0 °C for 10 min. The reaction vessel was sealed and heated at 110–120 °C. After 3 h, the heat was removed and after cooling the product was collected by filtration. The solid was rinsed with MeOH to yield after drying 100 mg (75%) of the desired material as an orange solid: mp 221–223 °C. IR (KBr): 3424, 1626, 1560, 1447, 1306, 1244, 1152, 1105, 729 cm^{-1}. ^1H NMR (DMSO-d_6) δ (ppm): 2.71 (s, 3 H), 3.03 (d, 3 H, J = 3.78 Hz), 4.38 (s, 2 H), 6.79 (d, 1 H, J = 7.54 Hz), 6.88 (d, 1 H, J = 7.48 Hz), 7.54–7.71 (m, 6 H), 7.93–7.99 (m, 6 H), 8.15 (m, 1 H).

Acknowledgment. We would like to thank the members of the Crystallography, Computational Chemistry, and Medicinal Chemistry Groups for both their intellectual and technical assistance throughout this work. We thank Dottie Olson for her expert assistance in preparing this manuscript.

Registry No. 3·2HCl, 138384-41-5; 3 free base, 138384-42-6; 4, 138384-43-7; 5, 138384-44-8; 6, 138384-45-9; 7, 138384-46-0; 8, 138384-47-1; 9·maleate, 138384-49-3; 9 free base, 138384-48-2; 10, 138384-50-6; 11, 138384-51-7; 12, 138384-52-8; 13, 138384-53-9; 14, 138384-54-0; 15, 138384-55-1; 16, 138384-56-2; 17, 138384-57-3; 18, 138384-58-4; 19, 138384-59-5; 20, 138384-60-8; 21, 138384-61-9; 22 free base, 138384-62-0; 22·HCl, 138384-63-1; 23, 138384-64-2; 24, 138384-65-3; 25, 138384-66-4; 26, 138384-67-5; 27, 138384-68-6; 28, 138384-69-7; 29·$^1/_2$AcOH, 138384-71-1; 29 free base, 138384-70-0; 30, 138384-72-2; 31, 138384-73-3; 32, 138384-74-4; 33, 138384-75-5; 34, 138384-76-6; 35, 138384-77-7; 36, 138384-78-8; 37, 138407-36-0; 38·maleate, 138384-80-2; 38 free base, 138384-79-9; 39, 138384-81-3; 40, 138384-82-4; 41·xAcOH, 138384-84-6; 41 free base, 138384-83-5; 42·2AcOH, 138384-86-8; 42 free base, 138384-85-7; 43, 138384-87-9; 44·maleate, 138384-89-1; 44 free base, 138384-88-0; 45a, 130-00-7; 45b, 138384-90-4; 45c, 24950-29-6; 46a, 34599-42-3; 46b, 138384-91-5; 46c, 138384-92-6; 47a, 50964-11-9; 47b, 138384-93-7; 47c, 138384-94-8; 48, 138384-95-9; 49, 138384-96-0; 50, 10130-89-9; 51, 138384-97-1; 52, 138384-98-2; 52 alcohol, 138384-99-3; 52 carboxylic acid, 138385-00-9; 55a, 138384-73-3; 55b, 138385-01-0; 55c, 138385-02-1; 55d, 138384-50-6; 55e, 138385-03-2; 56, 6642-29-1; 57, 28434-96-0; 58, 65300-66-5; 59, 65300-69-8; 60, 74356-38-0; 61b, 6339-26-0; 62a, 7705-63-7; 62b, 138385-04-3; 63, 138385-05-4; phenyl p-tolyl sulfone, 640-57-3; *tert*-butyl 1-piperazinecarboxylate, 57260-71-6; 5-methylnaphthoyl azide, 138385-06-5; 5-methylnaphthoic acid, 4527-60-0; N-[4-(phenylsulfonyl)benzyl]-N-methyl-6-aminobenz[cd]indole-2-(1H)-thione, 138385-07-6; 1-chloro-2,4-dinitrobenzene, 97-00-7; thymidylate synthase, 9031-61-2.

4-Substituted 2-Alkoxytetrahydrofurans as Potent and Long-Lasting PAF Antagonists

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A series of 4-substituted 2-alkoxytetrahydrofuran derivatives featuring an acetal group were prepared and evaluated for PAF antagonist activity in the PAF-induced in vitro platelet-aggregation and in vivo hypotension tests. Compound 2-[[N-acetyl-N-[[[2-(octadecyloxy)tetrahydrofuran-4-yl]methoxy]carbonyl]amino]methyl]-1-ethylpyridinium chloride (**4e**, UR-11353) was selected for further development on the basis of its high activity and long-lasting action. The compound maintained a significant activity even 24 h after administration of a single dose of 1 mg/kg iv in the PAF-induced mortality test in mice and 10 h after administration of the same dose in the PAF-induced hypotension test in rats. Comparison with previously reported carba analogues suggests that the presence of the acetal group is the structural characteristic that confers its long-lasting activity.

Introduction

Platelet activating factor (PAF), an endogenous ether-linked phospholipid identified as 1-*O*-hexadecyl and 1-*O*-octadecyl-2-acetyl-*sn*-glyceryl-3-phosphocholine[1] has been receiving increasing attention as a potential mediator of several pathological conditions such as asthma, inflammation, anaphylactic shock, gastric ulceration, and transplant rejection.[2] Shortly after PAF's biological actions were described, a wide variety of compounds exhibiting potent PAF antagonist activity were discovered.

We have recently reported a new series of disubstituted tetrahydrofuran and dioxolane derivatives of formula **1a–e** as specific PAF antagonists (Figure 1).[3] We determined the influence of ring pattern on anti-PAF activity and studied the role of the nature of the lipophilic substituent R_1. The inhibitory effect of several of these compounds in the PAF-induced rabbit platelet aggregation test was higher than that of the structurally related compound 2-[[N-acetyl-N-[[2-methoxy-3-[(octadecylcarbamoyl)-oxy]propoxy]carbonyl]amino]methyl]-1-ethylpyridinium chloride (CV-6209, **2**).[4]

In connection with our research on the role of the central framework, we have recently described a new series of linear PAF antagonists of general formula **3** as simplified models of **1a–e** derivatives.[5] These compounds feature

† Department of Chemistry.
‡ Department of Pharmacology.

(1) (a) Demopoulos, C. A.; Pinckard, N. R.; Hanahan, D. J. Platelet-activating factor. Evidence for 1-*O*-alkyl-*sn*-glycerol-3-phosphocholine as the active component (a new class of lipid chemical mediators). *J. Biol. Chem.* **1979**, *254*, 9355–9358. (b) Benveniste, J.; Tence, M.; Varenne, P.; Bidault, J.; Boullet, C.; Polonsky, J. C. Semisynthèse et structure proposeé du facteur activant les plaquettes (P. A. F.): PAF-acether, un alkyl ether analogue de la lysophosphatidylcholine. *R. Acad. Sci. Paris* **1979**, *289*, 1037-1040.

(2) Hosford, D.; Braquet, P. Antagonists of Platelet-Activating Factor: Chemistry, Pharmacology and Clinical Applications. In *Progress in Medicinal Chemistry*; Ellis, G. P., West, G. B., Eds.; Elsevier Science Publisher: Amsterdam, 1990; Vol. 27, pp 325–380.

(3) Bartroli, J.; Carceller, E.; Merlos, M.; García-Rafanell, J.; Forn, J. 1,3 Disubstituted Tetrahydrofurans and Dioxolanes as PAF-Antagonists. *J. Med. Chem.* **1991**, *34*, 373–386.

(4) (a) Terashita, Z-i.; Imura, Y.; Takatani, M.; Tsushima, S.; Nishikawa, K. CV-6209, a Highly Potent Antagonist of Platelet Activating Factor *in Vitro* and *in Vivo*. *J. Pharmacol. Exp. Ther.* **1987**, *242*, 263–268. (b) Takatani, M.; Yoshioka, Y.; Tasaka, A.; Terashita, Z.-i.; Imura, Y.; Nishikawa, K.; Tsushima, S. Platelet Activating Factor Antagonists: Synthesis and Structure-Activity Studies of Novel PAF Analogues Modified in the Phosphorylcholine Moiety. *J. Med. Chem.* **1989**, *32*, 56–64.

