Spiro Derivatives of Tetrahydrothiophene. Synthesis of the Quinolizidine ⟨3-spiro-2′⟩tetrahydrothiophene System Using Solid/Liquid or Liquid/Liquid Phase-Transfer Catalysis

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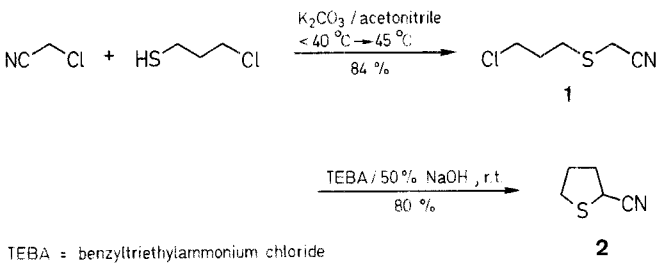
4-Oxooctahydroquinolizine⟨3-spiro-2′⟩tetrahydrothiophene 1′,1′-dioxide can be synthetized from 2-cyanotetrahydrothiophene by two independent routes, both of them using phase-transfer catalysis: the first one involves alkylation of 2-cyanotetrahydrothiophene under PTC conditions, the second one *N*-acylation of 2-(2-chloroethyl)piperidine with 2-chlorocarbonyltetrahydrothiophene with the final cycloalkylation being performed under PTC conditions. Two stereoisomers of the spiro compound are obtained.

A tetrahydrothiophene ring spiro-linked to a substituted quinolizidine skeleton is a characteristic fragment of some *Nuphar* alkaloids.[1] We have now attempted the partial and total synthesis of such alkaloids, taking into account both chemical and possible pharmacological aspects.

The synthesis of 4-oxooctahydroquinolizine⟨3-spiro-2′⟩tetrahydrothiophene 1′,1′-dioxide **(6)** was achieved by two different procedures, both starting with 2-cyanotetrahydrothiophene **(2)** which was prepared by a two-step PTC method[2] involving *S*-cyanomethylation of 3-chloropropanethiol with chloroacetonitrile and alkaline cyclization of the resultant (3-chloropropylthio)acetonitrile.



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Route A: Hydrogen peroxide oxidation of 2-cyanotetrahydrothiophene[3] **(2)** affords its *S,S*-dioxide **(3)** in which the active H-atom in position 2 is susceptible to alkylation. Thus, reaction of **3** with 2-(2-bromoethyl)pyridine **(11)** affords the nitrile **4** which represents a suitable precursor of the target spiro system **6**. This *C*-alkylation was performed under PTC conditions using Aliquat 336® (tricaprylylmethylammonium chloride) as catalyst.[4] The alkylated product **4** has already the proper skeleton to prepare the spiro system. Hydrolysis of its cyano group followed by esterification and reduction-cyclization affords the octahydroquinolizine-spiro-tetrahydrothiophene derivative **6** as a mixture of two isomers A and B, which can be separated by fractional crystallization.

Route B: This procedure consists of hydrolysis 2-cyanotetrahydrothiophene **(2)** to tetrahydrothiophene-2-carboxylic acid, conversion of the acid into its chloride **(8)**, *N*-acylation of 2-(2-chloroethyl)piperidine **(12)** with chloride **8**, oxidation of the resultant tetrahydrothiophene-2-carboxamide **9** to the sulfone **10**, and cyclization of **10** using base in the presence of benzyltriethylammonium chloride (PTC conditions). Route B furnishes the isomer A of spiro compound **6**.

In both isomers (A and B), the configurational assignment of the ring junction is based on the chemical shifts of protons 6-H and 9a-H[5] in the ^{1}H-NMR, spectrum as well as on the ^{13}C-NMR spectrum (cf. Lit.[6]). However, the downfield shift of the C-6 signal suggests some deformation.

Isomers A and B are epimeric on the spiro C-atom. The ^{13}C-NMR spectrum suggests that in isomer B the atom C-3′ in the tetrahydrothiophene ring is pseudo-equatorial (δ = 26.7 ppm), whereas in isomer A it is pseudo-axial (δ = 25.4 ppm). The ratio of isomers A:B is 3:1.

