Platelet Activating Factor Antagonists: Synthesis and Structure–Activity Studies of Novel PAF Analogues Modified in the Phosphorylcholine Moiety[1]

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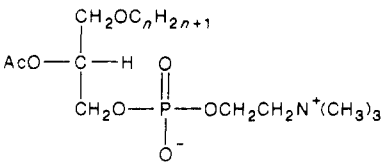
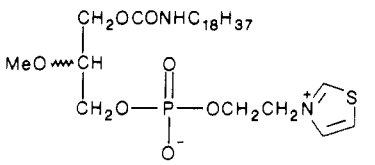
New analogues of platelet activating factor (PAF), in which the phosphate and trimethylammonium moieties were replaced with an acylcarbamoyl moiety and a quaternary cyclic ammonium group, were synthesized. Their biological activities as PAF antagonists were evaluated by the inhibition of PAF-induced rabbit platelet aggregation in vitro and protective effects on PAF-induced hypotension in rats and PAF-induced death in mice. Investigation of structure–activity relationships revealed that PAF antagonist activity is strongly influenced by the acyl substituent of the nitrogen atom on the carbamoyl group and the nature of the polar head group at the 3-position of the glycerin backbone. Among the compounds tested, 2-[[*N*-acetyl-*N*-[[2-methoxy-3-[(octadecylcarbamoyl)oxy]propoxy]-carbonyl]amino]methyl]-1-ethylpyridinium chloride (**21**, CV-6209) was one of the most potent compounds in the in vitro assay ($IC_{50} = 7.5 \times 10^{-8}$ M) and the most potent and long-lasting in the in vivo assays. (*R*)-(−)-**21** and (*S*)-(+)-**21** were also synthesized, and no significant differences were observed in PAF antagonist activity in vitro and an inhibitory effect on PAF induced hypotension in vivo between (*RS*)-**21** and its enantiomers.

Platelet activating factor (PAF), a phospholipid mediator released from rabbit basophils through an IgE-dependent mechanism,[2,3] has been identified as 1-*O*-alkyl-2-*O*-acetyl-*sn*-glycero-3-phosphocholine[4,5] (**1**). This compound exerts diverse biological actions such as platelet aggregation, hypotension, bronchoconstriction, and increase of vascular permeability;[6] however, its precise pathophysiological roles remain to be clarified. In this respect, PAF specific antagonists might represent important tools in the investigation of the role of PAF in various pathophysiological conditions.[7] In 1983, we reported the first PAF specific antagonist, CV-3988 (**2**),[8] which selec-



1: n = 16 or 18



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tively inhibited biological actions of PAF in vitro and in vivo. Recent studies utilizing CV-3988 have suggested that PAF might play important roles in various diseases such as endotoxin shock,[9] anaphylactic shock,[10] and disseminated intravascular coagulation.[11]

In a continuation of our effort to prepare more potent PAF antagonists, we were interested in the compounds in which the charged phosphate moiety of PAF was replaced with other functional groups.[12] As a part of this program, the synthesis of the carbamoyl analogue **9** was undertaken (Scheme I). Acetylation of compound **4** gave the diacetyl compound **5**, which was then converted to the quaternary derivative **6** by the reaction with methyl iodide. Compound **6** was found to have more potent PAF antagonist activity in vitro than that of CV-3988. The corresponding carbamoyl derivative **9** showed PAF antagonist activity in vitro, but was less potent than **6**. On the basis of this finding, a study was carried out to elucidate the structure–activity profile of the PAF analogues replaced with an acylcarbamoyl group as the PAF specific antagonists. In this paper, we report the synthesis and biological evaluation of a novel series of PAF antagonists.

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(3) Benveniste, J.; Henson, P. M.; Cochrane, C. G. *J. Exp. Med.* **1972**, *136*, 1356.
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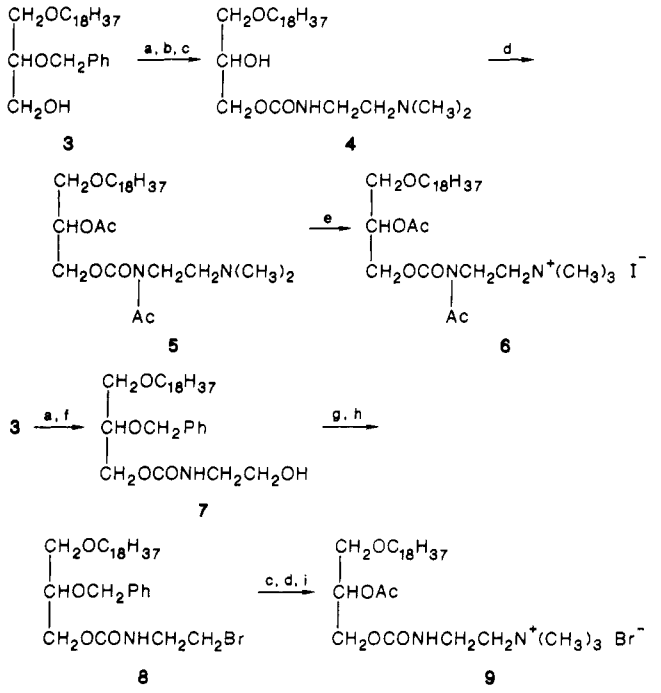
Scheme I[a]



[a] (a) $ClCO_2Ph$, pyridine; (b) $H_2NCH_2CH_2N(CH_3)_2$; (c) H_2, Pd/C; (d) Ac_2O, Et_3N; (e) CH_3I; (f) $H_2NCH_2CH_2OH$; (g) *p*-TsCl/Et_3N; (h) LiBr; (i) Me_3N/toluene.

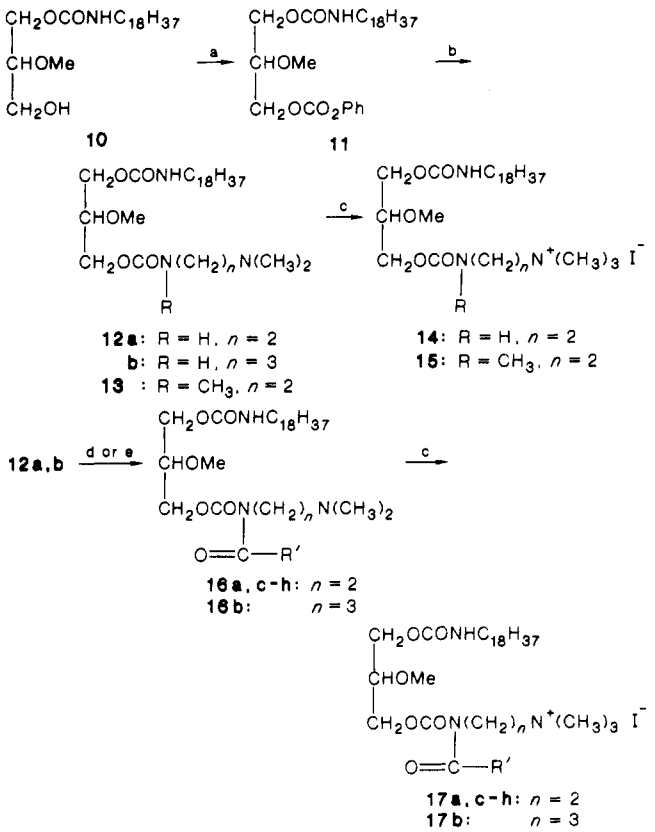
Chemistry

PAF analogues **6** and **9** were prepared as outlined in Scheme I. Reaction of 2-*O*-benzyl-1-*O*-octadecylglycerol (**3**)[13] with phenyl chloroformate in the presence of pyridine followed by coupling with *N*,*N*-dimethylethylenediamine and hydrogenolysis of the benzyl group on Pd/C gave compound **4**. Acetylation of **4** with acetic anhydride and triethylamine in chloroform at room temperature yielded the diacetyl derivative **5**, which was subsequently treated with methyl iodide to give compound **6**. The other PAF analogue **9** was prepared in a different manner. Reaction of **3** with phenyl chloroformate in the presence of pyridine followed by coupling with ethanolamine gave the alcohol **7**, which was then converted to compound **8** in a two-step process involving tosylation of the hydroxy group of **7** with *p*-toluenesulfonyl chloride in triethylamine followed by bromination with lithium bromide. Compound **8** was converted to **9** by hydrogenolysis of the benzyl group on Pd/C followed by acetylation with acetic anhydride in triethylamine and treatment with trimethylamine in toluene.