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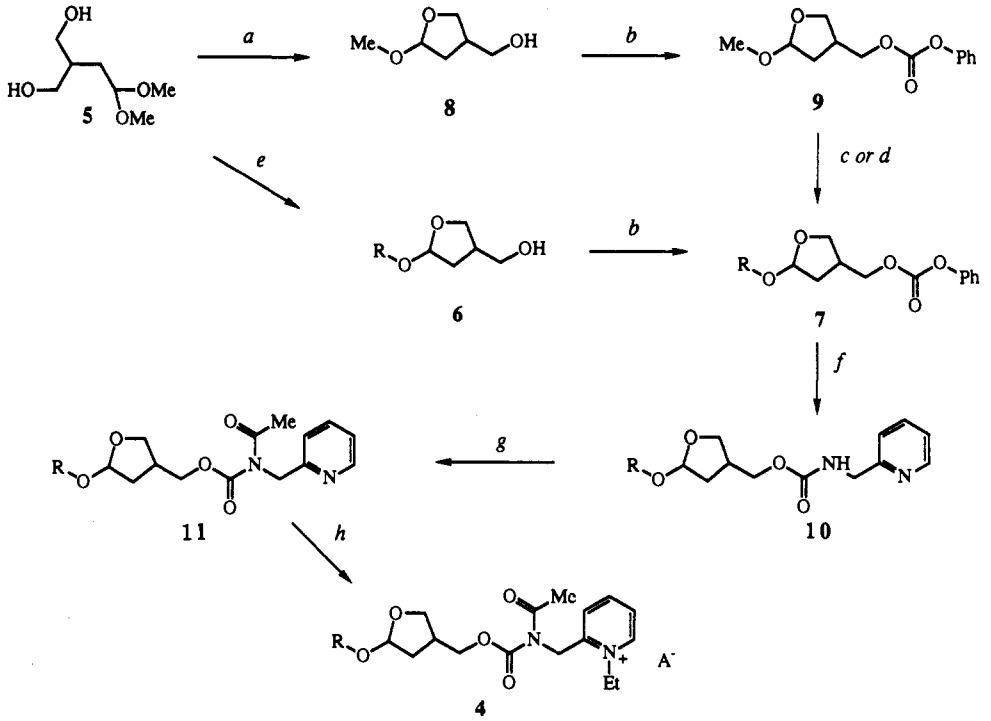
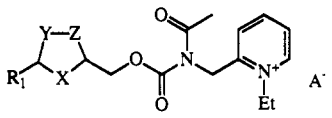
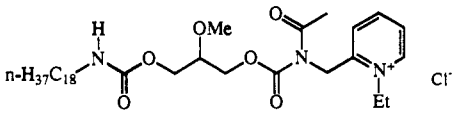
Scheme I[a]



[a] (a) Pyridinium 10-camphorsulfonate, CH_2Cl_2, room temperature, 18 h; (b) $ClCO_2Ph$, py, CH_2Cl_2, 0 °C, 2 h; (c) Dowex HCR-S H^+, THF–H_2O, reflux, 12 h, then MsCl, TEA, THF, -30 to 50 °C, ROH, 18 h, room temperature; (d) ROH, *p*-TsOH, toluene, 40 °C; (e) ROH, BF_2·Et_2O, CH_2Cl_2, 0–4 °C, 18 h; (f) 2-picolylamine, CH_3CN, reflux, 18 h; (g) AcCl, TEA, CH_2Cl_2, room temperature, 48 h; (h) EtI, CH_3CN, 70 °C, 24 h.



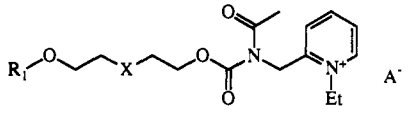
1a: X=O Y=Z=CH_2
1b: Y=O X=Z=CH_2
1c: Z=O X=Y=CH_2
1d: X=Y=O Z=CH_2
1e: X=Z=O Y=CH_2



2

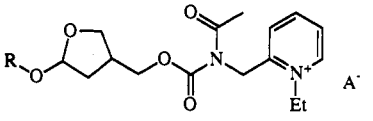
Figure 1.

a straightforward synthesis and are devoid of asymmetric centers.



3 (X=O,S)

High potency and long-lasting activity are both desirable in therapeutics. Thus, having achieved high levels of activity with compounds **1a–e** and **3**, we focused our efforts on improving their duration of action in vivo. As a result of preliminary screening of different structural modifications of our previously reported structures, we identified 4-substituted 2-alkoxytetrahydrofuran derivatives **4** as the most promising long-lasting compounds.[6]



4

In the present report, we describe the synthesis and PAF antagonist activities of the above compounds assessed by their ability to inhibit in vitro PAF-induced rabbit platelet aggregation and in vivo PAF-induced hypotension in rats. Furthermore, we compare the duration of effect of some selected compounds to that of the carba analogues **1**. The comparison is extended to **2**, a compound that shares the acyl carbamate substituent and is one of the most long-lasting charged PAF antagonists.[4a] The duration of action has been measured by the PAF-induced mortality test in mice and the PAF-induced hypotension test in rats.

The pharmacological tests have been carried out on the final products as cis–trans diastereomeric mixtures. However, in order to evaluate the effect of stereochemistry on the pharmacological activity, we have independently synthesized the cis and trans forms of a representative compound, **4d**.

Chemistry

The synthesis of acetals **4a–n** was accomplished as illustrated in Scheme I. The starting material, 2-(hydroxymethyl)-4,4-dimethoxybutan-1-ol, **5**,[7] was cyclized to

(5) Bartrolí, J.; Carceller, E.; Merlos, M.; Giral, M.; García-Rafanell, J.; Forn, J. Design of Potent Linear PAF Antagonists. *J. Med. Chem.* **1991**, *34*, 3328–3334.

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alcohol 6 upon treatment with excess of the corresponding fatty alcohol under boron trifluoride etherate catalysis in methylene chloride at 0 °C in 30–40% yield working on a few-gram scale. However, trying to increase the scale resulted in lower yields and tedious chromatographic separations of the excess fatty alcohol. We therefore looked for more reliable methods.

Attempts at monoprotection of diol 5 as the phenyl carbonate led to a complex mixture of mono- and dicarbonate derivatives together with polymerization products from the starting diol. Finally, we found a more practical route to 7 involving a clean transacetalization of diol 5 to alcohol 8 by treatment with a mild acid catalyst, pyridinium 10-camphorsulfonate, in methylene chloride at room temperature, followed by the reaction of crude alcohol 8 with phenyl chloroformate in pyridine to afford 9 as a 3:2 anomeric mixture (as determined by ^{13}C NMR). Protecting the hydroxy group of 8 as the phenyl carbonate both prevented polymerization and introduced an activated carboxyl group for further urethane formation.

Introduction of the fatty chain on 9 was achieved either via hydrolysis of the methyl acetal and dihydrofuran formation, or directly through a transacetalization process. Thus, heating 9 at reflux with Dowex HCR-S H^+ in a 1:1 mixture of tetrahydrofuran–water followed by reaction of the resulting lactol with mesyl chloride in triethylamine[8] at −30 to 50 °C, and treatment with the fatty alcohol afforded 7 again as a 3:2 (^{13}C NMR) anomeric mixture in a 55–60% yield. The conversion of 9 to 7 was also carried out in a similar yield via toluene/methanol azeotrope removal under reduced pressure, keeping the temperature below 40 °C, in the presence of catalytic *p*-toluenesulfonic acid.

Acetals **4a–n** were obtained from carbonate 7 according to the method described in the literature.[3,4b] Treatment of 7 with 2-picolylamine yielded carbamate 10. This was reacted with acetyl chloride and the resulting *N*-acetylcarbamate 11 was treated with ethyl iodide to afford the pyridinium salts. When desired, the iodide was converted to chloride by ion exchange chromatography.

The observation that the cis and trans isomers of *N*-acetylcarbamate 11 were separable on analytical TLC plates prompted us to carry out the preparation of pure *cis*- and *trans*-**4d**. The two diastereomers of **11d** were separated by preparative column chromatography eluting with a 1:4 mixture of ethyl acetate and hexane. Complete cis–trans equilibration was observed when alkylation was performed using commercial ethyl iodide, presumably due to the presence of traces of HI. This could be completely avoided by carrying out the reaction at 60 °C in a mixture of ethyl iodide–acetonitrile previously filtered through an alumina pad. Under these conditions no trace of the contaminant isomer was observed in the ^{13}C NMR spectrum.

The relative stereochemistry of *cis*-**11d** and *trans*-**11d** was determined by ^1H NMR analysis and NOE measurements (see Figure 2). In the more polar isomer, irradiation of H_2 and H_4 enhanced H_{3a} and irradiation of H_{3a} enhanced H_2 and H_4, indicating that H_2, H_{3a}, and H_4 are all on the same ring face. Therefore, the alkoxy chain and the polar substituent must be cis oriented. Irradiation of H_4 in the less polar isomer enhanced H_{3a} and irradiation of H_{3b} enhanced H_2, which confirms a trans relationship between the two substituents. Furthermore, the coupling constant between H_{3a} and H_2 in the less polar isomer (*trans*-**11d**) was <1 Hz, characteristic of a trans relationship[9] for neighboring hydrogens, while $J_{3a,2}$ was 5.5 Hz in the more polar isomer (*cis*-**11d**).

