.67% H, 10.87% N.

*N-(1-Cyano-1-cyclohexyl)-N-[2-(3,4-dimethoxyphenyl)ethyl]methylamine* (Ve): Reaction of cyclohexanone with [2-(3,4-dimethoxyphenyl)ethyl]methylamine (21.5 g, 0.11 mol) afforded 24.2 g (80%) of *Ve*, m.p. 66 – 68 °C (cyclohexane). IR spectrum (Nujol): 810, 816, 880 (Ar-H); 1 140, 1 153, 1 227, 1 255 (ArOR); 1 511, 1 590, 1 604, 3 010 (Ar); 2 210 (CN); 2 785 (N–$CH_3$). $^1$H NMR spectrum ($CDCl_3$): 1.30 – 2.20 m, 10 H (5 × $CH_2$ of cyclohexyl); 2.40 s, 3 H ($NCH_3$); 2.75 m, 4 H

($ArCH_2CH_2N$); 3.84 s and 3.85 s, 2 × 3 H (2 × $OCH_3$); 6.75 m, 3 H (Ar-H). $^{13}C$ NMR spectrum ($CDCl_3$): 2 × 22.18 t (C-3, C-5); 24.80 t (C-4); 34.43 t ($ArCH_2$); 2 × 34.66 t (C-2, C-6); 36.15 q (N–$CH_3$); 53.71 t ($CH_2N$); 2 × 55.80 q (2 × $OCH_3$); 61.62 s (C-1); 111.30 d (ArC-6); 112.19 d (ArC-2); 119.96 s (CN); 120.63 d (ArC-5); 132.66 s (ArC-1); 147.45 s (ArC-4); 148.79 s (ArC-3).

*3-Cyano-3-(1-piperidinyl)-3,4,5,6-tetrahydro-2H-thiopyran* (VIa): Reaction of 3,4,5,6-tetrahydro-2*H*-thiopyran-3-one with piperidine (9.4 g, 0.11 mol) afforded 19.3 g (92%) of *VIa*, m.p. 97 – 99 °C (benzene–light petroleum). $^{13}C$ NMR spectrum ($CDCl_3$): 24.05 t (C-5); 24.65 t (C-4′); 2 × 26.14 t (C-3′ and C-5′); 27.71 t (C-6); 33.99 t (C-4); 34.88 t (C-2); 2 × 47.51 t (C-2′ and C-6′); 61.25 s (C-3); 118.09 s (CN). For $C_{11}H_{18}N_2S$ (210.3) calculated: 62.81% C, 8.63% H, 13.32% N, 15.24% S; found: 62.78% C, 8.57% H, 13.54% N, 15.26% S.

*3-Cyano-3-[4-(2-hydroxyethyl)-1-piperazinyl]-3,4,5,6-tetrahydro-2H-thiopyran* (VIb): Similar reaction of 3,4,5,6-tetrahydro-2*H*-thiopyran-3-one with 1-(2-hydroxyethyl)piperazine (14.3 g, 0.11 mol) gave 23.2 g (91%) of oily *VIb*. Neutralization of the base with a solution of maleic acid in acetone gave hydrogen maleate, m.p. 118 – 123 °C (acetone). $^{13}C$ NMR spectrum: 24.55 t (C-5); 26.44 t (C-6); 32.64 t (C-4); 33.24 t (C-2); 2 × 43.40 t (C-2′ and C-6′); 2 × 51.47 t (C-3′ and C-5′); 55.05 t (N–$CH_2$); 57.37 s (C-3); 60.35 t ($CH_2OH$); 117.65 s (CN); 2 × 135.72 d (CH=CH of maleate); 2 × 167.24 s (COOH). For $C_{16}H_{25}N_3O_5S$ (371.5) calculated: 51.73% C, 6.78% H, 11.31% N, 8.63% S; found: 51.61% C, 6.72% H, 11.01% N, 8.30% S.