Boiling and melting points are uncorrected. Melting points were determined on a Boetius apparatus (Carl Zeiss, Jena). Microanalyses were carried out in the Microanalytical Laboratory of the Technical University Warsaw. Mass spectra (70 eV) were recorded on a LKB 9000 spectrometer. IR spectra were recorded on a UR-20 (Carl Zeiss, Jena) spectrometer. ^{1}H-NMR spectra were recorded either on Tesla 100 MHz or Bruker W.M. 250 spectrometers, the ^{13}C-NMR spectra on either Jeol FX 90 Q or IBM 200 SY (at 50.3 MHz) Fourier transform spectrometers.

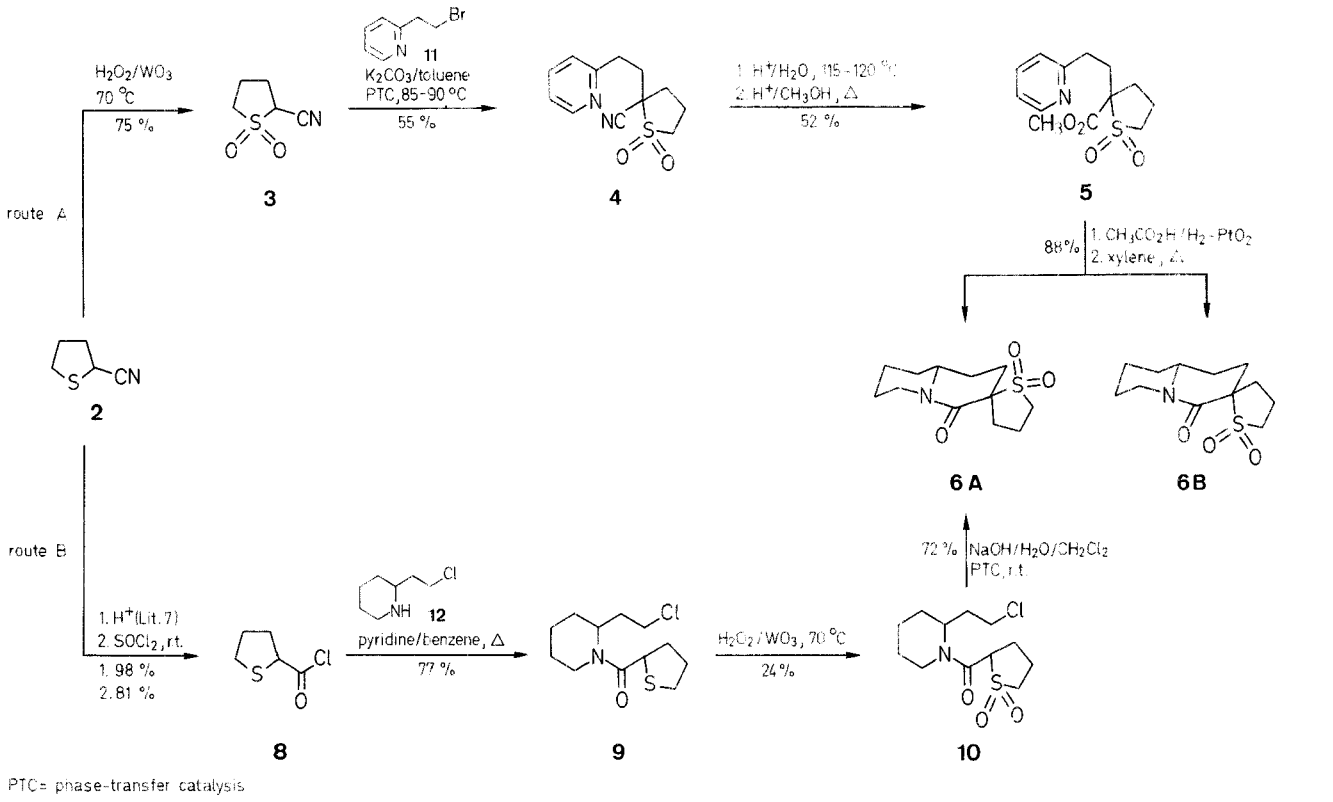

Table. NMR Data (TMS_{int}) of the Isolated Isomers A and B of Compound **6** and, for Comparison, Reported NMR Data of 4-Oxooctahydroquinolizine[5,6]

