Synthesis of positively charged lipids containing a 1,3-oxathiolane cycle

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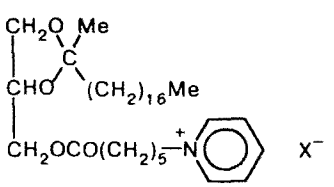
Positively charged lipids of the 1,3-oxathiolane series were synthesized by interaction of 2-pentadecyl-5-tosyloxymethyl- or -5-iodomethyl-1,3-oxathiolane with 2-(*N*,*N*-dimethylamino)ethanol.

Key words: cationic lipids, 1,3-oxathiolane; platelet activating factor (PAF), PAF antagonists.

Platelet activating factor (PAF), 1-*O*-alkyl-2-*O*-acetyl-*sn*-glycero-3-phosphocholine, is a lipid bioregulator that is capable of generating various pathological states: anaphylaxis, bronchospasm, thrombosis, hypotension, *etc.*[1] The response of targeted cells to the action of PAF can be blocked by both nonspecific and specific inhibitors. Nonspecific inhibitors change the intracellular concentration of Ca^{2+} directly (antagonists of Ca channels, chelating agents, and local anesthetics) or indirectly by changing the concentration of cyclic nucleotides (prostaglandins PGI and PGE, β_2-antagonists, *e.g.*, salbutamol, inhibitors of phosphodiesterase, *etc.*)[2,3] Specific antagonists act by competitive addition to PAF-receptors. Most of them possess highly specific biological effects. These compounds can be used to prevent pathological effects caused by PAF.[4,5]

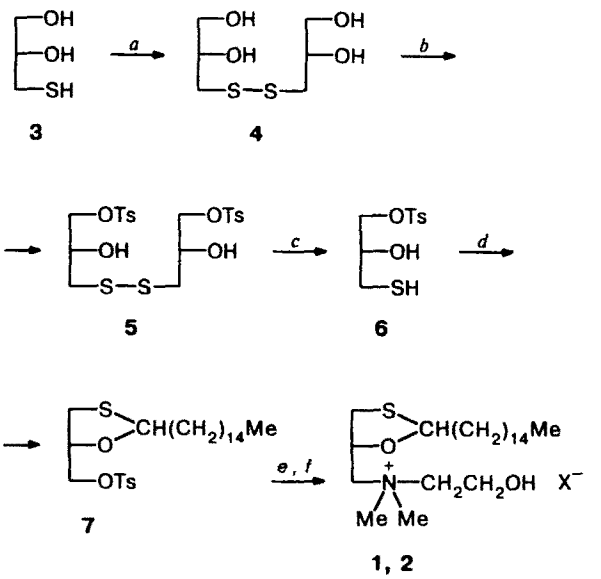
Numerous highly effective PAF antagonists of diverse structure have been synthesized to date.[6—11] Several cyclic structures sterically similar to the PAF molecule, *e.g.*, tetrahydropyran,[12] piperidine,[13] and THF derivatives,[14,15] are highly antagonistic to PAF. Cationic lipids having a dioxolane group are PAF antagonists.[16—19] The antagonist BN52111, for example, exhibits high activity.[20]



BN52111

In a continuation of our studies in this area, we have synthesized a cationic lipid bearing a 1,3-oxathiolane ring (Scheme 1) with two different anions, *viz.*, tosylate (compound **1**) and iodide anions (compound **2**).

Scheme 1



$X^- = TsO^-$ (**1**), I^- (**2**)

Reagents and conditions: *a*. 30 % H_2O_2, 10 °C, 4 h; *b*. TsCl, anhydrous $CHCl_3$, C_5H_5N, 5 °C, 20 °C, 10 h; *c*. $HSCH_2CH(OH)CH(OH)CH_2SH$, EtOH, 20 °C, 30 min; *d*. $Me(CH_2)_{14}CHO$, $BF_3 \cdot Et_2O$, anhydrous PhMe, 20 °C, 2 h; *e*. $Me_2NCH_2CH_2OH$, anhydrous DMSO, 60—70 °C, 5 h; *f*. (1) KI, anhydrous DMSO, 70—80 °C, 2 h; (2) $Me_2NCH_2CH_2OH$, 70—80 °C, 5 h.

