($C_{16}H_{25}ClNO_2$) (monohydrate) C, H, N, Cl.

Method B. An acetone solution (150 mL) of 1-amino-2-hydroxy-1-methyl-1,2,3,4-tetrahydronaphthalene (**14**) (2.5 g, 0.014 mol) and 1,5-dibromopentane (3.22 g, 0.014 mol) was refluxed for 48 h. After cooling, sodium carbonate (1.5 g, 0.014 mol) was added and the mixture was refluxed for an additional 48 h. The mixture was cooled and filtered and the solvent removed in vacuo. Water (20 mL) was added, and the solution was acidified with 4 M HCl. After washing with ether (3 × 50 mL), the remaining aqueous phase was basified (4 M NaOH) and extracted with chloroform (3 × 100 mL). The combined chloroform layers were dried ($MgSO_4$), and the solvent was removed in vacuo, leaving an oil, yield 1.4 g (41.3%).

1-Methyl-1-piperidyl-2-tetralone (19). By the same procedure described for the synthesis of **4** (method A), a 37% yield of **19** was obtained from the oxidation of 2-hydroxy-1-methyl-1-piperidyl-1,2,3,4-tetrahydronaphthalene (**18**): IR (neat) 1710 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.40 (m, 9, 1-CH_3 and piperidyl (3-, 4-, and 5-CH_2)), 2.15–3.15 (m, 8, 3-CH_2, 4-CH_2, and piperidyl (2- and 6-CH_2)), 7.11–7.60 (m, 4, aromatic); MS m/z 243 (M^+), 215, 200, 131 (base), 84. Hydrochloride: mp 246–268 °C. (ethanol). Anal. ($C_{16}H_{22}ClNO$) C, H, N, Cl.

2-Amino-2-methyl-1-tetralone (5). Concentrated sulfuric acid (25 mL) was added dropwise over a period of 1 h to 2-amino-2-cyano-4-phenylbutane[18] (22.0 g, 0.13 mol). The mixture was stirred at room temperature for 24 h and then cautiously poured into water (200 mL). The solution was neutralized with sodium hydroxide pellets and extracted with ether (3 × 100 mL). The ether was dried ($MgSO_4$) and removed in vacuo, leaving a yellow oil: yield 3.5 g (15.8%); IR (neat) 3290–3350 (NH_2), 1680 cm^{-1} (C=O); NMR ($CHCl_3$) δ 1.30 (s, 3, 2-CH_3), 1.85–2.35 (m, 4, 3-CH_2 and NH_2, exchangeable with D_2O), 3.05 (t, J = 2 2 Hz, 2, 4-CH_2), 7.15–7.50 (m, 3, aromatic), 7.90–8.10 (m, 1, aromatic 8-CH); MS m/z 175 (M^+), 148 (base). Hydrochloride: mp 256–257 °C (ethanol). Anal. ($C_{11}H_{14}ClNO$) C, H, N, Cl.

2-(Dimethylamino)-2-methyl-1-tetralone (21). Eschweiler–Clarke methylation[17] of **19** resulted in an 83% yield of **20**: IR (neat) 1680 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.20 (s, 3, 2-CH_3), 1.60–2.80 (m, 10, 3-CH_2, 4-CH_2, and 2-$N(CH_3)_2$), 7.20–8.05 (m, 4, aromatic); MS m/z 203 (M^+), 148 (base).

Evaluation of Spontaneous Locomotor Activity and Loss of Righting Reflex. Male, Swiss–Webster mice (25–35 g) were provided Purina rodent laboratory chow and water ad libitum. Temperature was maintained at 20–24 °C with a light period from 06.00 to 18.00 h. Animals were housed in wire mesh cages (16 × 18 × 24 cm) containing five mice each. Drug solutions were prepared in distilled water such that all doses were given in a volume of 20 mg/mL. All compounds were administered intraperitoneally in 50, 100, 150, and 200 mg kg^{-1} doses. Control animals received a comparable volume of normal saline. Spontaneous locomotor activity was measured with a Stoelting electronic activity monitor system (Stoelting Instruments, Chicago, IL). The average number of activity counts was measured for 5-min intervals up to a total time of 90 min following injection. All animal experiments were conducted between 13.00 and 17.00 h. Comparison of treatment groups by Duncan's multiple-range test was used to test the significance of the results.[19] Following injection, animals were observed for loss of righting reflex which was determined to occur when an animal could not right itself when placed on its back. Righting reflex was judged to be regained when an animal was able to turn over three times in a 10-s period.