General Procedure for Preparation of Cyclohexanes *VIIa – VIIf* and Thiopyranes *VIIIa* and *IX*

Grignard reagent was prepared either from 2-bromothiophene (13.0 g, 0.08 mol) or 2,5-dibromothiophene (19.4 g, 0.08 mol) and Mg (2.0 g, 0.08 mol) in ether (60 ml). After 1 h of refluxing, the solution of the reagent was treated dropwise under stirring with solution of aminonitriles *Va – Vf*, *VIa*, and *VIb* in ether (40 ml). The mixture was refluxed for further 5 h, decomposed with 20% solution of $NH_4Cl$ (70 ml), the aqueous layer was separated and extracted with ether (100 ml). The ethereal solutions where combined and the bases were extracted into 10% hydrochloric acid (150 ml). The acid aqueous layers were made alkaline with 20% NaOH and the bases were extracted with ether (200 ml). After processing of the extract, the residue was either dissolved in benzene and the solution filtered through a layer of $Al_2O_3$ (50 g), or was crystallized from a mixture of benzene and light petroleum. Bases obtained were transformed by neutralization with suitable acids to the corresponding salts.

*N′-[1-(2-Thienyl)-1-cyclohexyl]-N,N-diethylethylenediamine* (VIIa): Grignard reagent, prepared from 2-bromothiophene, reacted with the amino nitrile *Va* (6.7 g, 0.03 mol) and gave 4.5 g (53%) of oily *VIIe* which was transformed to the dihydrochloride monohydrate, m.p. 175 – 178 °C (ethanol–ether). $^1H$ NMR spectrum: 1.22 t, 6 H ($CH_3$); 7.15 dd, 1 H, $J$(4,5) = 5.0, $J$(3,4) = 3.0 (H-4 of thienyl); 7.50 d, 1 H, $J$(3,4) = 3.0 (H-3 of thienyl); 7.70 d, 1 H, $J$(4,5) = 5.0 (H-5 of thienyl). For $C_{16}H_{32}Cl_2N_2OS$ (371.4) calculated: 51.74% C, 8.69% H, 19.09% Cl, 7.54 % N, 8.63% S; found: 51.92% C, 8.20% H, 19.48% Cl, 7.51% N, 8.77% S.

*N-[1-(5-Bromo-2-thienyl)-1-cyclohexyl]-N-benzylmethylamine* (VIIb): Grignard reagent, prepared from 2,5-dibromothiophene was treated with the amino nitrile *Vb* (13.7 g, 0.06 mol) and gave 12.25 g (56%) of *VIIb*. $^{13}C$ NMR spectrum ($CDCl_3$): 2 × 22.26 t (C-3 and C-5); 25.99 t (C-4); 33.76 q ($CH_3$); 2 × 36.00 t (C-2 and C-6); 54.45 t ($NCH_2$); 60.73 s (C-1); 109.73 s (C-5 of thienyl); 124.52 d (C-3 of thienyl); 126.53 d (C-4 of benzyl); 2 × 128.18 d (C-2 and C-6 of benzyl); 2 × 128.33 d (C-3 and C-5 of benzyl); 129.00 d (C-4 of thienyl); 140.95 s (C-1 of benzyl); 148.94 s (C-2 of thienyl).

Neutralization with oxalic acid afforded the hydrogen oxalate, m.p. 188 – 189 °C (aqueous ethanol). $^1H$ NMR spectrum: 1.20 – 2.20 m, 10 H (5 × $CH_2$ of cyclohexyl); 2.08 s, 3 H (N–$CH_3$); 3.50 s, 2 H (N–$CH_2$); 7.00 d, 1 H, $J$(3,4) = 5.0, (H-3 of thienyl); 7.21 d, 1 H $J$(3,4 = 5.0 (H-4 of thienyl); 7.32 s,

5 H ($\mathbf{C_6H_5}CH_2$). Mass spectrum, *m*/*z* (%): 363 (9), 320 (5), 272 (4), 243 (60), 175 (46), 120 (22), 97 (19), 91 (100), 81 (32), 45 (42). For $C_{20}H_{24}BrNO_4S$ (454.4) calculated: 52.86% C, 5.32% H, 17.59% Br, 3.08% N, 7.06% S; found: 52.71% C, 5.50% H, 17.38% Br, 3.14% N, 6.95% S.