Compound	^{1}H-NMR δ (ppm)		^{13}C-NMR δ (ppm)
	$CDCl_3$	C_6D_6	$CDCl_3$
4-Oxooctahydroquinolizine	(Lit. [5]): 2.28 (m, 1H, 6-H$_{ax}$); 3.17 (m, 1H, 9a-H$_{ax}$)[a]; 4.63 (d, 1H, 6-H$_{eq}$)		(Lit. [6]): 19.5 (C-2); 24.7 (C-8); 25.6 (C7); 30.7 (C-1); 33.1 (C-3); 34.1 (C-9); 42.0 (C-6); 56.8 (C-9a)[b]
Isomer A of **6**	1.49–2.20 (m, 10H); 2.28–2.80 (m, 5H, 3′,3′-H$_2$, 4′,4′-H$_2$, 6-H$_{ax}$); 3.10 (m, 1H, 9a-H$_{ax}$); 3.50 (m, 2H, 5′,5′-H$_2$); 4.75 (d, 1H, J = 12 Hz, 6-H$_{eq}$)	0.82–2.75 (m, 17H); 3.15 (m, 1H, $W_{\frac{1}{2}}$ = 20 Hz, 9a-H$_{ax}$); 4.85 (dd, 1H, J = 15 Hz, 6-H$_{eq}$)	18.2 (t, C-4′); 24.7 (t, C-1); 25.2 (t, C-7); 25.2 (t, C-8); 25.4 (t, C-3′); 32.9 (t, C-2); 34.0 (t, C-9); 44.2 (t, C-6); 50.0 (t, C-5′); 56.8 (d, C-9a); 65.3 (s, C_{spiro}); 165.4 (s, C-4)
Isomer B of **6**	1.22–2.06 (m, 10H); 2.34–2.78 (m, 5H, 3′,3′-H$_2$, 4′,4′-H$_2$, 6-H$_{ax}$); 3.06–3.53 (m, 3H, 5′,5′-H$_2$, 9a-H$_{ax}$); 4.73 (d, 1H, J = 15 Hz, 6-H$_{eq}$)	0.93–2.55 (m, 17H); 3.10 (m, 1H, $W_{\frac{1}{2}}$ = 20 Hz, 9a-H$_{ax}$); 4.97 (dd, 1H, J = 15 Hz, 6-H$_{eq}$)	18.2 (t, C-4′); 23.9 (t, C-1); 25.2 (t, C-7); 25.2 (t, C-8); 26.7 (t, C-3′); 33.8 (t, C-2); 34.3 (t, C-9); 43.1 (t, C-6); 50.1 (t, C-5′); 56.9 (d, C-9a); 65.6 (s, C_{spiro}); 165.6 (s, C-4)

[a] "10-H" in Lit. [5]
[b] "C-10" in Lit. [6]

(3-Chloropropylthio)acetonitrile (1):
To a stirred solution of chloroacetonitrile (177.9 g, 2.38 mol) in acetonitrile (840 ml), anhydrous potassium carbonate (167 g, 1.21 mol) is added in one portion. A solution of 3-chloropropanethiol (131 g, 1.19 mol) in acetonitrile (260 ml) is added dropwise at such a rate that the temperature is kept below 40 °C. After 1 h, the mixture is heated with stirring to 45 °C for 2 h. The inorganic salts are filtered off and the solvent is removed in vacuo. The residue is distilled in vacuo; yield of **1**: 149 g (84 %); b.p. 145–148 °C/20 torr.

C_5H_8ClNS (149.6) calc. C 40.13 H 5.39 N 9.36
found 40.32 5.66 9.12

MS: m/e (%) = 155 (15.84), 150 (5.29), 149 (M^+, 41.44), 114 (11.72), 111 (5.91), 109 (15.86), 78 (10.23), 76 (29,92), 41 (100).

IR (film): ν = 2980, 2255, 1440, 1410, 1280 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 2.18 (q, 2H, 2,2-H$_2$); 2.98 (t, 2H, 1,1-H$_2$); 3.42 (s, 2H, 4,4-H$_2$); 3.75 ppm (t, 2H, 3,3-H$_2$).