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Registry No. **4**, 96866-37-4; **4**·HCl, 96866-38-5; **5**, 96866-39-6; **5**·HCl, 75834-65-0; **7**, 565-07-1; **8**, 24539-99-9; **9**, 24540-00-9; **10**, 96866-40-9; **11**, 3480-56-6; **12**, 91335-38-5; **13**, 96866-41-0; **13**·HCl, 96866-42-1; **14**, 96866-43-2; **14**·HCl, 96866-44-3; **15**, 96866-45-4; **15**·HCl, 96866-46-5; **16**, 96866-47-6; **16**·HCl, 96866-48-7; **17**, 96866-49-8; **17**·HCl, 96866-50-1; **18**, 96866-51-2; **18**·HCl, 96866-52-3; **19**, 96866-53-4; **19**·HCl, 96866-54-5; **21**, 96866-56-7; 2-amino-2-cyano-4-phenylbutane, 96866-55-6; phthalic anhydride, 85-44-9; 1,5-dibromopentane, 111-24-0.

Analogues of Platelet Activating Factor. 3.[1] Replacement of the Phosphate Moiety with a Sulfonylbismethylene Group

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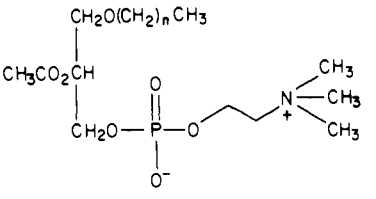
An analogue of platelet activating factor (PAF) in which the phosphate moiety has been replaced with a sulfonylbismethylene group (**8**) has been prepared. A key step in the synthetic sequence is the preparation of 4-[[3-(dimethylamino)propyl]thio]-1-(hexadecyloxy)-2-butanol (**5**) via a one-pot reaction involving a sequential Michael addition and reduction. In comparison to racemic C_{16}-PAF, **8** showed no platelet aggregating activity and substantially reduced hypotensive activity.

Platelet activating factor (PAF), a phospholipid of structure **1** composed primarily of the C_{16} and C_{18} homologues,[2] has a variety of interesting biological properties, among which is its potent ability to aggregate platelets and to lower blood pressure.[3] In a continuation of our study[1]



1, n = 15 or 17

of the structure–activity profile of analogues of this important substance, we have prepared a number of compounds in which the phosphocholine portion of the mol-

(1) For previous papers in this series, see: (a) Wissner, A.; Sum, P-E.; Schaub, R. E.; Kohler, C. A.; Goldstein, B. M. *J. Med. Chem.* **1984**, *27*, 1174. (b) Wissner, A.; Sum, P. E.; Schaub, R. E.; Kohler, C. A.; Goldstein, B. M. *J. Med. Chem.*, companion paper in this issue.

(2) (a) Benveniste, J.; Tence, M.; Varenne, P.; Bidault, J.; Boullet, C.; Polonsky, J. *C. R. Hebd. Seances Acad. Sci, Ser. D* **1979**, 289, 1037. (b) Polonsky, J.; Tence, M.; Varenne, P.; Das, B. C.; Lunel, J.; Benveniste, J. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 7019. (c) Demopoulos, C. A.; Pinckard, R. N.; Hanahan, D. J. *J. Biol. Chem.* **1979**, *254*, 9355. (d) Hanahan, D. J.; Demopoulos, C. A.; Liehr J.; Pinckard, R. N. *J. Biol. Chem.* **1980**, *255*, 5514.

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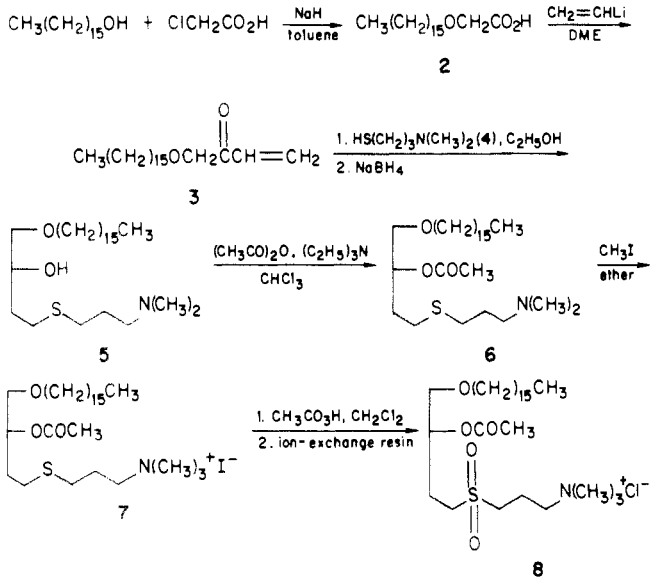
0022-2623/85/1828-1365$01.50/0

Scheme I



ecule has been altered. In this paper, we describe the preparation of one such compound (8) in which the charged phosphate moiety of PAF has been replaced with a neutral sulfonylbismethylene group.