*N-[1-(2-Thienyl)-1-cyclohexyl]-N-(2-phenylethyl)methylamine* (VIIc): Reaction of the Grignard reagent, prepared from 2-bromothiophene, with amino nitrile *Vc* (14.55 g, 0.06 mol) afforded 13.7 g (76%) of oily *VIIc* which was neutralized with maleic acid and gave the hydrogen maleate monohydrate, m.p. 117 – 119 °C (ethanol–ether). $^{13}$C NMR spectrum: 2 × 22.48 t (C-3 and C-5); 24.20 t (C-4); 31.37 t ($\mathbf{C}H_2$ of benzyl); 2 × 33.09 t (C-2 and C-6); 34.14 q ($CH_3$); 51.39 t ($NCH_2$); 68.05 s (C-1); 126.76 d (C-3 of thienyl); 127.80 d (C-4 of phenethyl); 2 × 128.55 d (C-2 and C-6 of phenethyl); 2 × 128.85 t (C-3 and C-5 of phenethyl); 130.34 d (C-4 of thienyl); 2 × 135.35 d (CH=CH of maleate); 2 × 137.37 s (C-2 of thienyl and C-1 of phenethyl); 2 × 167.24 s (2 × C=O of maleate). For $C_{23}H_{31}NO_5S$ (433.6) calculated: 63.72% C, 7.21% H, 3.23% N, 7.40% S; found: 63.92% C, 6.91% H, 3.45% N, 7.62% S.

*N-[1-(2-Thienyl)-1-cyclohexyl]-N-(3-phenylpropyl)methylamine* (VIId): Reaction of the Grignard reagent, prepared from 2-bromothiophene, was reacted with the amino nitrile *Vd* (15.4 g, 0.06 mol) and gave 15.4 g (82%) of oily *VIId* which was transformed to the hydrogen oxalate, m.p. 127 – 129 °C (acetone–ethanol–ether). $^{13}$C NMR spectrum: 2 × 22.48 t (C-3 and C-5); 24.20 t (C-4); 27.04 t (C–$\mathbf{C}H_2$–C of 3-phenylpropyl); 32.42 t (Ph-$\mathbf{C}H_2$); 2 × 33.24 t (C-2 and C-6); 33.76 q (N–$CH_3$); 49.60 t (N–$CH_2$); 66.78 s (C-1); 125.94 d (C-3 of thienyl); 127.58 d (C-4 of phenyl); 128.07 d (C-5 of thienyl); 4 × 128.33 d (C-2, C-3, C-5 and C-6 of phenyl); 129.60 d (C-4 of thienyl); 138.04 s (C-1 of phenyl); 141.03 s (C-2 of thienyl); 2 × 164.41 s (2 × COOH of oxalate). Mass spectrum, *m*/*z* (%): 313 ($M^+$, $C_{20}H_{27}NS$, 0.4), 270 (0.5), 242 (0.7), 165 (8), 97 (13), 44 (100). For $C_{22}H_{29}NO_4S$ (403.5) calculated: 65.48% C, 7.24% H, 3.47% N, 7.95% S; found: 65.29% C, 7.32% H, 3.77% N, 8.25% S.

*N-[1-(2-Thienyl)-1-cyclohexyl]-N-[2-(3,4-dimethoxyphenyl)ethyl]methylamine* (VIIe): Reaction of 2-thienylmagnesium bromide with the amino nitrile *Ve* (18.15 g, 0.06 mol) gave 13.0 g (60%) of *VIIe*, m.p. 90 – 91 °C (benzene–light petroleum). IR spectrum (Nujol): 713, 801, 817 854 (Ar-H); 1 028, 1 145, 1 231, 1 266 (ArOR); 1 515, 1 591, 1 606, 3 005, 3 065, 3 093 (Ar); 2 798, 2 815 ($CH_3$). $^{13}$C NMR spectrum ($CDCl_3$): 2 × 22.33 t (C-3 and C-5); 25.99 t (C-4); 34.28 q (N–$CH_3$); 35.78 t (Ar-$\mathbf{C}H_2$); 2 × 36.45 t (C-2 and C-6); 52.66 t (N–$CH_2$); 2 × 55.87 q ($OCH_3$); 60.58 s (C-1); 111.30 d (C-5 of $C_6H_3$), 112.48 d (C-2 of $C_6H_3$); 120.78 d (C-6 of $C_6H_3$); 122.95 d (C-5 of thienyl); 124.14 d (C-3 of thienyl); 126.01 d (C-4 of thienyl); 133.78 s (C-1 of $C_6H_3$); 147.08 s and 147.30 s (C-3 and C-4 of $C_6H_3$); 148.79 s (C-2 of thienyl). For $C_{21}H_{29}NO_2S$ (359.5) calculated: 70.15% C, 8.13% H, 3.90% N, 8.92% S; found: 70.27% C, 8.24% H, 4.08% N, 8.94% S.