2-Cyanotetrahydrothiophene (2):
Aqueous 50 % sodium hydroxide (327 ml) is added dropwise to a stirred slurry of (3-chloropropylthio)acetonitrile (**1**; 73.3 g, 0.49 mol) and benzyltriethylammonium chloride (3.34 g, 0.015 mol). After an exothermic reaction, the mixture is stirred for 1 h. The upper, dark brown layer is separated and the alkaline aqueous layer is diluted with water (90 ml) and extracted with benzene (4 × 100 ml). The combined organic layers are washed with aqueous 10 % hydrochloric acid (2 × 30 ml) and with water (20 ml), and are dried with magnesium sulfate. Benzene is evaporated and the residue distilled in vacuo to give product **2** as a colorless liquid; yield: 44.4 g (80 %); b.p. 110–112 °C/15 torr.

C_5H_7NS (113.1) calc. C 53.06 H 6.23 N 12.38 S 28.33
found 53.26 6.26 12.50 28.17

MS: m/e (%) = 113 (M^+, 28.85), 85 (47.39), 60 (35.70), 45 (40.39), 41 (100), 39 (36.34), 28 (45.29), 27 (51.50).

IR (film): ν = 2960, 2880, 2245, 1445, 1270 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 2.32 (m, 4H, 3,3-H_2, 4,4-H_2); 3.10 (m, 2H, 5,5-H_2); 4.08 ppm (m, 1H, 2-H).

^{13}C-NMR ($CDCl_3$): δ = 30.3 (t, C-4); 32.9 (t, C-5); 36.2 (t, C-3); 36.2 (d, C-2); 120.8 ppm (s, C≡N).

2-Cyanotetrahydrothiophene 1,1-Dioxide (3):

To a stirred solution of tungstic acid catalyst [$WO_3 \cdot H_2O$ (75 mg, 0.3 mmol) in water (25 ml), pH = 5.6] is added 2-cyanotetrahydrothiophene (**2**; 6.79 g, 0.06 mol) and the mixture is heated at 63 °C. Then, 30% hydrogen peroxide (17 ml) is added dropwise at such a rate that the temperature does not exceed 70 °C. The mixture is kept at 70 °C for 1.5 h, and then left stand overnight. The organic layer is separated and the water layer is extracted with benzene (5 × 25 ml) and with chloroform (4 × 25 ml). The combined organic extracts are dried with sodium sulfate, the solvents are evaporated, and the colorless crystalline residue is recrystallized from benzene; yield: 6.50 g (75%); m.p. 47–48 °C.

$C_5H_7NSO_2$	calc.	C 41.37	H 4.86	N 9.65	S 22.05
(145.1)	found	41.44	4.50	9.85	22.16

MS: *m/e* (%): 145 (M^+, 3.12), 81 (10.14), 80 (12.02), 54 (100), 28 (35.53).

IR (KBr): ν = 3020, 2955, 2900, 2255, 1330, 1140 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 2.27–2.70 (br.m, 4H, 3,3-H_2, 4,4-H_2); 3.28 (m, 2H, 5,5-H_2); 4.08 ppm (t, 1H, 2-H, J = 13.4 Hz).

^{13}C-NMR ($CDCl_3$): δ = 20.8 (t, C-4); 28.6 (t, C-3); 51.5 (t, C-5); 51.6 (d, C-2); 113.8 ppm (C≡N).

2-(2-Bromoethyl)pyridine Hydrobromide (11 · HBr):

A mixture of 2-(2-hydroxyethyl)pyridine (7.39 g, 0.06 mol) and 48% hydrobromic acid (60 ml) is slowly distilled to remove water and excess hydrogen bromide. The solid residue is recrystallized from isopropanol to give colorless **11** · HBr; yield: 15.22 g (95%); m.p. 133–135 °C.

$C_7H_9Br_2N$	calc.	C 31.49	H 3.40	N 5.25
(266.95)	found	31.72	3.42	5.39

IR (KBr): ν = 3260, 3090, 3050, 3020, 2800–2600, 1640, 1620, 1550, 1470, 1450, 1330, 1240, 780 cm^{-1}.

^{1}H-NMR (D_2O/TMS_{ext}): δ = 3.25 (m, 2H, CH_2–CH_2Br); 3.45 (m, 2H, CH_2–Br); 7.65 (m, 2H, 3-H, 5-H); 8.20 (d, 1H, 4-H); 8.35 ppm (m, 1H, 6-H).