Chemistry. Alkylation of 1-hexadecanol with chloroacetic acid (Scheme I) was accomplished by first forming the sodium salt of the acid in toluene by using an excess of sodium hydride and then adding the alcohol and refluxing for 40 h to give, after workup, the carboxylic acid 2. The reaction of 2 with an excess of vinyllithium in dimethoxyethane gave the unsaturated ketone 3. Compound 5 was prepared in a one-pot reaction involving a sequential Michael addition and reduction. Thus, addition of an excess of *N,N*-dimethyl-3-aminopropanethiol (4) to an ethanolic solution of 3 followed by the portionwise addition of sodium borohydride gave 5 in 37% yield after purification. Acetylation of 5 with acetic anhydride and triethylamine gave the acetate 6. The amino group of 6 was quaternized to give 7 in 80% yield by the reaction of an ethereal solution of 6 with 1 equiv of methyl iodide at room temperature for 5 days. Finally, oxidation of 7 to the sulfone was accomplished in 84% yield with 40% peracetic acid in methylene chloride at room temperature to give, after treatment with a chloride ion exchange resin, the desired racemic analogue 8, in which the phosphate group of PAF has been replaced with a sulfonylbismethylene moiety.

Biological Results

In contrast to racemic PAF (1, n = 15), 8 did not aggregate rabbit platelets at concentrations as high as 1.8×10^{-4} M. Furthermore, 8 is considerably less potent than PAF in its ability to lower blood pressure in the SHR rat; a dose of 10 mg/kg iv of 8 results in only a 20-mm decrease in the mean arterial blood pressure while for racemic PAF (1, n = 15) a dose of 0.3 μg/kg iv results in the same decrease.

While a sulfonylbismethylene group would be expected to have steric requirements similar to a phosphate group, it is, nevertheless, apparent that incorporation of the former moiety into the PAF structure results in a substantial decrease in biological activity. Since these two groups differ electronically, it is tempting to speculate that it is the ability of the phosphate group to bear a negative charge that is responsible for its contribution to the activity of PAF.[4]

Experimental Section

General Methods. Melting points were determined on a Mel-Temp capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on Varian FT-80 or Nicolet NT-300 WB spectrometers and chemical shifts are reported in parts per million (ppm) with tetramethylsilane as an internal reference. Infrared (IR) spectra were obtained with a Nicolet FT-700 spectrophotometer and mass spectra (MS) were obtained with a Finnegan-MAT Model CH7 or Kratos MS-50 mass spectrometer.

Biological Assays. Platelet aggregation studies were conducted with use of rabbit platelet-rich plasma. Compound 8 was tested at five concentrations ranging from 1×10^{-7} to 1.8×10^{-4} M with two to four replicates at each concentration level. We were unable to observe any platelet aggregation induced by 8 over this range of concentrations.

Blood pressure studies were conducted with spontaneously hypertensive rats (SHR). Analogue 8 was administered intravenously at five separate doses and a dose–response curve was generated from which the value that decreased the mean arterial blood pressure 20 mmHg was determined by using a least-squares regression analysis.

Full experimental details concerning the biological methods have been described previously.[1a]

1-(Hexadecyloxy)acetic Acid (2). To a suspension of 44.5 g (0.93 mol) of washed (hexane) 50% sodium hydride mineral oil dispersion in 500 mL of toluene was added with mechanical stirring under argon a solution of 46.8 g (0.49 mol) of chloroacetic acid in 200 mL of toluene over 1 h. A solution of 100 g (0.41 mol) of 1-hexadecanol in 200 mL of toluene was then added over 15 min. The mixture was stirred at reflux for 40 h, cooled to room temperature, and acidified with dilute HCl. The mixture was heated until all solid dissolved. The hot organic layer was dried ($MgSO_4$) and cooled, giving 84.5 g (68%) of 2 as a colorless solid: mp 64–66 °C (lit.[5] mp 64.3 °C); NMR ($CDCl_3$) δ 7.78 (brs, 1 H, CO_2H), 4.18 (s, 2 H, OCH_2CO_2), 3.60 (t, 2 H, OCH_2CH_2), 1.30 (m, 28 H, $(CH_2)_{14}$), 0.93 (m, 3 H, terminal CH_3); IR (KBr) 1695 cm^{-1} (C=O); MS, m/z 300 (M^+). Anal. ($C_{18}H_{36}O_3$) C; H: calcd, 12.08; found, 11.64.