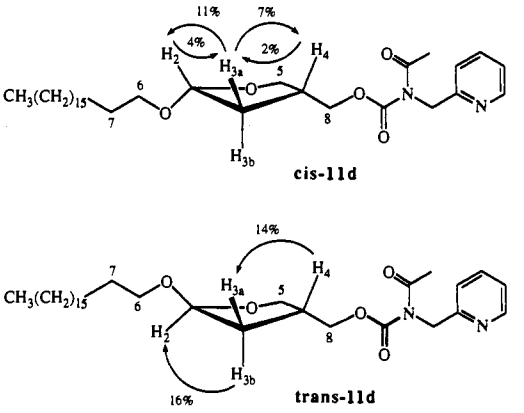

Figure 2. Selected NOE enhancements (%) measured in the 500-MHz spectra ($CDCl_3$) of *cis*-**11d** and *trans*-**11d**.

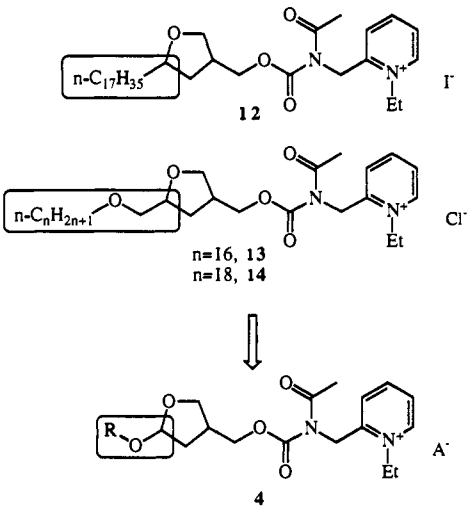

Figure 3.

Results and Discussion

The first screening for PAF antagonist activity was based on the in vitro PAF-induced rabbit platelet aggregation test and the in vivo PAF-induced hypotension test in rats. Results are summarized in Table I.

In our previous work on structure **1b**, we varied the nature of R_1, using a pure polymethylene chain (see, for example, compound **12**, Figure 3) or one carrying an ether or urethane function with a methylene residue between the ring and the oxygen (see, for example, compounds **13** and **14**). The direct linkage of the alkoxy chain to the ring furnished compound **4**, featuring an acetal function (see Figure 3).

Indeed, when we tested compounds **4c**, **4d**, and **4f**, carrying a fatty chain, we found similar in vitro and in vivo activities to that of their carba counterparts **13** and **14** and reference compound **2**. Encouraged by this observation, we prepared a number of acetal derivatives of formula **4** carrying a variety of R chains.

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(8) Bamford, M. J.; Humber, D. C.; Storer, R. Synthesis of (±)-2′-Oxa-carbocyclic-2′,3′-Dideoxynucleosides as potential anti-HIV Agents. *Tetrahedron Lett.* **1991**, *32*, 271–274.

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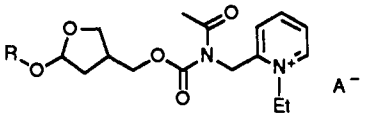
Table I. PAF Antagonist Activities of 2-Alkoxytetrahydrofuran Derivatives



compd	R	A	platelet agregation: IC_{50},[a] μM	blood pressure: ID_{50},[b] mg/kg, iv	formula[c]	anal.[d]
4a	C_2H_5	I	2.8 (2.3-3.4)	2.3 (0.8-6.4)	$C_{18}H_{27}IN_2O_5$	C,H,N
4b	$(CH_3)_2CH(CH_2)_2$	I	0.69 (0.66-0.72)	0.21 (0.14-0.30)	$C_{21}H_{33}IN_2O_5 \cdot H_2O$	C,H,N
4c	n-$C_{16}H_{33}$	I	0.0097 (0.0081-0.011)	0.010 (0.009-0.012)	$C_{32}H_{55}IN_2O_5 \cdot H_2O$	C,H,N
4d	n-$C_{18}H_{37}$	I	0.013 (0.0098-0.016)	0.026 (0.018-0.037)	$C_{34}H_{59}IN_2O_5 \cdot {}^1/_4H_2O$	C,H,N
trans-**4d**	n-$C_{18}H_{37}$	I	0.016 (0.013-0.020)	0.013 (0.009-0.020)	$C_{34}H_{59}IN_2O_5 \cdot {}^1/_4H_2O$	C,H,N
cis-**4d**	n-$C_{18}H_{37}$	I	0.031 (0.027-0.036)	0.066 (0.049-0.089)	$C_{34}H_{59}IN_2O_5 \cdot {}^1/_4H_2O$	C,N; H[e]
4e	n-$C_{18}H_{37}$	Cl	0.012 (0.0090-0.014)	0.025 (0.022-0.029)	$C_{34}H_{59}ClN_2O_5 \cdot 2H_2O$	C,H,N
4f	n-$C_{20}H_{41}$	I	0.040 (0.028-0.056)	0.048 (0.039-0.059)	$C_{34}H_{59}IN_2O_5 \cdot {}^1/_4H_2O$	C,H,N
4g	$Ph(CH_2)_3$	I	0.19 (0.094-0.38)	0.12 (0.08-0.18)	$C_{25}H_{33}IN_2O_5 \cdot H_2O$	C,H,N
4h	$Ph_2CH(CH_2)_2$	I	0.26 (0.22-0.32)	0.11 (0.07-0.18)	$C_{31}H_{37}IN_2O_5 \cdot 2H_2O$	C,H,N
4i	$CH_3O(CH_2)_{16}$	I	0.0021 (0.0016-0.0028)	0.040 (0.018-0.089)	$C_{33}H_{57}IN_2O_6 \cdot {}^3/_2H_2O$	C,H,N
4j	$CH_3(CH_2)_9O(CH_2)_6$	I	0.0041 (0.0028-0.0060)	0.0040 (0.0030-0.0070)	$C_{32}H_{55}IN_2O_8$	C,H,N
4k	$CH_2{=}CH(CH_2)_6O(CH_2)_6$	I	0.025 (0.018-0.036)	0.063 (0.046-0.086)	$C_{30}H_{49}IN_2O_6 \cdot 2H_2O$	C,H,N
4l	$Ph(CH_2)_3O(CH_2)_6$	I	0.051 (0.040-0.064)	0.060 (0.038-0.095)	$C_{31}H_{45}IN_2O_6 \cdot H_2O$	C,H,N
4m	$Ph(CH_2)_5O(CH_2)_6$	I	0.015 (0.0098-0.023)	0.021 (0.016-0.038)	$C_{33}H_{49}IN_2O_6 \cdot H_2O$	C,H,N
4n	4-biphenylyl-$CH_2O(CH_2)_6$	I	0.015 (0.012-0.019)	0.012 (0.0060-0.022)	$C_{35}H_{45}IN_2O_6 \cdot 2H_2O$	C,H,N
12			0.21 (0.16-0.31)	0.052 (0.041-0.067)	$C_{33}H_{57}IN_2O_4 \cdot {}^1/_2H_2O$	C,H,N
13			0.0086 (0.0071-0.012)	0.027 (0.023-0.033)	$C_{33}H_{57}ClN_2O_5 \cdot H_2O$	C,H,N
14			0.011 (0.0083-0.016)	0.011 (0.0070-0.017)	$C_{35}H_{61}ClN_2O_5 \cdot {}^5/_2H_2O$	C,H; N[f]
2			0.012 (0.010-0.014)	0.0078 (0.0053-0.011)	$C_{34}H_{60}ClN_3O_6 \cdot H_2O$	C,H,N

[a] Concentration required to inhibit PAF-induced maximum aggregation by 50%. Parentheses contain 95% confidence limits. [b] Dose required to reduce the lowering of the arterial blood pressure caused by PAF by 50%. Parentheses contain 95% confidence limits. [c] Empirical formula with amount of water of hydration. [d] Analytical results for the indicated elements are within ±0.4% of the calculated values, unless indicated otherwise. [e] H: calcd, 8.47; found, 8.96. [f] N: calcd, 4.12; found, 4.59.

First, compounds **4a** and **4b** were prepared to characterize the limitations of the R size. Those compounds, which had a medium-size alkyl chain, were 1-2 orders of magnitude less potent in both tests than those having a fatty chain. Compounds **4g** and **4h** carrying a 3-phenylpropyl and a 3,3-diphenylpropyl radical, respectively, were also significantly less active.