2-Cyano-2-[2-(2-pyridinyl)ethyl]tetrahydrothiophene 1,1-Dioxide (4):

2-(2-Bromoethyl)pyridine (**11**): 2-(2-Bromoethyl)pyridine hydrobromide (**11** · HBr; 12.814 g, 0.048 mol) is dissolved in aqueous 20% sodium hydroxide (15 ml) and extracted with benzene (5 × 20 ml). The organic extract is washed with water (1 × 5 ml) and filtered through anhydrous sodium sulfate. The solvent is evaporated. The residual **11** is a yellow liquid; yield: 8.484 g (95%).

2-Cyano-2-[2-(2-pyridinyl)ethyl]tetrahydrothiophene 1,1-Dioxide (**4**):

A solution of 2-(2-bromoethyl)pyridine (**11**; 8.484 g, 0.046 mol) in dry toluene (30 ml) is added to a stirred mixture of 2-cyanotetrahydrothiophene 1,1-dioxide (**3**; 5.807 g, 0.04 mol), anhydrous potassium carbonate (20.7 g, 0.15 mol), and Aliquat 336® (1.867 g). This mixture is heated to boiling (85–90 °C) with stirring for 10 h. The inorganic salts are then filtered off and the dark filtrate is passed through silica gel (Merck; 70–230 mesh) to remove polar impurities. The solvent is evaporated and the residue is recrystallized twice from benzene to give the colorless product **4**: yield: 5.508 g (55%); m.p. 94–95 °C.

$C_{12}H_{14}N_2O_2S$	calc.	C 55.57	H 5.64	N 11.19	S 12.81
(250.3)	found	57.35	5.43	11.39	12.66

MS: *m/e* (%) = 250 (M^+, 0.6), 186 (25.67), 170 (31.63), 159 (38.38), 158 (29.66), 157 (24.29), 132 (15.78), 131 (13.72), 130 (12.59), 106 (99.82), 93 (100), 92 (17.87).

IR (KBr): ν = 3090, 3020, 2960, 2245, 1600, 1575, 1485, 1460, 1440, 1325, 1140, 1000 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 2.20–2.60 (br. m, 6H, 3,3-H_2, 4,4-H_2, pyr-CH_2–CH_2); 3.10–3.50 (br. m, 4H, 5,5-H_2, pyr-CH_2–CH_2); 7.21 (m, 2H, 3-H_{pyr}, 5-H_{pyr}); 7.63 (m, 1H, 4-H_{pyr}); 8.53 ppm (dd, 1H, J = 4.9 Hz, 6-H_{pyr}).

^{13}C-NMR ($CDCl_3$): δ = 18.8 (t, C-4); 31.4, 33.5, 34.7 (3 t, pyr-CH_2–CH_2, C-3); 50.7 (t, C-5); 61.5 (s, C-2); 116.2 (s, C≡N); 121.9 (d, C-5_{pyr}); 123.1 (d, C-3_{pyr}); 136.7 (d, C-4_{pyr}); 149.4 (d, C-6_{pyr}); 158.7 ppm (s, C-2_{pyr}).

2-Methoxycarbonyl-2-[2-(2-pyridinyl)ethyl]tetrahydrothiophene 1,1-Dioxide (5):

The nitrile **4** (5.007 g, 0.02 mol) is dissolved in a mixture of water (5 ml), glacial acetic acid (5 ml), and concentrated sulfuric acid (5 ml) and this solution is heated to boiling (115–120 °C) for 5 h. Water and acetic acid are then distilled off in vacuum and methanol (30 ml) and concentrated sulfuric acid (3 ml) are added to the residue. This mixture is refluxed for 6 h, the solvent is evaporated, methanol (30 ml) and concentrated sulfuric acid (3 ml) are added, the mixture is again refluxed for 6 h, and the solvent is evaporated in vacuum. The residue is dissolved in aqueous 10% sodium hydrogen carbonate (20 ml) and this solution is extracted with benzene (1 × 25 ml) and chloroform (5 × 25 ml). The combined extracts (dried over anhydrous sodium sulfate) are filtered through silica gel (Merck; 70–230 mesh) to remove polar impurities. The solvent is evaporated and the colorless solid residue recrystallized from benzene: yield: 2.947 g (52%); m.p. 68–69 °C.

$C_{13}H_{17}NO_4S$	calc.	C 55.11	H 6.05	N 4.94	S 11.32
(283.3)	found	55.40	6.05	5.26	11.33

MS: *m/e* (%) = 283 (M^+, 0.51), 219 (5.32), 190 (13.96), 191 (16.69), 107 (11.96), 106 (100), 93 (95.1).