1-(Hexadecyloxy)-3-buten-2-one (3). To a solution of 88 g (0.29 mol) of 2 in 800 mL of dimethoxyethane (DME) was added dropwise under argon with stirring at 0 °C 280 mL of 2.3 M vinyllithium in THF. The mixture was stirred at 40 °C overnight. TLC of an aliquot quenched with dilute HCl indicated that some 2 remained unreacted. The solution was cooled to room temperature and another 180 mL of vinyllithium solution was added. The mixture was maintained at 40 °C for 18 h. The mixture was cooled to room temperature and pumped with the use of a double-tip needle into dilute HCl with ice cooling under argon. The mixture was saturated with NaCl and the organic layer was separated. The aqueous layer was extracted with ether. The combined organic solutions were dried ($MgSO_4$), and the solvent was removed. The product was chromatographed via preparative HPLC (hexane–ether, 9:1), giving 26.7 g of a white solid. TLC showed a major component that gave a yellow spot on treatment with (2,4-dinitrophenyl)hydrazine spray and a minor, more polar, component that did not react with the reagent spray. Obtained in this manner, 3 was used in the next step without additional purification.

4-[[3-(Dimethylamino)propyl]thio]-1-(hexadecyloxy)-2-butanol (5). A solution of 26.5 g (85.3 mmol) of impure 3 in 200 mL of EtOH was warmed on a steam bath until all solid dissolved. To the solution was added 26.9 g (0.26 mol) of *N,N*-dimethyl-3-aminopropanethiol (4). After the solution was stirred for 1 h, 3.23 g (85.3 mmol) of solid $NaBH_4$ was added portionwise over 30 min. After being stirred an additional 1.5 h, the solution was poured into H_2O and extracted with ether. The organic solution was dried

(4) Recently a phosphonate analogue of PAF was reported [Moschidis, M. C.; Demopoulos, C. A.; Kritikou, L. G. *Chem. Phys. Lipids* **1983**, *33*, 87]. This compound is only 30 times less potent than the natural product with respect to platelet activity.

(5) Hato, M.; Shinoda, K.; Myagama, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1257.

($MgSO_4$). Solvent and excess 4 were removed at reduced pressure. The residue was chromatographed on silica gel via preparative HPLC, eluting with chloroform–methanol (9:1), giving 13.7 g (37%) of **5** as a colorless solid: mp 30–32 °C; NMR ($CDCl_3$) δ 3.90 (m, C*H*OH), 3.43 (m, 4 H, CH_2OCH_2), 2.85–2.20 (m, 7 H, CH_2SCH_2, CH_2N, OH), 2.25 (s, 6 H, $N(CH_3)_2$), 2.1–1.15 (m, 32 H, $(CH_2)_{14}$, $S(CH_2CH_2)_2$),0.90 (m, 3 H, terminal CH_3); IR (neat) 3500 cm^{-1} (OH); MS, *m/z* 431 (M^+). Anal. ($C_{25}H_{53}O_2SN$) C, H, N, S.

4-[[3-(Dimethylamino)propyl]thio]-1-(hexadecyloxy)-2-butanol Acetate (6). A solution of 12.5 g (29 mmol) of **5**, 73.9 g (0.72 mol) of acetic anhydride, and 29.3 g (0.29 mol) of Et_3N in 700 mL of $CHCl_3$ was refluxed for 35 h. Solvent and excess anhydride were removed at reduced pressure. TLC (silica gel, $CHCl_3$–MeOH–H_2O, 70:30:5) indicated that some unreacted **5** remained; 40 mL of acetic anhydride and 0.2 g of sodium acetate were added, and the mixture was refluxed for 15 min. The excess anhydride was removed at reduced pressure at 40–60 °C. The residue was dissolved in ether–methanol (1:1), treated with Norite, and filtered through a pad of silica gel. Solvent was removed, giving 13.2 g (96%) of **6** as a yellow oil, homogeneous on TLC: NMR ($CDCl_3$) δ 5.08 (m, 1 H, C*H*OAc), 3.44 (m, 4 H, CH_2OCH_2), 2.51 (m, 6 H, CH_2SCH_2, CH_2N), 2.31 (s, 6 H, $N(CH_3)_2$), 2.07 (s, 3 H, $COCH_3$), 1.86 (m, 4 H, $S(CH_2CH_2)_2$), 1.54 (m, 2 H, OCH_2CH_2), 1.25 (m, 26 H, $(CH_2)_{13}$), 0.88 (m, 3 H, terminal CH_3); IR (neat) 1740 cm^{-1} (C=O); MS, *m/z* 473 (M^+). Anal. ($C_{27}H_{55}O_3SN$) C, H, N, S; C: calcd, 68.45; found, 66.85.