ω-Oxidation of the polymethylene chain followed by subsequent β-oxidation has been described as one of the metabolic processes after iv administration of 3-(4-hydroxy-7-methoxy-10-oxo-3,5,9-trioxa-11-aza-4-phosphanonacos-1-yl)thiazolium hydroxide, inner salt, *P*-oxide (CV-3988).[10] Thus, in an attempt to further improve the duration of activity of these compounds we functionalized the terminal carbon of the lipophilic chain in an attempt to block metabolism.

Our first modification of the ω-1 position consisted in the placement of an ether function. This led to an important increase in activity in the in vitro test, whereas the activity in the in vivo test decreased slightly (**4i** compared to **4d**).

For synthetic convenience, we next introduced an ether function at a distance of six carbon atoms from the acetal group together with different modifications at the end of the chain and we prepared compound **4j** in order to evaluate the effect of this modification. Surprisingly, this compound showed an increased potency of about 3-6-fold in both tests (**4j** compared with **4d** and **4c**). In fact, compound **4j** is one of the most potent PAF antagonists described so far. Next, we varied the functionality at the end of the chain placing a double bond or an aromatic ring while maintaining the ether group at six carbon atoms of distance from the acetal group. The compounds thus obtained, **4k**, **4l**, **4m**, and **4n**, were all less active than compound **4j**, but the latter two were equipotent to compound **4d**. Thus, the phenyl or biphenylyl substitution at the end of the alkyl chain does not produce significant impairment of activity. The overall length of the substituent was important, as can be seen by comparing compounds **4l** and **4m**.

The effect of the relative stereochemistry of the five-membered ring on activity was studied in compound **4d**. The trans isomer was twice as active as the cis isomer in the in vitro test and five times as active in the in vivo test. These results were in accordance with those reported on tetrahydrofuran derivatives **1b**.[3] Thus, the relative stereochemistry of the substituents seems to play only a minor role in activity.

Compound **4e**, the Cl^- form of **4d**, was also prepared as a pharmaceutically more acceptable salt. As expected, no difference in activity was observed between the two salts.

Additional pharmacological tests showed that these compounds are selective inhibitors of PAF-induced responses (e.g. compound **4e** inhibits PAF-, ADP-, and AA-induced platelet aggregation with IC_{50} values of 0.012, >200, and 107 μM, respectively).

Some of the more potent compounds were selected for a further study of duration of activity to determine the influence of R. We also found it of interest to compare the tetrahydrofuran derivatives **12-14** (see Figure 3) with compound **4e**. They differ in the presence or position of an oxygen atom whereas the overall length of the lipophilic chain was kept similar throughout the four compounds. Thus, the effect of the presence of the acetal group on the duration of activity can be directly infered. Furthermore, compounds **4e**, **13**, and **14** are almost equipotent in the in vitro and in vivo tests (Table I), and they also share similar ID_{50} values in the PAF-induced mortality test in mice (Table II), which makes the comparison more illustrative.

This study was based on two pharmacological tests, i.e. PAF-induced mortality in mice and PAF-induced hypotension in rats. Regarding the former (Table II), the pharmacological duration of **4e** seems very favorable, as

(10) Kobayashi, T.; Hohnoki, H.; Esumi, Y.; Ohtsuki, T.; Washino, T.; Tanayama, S. *Xenobiotica* **1988**, *18*, 49-59.

Table II. Percent Protection of PAF-Induced Mortality in Mice

compd	ID_{50},[a] mg/kg iv	percent protection at time (h)[b] 0.5	2	3	5	7	17	24
4c	0.024	100	100	88	61	64	65	44
trans-4d	0.012	-	-	-	100	100	93	60
cis-4d	0.030	-	-	-	-	100	67	38
4e	0.023	100	100	100	100	95	81	48
4i	0.0076	100	100	66	59	NP	-	-
4j	0.0064	100	100	100	100	88	40	51
4k	0.024	-	100	88	63	40	20	-
4l	0.073	-	100	50	NP	-	-	-
4m	0.0083	100	100	100	89	80	38	38
12	0.36	100	16	16	NP	-	-	-
13	0.031	-	100	75	54	65	44	17
14	0.026	-	-	100	100	100	44	33
2	0.022	100	100	100	100	100	95	48

[a] Dose required to inhibit PAF-induced mortality in mice by 50%. [b] Compounds were administered as a single dose of 1 mg/kg iv at time 0. PAF (100 μg/kg) plus propanolol (1 mg/kg) was administered at the given time. Ten to forty animals were used for each time point. NP indicates no protection; - means not tested.

this compound maintained a significant activity even 24 h after administration of a single dose of 1 mg/kg iv. The carba analogues **13** and **14** were somewhat less effective, and **12** showed a considerable drop in the duration of activity, which could be attributed, at least in part, to its lower potency in this test. Pure *cis*- and *trans*-**4d** showed a similar duration of activity, the trans isomer being slightly longer-lasting. In general, **4e** and both isomers of **4d** could be regarded as similar to the reference compound **2** in the duration of activity in this test.

Attempts to prolong the protective action of **4d** by modifying the nature of the fatty chain were unsuccessful. Indeed, the presence of an ether group in the alkyl chain seemed not to favor duration of activity, in spite of the enhanced pharmacological activity seen in some cases, particularly with **4i** and **4j** (see Table I and second column of Table II). In particular, the presence of an oxygen atom in the ω-1 position (**4i**) proved to be more deleterious than when a nearer position with respect to the acetal group (**4j**).

There is no clear relationship between blocking ω-oxidation of the polymethylene chain by insertion of a terminal aromatic group and an increase in the duration of action, as **4m** is slightly inferior to **4d** and similar to **4j**. Neither did the presence of a terminal olefin increase the duration (see entry **4k**). It can be postulated that other metabolic pathways are involved in the biological degradation of these products or, should ω-oxidation be really important, the presence of a new phenyl group or a double bond would provide an additional point of attack for metabolism, thus resulting in a molecule which is, as a whole, more easily biotransformable. In fact, it has been reported that in some related compounds only minor improvements of duration of activity were found after blocking of the ω-1 position by substitution of the terminal methyl group by a *tert*-butyl or trimethylsilyl group.[11]

When we analyzed the results of the hypotension test in rats, a different picture emerged (Figure 4). When a single dose of 1 mg/kg iv was given at time 0, activity of compounds **13** and **14** lasted for less than 4 h, independently of the nature or length of the substitution. In contrast, **4e** showed inhibition even 17–24 h after administration. In this case, the duration of activity profile of **4e**

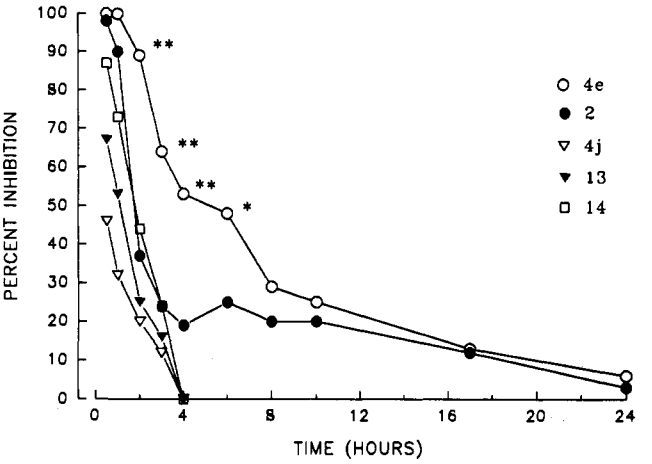


Figure 4. Time course of inhibitory effect on PAF-induced hypotension in normotensive rats. Compounds were given at a single dose of 1 mg/kg iv at time 0. C18-PAF 0.5 μg/kg iv was administered at different times (3–9 rats per time) and percent inhibition at each time was recorded. The asterisks indicate statistically significant differences between **4e** and **2** (Mann-Whitney's *U*-test); (*) $P < 0.05$, (**) $P < 0.005$.

was superior to that of reference compound **2**, which showed a rapid drop in activity in the period between 1 and 3 h, followed by a very smooth decay of inhibition in the succeding hours. Surprisingly, **4j** showed a short duration of activity in rats, comparable to that of **13** and **14**.

From the above results, it is reasonable to postulate a species-dependent metabolism of the described compounds. Thus, to have a reliable approach to the problem, the duration of activity should be compared in more than one animal species. At any rate, we can conclude from the present study that the presence of an acetal group is frankly beneficial as to duration of activity, as acetal **4e** shows a better overall profile compared with its carba analogues **13** and **14** in the two models tested.