The different types of PAF analogues modified in the phosphate moiety were synthesized by the method shown in Scheme II. Reaction of **10**[14] with phenyl chloroformate in the presence of pyridine gave carbonate **11**, which was converted to **12a** by heating with *N*,*N*-dimethylethylenediamine at 70 °C. Acetylation of **12a** with acetic anhydride in chloroform in the presence of triethylamine (method A) or in pyridine (method B) at room temperature gave the acetyl derivative **16a**, which was treated with methyl iodide to afford **17a**. To confirm the contribution of the acetyl group on the carbamoyl moiety to PAF antagonist activity, compound **12a** was converted to the quaternary derivative **14** with methyl iodide. To examine the effect of the distance between the *N*-acetylcarbamoyl group and the polar head moiety, **17b** was synthesized from **11** by the reaction with 3-(dimethylamino)propylamine followed by acetylation with acetic anhydride in pyridine at 100 °C and treatment with methyl iodide.

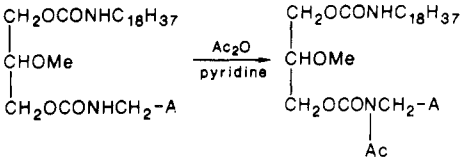
To investigate the effects of the N-substituent on the carbamoyl moiety at the 3-position, the acetyl group was replaced with methyl, propionyl, butyryl, methoxycarbonyl, and some carbamoyl groups (Table II). The alkyl derivative **15** was obtained by the reaction of **11** with *N*,*N*,*N*′-trimethylethylenediamine followed by treatment

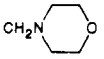
Scheme II[a]



[a] (a) $ClCO_2Ph$, pyridine; (b) $RNH(CH_2)_nNMe_2$; (c) CH_3I; (d) $(R'CO)_2O$/pyridine or R′COCl/pyridine; (e) (1) $ClCO_2Ph$/pyridine, (2) $HNMe_2$ or pyrrolidine or *n*-$PrNH_2$. R′: **a**,**b**, Me; **c**, Et; **d**, *n*-Pr; **e**, OMe; **f**, NMe_2; **g**, pyrrolidino; **h**, NH-*n*-Pr.

Table I. N-Acetylation of the Carbamoyl Group at the 3-Position with Acetic Anhydride in Pyridine



compd	A	reactn condit	yield,[a] %
12a	CH_2NMe_2	RT,[b] 6 h	95
12b	$CH_2CH_2NMe_2$	RT[b]	NR[c]
		100 °C, 24 h	29
18a		RT,[b] 6 h	89
18c		RT[b]	NR[c]
		100 °C, 24 h	43
18e		110 °C, 72 h	80

[a] Yields were not optimized. [b] RT = room temperature. [c] NR = no reaction.

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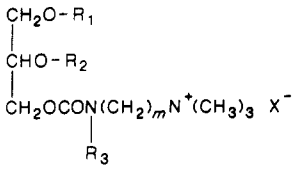
(14) Tsushima, S.; Yoshioka, Y.; Tanida, S.; Nomura, H.; Nojima, S.; Hozumi, M. *Chem. Pharm. Bull.* **1984**, *32*, 2700.

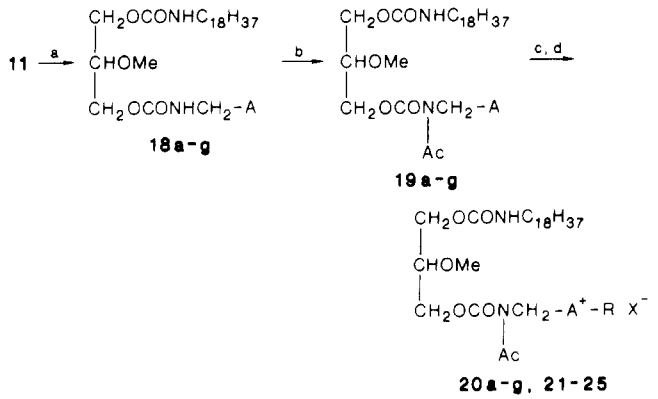
Table II. Inhibitory Activity on PAF-Induced Rabbit Platelet Aggregation



compd	R_1	R_2	R_3	X	m	platelet IC_{50},[a] μM	formula[b]	anal.[c]
2 (CV-3988)						7.8 (n = 6)[d]		
6	$C_{18}H_{37}$	Ac	Ac	I	2	0.88 (n = 2)	$C_{31}H_{61}N_2O_6I$ (1.5H_2O)	C, H, N; I[e]
9	$C_{18}H_{37}$	Ac	H	Br	2	8.4 (n = 2)	$C_{29}H_{59}N_2O_5Br$ (0.5H_2O)	C, H, N, Br
14	$CONHC_{18}H_{37}$	Me	H	I	2	14 (n = 2)	$C_{29}H_{60}N_3O_5I$ (1.5H_2O)	C, H, N
15	$CONHC_{18}H_{37}$	Me	Me	I	2	8.2 (n = 2)	$C_{30}H_{62}N_3O_5I$ (H_2O)	C, H, N
17a	$CONHC_{18}H_{37}$	Me	Ac	I	2	1.5 (n = 2)	$C_{31}H_{62}N_3O_6I$ (H_2O)	C, H, N, I
17b	$CONHC_{18}H_{37}$	Me	Ac	I	3	8.5 (n = 2)	$C_{32}H_{64}N_3O_6I$ (0.5H_2O)	C, H, N
17c	$CONHC_{18}H_{37}$	Me	COEt	I	2	5.6 (n = 2)	$C_{32}H_{64}N_3O_6I$ (2.6H_2O)	C, H, N
17d	$CONHC_{18}H_{37}$	Me	COnPr	I	2	7.8 (n = 2)	$C_{33}H_{66}N_3O_6I$ (H_2O)	C, H, N, I
17e	$CONHC_{18}H_{37}$	Me	CO_2Me	I	2	2.3 (n = 2)	$C_{31}H_{62}N_3O_7I$ (1.5H_2O)	C, H, N
17f	$CONHC_{18}H_{37}$	Me	$CONMe_2$	I	2	5.8 (n = 2)	$C_{37}H_{65}N_4O_6I$ (2H_2O)	C, H, N
17g	$CONHC_{18}H_{37}$	Me		I	2	8.6 (n = 2)	$C_{34}H_{67}N_4O_6I$ (2H_2O)	C, H, N
17h	$CONHC_{18}H_{37}$	Me	CONH-n-Pr	I	2	>30 (n = 2)	$C_{33}H_{67}N_4O_6I$ (2.5H_2O)	C, H, N

[a] Micromolar concentration of a test compound for 50% inhibition of rabbit platelet aggregation induced by PAF. The n values are the number of experiments in which a dose–response curve was determined from two to six replicates per dose level. [b] Parentheses contain the moles of water of hydration. [c] Analytical results are with ±0.4% of theoretical values unless indicated otherwise. [d] Reference 7. [e] I: calcd, 17.83; found, 17.09.

Scheme III[a]

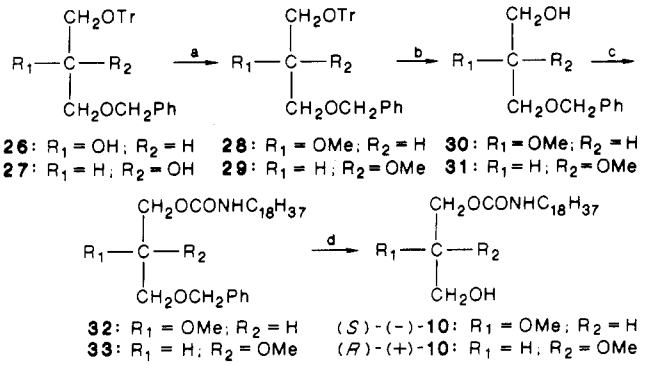


[a] (a) H_2NCH_2-A; (b) Ac_2O; (c) RX; (d) ion exchange. A: **a**, pyrrolidinomethyl; **b**, piperidinomethyl; **c**, morpholinomethyl; **d**, 2-pyrrolidinyl; **e**, 2-pyridyl; **f**, 2-thiazolyl; **g**, 4-thiazolyl.

with methyl iodide. The acyl derivatives **17c,d** were obtained by the acylation of **12a** with propionyl chloride and butyric anhydride in pyridine, respectively, followed by the reaction with methyl iodide. The alkoxycarbonyl derivative **17e** was obtained by the reaction of **12a** with methyl chloroformate in the presence of triethylamine followed by treatment with methyl iodide. The carbamoyl derivatives **17f,g,h** were obtained in a three-step process involving the conversion of **12a** to a phenyl carbonate derivative with phenyl chloroformate and pyridine in methylene chloride followed by treatment with an appropriate amine (dimethylamine, pyrrolidine, and n-propylamine) and the reaction with methyl iodide.