To protect the mercapto group, the starting *rac*-3-mercaptopropane-1,2-diol (**3**) was oxidized with 30% H_2O_2 into 3,3′-dithiobis(propane-1,2-diol)[21] (**4**), which was transformed into tosyl derivative **5** without purification. According to TLC data, the reaction involves preferably the primary OH groups of compound **4** under

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the conditions chosen. The thus prepared 3,3′-dithiobis(1-*O*-tosylpropane-1,2-diol) (**5**) was introduced into the thiol-disulfide exchange with 1,4-dithiothreitol in EtOH, and *rac*-3-mercapto-1-*O*-tosylpropane-1,2-diol (**6**) was obtained in a yield of 33% (based on starting **3**). In the ^{1}H NMR spectrum of compound **6**, the signal of the $C\underline{H}_2OTs$ group is shifted downfield (δ 4.06) *vs.* the signal of the proton of the methine group >C<u>H</u>OH (δ 3.88). This confirms the selectivity of tosylation of compound **4** at the primary OH groups.

The *rac*-3-mercapto-1-*O*-tosylpropane-1,2-diol thus obtained reacted with palmitaldehyde in toluene in the presence of $BF_3 \cdot Et_2O$. After chromatographic purification, the yield of a diastereomeric mixture of 2-pentadecyl-5-tosyloxymethyl-1,3-oxathiolane (**7**) was 34%. A cationic lipid with tosylate anion **1** was prepared by heating substituted 1,3-oxathiolane **7** with an excess of $Me_2NCH_2CH_2OH$ in anhydrous DMSO, and the yield of a diastereomeric mixture **1** was 24%.

Lipid **2** was synthesized by the interaction of tosyl derivative **7** with KI followed by treatment with $Me_2NCH_2CH_2OH$ in anhydrous DMSO. The yield of mixture of diastereomers **2** was 42%.

The homogeneity and the structure of all the compounds synthesized were confirmed by TLC, ^{1}H NMR and IR spectroscopy data, and elemental analysis.

Experimental

n-Hexadecanol was purchased from Reanal, 3-mercaptopropane-1,2-diol, and 1,4-dithiothreitol were purchased from Serva, and the other reagents were manufactured in Russia. *p*-Toluenesulfonylchloride was recrystallized from hexane in the presence of $SOCl_2$. Palmitaldehyde was synthesized by oxidation of *n*-hexadecanol with DMSO in the presence of P_2O_5 (see Ref. 22).

Reactions were monitored by TLC on Silufol plates in the following solvent systems: $CHCl_3$—MeOH, 4 : 1 (v/v) (*A*); light petroleum—ether, 2 : 1 (*B*) and 3 : 1 (*C*), and $CHCl_3$—MeOH—H_2O, 65 : 25 : 4 (*D*). Spots were revealed by charring. Solvents were removed on a rotor evaporator at a residual pressure of 10—15 Torr and bath temperature not higher than 40 °C. Silica gel L 100/160 mm (Chemapol, Czechoslovakia) and silicic acid (Russia) were used for chromatography. Melting points were determined with a Boetius heating stage (Germany). The IR spectra were recorded with a Shimadzu IR-435 spectrometer (Japan) in a film for liquid compounds and in nujol for others. The ^{1}H NMR spectra were recorded with a Bruker MSL-200 pulse Fourier spectrometer (200 MHz) in $CDCl_3$ or in a 1 : 1 $CDCl_3$—CD_3OD mixture.

3,3′-Dithiobis(propane-1,2-diol) (4). 30% H_2O_2 (18 mL) was added dropwise to 3-mercaptopropane-1,2-diol (**3**) (10 g, 92 mmol) with stirring and cooling (0 °C) (the temperature of the reaction mixture increased to 25—35 °C), and the mixture was stirred at 20 °C for 4 h. After removal of water *in vacuo* (15 Torr, 35 °C), the compound was dried in a vacuum dessicator over P_2O_5. Disulfide **4** (10 g, R_f 0.21, *A*) obtained was used at the next stage without further purification. Found (%): C, 31.33; H, 6.01. $C_6H_{14}O_4S_2 \cdot H_2O$. Calculated (%): C, 31.02; H, 6.94. IR, ν/cm^{-1}: 3250, 2900, 1390, 1300, 1090, 1030, 920, 875, 710, 620, 525.