IR (KBr): ν = 3000, 2970, 2900, 2860, 1745, 1595, 1575, 1480, 1440, 1305, 1200, 1130, 1000 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 2.08–2.32 (m, 4H, 3,3-H_2, 4,4-H_2); 2.65–3.24 (br. m, 6H, 5,5-H_2, pyr-CH_2–CH_2); 3.82 (s, 3H, OCH_3); 7.16 (m, 2H, 3-H_{pyr}, 5-H_{pyr}); 7.62 (m, 1H, 4-H_{pyr}); 8.53 ppm (dd, 1H, J = 5.7 Hz, 6-H_{pyr}).

^{13}C-NMR ($CDCl_3$): δ = 18.5 (t, C-4); 31.3, 32.8, 33.9 (3 t, CH_2–CH_2, C-3); 51.1 (t, C-5); 53.3 (q, OCH_3); 70.9 (s, C-2); 121.6 (d, C-5_{pyr}); 122.9 (d, C-3_{pyr}); 136.0 (d, C-4_{pyr}); 149.3 (d, C-6_{pyr}); 159.8 (s, C-2_{pyr}); 168.0 ppm (C=O).

4-Oxooctahydroquinolizine⟨3-spiro-2′⟩tetrahydrothiophene 1′,1′-Dioxide (6):

Route A: A solution of ester **5** (0.850 g, 0.003 mol) in glacial acetic acid (20 ml) is added to pre-reduced platinum(IV) oxide (400 mg) in glacial acetic acid (100 ml). The mixture is stirred under a hydrogen atmosphere until hydrogen uptake has ceased. The catalyst is filtered off and most of the solvent is removed in vacuo. The residue is dissolved in saturated sodium hydrogen carbonate solution (10 ml) and this solution is extracted with chloroform (4 × 20 ml). The organic layer is dried with sodium sulfate, and the solvent evaporated. The residual oil is dissolved in xylene (30 ml) and this solution is refluxed for 4 h and then allowed to stand overnight. Xylene is removed in vacuo and the remaining dark solid is column-chromatographed on silica gel (Merck; 200–300 mesh; eluent: chloroform/hexane/acetone 1:2:1) to give spiro compound **6** as a mixture of two stereoisomers which are separated by fractional crystallization from benzene/hexane (1:1); yield of isomer mixture **6**A + **6**B: 0.676 g (88%).

Isomer **6**A is obtained as colorless needles; yield: 0.451 g; m.p. 149–150 °C.

Isomer **6**B is obtained as colorless crystals; yield: 0.148 g; m.p. 94–95 °C.

$C_{12}H_{19}NO_3S$	calc.	C 56.01	H 7.44	N 5.44	S 12.46
(257.3)	found for **6**A	56.21	7.34	5.41	12.70
	found for **6**B	56.20	7.45	5.38	12.20

Isomer **6**A:

MS: *m/e* (%) = 257 (M^+, 0.91), 230 (10.58), 193 (44.76), 192 (18.00), 165 (57.10), 164 (100), 137 (19.09), 136 (84.10), 117 (22.18), 116 (15.29), 84 (21.16), 83 (13.88), 82 (10.54), 81 (10.58).

IR (KBr): ν = 3000, 2950, 2890–2860, 1645, 1470, 1450, 1300, 1125 cm^{-1}.

Isomer **6**B:

MS: *m/e* (%) = 258 (M^+ + 1, 10.15), 257 (M^+, 0.00), 193 (75.06), 192 (20.30), 166 (13.91), 165 (73.35), 164 (100), 150 (20.11), 137 (38.35), 136 (92.25), 123 (11.06), 122 (11.37), 108 (10.07), 84 (12.81), 83 (15.88), 82 (14.11), 81 (18.06), 80 (10.37).

IR (KBr): ν = 3020, 2950, 2880, 2860, 1640, 1480, 1450, 1310, 1140 cm^{-1}.

Tetrahydrothiophene-2-carboxylic Acid (7):

2-Cyanotetrahydrothiophene (**2**; 22.6 g, 0.2 mol) is hydrolyzed with concentrated hydrochloric acid (160 ml) and water (80 ml); yield: 25.8 g (98%); m.p. 50–51 °C (Lit.[7] m.p. 51 °C).