Hydrogen oxalate, m.p. 136 – 137 °C (ethanol–ether). Mass spectrum, *m*/*z* (%): 359 ($M^+$, $C_{21}H_{29}NO_2S$, 0.2), 278 (0.3), 208 (18), 165 (100), 97 (66), 44 (48). $^1$H NMR spectrum: 1.00 – 2.20 m, 10 H (5 × $CH_2$ of cyclohexyl); 2.68 s, 3 H (N–$CH_3$); 3.72 s and 3.74 s, 2 × 3 H (2 × $OCH_3$); 3.80 bs, 4 H (Ar–$CH_2CH_2$N); 6.70 – 7.40 m, 5 H ($C_6H_3$, H-3 and H-4 of thienyl); 7.68 d, 1 H, $J$(4,5) = 5.0 (H-5 of thienyl). For $C_{23}H_{31}NO_6S$ (449.6) calculated: 61.45% C, 6.95% H, 3.12% N, 7.13% S; found: 61.09% C, 6.83% H, 2.84% N, 6.96% S.

*1-[1-(5-Bromo-2-thienyl)-1-cyclohexyl]piperidine* (VIIf). Reaction of the Grignard reagent, prepared from 2,5-dibromothiophene, with 1-(1-piperidinyl)cyclohexane-1-carbonitrile[17] (*Vf*, 19.4 g, 0.06 mol) afforded a mixture of bases (12.4 g) whose crystallization from cyclohexane gave first the by-product, identified as 2,5-bis[1-(1-piperidinyl)-1-cyclohexyl]thiophene (*X*) (0.75 g, 6%). IR spectrum (Nujol): 791 (ArH); 1 588, 3 068, 3 085 (Ar); 2 665, 2 735, 2 780, 2 795 ($NCH_2$). $^1$H NMR spectrum ($CDCl_3$): 1.10 – 2.20 m, 32 H (10 × $CH_2$ of cyclohexyl and 4 × H-3, 4 × H-4, 4 × H-5 of piperidyl); 2.34 bm, 8 H (4 × H-2, 4 × H-6 of piperidyl); 6.66 s, 2 H (H-3 and H-4 of thienyl). $^{13}$C NMR spectrum ($CDCl_3$): 4 × 22.41 t (2 × C-3, 2 × C-5 of cyclohexyl); 2 × 25.26 t (2 × C-4 of piperidyl); 2 × 26.37 t (2 × C-4 of cyclohexyl); 4 × 27.34 t (2 × C-3, 2 × C-5 of piperidyl); 4 × 36.08 t, (2 × C-2, 2 × C-6

of cyclohexyl); 4 × 46.68 t (2 × C-2, 2 × C-6 of piperidyl); 2 × 60.20 s (2 × C-1 of cyclohexyl); 2 × 122.58 d (C-3, C-4 of thienyl); 2 × 144.61 s (C-2, C-5 of thienyl). Mass spectrum, *m*/*z* (%): 414 ($M^+$, $C_{26}H_{42}N_2S$, 3), 310 (43), 247 (14), 245 (34), 177 (10), 166 (71), 165 (100), 97 (32), 84 (25), 81 (22), 55 (11), 41 (17). For $C_{26}H_{42}N_2S$ (414.7) calculated: 75.30% C, 10.21% H, 6.76% N, 7.73% S; found: 75.35% C, 10.19% H, 6.53% N, 7.98% S.

Neutralization of *X* with HCl in ether gave the dihydrochloride sesquihydrate, m.p. 202 – 204 °C (ethanol–ether). For $C_{26}H_{44}44Cl_{22}NS + 1.5\ H_2O$ (514.7) calculated: 60.68% C, 9.20% H, 13.78% Cl, 5.44% N; found: 60.76% C, 8.96% H, 13.46% Cl, 5.17% N, 6.18% S.