To evaluate the effects of the polar head base on PAF antagonist activity, compounds possessing a cyclic ammonium moiety as the polar head group were synthesized as shown in Scheme III. The reaction of **11** with an appropriate diamine (H_2NCH_2A; A = **a**–**g**, Scheme III) gave a series of amines **18a–g**. These were then converted to the acetylcarbamoyl derivatives by the reaction with acetic anhydride in pyridine (**19a,c**), or in chloroform in the presence of triethylamine at reflux (**19b,d**), or in toluene in the presence of 4-(dimethylamino)pyridine at 80 °C (**19f,g**). The reaction of **19a–g** with methyl iodide (followed by treatment with ion-exchange resin in the case of **19e**) gave a series of the quaternary ammonium derivatives **20a–g**.

Scheme IV[a]



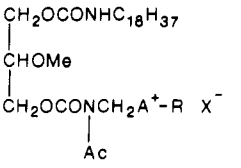
[a] (a) CH_3I/KOH/DMSO; (b) 80% AcOH/H_2O; (c) $C_{18}H_{37}N$=C=O/pyridine; (d) H_2, Pd/C. Tr = trityl.

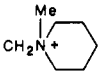
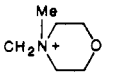
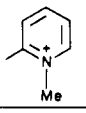
To investigate the effects of the substituent on the nitrogen atom of the pyridinium moiety, compounds **21–23** were prepared by the reaction of **19e** with ethyl iodide, n-propyl iodide, and n-butyl iodide, respectively, followed by treatment with ion-exchange resin. The thiazolium derivatives **24** and **25** which were substituted with an ethyl group at the nitrogen atom of the polar head moiety were also synthesized by the reaction of **19f,g** with ethyl iodide followed by treatment with ion-exchange resin (in the case of **19g**).

In order to examine the enantiospecificity at the 2-position in PAF antagonist activities, (*R*)-(−)-**21** and (*S*)-(+)-**21** were synthesized from (*S*)-(−)-**10** and (*R*)-(+)-**10**, which were prepared as outlined in Scheme IV. Alkylation of 3-*O*-benzyl-1-*O*-trityl-*sn*-glycerol[15] (**26**) with methyl iodide and sodium hydroxide in DMSO gave compound **28**. Deprotection of the trityl group of **28** with acetic acid gave **30**, which was treated with octadecyl isocyanate to afford **32**. Hydrogenolysis of the benzyl group in the

(15) Hirth, G.; Barner, R. *Helv. Chim. Acta* **1982**, *65*, 1059.

Table III. Inhibitory Activity of PAF-Induced Rabbit Platelet Aggregation



compd	A^+–R	X	platelet IC_{50},[a] μM	formula[b]	anal.[c]
20a		I	1.1 (n = 2)	$C_{33}H_{64}N_3O_6I$ (H_2O)	C, H, N, I
20b		I	5.4 (n = 2)	$C_{34}H_{66}N_3O_6I$ (0.5H_2O)	C, H, N, I
20c		I	9.2 (n = 2)	$C_{33}H_{64}N_3O_7I$ (0.5H_2O)	C, H, N
20d		I	0.67 (n = 2)	$C_{34}H_{66}N_3O_6I$ (0.5H_2O)	C, H, N
20e		Cl	0.20 (n = 2)	$C_{33}H_{58}N_3O_6Cl$ (H_2O)	C, H, N, Cl

[a] Micromolar concentration of a test compound for 50% inhibition of rabbit platelet aggregation induced by PAF. The n values are the number of experiments in which a dose–response curve was determined from two to six replicates per dose level. [b] Parentheses contain the moles of water of hydration. [c] Analytical results are within ±0.4% of theoretical values unless indicated otherwise.

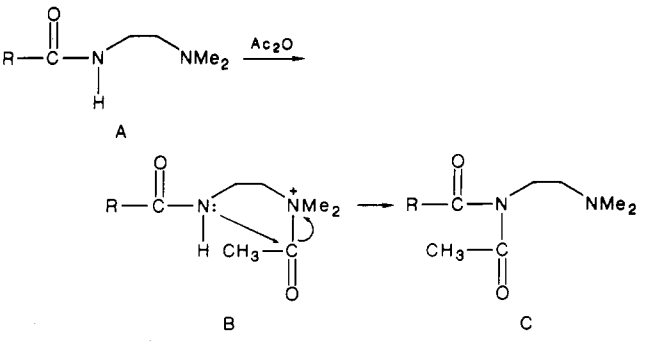
presence of 5% Pd–C catalyst gave (*S*)-(−)-**10**. In an identical manner, (*R*)-(+)-**10** was prepared from 1-*O*-benzyl-3-*O*-trityl-*sn*-glycerol (**27**) via compounds **29**, **31**, and **33**. The chiral purity of (*S*)-(−)-**10** and (*R*)-(+)-**10** was examined by ^{13}C NMR with the Mosher's ester derivatives[16] of both enantiomers and estimated to be greater than 97% (see the Experimental Section). Preparations of (*R*)-(−)-**21** and (*S*)-(+)-**21** from (*S*)-(−)-**10** and (*R*)-(+)-**10** were accomplished by the same procedure with (*RS*)-**21**.

Results and Discussion

The mechanism of acetylation on the carbamoyl group at the 3-position was not further investigated; however, it was revealed that the reaction rate was strongly affected by the nature of the amino group, the basicity of the tertiary amine, and the distance between the carbamoyl group and the amino group (Table I). Thus the acetylation of compounds **18c,e** bearing a weakly basic amino group as the polar head moiety required considerably longer reaction time and higher reaction temperature than that of compounds **12a** and **18a**, which possess a more basic amino group. The reaction rate of the (dimethylamino)-ethyl derivative **12a** was much faster than that of the (dimethylamino)propyl derivative **12b**. In the case of acetylation of **12a,b** and **18a–g**, the carbamoyl group at the 1-position was not acetylated under each reaction condition. From these results, the mechanism of this acetylation reaction might be explained as shown in Scheme V. The tertiary amino group of A is acetylated with acetic anhydride to afford the quaternary ammonium salt (B) and then the acetyl group is transferred to the carbamoyl group by an intramolecular rearrangement to give the acetylcarbamoyl derivative (C). A similar rearrangement reaction of quaternary ammonium salt has been reported.[17]

The inhibitory effect of the compounds on PAF-induced rabbit platelet aggregation in vitro was examined as a first

Scheme V



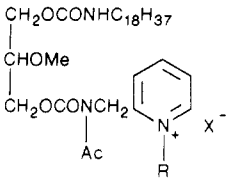
screening using the method of Born[18] (Tables II–IV). The carbamoyl derivatives of PAF (**9** and **14**) showed comparable PAF antagonist activity in vitro to that of CV-3988. It was evident that introduction of an acetyl group into the carbamoyl moiety at the 3-position resulted in a large increase in potency in blocking PAF-induced platelet aggregation in vitro (**6** and **17a**, compared with **9** and **14**, respectively). Since variation of the substituents R_1 and R_2 did not cause marked change in inhibitory activity in comparison of **17a** with **6**, modification of the substituent at the 3-position was explored with use of the same substituent pattern at the 1- and 2-positions with CV-3988 in subsequent studies.

Increasing the distance between the acetylcarbamoyl group and the polar head moiety (compound **17b**) resulted in a decrease of PAF-induced platelet aggregation in vitro, compared to **17a**.

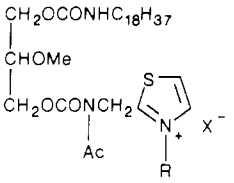
Replacement of the acetyl group on the carbamoyl moiety by methyl, propionyl, butyryl, methoxycarbonyl, and some carbamoyl groups resulted in a decrease in PAF antagonist potency. Especially, introduction of methyl or larger acyl substituents such as butyryl, pyrrolidinocarbonyl, and *n*-propylcarbamoyl led to greater decreases

(16) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
(17) Willstatter, R. *Ber.* **1902**, *35*, 584.
(18) Born, G. V. R. *Nature (London)* **1962**, *194*, 927.