3,3′-Dithiobis(1-*O*-tosylpropane-1,2-diol) (5). TsCl (10.9 g, 57 mmol) was added to a mixture of disulfide **4** (6.12 g, 28.5 mmol), anhydrous C_5H_5N (15 mL), and anhydrous $CHCl_3$ (200 mL) for 1 h with stirring and cooling (5 °C). The mixture was stirred at 20 °C for 10 h, then diluted with $CHCl_3$ (200 mL), washed with water (2×150 mL), and dried with Na_2SO_4. After removal of the solvent, the product (16.1 g, R_f 0.75, *A*) was used at the next stage without further purification.

***rac*-3-Mercapto-1-*O*-tosylpropane-1,2-diol (6).** 1,4-Dithiothreitol (5.3 g, 34.3 mmol) and conc. NH_4OH (0.2 mL) were added to a solution of 3,3′-dithiobis(1-*O*-tosylpropane-1,2-diol) (**5**) (16 g, 30.6 mmol) in EtOH (150 mL) with stirring (20 °C), and stirring was continued for 30 min at the same temperature. The product was extracted with $CHCl_3$ (200 mL), and the extract was washed with water (2×150 mL) and dried with Na_2SO_4. The solvent was removed *in vacuo*, the residue was chromatographed on a column with silicic acid in a 4 : 1 light petroleum—ether solvent system. The solvent was removed *in vacuo*, and the residue was dried *in vacuo* (1 Torr) at 50 °C for 1 h to yield compound **6** (5.23 g, 33%), R_f 0.26 (*B*). Found (%): C, 45.69; H, 5.41. $C_{10}H_{14}O_4S_2$. Calculated (%): C, 45.78; H, 5.38; IR, ν/cm^{-1}: 3420, 3020, 2910, 2580, 1925, 1820, 1770, 1600, 1490, 1460, 1390, 1350, 1290, 1175, 1090, 975, 660. ^{1}H NMR, δ: 2.44 (s, 3 H, $-C_6H_4C\underline{H}_3$); 2.63 (m, 2 H, $-C\underline{H}_2SH$); 3.88 (m, 1 H, >C<u>H</u>OH); 4.06 (d, 2 H, $-CH_2OTs$, J = 5 Hz); 7.35 (d, 2 H, 3,5-H(Ar), J = 8 Hz); 7.79 (d, 2 H, 2,6-H (Ar), J = 8 Hz).

2-Pentadecyl-5-tosyloxymethyl-1,3-oxathiolane (7). $BF_3 \cdot Et_2O$ (1.88 mL) was added to a solution of *rac*-3-mercapto-1-*O*-tosylpropane-1,2-diol (**6**) (5.0 g, 19 mmol) and palmitaldehyde (3.5 g, 14.5 mmol) in anhydrous toluene (100 mL) with stirring (20 °C). The reaction mixture was stirred at 20 °C for 2 h, then $CHCl_3$ (200 mL) was added, and the resulting solution was washed with water (2×100 mL) and dried with Na_2SO_4. The solvent was removed *in vacuo*, the residue was chromatographed on a column with silica gel L (100/160), impurities were eluted with a 20 : 1 light petroleum—ether mixture, and the reaction product was eluted with a 10 : 1 light petroleum—ether mixture. The solvent was removed *in vacuo*, and the residue was dried *in vacuo* (1 Torr) at 45 °C for 2 h yielding compound **7** (3.12 g, 34%), R_f 0.42 (*C*, silica gel 60, Merck). Found (%): C, 64.86; H, 9.03. $C_{26}H_{44}O_4S_2$. Calculated (%): C, 64.42; H, 9.15. IR, ν/cm^{-1}: 2900, 1600, 1500, 1460, 1365, 1380, 1175, 1100, 1075, 980, 925, 840, 830, 810, 710, 660, 550. ^{1}H NMR, δ: 0.88 (t, 3 H, CH_3); 1.26 (m, 28 H, $(CH_2)_{14}$); 2.45 (s, 3 H, $-C_6H_4C\underline{H}_3$); 2.78, 3.05 (both m, 2 H, $-CH_2S$); 4.05 (m, 1 H, $(CH_2)_2C\underline{H}O-$); 4.12 (m, 2 H, $-C\underline{H}_2OTs$); 5.02 (m, 1 H, —SCHO—); 7.34 (d, 2 H, 3,5-H (Ar), J = 8 Hz); 7.79 (d, 2 H, 2,6-H(Ar), J = 8 Hz).