In conclusion, we have prepared and optimized a new series of potent PAF antagonists, the main feature of which is the presence of an acetal group. This structural characteristic seems to confer a longer-lasting activity. Based on the results of the biological evaluation, 2-[[*N*-acetyl-*N*-[[[2-(octadecyloxy)tetrahydrofuran-4-yl]methoxy]carbonyl]amino]methyl]-1-ethylpyridinium chloride (**4e**) (UR-11353) was selected for further pharmacological development.

Experimental Section

A. Chemistry. Melting points were determined with a Mettler FP 80 central processor melting point apparatus and are un-

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corrected. Melting points of organic salts varied, depending on the amount of water of the sample and should be regarded as approximated. Infrared spectra were recorded on a Perkin-Elmer 983 spectrophotometer. ^{1}H NMR (80 MHz) and ^{13}C NMR (20.1 MHz) spectra were recorded on a Brücker AC80 spectrometer and are reported in ppm on the δ scale, from the indicated reference. ^{1}H NMR (500 MHz) spectra were recorded on a VXR-500 spectrometer and are also reported in ppm on the δ scale, from the indicated reference. Combustion analyses were performed with a Carlo Erba 1106 analyzer. Liquid chromatography was performed with a forced flow (flash chromatography) of the indicated solvent system on SDS silica gel chromagel 60 a CC (230–400 mesh). Analytical thin-layer chromatography (TLC) was performed using Macherey-Nagel 0.25-mm silica gel SIL G-25 plates. When necessary, solvents and reagents were dried prior to use. Tetrahydrofuran, diethyl ether, and toluene were distilled from sodium metal/benzophenone ketyl. Dichloromethane and triethylamine were distilled from calcium hydride. Dimethyl sulfoxide and dimethylformamide were distilled under reduced pressure from calcium hydride and stored over activated 4-Å molecular sieves. Unless otherwise specified, all nonaqueous reactions were conducted under a rigorously dried argon atmosphere, using oven-dried glassware.

C-18-PAF-acether was synthesized from (*S*)-batyl alcohol[12] following a published procedure.[13] Compound **2** was prepared according to the literature[4b] and was selected as the reference compound.

4-[[(Phenoxycarbonyl)oxy]methyl]-2-methoxytetrahydrofuran (9). To a solution of 2-(hydroxymethyl)-4,4-dimethoxybutan-1-ol (**5**) (27.2 g, 0.16 mol) in dichloromethane (300 mL) was added a 0.22 M solution containing pyridinium 10-camphorsulfonate in dichloromethane (15 mL). The mixture was then stirred for 18 h. The volatiles were removed in vacuo, and the residue was redissolved in dichloromethane (200 mL) and pyridine (18 mL), cooled to 0 °C, and treated dropwise with phenyl chlorocarbonate (23.0 mL, 0.183 mol) in dichloromethane (60 mL). After stirring for 1 h at room temperature, the mixture was washed with water (2 × 60 mL) and 10% sodium bicarbonate aqueous solution (60 mL). Anhydrous sodium sulfate was added, the mixture was filtered, and the filtrate was concentrated in vacuo to an oil (42.0 g), which was purified by flash chromatography (1:4 ethyl acetate/hexane) to give a colorless oil (35.3 g) in 84% yield. ^{13}C NMR analysis indicated a roughly 3:2 mixture of diastereomers: IR (NaCl) ν 2949, 2827, 1756, 1488, 1247, 1098 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 7.23 (m, 5 H), 5.03 (d, J = 5.6 Hz, 1 H, CHOMe), 4.4–3.6 (m, 4 H), 3.32 (s, 3 H, OMe), 2.75 (m, 1 H), 2.2–1.6 (m, 2 H); ^{13}C NMR (20.15 MHz, $CDCl_3$) δ (TMS) 153.05 (C), 150.84 (C), 128.09 (CH), 125.52 (CH), 120.56 (CH), 104.54 (CH, CHOMe, min), 104.41 (CH, CHOMe, maj), 70.18 (CH_2, min), 69.61 (CH_2, maj), 68.74 (CH_2, min), 68.00 (CH_2, maj), 53.95 (CH_3), 36.47 (CH, min), 36.15 (CH, maj), 35.08 (CH_2, maj), 34.97 (CH_2, min).

4-[[(Phenoxycarbonyl)oxy]methyl]-2-(octadecyloxy)tetrahydrofuran (7d). Method A. A solution of methyl acetal **9** (19.36 g, 0.076 mol) in tetrahydrofuran (190 mL) and water (190 mL) was treated with Dowex HCR-S H$^+$ (5 g) at 80 °C for 18 h. The resin was filtered, the filtrate was concentrated, and the resulting aqueous phase was extracted with chloroform (2 × 80 mL). The combined organic phases were dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated in vacuo to a pale brown oil (17.2 g) which was purified by flash chromatography (1:1 ethyl acetate/hexane) to afford 4-[[(phenoxycarbonyl)oxy]methyl]-2-hydroxytetrahydrofuran as a colorless oil (12.02 g, 66%): IR (NaCl) ν 3464, 1756, 1487, 1210, 1172, 1069 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 7.25 (m, 5 H), 5.53 (d, J = 4.9 Hz, 1 H, CHOH), 4.10 (m, 5 H), 2.85 (m, 1 H), 1.90 (m, 2 H).

Next, a cooled (−30 °C) solution containing this lactol (12.0 g, 0.05 mol) and triethylamine (7.6 mL, 0.054 mol) in tetrahydrofuran (200 mL) was treated with a solution of methanesulfonyl chloride (3.98 mL, 0.05 mol). The mixture was stirred 30 min at room temperature and then was heated at 50 °C for 30 min. After cooling to room temperature, the mixture was treated dropwise with a solution of octadecyl alcohol (15.93 g, 0.058 mol) in tetrahydrofuran (80 mL). After stirring for 18 h at room temperature, the volatiles were removed in vacuo to give an oil that was purified by flash chromatography (1:9 ethyl acetate/hexane) to afford a white solid (22.9 g, 82% yield): mp 43.2–44.2 °C; IR (KBr) ν 2911, 2844, 1758, 1587, 1483, 1461, 1343, 1269, 1242, 1200 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 7.23 (m, 5 H), 5.14 (d, J = 4.9 Hz, 1 H, OCHO), 4.4–3.3 (m, 6 H), 2.76 (m, 1 H), 2.2–0.6 (m, ca. 37 H); ^{13}C NMR (20.15 MHz, $CDCl_3$) δ (TMS) 153.39 (C, maj), 153.33 (C, min), 151.10 (C), 129.26 (CH), 125.78 (CH), 120.80 (CH), 103.59 (CH, CHOMe, min), 103.53 (CH, CHOMe, maj), 70.66 (CH_2, min), 70.01 (CH_2, maj), 69.10 (CH_2, min), 68.27 (CH_2, maj), 67.27 (CH_2), 36.81 (CH, min), 36.58 (CH, maj), 35.56 (CH_2, maj), 35.44 (CH_2, min), 31.80 (CH_2), 29.56 (CH_2), 29.29 (CH_2), 29.23 (CH_2), 26.10 (CH_2), 22.53 (CH_2), 13.91 (CH_3). Anal. ($C_{30}H_{50}O_5$) C, H.

Method B. A solution containing methyl acetal **9** (6.8 g, 0.020 mol), octadecyl alcohol (6.5 g, 0.024 mol), and *p*-toluenesulfonic acid (0.6 g) in toluene (200 mL) was heated at 40 °C in vacuo (15 mmHg). Additional toluene was added, and the solution was concentrated again. The resulting residue was purified by flash chromatography (1:9 ethyl acetate/hexane) to afford the title compound as a white solid (6.8 g, 54% yield) analytically identical to that described above.

2-[[*N*-[[[2-(Octadecyloxy)tetrahydrofuran-4-yl]methoxy]carbonyl]amino]methyl]pyridine (10d). To a solution of phenyl carbonate **7d** (34.49, 0.07 mol) in acetonitrile (240 mL) was added 2-(aminomethyl)pyridine (7.6 mL, 0.074 mol), and the resulting mixture was heated at reflux for 12 h. After cooling, the volatiles were removed under reduced pressure, and the residue was partitioned between chloroform (140 mL) and water (50 mL). The organic phase was washed twice with 1 N aqueous sodium hydroxide (40 mL) and water (40 mL) and dried over anhydrous sodium sulfate. Removal of the solvent afforded 32 g of an oil that was purified by flash chromatography (1:1 ethyl acetate/hexane) to afford 27.3 g of the title compound as a white solid in 77% yield: mp 59.2–63.0 °C; IR (KBr) ν 3326, 2957, 2912, 2845, 1702, 1589, 1524, 1463, 1259, 1089 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.45 (d, J = 5.4 Hz, 1 H, py), 7.58 (t of d, J = 2 Hz, J = 7.8 Hz, 1 H, py), 7.12 (m, 2 H, py), 5.85 (1 H, NH), 5.00 (m, 1 H), 4.39 (d, J = 5.6 Hz, 2 H), 3.1–4.1 (m, 6 H), 2.5 (m, 1 H), 1.18 (m, 34 H), 0.8 (m, 3 H). Anal. ($C_{30}H_{52}N_2O_4$) C, H, N.