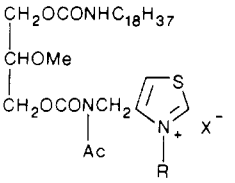
Table IV. Inhibitory Activity of PAF-Induced Rabbit Platelet Aggregation and PAF-Induced Hypotension in Rats



20e, 21-23



20f, 24



20g, 25

compd	R	X	platelet IC_{50},[a] μM	inhibition of PAF hypotension,[b] % dose, mg/kg	5 min	60 min	120 min	formula[c]	anal.[d]
20e	Me	Cl	0.20 (n = 2)	1.0 (n = 2)	82	39	33	$C_{33}H_{58}N_3O_6Cl$ (H_2O)	C, H, N, Cl
21	Et	Cl	0.075 (n = 8)	0.1 (n = 5)	100	55	34	$C_{34}H_{60}N_3O_6Cl$ (1.5H_2O)	C, H, N, Cl
(*R*)-(−)-**21**	Et	Cl	0.084 (n = 2)	0.1 (n = 3)	100	36	20	$C_{34}H_{60}N_3O_6Cl$ (2H_2O)	C, H, N
(*S*)-(+)-**21**	Et	Cl	0.091 (n = 2)	0.1 (n = 2)	100	54	17	$C_{34}H_{60}N_3O_6Cl$ (2H_2O)	C, H, N
22	n-Pr	Cl	0.094 (n = 2)	0.1 (n = 2)	45	0		$C_{35}H_{62}N_3O_6Cl$ (1.5H_2O)	C, H, N; Cl[e]
23	n-Bu	Cl	0.11 (n = 2)	1.0 (n = 2)	100	0		$C_{36}H_{64}N_3O_6Cl$ (H_2O)	C, H, N, Cl
20f	Me	I	0.41 (n = 2)	1.0 (n = 1)	100	100	30	$C_{31}H_{56}N_3O_6SI$ (0.5H_2O)	C, H, N, S
				0.1 (n = 2)	43	6	0		
24	Et	I	0.096 (n = 2)	0.1 (n = 2)	100	3	0	$C_{32}H_{58}N_3O_6Si$ (0.5H_2O)	C, H, N, S
20g	Me	I	0.10 (n = 2)	1.0 (n = 2)	92	29	4	$C_{31}H_{56}N_3O_6SI$ (1.5H_2O)	C, H, N, S
25	Et	Cl	0.092 (n = 2)	0.1 (n = 2)	100	40	14	$C_{32}H_{58}N_3O_6Cl$ (H_2O)	C, H, N, S

[a] Micromolar concentration of a test compound for 50% inhibition of rabbit platelet aggregation induced by PAF. The n values are the number of experiments in which a dose–response curve was determined from two to six replicates per dose level. [b] PAF (0.3 μg/kg, iv) was first injected twice at an interval of 20 min. Twenty minutes after the second injection, test compounds (one dose per rat for one compound) were given iv and PAF was injected 5, 60, and 120 min after the compound. The hypotension induced by the second injection of PAF (about 50 mmHg) was defined as 100 and the percent inhibition of the PAF-induced hypotension by test compounds was estimated. The n values are the number of experiments. The standard deviation of the mean of these results less than 5%. [c] Parentheses contain the moles of water of hydration. [d] Analytical results are with in ±0.4% of theoretical values unless indicated. [e] Cl: calcd, 5.19; found, 5.61.

in potency (**15**, **17d**, and **17h**).

The effects of the polar head base on PAF antagonist activity were shown in Tables III and IV. Compounds **20d,e** in which the nitrogen atom of the polar head was incorporated into the ring system showed more potent PAF antagonist activity than the trimethylammonium derivative **17a**. Especially, the pyridinium methyl derivative **20e** was 10 times more potent than **17a** (Table III). Since the thiazolium group was the best polar head base for PAF antagonist activity in the case of CV-3988, the thiazolium derivatives **20f** and **20g** were synthesized. These compounds showed approximately equivalent potency to the corresponding pyridinium derivative **20e**. Modification of the substituent on the nitrogen atom of the pyridinium moiety resulted in an increase in reducing PAF-induced platelet aggregation (**21–23**) and the ethyl group appeared to be optimal. Similarly, the thiazolium derivatives substituted with an ethyl group at the nitrogen atom also had strong PAF antagonist activity (**24**, **25**) (Table IV).

Compounds with strong PAF antagonist activity in vitro were further evaluated by measuring the inhibitory effect on PAF-induced hypotension in rats. As shown in Table IV, compounds **21**, **24**, and **25** completely inhibited PAF-induced hypotension at a dose of 0.1 mg/kg after 5 min. It was noteworthy that these *N*-ethyl derivatives were about 10 times more potent than that of the corresponding *N*-methyl derivatives. Consequently, compounds **21** and **25** were selected for further evaluation of the protecting effect on PAF-induced sudden death in mice. Since a long-lasting effect is desirable for pharmaceutical usage, the duration of action was evaluated in this assay. As shown in Table V, the duration of action of the pyridinium derivative **21** was longer than that of the thiazolium derivative **25**. The protective effect of **21** at a dose of 1 mg/kg continued even after 24 h.

No significant differences were observed in PAF antagonist activity in vitro and an inhibitory effect on PAF-induced hypotension in vivo between (*RS*)-**21** and its stereoisomers (*R*)-(−)-**21** and (*S*)-(+)-**21**. Similar results have been reported on PAF antagonists SRI 63-072 and SRI 63-119.[7j]

Table V. Time Course of Protecting Effect of **21** and **25** on PAF-Induced Death in Mice

compd	dose, mg/kg	survival rate,[a] % 8 h	24 h
21	1	100**[b]	69**
25	1	75**	25

[a] Test compounds were given iv 8 and 24 h before the injection of PAF (50 μg/kg, iv). Numbers of mice were 142 (control) and 16 (**21** and **25**). The survival rate was recorded 60 min after the injection of PAF and was 22% for control. [b] (**) $p < 0.01$, χ^2 test: vs the value of the control.

From the results of biological evaluation, 2-[[*N*-acetyl-*N*-[[2-methoxy-3-[(octadecylcarbamoyl)oxy]propoxy]-carbonyl]amino]methyl]-1-ethylpyridinium chloride (**21**) (CV-6209) was selected for further pharmacological characterization.[19]

Experimental Section

Melting points were determined on a Yanaco micro-melting apparatus and are uncorrected. ^1H NMR spectra were taken with a Varian EM-390 or a Varian T-60 spectrometer, while ^{13}C NMR spectra were determined with a JEOL GX-400 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. Unless otherwise indicated, ^1H NMR spectra were measured at 90 MHz. Infrared spectra were recorded on a Hitachi 215 spectrometer. Where analyses are indicated by symbols of elements, the analytical results were within ±0.4% of the theoretical values. Column chromatography was carried out on silica gel (E. Merck, particle size 70–230 mesh).

The diamines required for the preparation of **18a–e** are commercially available; however, the diamines needed for compounds **18f** and **18g** were prepared in a manner similar to that described in the literature.[20]

(19) Terashita, Z-i.; Imura, Y.; Takatani, M.; Tsushima, S.; Nishikawa, K. *J. Pharmacol. Exp. Ther.* **1987**, *242*, 263.

3-*O*-[[2-(Dimethylamino)ethyl]carbamoyl]-1-*O*-octadecylglycerol (4). To a solution of 2-*O*-benzyl-1-*O*-octadecylglycerol (**3**)[13] (1.88 g, 4.33 mmol) and pyridine (0.68 g, 8.65 mmol) in 12 mL of methylene chloride was added phenyl chloroformate (0.75 g, 4.76 mmol) with stirring at 0 °C. After stirring for 1.5 h, the mixture was washed with 1% $NaHCO_3$ solution and dried ($MgSO_4$). Solvent was removed at reduced pressure, giving the crude carbonate as an oil which was used in the next step without additional purification: NMR ($CDCl_3$) δ 0.86 (3 H, s), 1.27 (30 H, s), 1.4–1.7 (2 H, m), 3.43 (2 H, t, J = 6 Hz), 3.55 (2 H, d, J = 5 Hz), 3.84 (1 H, m), 4.40 (2 H, m), 4.70 (2 H, s), 7.08–7.57 (10 H, m); IR (neat) 1760, 1235, 1210 cm^{-1}.