[(2-Pentadecyl-1,3-oxathiolan-5-yl)methyl]-(2-hydroxyethyl)-*N,N*-dimethylammonium tosylate (1). A mixture of compound **7** (0.91 g, 1.9 mmol) and $Me_2NCH_2CH_2OH$ (3.60 g, 40 mmol) in anhydrous DMSO (7 mL) was heated at 60—70 °C for 5 h. The excess amine and DMSO were removed *in vacuo* (1 Torr, 70 °C). The residue was dissolved in $CHCl_3$ (60 mL), and the solution was washed with water (2×40 mL) and dried with Na_2SO_4. The solvent was removed *in vacuo*, and the residue was chromatographed on a column with silica gel L (100/160). Impurities were eluted with $CHCl_3$ and the product was eluted with a $CHCl_3$—MeOH (30 : 1 → 20 : 1 → 10 : 1) mixture. Compound **1** was dried *in vacuo* (1 Torr, 50 °C) for 2 h; yield 0.26 g (24%), R_f 0.45 (*D*), m.p. 188—190 °C. Found (%): N, 2.36; S, 9.70. $C_{30}H_{55}NO_5S_2$. Calculated (%): N, 2.44; S, 11.17. IR, ν/cm^{-1}: 3360, 2885, 1500,

1460, 1380, 1220, 1180, 1120, 1075, 1035, 1010, 960, 810, 710, 680, 560. ^{1}H NMR, δ: 0.86 (t, 3 H, CH_3); 1.24 (m, 28 H, $(CH_2)_{14}$); 2.33 (s, 3 H, $-C_6H_4C\underline{H}_3$); 2.65, 3.18 (both m, 2 H, $-CH_2S$); 3.35 (s, 6 H, $>N^+Me_2$); 3.78 (m, 2 H, $-\underline{CH}_2N^+Me_2$); 4.00—4.34 (m, 4 H, $Me_2N^+-C\underline{H}_2CH_2OH$, $-CH_2C\underline{H}_2OH$); 4.44, 4.70 (both m, 1 H, $(CH_2)_2C\underline{H}O-$); 5.09, 5.18 (both t, 1 H, —SCHO—); 7.16 (d, 2 H, 3,5-H(Ar), J = 8 Hz); 7.72 (d, 2 H, 2,6-H(Ar), J = 8 Hz).

[(2-Pentadecyl-1,3-oxathiolan-5-yl)methyl]-(2-hydroxyethyl)-*N,N*-dimethylammonium iodide (2). A mixture of compound 7 (0.56 g, 1 mmol) and KI (1.15 g, 6 mmol) in anhydrous DMSO (10 mL) was heated to 70—80 °C for 2 h. $Me_2NCH_2CH_2OH$ (2.05 g, 23 mmol) was added and the mixture was heated at 70—80 °C for 5 h with stirring. After cooling, $CHCl_3$ (80 mL) was added to the reaction mixture, and the solution was washed with water (3×40 mL) and dried with Na_2SO_4. The solvent was removed *in vacuo*, and the residue was chromatographed on a column with silica gel L (100/160) eluting with a $CHCl_3$—MeOH mixture (40 : 1 → 30 : 1 → 20 : 1 → 10 : 1). The product was dried *in vacuo* (1 Torr) at 50 °C for 2 h, yielding compound **2** (0.25 g, 42%), R_f 0.62 (*D*), m.p. 185—189 °C (sinters at 65 °C). Found (%): N, 2.44; S, 5.44. $C_{23}H_{48}INO_2S$. Calculated (%): N, 2.64; S, 6.05. IR, ν/cm^{-1}: 3300, 2900, 1460, 1380, 1260, 1225, 1140, 1100, 1075, 1020, 950, 930, 716. ^{1}H NMR, δ: 0.87 (t, 3 H, CH_3); 1.24 (m, 28 H, $(CH_2)_{14}$); 2.80, 3.39 (both m, 2 H, $-CH_2S$); 3.47 (s, 6 H, $>N^+Me_2$); 3.88 (m, 2 H, $-\underline{CH}_2N^+Me_2$); 4.07—4.38 (m, 4 H, $Me_2N^+-C\underline{H}_2CH_2OH$, $-CH_2C\underline{H}_2OH$); 4.56, 4.79 (both m, 1 H, $(CH_2)_2C\underline{H}O-$); 5.22, 5.28 (both t, 1 H, —SCHO—).

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