2-[[*N*-Acetyl-*N*-[[[2-(octadecyloxy)tetrahydrofuran-4-yl]methoxy]carbonyl]amino]methyl]pyridine (11d). To a cooled solution (0 °C) of compound **10d** (29.4 g, 0.058 mol) in dichloromethane (100 mL) was slowly added acetyl chloride (4.3 mL, 0.06 mol), and the mixture was stirred at room temperature for 18 h. The solution was then cooled (0 °C) and treated with triethylamine (12.9 mL) and additional acetyl chloride (2.15 mL, 0.03 mol). After stirring for 20 h at room temperature, triethylamine (6.5 mL) was added and the mixture was washed with water (2 × 50 mL) and brine (50 mL). The organic layer was decanted and dried over anhydrous sodium sulfate, the drying agent was filtered off, and the filtrate was concentrated in vacuo and purified by flash chromatography (1:1 ethyl acetate/hexane) to afford the title compound as a white solid (24.94 g, 78%). ^{13}C NMR analysis indicated a roughly 3:2 mixture of diastereomers (R_f 0.31 and R_f 0.41 in 1:1 ethyl acetate/hexane): mp 58.2–60.2 °C; IR (KBr) ν 2911, 2846, 1732, 1693, 1588, 1430, 1391, 1372, 1343, 1222 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.5 (dt, J = 4.8 Hz, J = 0.9 Hz, 1 H, py), 7.60 (td, J = 7.2 Hz, J = 1.6 Hz, 1 H, py), 7.14 (m, 2 H, py), 5.07 (s, 2 H), 5.00 (m, 1 H), 3.3–4.3 (m, 6 H), 2.62 (s, 3 H), 2.5 (m, 1 H), 1.26 (m, 34 H), 0.87 (m, 3 H). Anal. ($C_{32}H_{54}N_2O_5$) C, H, N.

***cis*- and *trans*-2-[[*N*-Acetyl-*N*-[[[2-(octadecyloxy)tetrahydrofuran-4-yl]methoxy]carbonyl]amino]methyl]pyridine (*cis*- and *trans*-11d).** The above diastereomeric mixture (8 g) was chromatographed twice on silica gel (150 g) and eluted with 1:4 ethyl acetate/hexane, and each fraction was then chromatographed to afford 3.0 g of the less polar diastereomer *trans*-**11d** and 0.67 g of the more polar diastereomer *cis*-**11d** as white solids.

***trans*-11d:** mp 64.7 °C; IR (KBr) ν 2948, 2910, 2844, 1727, 1695, 1588, 1467, 1443, 1366, 1351 cm^{-1}; ^{1}H NMR (499.9 MHz, $CDCl_3$) δ (TMS) 8.49 (br d, J = 4.5 Hz, 1 H, py), 7.60 (td, J =

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8 Hz, J = 2 Hz, 1 H, py), 7.12 (dd, J = 7.5 Hz, J = 5 Hz, 1 H, py), 7.08 (d, J = 8 Hz, 1 H, py), 5.066 and 5.038 (AB system, J = 16 Hz, 2 H, CH_2-py), 4.98 (d, J = 4.5 Hz, H_2), 4.07 (dd, J = 6 Hz, J = 10.5 Hz, H_{8a}), 3.98 (dd, J = 11 Hz, J = 8 Hz, H_{8b}), 3.73 (br t, J = 8.5 Hz, H_{5a}), 3.55 (dt, J = 9.5 Hz, J = 7 Hz, H_{6a}), 3.36 (dd, J = 8.5 Hz, J = 4.5 Hz, H_{5b}), 3.28 (dt, J = 9.5 Hz, J = 7 Hz, H_{6b}), 2.61 (s, 3 H, CH_3CO), 2.55 (m, H_4), 1.84 (br dd, J = 7.5 Hz, J = 13 Hz, J = <1 Hz, H_{3a}), 1.49 (br q, J = 7 Hz, H_{7a}, H_{7b}, and H_{3b}), 1.23 (m, ca. 30 H), 0.86 (t, J = 7.5 Hz, 3 H, CH_3); ^{13}C NMR (20.15 MHz, $CDCl_3$) δ (TMS) 172.78 (C), 156.92 (C), 154.43 (C), 149.25 (CH), 136.36 (CH), 121.91 (CH), 120.33 (CH), 103.57 (CH, CHOMe), 68.28 (2 CH_2), 67.32 (CH_2), 48.34 (CH_2), 36.41 (CH), 35.48 (CH_2), 31.87 (CH_2), 29.62 (CH_2), 29.38 (CH_2), 26.33 (CH_3), 26.14 (CH_2), 22.62 (CH_2), 14.01 (CH_3). Anal. ($C_{32}H_{54}N_2O_5$) C, H, N.

***cis*-11d**: mp 61.8–63.2 °C; IR (KBr) ν 2910, 2845, 1735, 1691, 1587, 1468, 1431, 1371 cm^{-1}; ^1H NMR (499.9 MHz, $CDCl_3$) δ (TMS) 8.49 (br d, J = 4.5 Hz, 1 H, py), 7.60 (td, J = 7.5 Hz, J = 1.5 Hz, 1 H, py), 7.12 (dd, J = 7.5 Hz, J = 5 Hz, 1 H, py), 7.08 (d, J = 8 Hz, 1 H, py), 5.05 (s, 2 H, CH_2-py), 5.01 (dd, J = 5 Hz, J = <1 Hz, H_2), 4.22 (dd, J = 10.5 Hz, J = 6.5 Hz, H_{8a}), 4.12 (dd, J = 10.5 Hz, J = 8.5 Hz, H_{8b}), 3.69 (t, J = 8 Hz, H_{5a}), 3.55 (dt, J = 9.5 Hz, J = 7 Hz, H_{6a}), 3.38 (dd, J = 9 Hz, J = 7 Hz, H_{5b}), 3.27 (dt, J = 9.5 Hz, J = 6.5 Hz, H_{6b}), 2.61 (s, 3 H, CH_3CO), 2.40 (m, H_4), 1.97 (ddd, J = 14.0 Hz, J = 10.5 Hz, J = 5.5 Hz, H_{3a}), 1.49 (m, H_{7a}, H_{7b}, and H_{3b}), 1.23 (m, ca. 30 H), 0.86 (t, J = 7 Hz, 3 H, CH_3); ^{13}C NMR (20.15 MHz, $CDCl_3$) δ (TMS) 172.78 (C), 157.09 (C), 154.37 (C), 149.27 (CH), 136.34 (CH), 121.88 (CH), 120.33 (CH), 103.68 (CH, CHOMe), 69.01 (CH_2), 68.83 (CH_2), 67.40 (CH_2), 48.38 (CH_2), 36.78 (CH), 35.38 (CH_2), 31.90 (CH_2), 29.66 (CH_2), 29.34 (CH_2), 26.32 (CH_3), 26.20 (CH_2), 22.63 (CH_2), 14.00 (CH_3). Anal. ($C_{32}H_{54}N_2O_5$) C, H, N.

2-[[*N*-Acetyl-*N*-[[[2-(octadecyloxy)tetrahydrofuran-4-yl]methoxy]carbonyl]amino]methyl]-1-ethylpyridinium Iodide (4d). A solution containing a 3:2 mixture of *trans*/*cis*-acylcarbamates **11d** (17.24 g, 0.032 mol), ethyl iodide (50 mL), and acetonitrile (25 mL) was heated at 80 °C for 18 h. After cooling, the volatiles were removed in vacuo and the residue was recrystallized from dichloromethane/diethyl ether to yield 22 g of the title compound as a yellow solid (99% yield): mp 58.6–69.3 °C; IR (KBr) ν 3440, 2913, 2846, 1737, 1682, 1625, 1579, 1508, 1463, 1212 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 9.61 (d, J = 6 Hz, 1 H, py), 8.45 (t, J = 8 Hz, 1 H, py), 8.04 (t, J = 8.2 Hz, 1 H, py), 7.73 (d, J = 8.2 Hz, 1 H, py), 5.43 (s, 2 H), 5.05 (m, 3 H), 4.5–3.3 (complex signal, 6 H), 2.7 (m, 1 H), 2.64 (s, 3 H), 1.73 (t, J = 7.2 Hz, 3 H), 1.25 (m, 34 H), 0.87 (m, 3 H). Anal. ($C_{34}H_{59}IN_2O_5 \cdot 0.25H_2O$) C, H, N.