Evaporation of the mother liquor after isolation of *X* and crystallization of the residue from ethanol afforded 9.6 g (49%) of *VIIf*, m.p. 50 – 52 °C. $^1$H NMR spectrum ($CDCl_3$): 1.20 – 2.00 m, 16 H (5 × $CH_2$ of cyclohexyl and 2 × H-3, 2 × H-4, 2 × H-5 of piperidyl); 2.30 bt, 4 H (2 × H-2, 2 × H-6 of piperidyl); 6.55 d, 1 H, *J*(3,4) = 5.0 (H-3 of thienyl); 6.94 d, 1 H, *J*(3,4) = 5.0 (H-4 of thienyl). $^{13}$C NMR spectrum ($CDCl_3$): 2 × 22.11 t (C-3, C-5 of cyclohexyl); 24.87 t (C-4 of piperidyl); 25.99 t (C-4 of cyclohexyl); 2 × 27.04 t (C-3, C-5 of piperidyl); 2 × 35.80 t (C-2, C-6 of cyclohexyl); 2 × 46.31 t (C-2, C-6 of piperidyl); 60.58 s (C-1 of cyclohexyl); 109.28 s (C-5 of thienyl); 124.29 d (C-3 of thienyl); 128.92 d (C-4 of thienyl); 148.94 s (C-2 of thienyl). Mass spectrum, *m*/*z* (%): 329 ($M^+$, $C_{15}H_{22}BrNS$, 23), 327 (24), 286 (28), 284 (31), 245 (100), 244 (45), 243 (98), 242 (30), 203 (13), 201 (12), 177 (83), 175 (73), 166 (13), 165 (19), 164 (17), 163 (18), 122 (21), 108 (10), 97 (17), 86 (17), 84 (17), 81 (62), 55 (42), 41 (63). Hydrogen maleate, m.p. 134 – 135.5 °C (ether). For $C_{19}H_{26}BrNO_4S$ (444.4) calculated: 51.35% C, 5.90% H, 17.98% Br, 3.15% N, 7.22% S; found: 51.06% C, 5.92% H, 17.90% Br, 3.39% N, 7.30% S.

*1-[3-(2-Thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-3-yl]piperidine* (IX): Reaction of the Grignard reagent, prepared from 2-bromothiophene with the amino nitrile *VIa* (12.55 g, 0.06 mol) gave 12.6 g (79%) of oily *IX* which was transformed to the hydrochloride, m.p. 203 – 205 °C (ethanol). Mass spectrum, *m*/*z* (%): 267 ($M^+$, $C_{14}H_{21}NS_2$, 12), 220 (6), 206 (100), 192 (29), 183 (14), 149 (16), 123 (16), 110 (25), 99 (13), 97 (19), 84 (41), 55 (10), 45 (14). For $C_{14}H_{22}ClNS_2$ (303.9) calculated: 55.3% C, 7.3% H, 11.6% Cl, 4.6% N, 21.1% S; found: 55.2% C, 7.2% H, 11.7% Cl, 4.4% N, 20.8% S.

*2-{4-[3-(2-Thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-3-yl]-1-piperazinyl}ethanol* (VIIIa): Grignard reagent, prepared from 2-bromothiophene was reacted with the amino nitrile *VIb* (7.7 g, 0.03 mol) and gave 5.0 g (53%) of *VIIIa*, m.p. 115.5 – 116.5 °C (benzene–cyclohexane). IR spectrum (Nujol): 719, 822, 840 (Ar-H); 1 051, 3 170 (OH); 2 700, 2 775 ($NCH_2$); 3 060 (Ar). $^{13}$C NMR spectrum ($CDCl_3$): 29.90 t (C-5); 28.38 t (C-6); 35.70 t (C-4); 36.30 t (C-2); 2 × 45.12 t (C-3 and C-5 of piperazinyl); 57.74 t ($NCH_2$); 58.49 s (C-3); 59.23 t ($CH_2OH$); 123.70 d (C-5 of thienyl); 125.12 d (C-3 of thienyl); 126.24 d (C-4 of thienyl); 145.43 s (C-2 of thienyl). For $C_{15}H_{24}N_2OS_2$ (312.5) calculated: 57.65% C, 7.74% H, 8.96% N, 20.52% S; found: 57.88% C, 7.72% H, 8.81% N, 20.40% S. Hydrogen oxalate, m.p. 181 – 183 °C (aqueous ethanol–ether). For $C_{17}H_{26}N_2O_5S_2$ (402.5) calculated: 50.72% C, 6.51% H, 6.96% N, 15.93% S; found: 50.62% C, 6.51% H, 7.08% N, 15.88% S.