$C_5H_8O_2S$ (132.1)

MS: *m/e* (%) = 132 (M^+, 26.10), 87 (100), 85 (11.80), 60 (6.88), 45 (39.82).

IR (KBr): ν = 2950, 1720, 1420, 1310 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 2.12 (m, 4H, 3,3-$\underline{H}_2$, 4,4-$\underline{H}_2$); 2.88 (m, 2H, 5,5-$\underline{H}_2$); 3.88 (t, 1H, 2-$\underline{H}$); 11.56 ppm (s, 1H, COO$\underline{H}$).

^{13}C-NMR ($CDCl_3$): δ = 30.8 (t, C-4); 33.2 (t, C-5); 33.3 (t, C-3); 47.5 (d, C-2); 180.1 ppm (s, C=O).

2-Chlorocarbonyltetrahydrothiophene (8):

Tetrahydrothiophene-2-carboxylic acid (**7**; 7.93 g, 0.06 mol) is dissolved in thionyl chloride (28.6 g, 0.24 mol) and this solution is allowed to stand overnight. Excess thionyl chloride is then removed at ambient pressure and the residue is distilled in vacuum; yield of **8**: 7.32 g (81%); colorless liquid, b.p. 113–114 °C/25 torr.

For analysis, *tetrahydrothiophene-2-carboxanilide* is prepared by reaction of acid chloride **8** with aniline; m.p. 125–126 °C (ethanol).

$C_{11}H_{15}NOS$	calc.	C 63.16	H 7.18	N 6.70	S 15.31
(209.25)	found	63.27	6.98	6.18	15.08

2-(2-Chloroethyl)piperidine Hydrochloride (12 · HCl):

This compound is prepared from 2-(2-hydroxyethyl)piperidine and thionyl chloride according to Lit.[8]; yield: 90%; m.p. 163–164 °C (Lit.[8] m.p. 148–150 °C).

$C_7H_{14}ClN \cdot HCl$ (184.1)

MS: *m/e* (%) = 84 (100), 56 (19.23), 36 (14.46).

IR (KBr): ν = 2960–2740, 2580, 2520, 2450, 2410, 1590, 1460, 1440, 1340, 1310, 1290, 660 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.87 (m, 6H, 3,3-$\underline{H}_2$, 4,4-H_2, CH_2-CH_2Cl); 2.17–4.30 (br.m, 7H, 2-$\underline{H}$, 5,5-$\underline{H}_2$, 6,6-$\underline{H}_2$, $CH_2-C\underline{H}_2Cl$); 9.60 ppm (m, 2H, $\overset{+}{N}\underline{H}_2$).

2-(2-Chloroethyl)-1-(tetrahydrothiophen-2-ylcarbonyl)-piperidine (9):

2-(2-Chloroethyl)piperidine (**12**): The hydrochloride **12** · HCl (1.84 g, 0.01 mol) is dissolved in aqueous 20% sodium hydroxide (3 ml) and extracted with benzene (5 × 5 ml). The organic extract is washed with water (1 × 1 ml) and filtered through anhydrous sodium sulfate. The solvent is evaporated. The residual **12** is a yellow liquid; yield: 1.33 g (90%).

2-(2-Chloroethyl)-1-(tetrahydrothiophen-2-ylcarbonyl)-piperidine (**9**): In a two-necked flask sealed with a rubber septum, 2-(2-chloroethyl) piperidine (**12**; 1.33 g, 0.009 mol) is dissolved in a mixture of dry pyridine (5 ml) and dry benzene (20 ml). This solution is cooled in an ice bath and stirred and a solution of 2-chlorocarbonyltetrahydrothiophene (**8**; 0.75 g, 0.005 mol) in dry benzene (5 ml) is added by syringe. The mixture is gradually warmed to 50° and heated under reflux for 20 min. The solvents are evaporated and the oily residue is dissolved in benzene (50 ml), washed with 10% hydrochloric acid (10 ml), aqueous 10% sodium carbonate (10 ml), and water (10 ml). The organic layer is dried with sodium sulfate. The solvent is removed and the residue is column-chromatographed on silica gel (Merck; 100–200 mesh) using cyclohexane/ethyl acetate (5:1) as eluent; yield: 1.005 g (77%). Analytically pure product **9** is obtained as a colorless oil by preparative TLC on silica gel plates (Merck; 20 × 20 cm) using cyclohexane/ethyl acetate (1:1) for development.