3-[[3-(Acetyloxy)-4-(hexadecyloxy)butyl]thio]-*N*,*N*,*N*-trimethyl-1-propanaminium Iodide (7). A solution of 12.0 g (25.3 mmol) of **6** and 3.59 g (25.3 mmol) of methyl iodide in 200 mL of ether was allowed to stand at room temperature for 5 days. Solid was collected and washed with ether, giving 11.3 g of **7** as a colorless powder. From the filtrate was recovered 1.1 g of unreacted **6**. The yield is 80% after correcting for recovered **6**: NMR ($CDCl_3$) δ 5.13 (m, 1 H, C*H*OAc), 3.80 (m, 2 H, CH_2N), 3.47 (s, 9 H, $N(CH_3)_3$), 3.42 (m, 4 H, CH_2OCH_2), 2.61 (m, 4 H, CH_2SCH_2), 2.11 (m, 2 H, CH_2CH_2N), 1.89 (m, 2 H, CH_2CH_2S), 1.57 (m, 2 H, CH_2CH_2O), 1.26 (m, 26 H, $(CH_2)_{13}$), 0.88 (m, 3 H terminal CH_3); IR (KBr) 1736 cm^{-1} (C=O); MS (EI), *m/z* 473 (M – CH_3I). Anal. ($C_{28}H_{58}O_3SNI$) C, H, N, S, I.

3-[[3-(Acetyloxy)-4-(hexadecyloxy)butyl]sulfonyl]-*N*,*N*,*N*-trimethyl-1-propanaminium Chloride (8). To a solution of 3.5 g (5.7 mmol) of **7** in 150 mL of CH_2Cl_2 was added 9.0 g of 40% peracetic acid. After the solution was allowed to stand overnight, a saturated solution of $NaHSO_3$ was added until the iodine color disappeared. Solvent was removed. Ethanol and then CH_2Cl_2 were added and then evaporated to remove last traces of H_2O. The residue was mixed with CH_2Cl_2 and filtered. The solvent was removed from the filtrate and the residue was dissolved in 400 mL of CH_2Cl_2–CH_3OH (1:2). The solution was stirred with 100 g of chloride ion exchange resin (Bio-Rad AGI-X2) for 10 min. The mixture was filtered and the filtrate was stirred with another 50 g of resin. The mixture was filtered and solvent was removed. The residue was triturated with ether and 2.65 g (84%) of **8** was collected as a white powder, which did not have a well-defined melting point. Elemental analysis indicates a monohydrate: NMR ($CDCl_3$ + CD_3OD) δ 5.10 (m, 1 H, C*H*OAc), 3.72 (m, 2 H, CH_2N), 3.58–3.13 (m's, 8H, CH_2OCH_2, $CH_2SO_2CH_2$), 3.23 (s, 9 H, $N(CH_3)_3$), 2.35 (m, 2 H, CH_2CH_2N), 2.19 (m, 2 H, CH_2CH_2S), 2.10 (s, 3 H, $COCH_3$), 1.55 (m, 2 H, CH_2CH_2O), 1.23 (m, 26 H, $(CH_2)_{13}$), 0.88 (m, 3 H, terminal CH_3); IR (KBr) 1735, 1275, 1238, 1130 cm^{-1}; MS (FAB), *m/z* 520 (M – Cl). Anal. ($C_{28}H_{58}O_5SNCl·H_2O$) C, H, N, S, Cl.

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Registry No. 1 (*n* = 15), 85733-92-2; **2**, 58210-02-9; **3**, 97012-58-3; **4**, 42302-17-0; **5**, 97012-59-4; **6**, 97012-60-7; **7**, 97012-61-8; **8**, 97012-62-9; chloroacetic acid, 79-11-8; 1-hexadecanol, 36653-82-4; vinyllithium, 917-57-7.