2-{4-[3-(2-Thienyl)-3,4,5,6-tetrahydro-2*H*-thiopyran-3-yl]-1-piperazinyl}ethyl Acetate (*VIIIb*)

A solution of *VIIIa* (2.0 g, 6.4 mmol) in pyridine (10 ml) was treated with acetic anhydride (2.9 g, 29 mmol) and the mixture was stirred for 7 h at room temperature. It was then diluted with water and extracted with ether. Processing of the extract gave 1.13 g (51%) of oily *VIIIb* which was transformed to the bis(hydrogen maleate), m.p. 144 – 145 °C (acetone). IR spectrum (KBr): 702, 862 (Ar); 1 225, 3 378, 3 480 (COOH); 1 484, 2 942 ($CH_2$, $CH_3$); 1 362, 1 384, 1 572 ($COO^-$); 1 738 (ester); 2 707 – 2 611 ($NH^+$). For $C_{25}H_{34}N_2O_{10}S_2$ (586.7) calculated: 51.18% C, 5.84% H, 4.78% N, 10.93% S; found: 51.24% C, 6.09% H, 4.88% N, 10.88% S.

1-[3-(2-Thienyl)-3,4,5,6-tetrahydro-2*H*-thiopyran-3-yl]-4-(2-benzyloxyethyl)piperazine (*VIIIc*)

A solution of *VIIIa* (3.12 g, 10 mmol) in *N*,*N*-dimethylformamide (50 ml) was stirred and treated at 60 °C with an oily suspension of NaH (0.50 g, 16.6 mmol). The mixture was stirred for 30 min, treated with benzyl chloride (1.6 g, 12.6 mmol) and stirred at 60 °C for further 3 h. After dilution with water it was extracted with ether. Processing of the extract gave a mixture which was separated by chromatography on $Al_2O_3$ (100 g). Elution with benzene afforded 1.8 g (45%) of *VIIIc* which was transformed to the bis(hydrogen maleate), m.p. 142 – 145 °C (acetone–ether). For $C_{30}H_{38}N_2O_9S_2$ (634.8) calculated: 56.76% C, 6.03% H, 4.41% N, 10.10% S; found: 56.48% C, 6.09% H, 4.15% N, 10.18% S. Continued chromatography using elution with chloroform recovered 1.0 g (32%) of the starting *VIIIa*, m.p. 115.5 – 116.5 °C (benzene–cyclohexane).

5-[1-(1-Piperidinyl)-1-cyclohexyl]thiophene-2-carboxylic Acid (*XI*)

A stirred solution of *VIIf* (9.0 g, 27.4 mmol) in ether (80 ml) was treated dropwise at (–50) – (–60) °C over 2 min with 15% solution of butyllithium in hexane (25 ml, 40 mmol). The mixture was stirred for 2 min and poured into a suspension of solid $CO_2$ (ca 50 g) in ether (50 ml). After evaporation of the excessive $CO_2$, the mixture was washed with water and the undissolved solid *XI* was filtered and crystallized from 40% acetic acid; yield 2.2 g (27%), m.p. 175.5 – 178.5 °C. IR spectrum (Nujol): 1 700, 3 260, 3 360 (COOH); 1 530, 1 595 (Ar); 2 250 ($NH^+$). Mass spectrum, *m*/*z* (%): 293 ($M^+$, $C_{16}H_{23}NO_2S$, 18), 250 (48), 236 (11), 208 (302), 163 (32), 141 (57), 135 (24), 97 (16), 84 (100), 56 (18). For $C_{16}H_{23}NO_2S$ (293.4) calculated: 65.46% C, 7.90% H, 4.77% N, 10.93% S; found: 65.46% C, 7.77% H, 4.50% N, 11.18% S.