$C_{12}H_{20}ClNOS$	calc.	C 55.05	H 7.70	N 5.35
(261.7)	found	55.35	7.52	5.40

MS: *m/e* (%) = 263 (9.52), 261 (25.79 (M^+)); 226 (21.29), 174 (98.82), 146 (11.35), 138 (45.67), 114 (2.14), 87 (100), 84 (63.15)

IR (film): ν = 2950, 2870, 1645, 1430 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.50–1.80 (m, 12H, 3,3-$\underline{H}_{2tetrah.-th.}$, 4,4-$\underline{H}_{2tetrah.-th.}$, 3,3-$\underline{H}_{2piperidine}$, 4,4-$\underline{H}_{2piperidine}$, 5,5-$\underline{H}_{2piperidine}$, CH_2-CH_2Cl); 2.75–3.10 (m, 2H, 5,5-$\underline{H}_{2tetrah.-th.}$); 3.30–5.05 ppm (m, 6H, 2-$\underline{H}_{tetrah.-th.}$, 2-$\underline{H}_{piperidine}$, 6,6-$\underline{H}_{2piperidine}$, $CH_2-C\underline{H}_2Cl$).

2-(2-Chloroethyl)-1-(tetrahydrothiophen-2-ylcarbonyl)piperidine *S,S*-Dioxide (10):

30% Hydrogen peroxide (1.13 ml) is added to a solution of tungstic acid catalyst [$WO_3 \cdot H_2O$ (5 mg, 0.02 mmol) in water (2 ml)] and to this mixture, compound **9** (1.0472 g, 0.004 mol) is added dropwise and the mixture is stirred at 70 °C for 30 min. Then, 30% hydrogen peroxide (1.5 ml) is added, stirring at 70 °C is continued for 2 h, and the mixture allowed to stand at room temperature overnight. It is extracted with chloroform (2 × 8 ml), dried with sodium sulfate, and evaporated. The residue is column-chromatographed on silica gel (Merck; 100–200 mesh) using hexane/ethyl acetate (1:1) as eluent to give product **10** as an oil which solidifies in the refrigerator; yield: 0.283 g (24%).

$C_{12}H_{20}ClNO_3S$	calc.	C 49.06	H 6.86	N 4.77
(293.7)	found	48.75	7.01	4.52

MS: *m/e* (%) = 293 (M^+, 0.87), 295 (0.54), 230 (71.33), 223 (12.02), 192 (16.02), 174 (25.18), 146 (20.12), 118 (17.17), 106 (100), 93 (99.44), 84 (94.38).

IR (film): ν = 3020, 2980, 2940, 2870, 1645, 1450, 1310, 1160 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.50–2.95 (m, 12H); 3.00–3.30 (m, 2H, 5,5-$\underline{H}_{2tetrah.-th.}$); 3.38–5.10 ppm (m, 6H, $CH_2-C\underline{H}_2Cl$, 2-$\underline{H}_{tetrah.-th.}$, 2-$\underline{H}_{piperidine}$, 6,6-$\underline{H}_{2piperidine}$).

4-Oxooctahydroquinolizine⟨4-spiro-2′⟩tetrahydrothiophene 1′,1′-Dioxide (6):

Route B: A mixture of sulfone **10** (0.280 g, 0.95 mmol), benzyltriethylammonium chloride (25 mg), aqueous 50% sodium hydroxide (1 ml), and dichloromethane (1 ml) is stirred at room temperature for 1.5 h. The resultant mixture is diluted with water to a volume of 10 ml, and extracted with dichloromethane (5 × 5 ml). The organic extract is washed with 10% hydrochloric acid (5 ml), aqueous 10% sodium carbonate (5 ml), and water (5 ml) and is dried with sodium sulfate. The solvent is removed and the residue recrystallized from benzene/hexane (1:2) to give compound **6** (isomer A) as colorless needles; yield: 0.176 g (72%); m.p. 149–150 °C.

$C_{12}H_{19}NO_3S$	calc.	C 56.01	H 7.44	N 5.44	S 12.46
(257.3)	found	56.25	7.40	5.50	12.32

The spectral data of compound **6** (isomer A) thus obtained are identical with those reported for compound **6** (isomer A) obtained by Route A.

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