This carbonate was heated at 70 °C with *N,N*-dimethylethylenediamine for 5 h. After cooling, the reaction mixture was chromatographed on silica gel, with $CHCl_3$–MeOH (19:1) as eluent, to give 2.37 g (100%) of 2-*O*-benzyl-3-*O*-[[2-(dimethylamino)ethyl]carbamoyl]-1-*O*-octadecylglycerol as an oil that solidified on cooling: NMR ($CDCl_3$) δ 0.87 (3 H, br t, J = 7 Hz), 1.28 (30 H, s), 1.4–1.7 (2 H, m), 2.20 (6 H, s), 2.37 (2 H, t, J = 6 Hz), 3.23 (2 H, q, J = 6 Hz), 3.42 (2 H, t, J = 6 Hz), 3.53 (2 H, d, J = 5 Hz), 3.76 (1 H, quint, J = 5 Hz), 4.20 (2 H, m), 4.68 (2 H, s), 5.27 (1 H, br), 7.32 (5 H, s); IR (neat) 1725 cm^{-1}. This free base was converted to the HCl salt by treatment with HCl/ether for elemental analysis. Anal. ($C_{33}H_{61}N_2O_4Cl \cdot H_2O$) C, H, N.

A solution of 1.10 g (2 mmol) of the above free base in 5 mL of 90% AcOH and 5 mL of EtOH containing 250 mg of 10% Pd/C catalyst was subjected to hydrogenolysis for 14 h. The catalyst was removed by filtration and the solvent was removed at reduced pressure. The residue was chromatographed on silica gel, with $CHCl_3$–MeOH (6:1) as eluent, to afford 816 mg (89%) of **4** as a colorless wax: NMR ($CDCl_3$) δ 0.87 (3 H, t, J = 7 Hz), 1.27 (30 H, s), 1.4–1.7 (2 H, m), 2.24 (6 H, s), 2.40 (2 H, t, J = 6 Hz), 2.99 (1 H, br), 3.27 (2 H, q, J = 6 Hz), 3.45 (4 H, m), 3.97 (1 H, m), 4.14 (2 H, m), 5.48 (1 H, br); IR (neat) 3290, 1700, 1525, 1465 cm^{-1}. Anal. ($C_{26}H_{54}N_2O_4$) C, N; H: calcd, 11.87; found, 11.08.

2-*O*-Acetyl-3-*O*-[*N*-acetyl-*N*-[2-(dimethylamino)ethyl]carbamoyl]-1-*O*-octadecylglycerol (5). To a solution of **4** (1.417 g, 3.09 mmol) and 31 mL of triethylamine in $CHCl_3$ (15 mL) was added 4.6 mL (48.75 mmol) of acetic anhydride. The mixture was allowed to stand at room temperature for 21 h and concentrated at reduced pressure. The residue was diluted with $CHCl_3$ and washed with 5% $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$) and the solvent was removed. The residue was chromatographed on silica gel, with AcOEt–acetone (2:1) as eluent, to afford 1.608 g (96%) of **5** as a colorless oil: NMR ($CDCl_3$) δ 0.88 (3 H, br t, J = 7 Hz), 1.27 (30 H, s), 1.4–1.7 (2 H, m), 2.10 (3 H, s), 2.23 (6 H, s), 2.40 (2 H, t, J = 7 Hz), 2.50 (3 H, s), 3.46 (2 H, t, J = 6 Hz), 3.58 (2 H, d, J = 5 Hz), 3.85 (2 H, t, J = 7 Hz), 4.42 (2 H, m), 5.29 (1 H, m); IR (neat) 1745, 1710, 1234 cm^{-1}. This free base was converted to the HCl salt by treatment with HCl/ether for elemental analysis. Anal. ($C_{30}H_{59}N_2O_6Cl \cdot H_2O$) C, H, N.

2-[*N*-Acetyl-*N*-[[2-methoxy-3-(octadecyloxy)propoxy]carbonyl]amino]-*N,N,N*-trimethyl-1-ethanaminium Iodide (6). To a solution of **5** (1.10 g, 2.03 mmol) in 45 mL of ether was added 623 mg (4.37 mmol) of methyl iodide. The mixture was allowed to stand at room temperature for 72 h in the dark, and 1.22 g (88%) of **6** was collected by filtration as a white powder with no well-defined melting point (73–76 °C): NMR ($CDCl_3$) δ 0.87 (3 H, br t, J = 7 Hz), 1.27 (30 H, s), 1.4–1.7 (2 H, m), 2.12 (3 H, s), 2.52 (3 H, s), 3.33–3.7 (13 H, m), 3.80 (2 H, m), 4.22 (2 H, br t, J = 7 Hz), 4.51 (2 H, m), 5.42 (1 H, m); IR (KBr) 1740, 1680 (br) cm^{-1}. Anal. ($C_{31}H_{61}N_2O_6I \cdot 1.5H_2O$) C, H, N; I: calcd, 17.83; found, 17.09.

In a similar manner, compounds **14**, **15**, **17a–h**, **20a–d** were prepared.

2-*O*-Benzyl-3-*O*-[(2-hydroxyethyl)carbamoyl]-1-*O*-octadecylglycerol (7). The crude carbonate, prepared by a procedure identical with that described in the synthesis of **4** from 1.74 g (4 mmol) of 2-*O*-benzyl-1-*O*-octadecylglycerol, 632 mg (8 mmol) of pyridine, and 689 mg (4.4 mmol) of phenyl chloroformate, was dissolved in 10 mL of $CHCl_3$ and stirred with 293 mg (4.8 mmol) of ethanolamine at reflux for 21 h. The reaction mixture was concentrated at reduced pressure. The residue was chromatographed on silica gel, with *n*-hexane–AcOEt (1:1) as eluent, to afford 1.94 g (93%) of **7** as a white powder: mp 45–46 °C; NMR ($CDCl_3$) δ 0.89 (3 H, br t, J = 7 Hz), 1.27 (30 H, s), 1.4–1.7 (2 H, m), 2.82 (1 H, br t, J = 6 Hz), 3.15–3.91 (9 H, m), 4.22 (2 H, m), 4.68 (2 H, s), 5.37 (1 H, br t, J = 6 Hz), 7.33 (5 H, s); IR (KBr) 3335, 1700 cm^{-1}. Anal. ($C_{31}H_{55}NO_5$) C, H, N.

2-*O*-Benzyl-3-*O*-[(2-bromoethyl)carbamoyl]-1-*O*-octadecylglycerol (8). To a solution of 1.84 g (3.53 mmol) of **7** in 10 mL of triethylamine was added 0.88 g (4.59 mmol) of *p*-toluenesulfonyl chloride with stirring at 0 °C. After the mixture was stirred for 18 h at room temperature, 5% HCl solution (100 mL) was added slowly and the mixture was extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$) and the solvent was removed at reduced pressure. The residue was chromatographed on silica gel, with *n*-hexane–AcOEt (2.5:1) as eluent, to give 2.36 g (99%) of 2-*O*-benzyl-1-*O*-octadecyl-3-*O*-[[2-[(*p*-tolylsulfonyl)oxy]ethyl]carbamoyl]glycerol as a colorless oil: NMR ($CDCl_3$) δ 0.88 (3 H, br t, J = 7 Hz), 1.23 (30 H, s), 1.4–1.7 (2 H, m), 2.41 (3 H, s), 3.28–3.58 (6 H, m), 3.72 (1 H, quint, J = 5 Hz), 3.97–4.37 (4 H, m), 4.64 (2 H, s), 5.02 (1 H, br), 7.22–7.42 (7 H, m), 7.79 (2 H, d, J = 8 Hz); IR (neat) 1728, 1600 cm^{-1}.

This compound (2.36 g, 3.49 mmol) was dissolved in 22 mL of DMF and 0.73 g (6.98 mmol) of lithium bromide was added. The mixture was heated for 2 h at 60 °C and cooled to room temperature. Water was added and the mixture was extracted with ether. The organic layer was dried ($MgSO_4$) and the solvent was removed. The residue was chromatographed on silica gel, with *n*-hexane–AcOEt (4:1) as eluent, to give 1.86 g (91%) of **8** as an oil that crystallized on standing: mp 50–51 °C; NMR ($CDCl_3$) δ 0.87 (3 H, m), 1.26 (30 H, s), 1.4–1.7 (2 H, m), 3.29–3.92 (9 H, m), 4.22 (2 H, m), 4.66 (2 H, s), 5.06 (1 H, br), 7.30 (5 H, s); IR (KBr) 1720 cm^{-1}. Anal. ($C_{31}H_{54}NO_4Br$) C, H, N.