***trans*-2-[[*N*-Acetyl-*N*-[[[2-(octadecyloxy)tetrahydrofuran-4-yl]methoxy]carbonyl]amino]methyl]-1-ethylpyridinium Iodide (*trans*-4d)**. *trans*-Acylcarbamate **11d** (0.75 g, 1.37 mmol) was treated with 6 mL of a 2:1 mixture of ethyl iodide and acetonitrile previously filtered through an alumina pad. The resulting mixture was heated at 60 °C for 32 h, and *trans*-**4d** was isolated as above as a yellow solid (0.33 g, 34% yield): mp 97.3–108.5 °C; IR (KBr) ν 3477, 2912, 2845, 1740, 1691, 1621, 1444, 1219 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 9.62 (br d, J = 6 Hz, 1 H, py), 8.57 (br t, J = 8 Hz, 1 H, py), 8.09 (br t, J = 8.2 Hz, 1 H, py), 7.89 (d, J = 8.2 Hz, 1 H, py), 5.45 (s, 2 H), 5.08 (m, 3 H), 4.28 (d, J = 7.09 Hz, 2 H), 3.93 (t, J = 8.8 Hz, 1 H), 3.5 (m, 3 H), 2.75 (m, 1 H), 2.65 (s, 3 H), 1.73 (t, J = 7.2 Hz, 3 H), 1.25 (m, ca. 34 H), 0.87 (m, 3 H); ^{13}C NMR (20.15 MHz, $CDCl_3$) δ (TMS) 172.44 (C), 153.36 (C), 153.21 (C), 146.39 (CH), 145.94 (CH), 127.25 (CH), 126.19 (CH), 103.59 (CH, CHOMe), 70.39 (CH_2), 68.20 (CH_2), 67.45 (CH_2), 54.60 (CH_2), 45.10 (CH_2), 36.41 (CH), 35.86 (CH_2), 31.83 (CH_2), 29.60 (CH_2), 29.26 (CH_2), 26.65 (CH_3), 26.12 (CH_2), 22.59 (CH_2), 16.08 (CH_3), 13.99 (CH_3). Anal. ($C_{34}H_{59}IN_2O_5 \cdot 0.25H_2O$) C, H, N.

***cis*-2-[[*N*-Acetyl-*N*-[[[2-(octadecyloxy)tetrahydrofuran-4-yl]methoxy]carbonyl]amino]methyl]-1-ethylpyridinium Iodide (*cis*-4d)**. Using pure *cis*-acylcarbamate **11d** and following the same procedure as above gave *cis*-**4d** as a yellow solid (28% yield): mp 47.7–49.8 °C; IR (KBr) ν 3439, 2912, 2844, 1744, 1679, 1625, 1577, 1508, 1462, 1210 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 9.62 (br d, J = 6 Hz, 1 H, py), 8.56 (br t, J = 8 Hz, 1 H, py), 8.09 (br t, J = 8.2 Hz, 1 H, py), 7.83 (d, J = 8.2 Hz, 1 H, py), 5.46 (s, 2 H), 5.08 (m, 3 H), 4.39 (d, J = 7.5 Hz, 2 H), 3.99 (t, J = 8.5 Hz, 1 H), 3.5 (m, 3 H), 2.75 (m, 1 H), 2.66 (s, 3 H), 1.73 (t, J = 7.2 Hz, 3 H), 1.25 (m, ca. 34 H), 0.87 (m, 3 H); ^{13}C NMR (20.15 MHz, $CDCl_3$) δ (TMS) 172.52 (C), 153.39 (C), 153.05 (C), 146.44 (CH), 145.86 (CH), 127.27 (CH), 125.99 (CH), 103.70 (CH, CHOMe), 70.70 (CH_2), 69.05 (CH_2), 67.54 (CH_2), 54.65 (CH_2), 45.04 (CH_2), 36.61 (CH), 35.60 (CH_2), 31.81 (CH_2), 29.58 (CH_2), 29.25 (CH_2), 26.58 (CH_3), 26.10 (CH_2), 22.57 (CH_2), 16.05 (CH_3), 13.98 (CH_3). Anal. ($C_{34}H_{59}IN_2O_5 \cdot 0.25H_2O$) C, H, N.

2-[[*N*-Acetyl-*N*-[[[2-(octadecyloxy)tetrahydrofuran-4-yl]methoxy]carbonyl]amino]methyl]-1-ethylpyridinium Chloride (4e). A solution of iodide **4d** (3 g) in 85% methanol/water was passed through a column of Amberlite IRA-410 ion-exchange resin previously washed with 5% NaCl solution. The fractions containing the product were mixed, extracted with dichloromethane (2 × 30 mL), dried over sodium sulfate, and filtered, and the filtrate was concentrated to a white powder. Recrystallization from acetone afforded the title compound as a white solid (1.8 g, 70% yield): mp 54.0–55.1 °C; IR (KBr) ν 3427, 2914, 2846, 1744, 1677, 1625, 1463, 1370, 1351 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 10.18 (d, J = 6 Hz, 1 H, py), 8.39 (t, J = 6.6 Hz, 1 H, py), 8.04 (t, J = 5.8 Hz, 1 H, py), 7.61 (d, J = 6.7 Hz, 1 H, py), 5.42 (s, 2 H), 5.24 (q, J = 7.2 Hz, 2 H), 5.10 (m, 1 H), 3.3–4.5 (complex signal, 6 H), 2.66 (m, 1 H), 2.64 (s, 3 H), 1.74 (t, J = 7.2 Hz, 3 H), 1.26 (m, ca. 34 H), 0.88 (m, 3 H). Anal. ($C_{34}H_{59}ClN_2O_5 \cdot 2H_2O$) C, H, N.

2-[[*N*-Acetyl-*N*-[[[2-[(16-methoxyhexadecyl)oxy]tetrahydrofuran-4-yl]methoxy]carbonyl]amino]methyl]-1-ethylpyridinium Iodide (4i). The title compound was prepared from 16-methoxyhexadecanol and obtained as a yellow powder: mp 112.9–115.2 °C; IR (KBr) ν 3441, 2912, 2845, 1743, 1692, 1623, 1445, 1369, 1213 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 9.60 (br d, J = 5.5 Hz, 1 H, py), 8.42 (br t, J = 8.1 Hz, 1 H, py), 8.04 (br t, J = 6.2 Hz, 1 H, py), 7.70 (br d, J = 7.5 Hz, 1 H, py), 5.50 (m, 1 H, OCHO), 5.43 (s, 2 H, CH_2-py), 5.08 (m, 3 H), 4.4–3.1 (m, 7 H), 3.32 (s, 3 H, CH_3O), 2.70 (m, 1 H), 2.64 (s, 3 H, CH_3CO), 1.73 (t, J = 7.5 Hz, 3 H, CH_3CH_2), 2.1–1.2 (m, ca. 30 H). Anal. ($C_{33}H_{57}IN_2O_6 \cdot {}^3/_2H_2O$) C, H, N.

2-[[*N*-Acetyl-*N*-[[[2-[[6-(decyloxy)hexyl]oxy]tetrahydrofuran-4-yl]methoxy]carbonyl]amino]methyl]-1-ethylpyridinium Iodide (4j). The title compound was prepared from 6-(decyloxy)hexanol and obtained as a yellow powder: mp 67.3–71.9 °C; IR (NaCl) ν 2922, 2849, 1741, 1693, 1622, 1445, 1369, 1082 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 9.59 (br d, J = 5.9 Hz, 1 H, py), 8.50 (br t, J = 8.0 Hz, 1 H, py), 8.06 (br t, J = 6.3 Hz, 1 H, py), 7.79 (br d, J = 7.9 Hz, 1 H, py), 5.48 (m, 1 H, OCHO), 5.44 (s, 2 H, CH_2-py), 5.06 (m, 3 H), 4.32 (m, 2 H), 4.02 (m, 1 H), 3.7–3.2 (m, 4 H), 2.81 (m, 1 H), 2.64 (s, 3 H, CH_3CO), 1.73 (t, J = 7.5 Hz, 3 H, CH_3CH_2), 1.9–1.1 (m, ca. 28 H), 0.87 (t, J = 5.8 Hz, 3 H). Anal. ($C_{32}H_{55}IN_2O_6$) C, H, N.