Evaporation of the ethereal solution gave a mixture (4.1 g) which was separated by chromatography on silica gel (280 g). Elution with chloroform gave first the starting *VIIf* (1.25 g, 14%, m.p. 50 – 52 °C) and further a halogen-free product which was identified as 1-[1-(2-thienyl)-1-cyclohexyl]piperidine (*IV*) (1.26 g, 18%) which was transformed to the hydrochloride melting at 245 – 247 °C (ethanol–ether). Literature[18] gave for the hydrochloride the m.p. of 230 – 235 °C. IR spectrum (Nujol): 703, 810, 846 (ArH); 2 380, 2 440, 2 580 ($NH^+$); 3 055 (Ar). $^{13}C$ NMR spectrum: 21.81 t (C-4 of piperidyl); 2 × 22.48 t (C-3 and C-5 of cyclohexyl); 2 × 22.71 t (C-3 and C-5 of piperidyl); 23.98 t (C-4 of cyclohexyl); 2 × 32.12 t (C-2 and C-6 of cyclohexyl); 2 × 46.68 t (C-2 and C-6 of piperidyl); 68.42 s (C-1 of cyclohexyl); 127.88 d (C-3 of thienyl); 129.07 d (C-5 of thienyl); 130.94 d (C-4 of thienyl); 135.95 s (C-2 of thienyl). Mass spectrum, *m*/*z* (%): 249 ($M^+$, $C_{15}H_{23}NS$, 12), 206 (21), 165 (41), 164 (21), 97 (100), 84 (34). For $C_{15}H_{24}ClNS$ (285.9) calculated: 63.02% C, 8.46% H, 12.40% Cl, 4.90% N, 11.21% S; found: 62.80% C, 8.19% H, 12.56% Cl, 5.04% N, 10.96% S.

*The authors thank the following colleagues at the Research Institute for Pharmacy and Biochemistry for co-operation: Dr M. Cech, Mrs R. Svatosova and Mrs A. Svatonova (elemental analyses), Dr J. Taimr (NMR spectra), Dr M. Ryska (mass spectra), Dr E. Svatek and Mrs R. Hanusova (IR spectra), Dr R. Lapka, Mrs B. Moserova, Dr J. Sedlackova, and Mrs J. Brychnacova (pharmacology). This work was supported by the Grant No. Z 001/42-540 of the Ministry of Health and by the Grant No. 307/93 of the Grant Agency of the Czech Republic.*

## REFERENCES

1. Chen G. C., Ensor C., Russell D., Bohner B.: J. Pharmacol. Exp. Ther. *127*, 241 (1959).
2. Greinfestein F. E., Devault M., Yoshitake J., Gajewski J. E.: Anesthesia Anesth. Analg. *37*, 283 (1958).

3. Domino E. F.: Int. Rev. Neurobiol. *6*, 303 (1964).
4. Zukin S. R., Zukin R. S.: Proc. Natl. Acad. Sci. U.S.A. *76*, 5372 (1979).
5. Vincent J. P., Cavey D., Kamenka J. M., Geneste P., Lazdunski M.: Brain Res. *1952*, 176 (1978).
6. Smith R. C., Meltzer H. Y., Arora R. C., Davis J. M.: Biochem. Pharmacol. *26*, 1436 (1977).
7. Foster A. C., Fagg G. E.: Brain Res. Rev. *7*, 103 (1984).
8. Loo P. S., Braunwalder A. F., Lehmann J., Williams M., Sills M. A.: Mol. Pharmacol. *32*, 820 (1987).
9. Anis N. A., Bery S. C., Burton N. R., Lodge D.: Brit. J. Pharmacol. *79*, 565 (1983).
10. Steele J. E., Robinson T. N., Cross A. J., Bowen D. M.: J. Neurochem. *56*, 1248 (1991).
11. Zorbas M., Owens S. M., Plunkett L. M., Bui H.: Drug Metab. Dispos. *17*, 641 (1989).
12. Spath E., Epstein H.: Ber. Dtsch. Chem. Ges. *59*, 2796 (1926).
13. Buck J. S.: J. Am. Chem. Soc. *52*, 4119 (1930).
14. Fehnel E. A.: J. Am. Chem. Soc. *74*, 1569 (1952).
15. Schipper E. S. (Ethicon, Inc.): U.S. 2,971 021; Chem. Abstr. *55*, 18629 (1961).
16. Harper N. J., Veitch G. B. (Allen and Hansburys, Ltd.): Ger. Offen. 2,246 728 (1973); Chem. Abstr. *79*, 42204 (1973).
17. Maddox V. H., Godefroi E. F., Parcell R. F.: J. Med. Chem. *8*, 230 (1965).
18. Kalir A., Edery H., Pelah Z., Balderman D., Porath G.: J. Med. Chem. *12*, 473 (1969).