2-[[[2-Acetoxy-3-(octadecyloxy)propoxy]carbonyl]amino]-*N,N,N*-trimethyl-1-ethanaminium Bromide (9). A solution of **8** (949 mg, 1.62 mmol) in 40 mL of 90% AcOH–H_2O containing 250 mg of 10% Pd/C catalyst was subjected to hydrogenolysis for 2 h. The catalyst was removed by filtration, and the solvent was evaporated to give 785 mg (98%) of the alcohol as a white powder which was used in the next step without additional purification: mp 65–66 °C; NMR ($CDCl_3$) δ 0.88 (3 H, br t, J = 7 Hz), 1.24 (30 H, s), 1.4–1.7 (2 H, m), 2.85 (1 H, br), 3.31–3.72 (8 H, m), 4.00 (1 H, m), 4.17 (2 H, m), 5.33 (1 H, br); IR (KBr) 3415, 3305, 1698 cm^{-1}. Anal. ($C_{24}H_{48}NO_4Br$) C, H, N.

This compound (124 mg, 0.25 mmol) was dissolved in 3 mL of $CHCl_3$, and 2.5 mL of pyridine and 0.4 mL of acetic anhydride were added. The mixture was allowed to stand for 13 h at room temperature and 50 mL of ether was added. The mixture was washed with 5% $NaHCO_3$ and 5% HCl solution, and the organic layer was dried ($MgSO_4$) and concentrated at reduced pressure. The residue was chromatographed on silica gel, with *n*-hexane–AcOEt (4:1) as eluent, to give 117 mg (87%) of the acetate as a colorless syrup: NMR ($CDCl_3$) δ 0.89 (3 H, br t, J = 7 Hz), 1.27 (30 H, s), 1.4–1.7 (2 H, m), 2.08 (3 H, s), 3.35–3.73 (8 H, m), 4.28 (2 H, m), 5.04–5.41 (2 H, m); IR (neat) 1735, 1700, 1225 cm^{-1}.

The acetate (115 mg, 0.21 mmol) was dissolved in toluene and 4 mL of 20% trimethylamine–toluene solution was added. The mixture was allowed to stand at room temperature for 48 h and the solvent was removed at reduced pressure. The residue was triturated with $CHCl_3$–ether to afford 120 mg (94%) of **9** as a white powder: mp 61–62 °C; NMR ($CDCl_3$) δ 0.87 (3 H, br t, J = 7 Hz), 1.25 (30 H, s), 1.4–1.7 (2 H, m), 2.08 (3 H, s), 3.32–3.97 (17 H, m), 4.30 (2 H, m), 5.20 (1 H, m), 6.82 (1 H, m); IR (KBr) 1730, 1265, 1240 cm^{-1}. Anal. ($C_{29}H_{59}N_2O_5Br \cdot 0.5H_2O$) C, H, N, Br.

2-*O*-Methyl-1-*O*-(octadecylcarbamoyl)-3-*O*-(phenoxycarbonyl)glycerol (11). To a solution of 2-*O*-methyl-1-*O*-(octadecylcarbamoyl)glycerol[14] (40.16 g, 0.1 mol) and pyridine (16.18 mL, 0.2 mol) in 300 mL of methylene chloride was added phenyl chloroformate (15.06 g, 0.12 mol) at 0 °C. After the mixture was stirred at room temperature for 30 min, 5% $NaHCO_3$ solution (150 mL) was added. The organic layer was separated and the aqueous layer was extracted with methylene chloride. The combined organic layer was dried ($MgSO_4$) and the solvent was removed. The residue was recrystallized from *n*-hexane to give 47.51 g (91%) of **11** as colorless fine needles: mp 59.5–60.5 °C; NMR

(20) Berlin, A. Y.; Bronovitskaya, V. P. *Zh. Obshch. Khim.* **1961**, *31*, 1356.

($CDCl_3$) δ 0.86 (3 H, br t, J = 7 Hz), 1.26 (30 H, s), 1.4–1.7 (2 H, m), 3.15 (2 H, q, J = 6 Hz), 3.48 (3 H, s), 3.67 (1 H, m), 4.22 (2 H, d, J = 5 Hz), 4.33 (2 H, dd, J = 3, 5 Hz), 4.73 (1 H, br), 7.10–7.53 (5 H, m); IR (KBr) 3330, 1762, 1695, 1275, 1250, 1205 cm^{-1}. Anal. ($C_{30}H_{51}NO_6$) C, H, N.

3-*O*-[[2-(Dimethylamino)ethyl]carbamoyl]-2-*O*-methyl-1-*O*-(octadecylcarbamoyl)glycerol (12a). The mixture of **11** (2.09 g, 4 mmol) and *N,N*-dimethylethylenediamine (445 mg, 4.8 mmol) was heated at 70 °C for 5 h. After cooling, the reaction mixture was chromatographed on silica gel, with $CHCl_3$–MeOH (10:1) as eluent, to give 1.90 g (92% of **12a** as a colorless solid: mp 42–43 °C; NMR ($CDCl_3$) δ 0.88 (3 H, br t, J = 7 Hz), 1.27 (30 H, s), 1.4–1.7 (2 H, m), 2.20 (6 H, s), 2.39 (2 H, t, J = 6 Hz), 3.02–3.34 (4 H, m), 3.43 (3 H, s), 3.58 (1 H, quint, J = 5 Hz), 4.16 (4 H, br d, J = 5 Hz), 5.00 (1 H, br); IR (KBr) 3330, 1695 cm^{-1}. Anal. ($C_{28}H_{57}N_3O_5$) C, H, N.

In a similar manner, compounds **12b**, **13**, **18a–d,f,g** were prepared from appropriate diamines.

2-*O*-Methyl-3-*O*-[*N*-(2-pyridylmethyl)carbamoyl]-1-*O*-(octadecylcarbamoyl)glycerol (18e). The mixture of **11** (10.43 g, 20 mmol) and 2-(aminomethyl)pyridine (3.05 mL, 30 mmol) was heated at 90 °C for 1 h. After cooling, the mixture was diluted with methylene chloride and washed with 5% KOH solution. The organic layer was dried (K_2CO_3) and the solvent was removed. The residue was recrystallized from *n*-hexane–methylene chloride (10:1) to give 10.70 g (100%) of **18e** as colorless fine needles: mp 66.5–67.0 °C; NMR ($CDCl_3$) δ 0.86 (3 H, br t, J = 7 Hz), 1.25 (30 H, s), 1.4–1.7 (2 H, m), 3.15 (2 H, q, J = 6 Hz), 3.44 (3 H, s), 3.59 (1 H, quint, J = 5 Hz), 4.18 (4 H, m,), 4.50 (2 H, d, J = 6 Hz), 4.80 (1 H, br), 5.90 (1 H, br), 7.10–7.40 (2 H, m), 7.67 (1 H, dt, J = 2, 8 Hz), 8.56 (1 H, br d, J = 5 Hz); IR (KBr) 3320, 1695 cm^{-1}. Anal. ($C_{30}H_{53}N_3O_5$) C, H, N.

In a similar manner, (*R*)-(−)-**18e** and (*S*)-(+)-**18e** were prepared from (*S*)-(−)-**10** and (*R*)-(+)-**10** with phenyl chloroformate and pyridine followed by 2-(aminomethyl)pyridine, respectively. The compounds were identical (IR, NMR, TLC) with racemic **18e**. (*R*)-(−)-**18e**: mp 74–75 °C (from *n*-hexane–ether (4:1)); $[\alpha]^{26}_D$ −0.2° (*c* 1, $CHCl_3$). Anal. ($C_{30}H_{53}N_3O_5$) C, H, N. (*S*)-(+)-**18e**: mp 75–76 °C (from *n*-hexane–ether (4:1)); $[\alpha]^{26}_d$ +0.3° (*c* 1, $CHCl_3$). Anal. ($C_{30}H_{53}N_3O_5$) C, H, N.