2-[[*N*-Acetyl-*N*-[[[2-[[6-(7-octenyloxy)hexyl]oxy]tetrahydrofuran-4-yl]methoxy]carbonyl]amino]methyl]-1-ethylpyridinium Iodide (4k). The title compound was prepared from 6-(7-octenyloxy)hexanol and obtained as a yellow powder: mp 60.2–66.7 °C; IR (KBr) ν 3441, 2928, 1743, 1691, 1623, 1503, 1351, 1213 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 9.55 (d, J = 6.2 Hz, 1 H, py), 8.54 (td, J = 1.1 Hz, J = 7.8 Hz, 1 H, py), 8.08 (t, J = 6.4 Hz, 1 H, py), 7.84 (br d, J = 8 Hz, 1 H, py), 5.86 (m, 1 H, $CH{=}CH_2$), 5.44 (s, 2 H, CH_2-py), 5.00 (m, 5 H, CH_2N^+, $CH{=}CH_2$, OCHO), 4.37 (m, 2 H), 4.04 (m, 1 H), 3.74 (m, 2 H), 3.46 (m, 5 H), 2.80 (m, 1 H), 2.65 (s, 3 H, CH_3CO), 2.03 (H_2O), 1.73 (t, J = 7.2 Hz, 3 H), 1.36 (m, 20 H). Anal. ($C_{30}H_{49}IN_2O_6 \cdot 2H_2O$) C, H, N.

2-[[*N*-Acetyl-*N*-[[[2-[[6-[(5-phenylpentyl)oxy]hexyl]oxy]tetrahydrofuran-4-yl]methoxy]carbonyl]amino]methyl]-1-ethylpyridinium Iodide (4m). The title compound was prepared from 6-[(5-phenylpentyl)oxy]hexanol and obtained as a yellow powder: mp 34.7–45.9 °C; IR (KBr) ν 3439, 3020, 2926, 1743, 1691, 1623, 1446, 1368, 1351 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 9.60 (d, J = 6.1 Hz, 1 H, py), 8.53 (t, J = 7.6 Hz, 1 H, py), 8.07 (t, J = 6.4 Hz, 1 H, py), 7.83 (br d, J = 7.7 Hz, 1 H, py), 7.20 (m, 5 H, Ph), 5.44 (s, 3 H, CH_2-py, OCHO), 5.05 (m, 3 H), 4.32 (m, 2 H), 3.96 (m, 1 H), 3.69–3.30 (m, 6 H), 2.65 (m, 3 H), 2.64 (s, 3 H, CH_3CO), 2.2–1.15 (m, ca. 19 H). Anal. ($C_{33}H_{49}IN_2O_6 \cdot 1H_2O$) C, H, N.

2-[[*N*-Acetyl-*N*-[[[2-[[6-(4-biphenylylmethyl)hexyl]oxy]tetrahydrofuran-4-yl]methoxy]carbonyl]amino]-

methyl]-1-ethylpyridinium Iodide (4n). The title compound was prepared from 6-(4-biphenylylmethyl)hexanol and obtained as a yellow powder: mp 40.0–44.5 °C; IR (KBr) ν 3440, 2930, 1744, 1688, 1623, 1481, 1366, 1213 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 9.65 (br d, J = 5.6 Hz, 1 H, py), 8.39 (t, J = 7.0 Hz, 1 H, py), 8.00 (t, J = 7.0 Hz, 1 H, py), 7.53 (m, 11 H, py, Ar), 5.41 (m, 2 H), 5.07 (m, 3 H), 4.53 (s, 2 H, OCH_2Ar), 4.32 (dd, J = 7.3 Hz, J = 9.6 Hz, 2 H), 3.98 (m, 1 H), 3.57 (m, 4 H), 2.75 (m, 1 H), 2.63 (s, 3 H, CH_3CO), 1.56 (m, 13 H). Anal. ($C_{35}H_{45}IN_2O_6 \cdot 2H_2O$) C, H, N.

B. Biological Methods: Inhibition of Platelet Aggregation in Vitro. Platelet-aggregation studies were done by the method of Born.[14] Blood was collected in 3.16% sodium citrate (1 volume for 9 volume of blood) by cardiac puncture from male New Zealand rabbits (2–2.5 kg body weight). Platelet-rich plasma (PRP) was prepared by centrifuging the blood at 250g for 10 min at 4 °C. The PRP was diluted with platelet-poor plasma obtained by further centrifuging at 3000g for 10 min. The platelet number was adjusted to 3.5×10^5 cells/mm^3. Platelet aggregation was induced by C18-PAF (1.5×10^{-8} M) and measured by using a dual-channel aggregometer Chrono-log 500. Activity of the inhibitors was expressed as the IC_{50} value, i.e. the concentration required to inhibit platelet aggregatory response by 50%. The values shown in the tables were calculated by linear regression from a single experimental curve with no less than four data points, each point being the mean of the percentage inhibition at a given concentration obtained from one to three independent experiments.

Inhibition of PAF-Induced Hypotension in Normotensive Rats. Hypotension studies were performed as described by Baranes.[15] Male Sprague–Dawley rats, weighing 180–220 g, were anesthetized with sodium pentobarbital (50 mg/kg, ip). Blood pressure was recorded from the left carotid artery using a Beckman pressure transducer coupled to a Beckman R611 polygraph. Right and left femoral veins were catheterized to inject PAF (0.5 μg/kg) or the test compound. Test compounds were administered by intravenous injection (1 mL/kg, dissolved in saline) 3 min before PAF injection. Control animals received only the vehicle. Blood pressure was monitored and percentage inhibition of PAF-induced hypotension with respect to controls was calculated. The results were expressed as ID_{50} values, i.e. the dose of the test compound required to inhibit the PAF-induced hypotension by 50%. The results were calculated by linear regression from a single experimental curve with not less than four points, each point being the mean of the percentage inhibition at a given dose obtained from two or more independent experiments. For duration of activity studies, test compounds were given at a single dose of 1 mg/kg iv at time 0. C18-PAF was administered at a different times (3–9 rats per time) and percentage inhibition at each time was recorded.

Inhibition of PAF-Induced Mortality in Mice.[16] Groups of 10 male Swiss mice weighing 22–26 g were used. A dose of 100 μg/kg C18-PAF plus 1 mg/kg propanolol was administered through a lateral tail vein 5 min after iv administration of the test compounds (10 mL/kg) or saline (control group). Animals were observed 2 h after the PAF injection. Following this protocol we obtained a consistent mortality of 70–100% in control group. Percent inhibition of mortality due to the treatments in comparison with the control group was calculated. Results were given as ID_{50} values, i.e. the dose required to inhibit PAF-induced mortality by 50%. The results were calculated by linear regression from a single experimental curve with no less than four data points. For duration of activity studies, test compounds were given at a single dose of 1 mg/kg iv at time 0. C18-PAF plus propanolol was administered at different times (10–40 mice per time) and percentage inhibition at each time was recorded.

Statistics. Statistical analyses of pharmacological data were made using a standard pharmacology program implemented on an IBM PC.[17]

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Registry No. 4a, 138060-08-9; **4b**, 138060-09-0; **4c**, 138060-10-3; *trans*-**4d**, 138060-11-4; *cis*-**4d**, 138060-12-5; **4e**, 138060-13-6; **4f**, 138060-14-7; **4g**, 138060-15-8; **4h**, 138060-16-9; **4i**, 138060-17-0; **4j**, 138060-18-1; **4k**, 138060-19-2; **4l**, 138060-20-5; **4m**, 138060-21-6; **4n**, 138060-22-7; **5**, 99776-32-6; *cis*-**7d**, 138060-23-8; *trans*-**7d**, 138060-27-2; *cis*-**9**, 138060-24-9; *trans*-**9**, 138060-25-0; **10d**, 138060-26-1; *trans*-**11d**, 138060-27-2; *cis*-**11d**, 138060-28-3; pyridinium 10-camphorsulfonate, 78982-30-6; phenyl chlorocarbonate, 1885-14-9; 4-[[(phenoxycarbonyl)oxy]methyl]-2-hydroxytetrahydrofuran, 138060-29-4; octadecyl alcohol, 112-92-5; 16-methoxyhexadecanol, 138060-30-7; 6-(decyloxy)hexanol, 138060-31-8; 6-(7-octenyloxy)hexanol, 138060-32-9; 6-[(5-phenylpentyl)oxy]-hexanol, 138060-33-0; 6-(4-biphenylmethyl)hexanol, 138060-34-1; 2-(aminomethyl)pyridine, 3731-51-9.

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