3-*O*-[*N*-Acetyl-*N*-[2-(dimethylamino)ethyl]carbamoyl]-2-*O*-methyl-1-*O*-(octadecylcarbamoyl)glycerol (16a). Method A. To a solution of **12a** (202 mg, 0.39 mmol) and triethylamine (4.4 mL) in 15 mL of $CHCl_3$ was added 0.4 mL (4.24 mmol) of acetic anhydride with strirring. The mixture was allowed to stand at room temperature for 19 h and concentrated. The residue was dissolved in $CHCl_3$ and washed with 1% $NaHCO_3$ solution. The organic layer was dried (K_2CO_3) and the solvent was removed. The residue was chromatographed on silica gel, with AcOEt–acetone (1:1) as eluent, to give 206 mg (94%) of **16a** as an oil: NMR ($CDCl_3$) δ 0.89 (3 H, br t, J = 7 Hz), 1.25 (30 H, s), 1.4–1.7 (2 H, m), 2.25 (6 H, s), 2.43 (2 H, m), 2.48 (3 H, s), 3.13 (2 H, q, J = 6 Hz), 3.43 (3 H, s), 3.62 (1 H, br quint, J = 5 Hz), 3.86 (2 H, t, J = 8 Hz), 4.20 (2 H, d, J = 5 Hz), 4.30 (2 H, dd, J = 2, 5 Hz), 5.61 (1 H, br); IR (neat) 1738, 1710, 1690 cm^{-1}.

In a similar manner, compounds **19b,d** were prepared except the reactions were allowed to proceed at reflux for 24 h.

Method B. The mixture of **12a** (200 mg, 0.39 mmol), acetic anhydride (4 mL, 42.4 mmol), and pyridine (8 mL) was allowed to stand at room temperature for 6 h and concentrated under reduced pressure. Workup was the same as in method A and the yield of **16a** was 95%.

In a similar manner, compound **19a** was prepared. Compounds **16b**, **16d**, and **19c** were also prepared by method B except that the reactions were allowed to proceed at 100 °C for 24 h.

3-*O*-[*N*-[2-(Dimethylamino)ethyl]-*N*-propionylcarbamoyl]-2-*O*-methyl-1-*O*-(octadecylcarbamoyl)glycerol (16c). To a solution of **12a** (516 mg, 1 mmol) and pyridine (395 mg, 5 mmol) in a 10 mL of methylene chloride was added 185 mg (2 mmol) of propionyl chloride at 0 °C. The mixture was allowed to stand at room temperature for 24 h and washed with 5% $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4) and the solvent was removed. The residue was chromatographed on silica gel, with $CHCl_3$–MeOH (19:1) as eluent, to give 560 mg (98%) of **16c** as a colorless oil: NMR (60 MHz, $CDCl_3$) δ 0.90 (3 H, m), 1.17 (3 H, m), 1.25 (32 H, s), 2.28 (6 H, s), 2.43 (2 H, t, J = 6 Hz), 2.66 (2 H, q, J = 8 Hz), 3.08 (2 H, m), 3.43 (3 H, s), 3.72 (1 H, m), 3.92 (2 H, t, J = 6 Hz), 4.18 (2 H, d, J = 6 Hz), 4.30 (2 H, d, J = 6 Hz), 5.33 (1 H, br); IR (neat) 1735, 1705, 1675 cm^{-1}.

3-*O*-[*N*-[2-(Dimethylamino)ethyl]-*N*-(methoxycarbonyl)carbamoyl]-2-*O*-methyl-1-*O*-(octadecylcarbamoyl)glycerol (16e). To a solution of **12a** (500 mg, 0.97 mmol) and triethylamine (1 mL, 7.17 mmol) was added methyl chloroformate (0.5 g, 5.29 mmol) at 0 °C. The mixture was stirred for 10 min, diluted with 20 mL of ether, and then washed with 5% $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4) and the solvent was removed. The residue was chromatographed on silica gel, with $CHCl_3$–MeOH (19:1) as eluent, to give 350 mg (63%) of **16e** as a colorless oil: NMR (60 MHz, $CDCl_3$) δ 0.88 (3 H, m), 1.25 (32 H, s), 2.25 (6 H, s), 2.48 (2 H, t, J = 6 Hz), 3.10 (2 H, m), 3.45 (3 H, s), 3.67 (1 H, m), 3.75 (2 H, t, J = 6 Hz), 3.82 (3 H, s), 4.20 (2 H, d, J = 5 Hz), 4.30 (2 H, d, J = 5 Hz), 5.03 (1 H, br); IR (neat) 1790, 1750, 1725, 1705 cm^{-1}.

3-*O*-[*N*-[2-(Dimethylamino)ethyl]-*N*-(pyrrolidinocarbonyl)carbamoyl]-2-*O*-methyl-1-*O*-(octadecylcarbamoyl)glycerol (16g). To a solution of **12a** (1.03 g, 2 mmol) and pyridine (633 mg, 8 mmol) in 20 mL of methylene chloride was added phenyl chloroformate (470 mg, 3 mmol) at 0 °C. The mixture was stirred at room temperature for 4 h and washed with 2.5% $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4) and the solvent was removed at reduced pressure to give 1.27 g (100%) of 3-*O*-[*N*-[2-(dimethylamino)ethyl]-*N*-(phenoxycarbonyl)carbamoyl]-2-*O*-methyl-1-*O*-(octadecylcarbamoyl)glycerol as a colorless oil which was used in the next step without additional purification.

This compound (636 mg, 1 mmol) was heated with pyrrolidine (0.5 mL, 6.0 mmol) at 70 °C for 5 h. After cooling, the mixture was concentrated and the residue was chromatographed on silica gel, with $CHCl_3$–MeOH (19:1) as eluent, to give 613 mg (100%) of **16g** as a colorless oil: NMR (60 MHz, $CDCl_3$) δ 0.91 (3 H, m), 1.27 (32 H, s), 1.88 (4 H, m), 2.21 (6 H, s), 2.45 (2 H, t, J = 6 Hz), 3.08 (2 H, m), 3.42 (3 H, s), 3.53 (1 H, m), 3.66 (6 H, m), 4.17 (2 H, d, J = 5 Hz), 4.23 (2 H, d, J = 5 Hz), 5.05 (1 H, br); IR (neat) 1725, 1675 cm^{-1}.

In a similar manner, compounds **16f,h** were prepared.

3-*O*-[*N*-Acetyl-*N*-(2-pyridylmethyl)carbamoyl]-2-*O*-methyl-1-*O*-(octadecylcarbamoyl)glycerol (19e). The mixture of **18e** (5.36 g, 10 mmol), acetic anhydride (18.9 mL, 200 mmol), and pyridine (100 mL) was heated at 110 °C for 72 h and evaporated in vacuo. The residue was diluted with $CHCl_3$ and washed with 5% $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4) and the solvent was removed. The residue was chromatographed on silica gel, eluting with *n*-hexane–AcOEt (1:2), to give 4.62 g (80%) of **19e** as colorless fine needles: mp 63.0–63.5 °C (from *n*-hexane); NMR ($CDCl_3$) δ 0.86 (3 H, br t, J = 7 Hz), 1.27 (30 H, s), 1.4–1.7 (2 H, m), 2.62 (3 H, s), 3.12 (2 H, q, J = 6 Hz), 3.30 (3 H, s), 3.46 (1 H, quint, J = 6 Hz), 3.99 (2 H, d, J = 5 Hz), 4.23 (2 H, dd, J = 2, 5 Hz), 4.87 (1 H, br), 5.09 (2 H, s), 7.15 (2 H, m), 7.64 (2 H, dt, J = 2, 8 Hz), 8.52 (1 H, m); IR (KBr) 3370, 1740, 1700 cm^{-1}. Anal. ($C_{32}H_{55}N_3O_6$) C, H, N.

In an identical manner, (*R*)-(−)-**19e** and (*S*)-(+)-**19e** were prepared from (*R*)-(−)-**18e** and (*S*)-(+)-**18e**, respectively. Each isomer was identical (IR, NMR, TLC) with racemic **19e**. (*R*)-(−)-**19e**: mp 67–68 °C; $[\alpha]^{25}_D$ −3.1 (*c* 1, $CHCl_3$). Anal. ($C_{32}H_{55}N_3O_6$) C, H, N. (*S*)-(+)-**19e**: mp 69–69.5 °C; $[\alpha]^{25}_D$ +3.3° (*c* 1, $CHCl_3$). Anal. ($C_{32}H_{55}N_3O_6$) C, H, N.

3-*O*-[*N*-Acetyl-*N*-(2-thiazolylmethyl)carbamoyl]-2-*O*-methyl-1-*O*-(octadecylcarbamoyl)glycerol (19f). To a solution of **18f** (108 mg, 0.2 mmol) and 4-(dimethylamino)pyridine (122 mg, 1.0 mmol) in 0.5 mL of toluene was added 102 mg (1.0 mmol) of acetic anhydride. The mixture was heated at 80 °C for 4 h and concentrated at reduced pressure. The residue was chromatographed on silica gel, with $CHCl_3$–MeOH (39:1) as eluent, to give 110 mg (78%) of **19f** as a pale yellow powder: mp 47.5–48.0 °C; NMR (60 MHz, $CDCl_3$) δ 0.92 (3 H, m), 1.23 (32 H, s), 2.60 (3 H, s), 3.08 (2 H, m), 3.37 (3 H, s), 3.57 (1 H, m), 4.10 (2 H, d, J = 5 Hz), 4.27 (2 H, d, J = 5 Hz), 4.90 (1 H, br), 5.27 (2 H, s), 7.23 (1 H, d, J = 3 Hz), 7.67 (1 H, d, J = 3 Hz); IR (KBr) 1745, 1715 cm^{-1}. Anal. ($C_{30}H_{53}N_3O_6S \cdot {}^1/_2H_2O$) H, N, S; C: calcd, 60.78; found, 61.24.

In a similar manner, compound **19g** was prepared.

2-[[*N*-Acetyl-*N*-[[2-methoxy-3-[(octadecylcarbamoyl)oxy]propoxy]carbonyl]amino]methyl]-1-ethylpyridinium Chloride (21). The mixture of **19e** (5.78 g, 10 mmol) and ethyl iodide (30 mL) was stirred at reflux for 39 h in the dark and concentrated. The residue was dissolved in 70% MeOH/H_2O (150 mL) and passed through a column of Amberlite IRA-410 ion-exchange resin (200 mL wet volume) to give 5.72 g (89%) of **21** as a white powder: mp 49.5–50.0 °C (from acetone); NMR ($CDCl_3$) δ 0.88 (3 H, br t, J = 7 Hz), 1.25 (30 H, s), 1.4–1.6 (2 H, m), 1.71 (3 H, t, J = 7 Hz), 2.65 (3 H, s), 3.12 (2 H, q, J = 6 Hz), 3.38 (3 H, s), 3.66 (1 H, quint, J = 5 Hz), 4.02 (2 H, br d, J = 5 Hz), 4.37 (2 H, m), 5.20 (2 H, q, J = 7 Hz), 5.31 (1 H, br), 5.48 (2 H, br s), 7.75 (1 H, br d, J = 7 Hz), 8.06 (1 H, br t, J = 7 Hz), 8.47 (1 H, br t, J = 8 Hz), 10.00 (1 H, d, J = 6 Hz); IR (KBr) 1754, 1700 cm^{-1}. Anal. ($C_{34}H_{60}N_3O_6Cl·H_2O$), C, H, N.

In an identical manner, (*R*)-(−)-**21** and (*S*)-(+)-**21** were prepared. Each isomer was identical (IR, NMR, TLC) with racemic **21**. (*R*)-(−)-**21**: mp 49–50 °C; $[\alpha]^{25}_D$ −9.8° (*c* 1, $CHCl_3$). Anal. ($C_{34}H_{60}N_3O_6Cl·H_2O$). (*S*)-(+)-**21**: mp 49–50 °C; $[\alpha]^{25}_D$ +9.3° (*c* 1, $CHCl_3$). Anal. ($C_{34}H_{60}N_3O_6Cl·2H_2O$) C, H, N.

In a similar manner, compounds **20e–g**, **21–24** were prepared.

4-[[*N*-Acetyl-*N*-[[2-methoxy-3-[(octadecylcarbamoyl)oxy]propoxy]carbonyl]amino]methyl]-3-ethylthiazolium Chloride (25). The mixture of **19** g (3.0 g, 5.1 mmol) and ethyl iodide (20 mL) was heated at 120 °C overnight in a sealed tube. After cooling, the mixture was concentrated to give the iodide salt of **19g** (3.78 g, 100%). A solution of this compound (3.3 g, 4.46 mmol) in 150 mL of 70% MeOH–H_2O was passed through a column of Amberlite IRA-410 ion-exchange resin (150 mL wet volume) to give 2.8 g (97%) of **25** as a white powder after trituration from acetone–ether–*n*-hexane (1:1:10): mp 55–56 °C; NMR (60 MHz, $CDCl_3$) δ 0.87 (3 H, m), 1.23 (32 H, s), 1.72 (3 H, t, J = 7 Hz), 2.60 (3 H, s), 3.08 (2 H, m), 3.45 (3 H, s), 3.79 (1 H, m), 4.14 (2 H, d, J = 5 Hz), 4.42 (2 H, d, J = 5 Hz), 4.87 (2 H, q, J = 7 Hz), 5.07 (1 H, br), 5.20 (2 H, s), 8.25 (1 H, d, J = 2 Hz), 10.80 (1 H, d, J = 2 Hz); IR (KBr) 1750, 1705 cm^{-1}. Anal. ($C_{32}H_{58}N_3O_6SCl·H_2O$) C, H, N, S.

1-*O*-Benzyl-2-*O*-methyl-3-*O*-trityl-*sn*-glycerol (29). To a solution of 1-*O*-benzyl-3-*O*-trityl-*sn*-glycerol (**27**)[15] (10.7 g, 25 mmol) and methyl iodide (7.2 g, 50 mmol) in 54 mL of DMSO was added 5.7 g (100 mmol) of powdered KOH. The mixture was stirred at room temperature for 2 h, poured into water (450 mL), neutralized with HCl solution, and extracted with ether (500 mL). The organic layer was washed with water, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel, with *n*-hexane–AcOEt (9:1) as eluent, to give 9.51 g (87%) of **29** as a colorless oil: NMR (60 MHz, $CDCl_3$) δ 3.25 (2 H, d, J = 5 Hz), 3.42 (3 H, s), 3.62 (3 H, m), 4.53 (2 H, s), 7.30 (20 H, m); IR (neat) 3060, 3025, 2930, 2870, 1495, 1450, 1210, 1090, 750, 700 cm^{-1}; $[\alpha]^{22}_D$ +9.7° (c 1, $CHCl_3$). Anal. ($C_{30}H_{30}O_3$) C, H.

In an identical manner, 3-*O*-benzyl-2-*O*-methyl-1-*O*-trityl-*sn*-glycerol (**28**) was prepared from 3-*O*-benzyl-1-*O*-trityl-*sn*-glycerol: mp 49–50 °C (crystalized on standing); $[\alpha]^{23}_D$ −7.1° (*c* 1, $CHCl_3$).

1-*O*-Benzyl-2-*O*-methyl-*sn*-glycerol (31). Compound **29** (9.51 g, 21.7 mmol) in 80% AcOH–H_2O (200 mL) was stirred for 3 h at 60 °C. After removal of the solvent, the residue was chromatographed on silica gel, with $CHCl_3$–MeOH (97:3) as eluent, to give 4.25 g (100%) of **31** as a colorless oil: NMR (60 MHz, $CDCl_3$) δ 2.08 (1 H, br), 3.47 (3 H, s), 3.5–3.8 (5 H, m), 4.55 (2 H, s), 7.33 (5 H, s); IR (neat) 3450, 2940, 2870, 1450, 1360, 1080, 1030, 740, 700 cm^{-1}; $[\alpha]^{22}_D$ −19.6° (*c* 1, $CHCl_3$). Anal. ($C_{11}H_{16}O_3$) H; C: calcd, 67.32; found, 66.77.

In an identical manner, 3-*O*-benzyl-2-*O*-methyl-*sn*-glycerol (**30**) was prepared from **28**: $[\alpha]^{23}_D$ +20.3° (*c* 1, $CHCl_3$).

1-*O*-Benzyl-2-*O*-methyl-3-*O*-(octadecylcarbamoyl)-*sn*-glycerol (33). The mixture of **31** (1.96 g, 10 mmol), *n*-octadecyl isocyanate (3.25 g, 11 mmol), pyridine (2 mL), and 25 mL of methylene chloride were allowed to stand at room temperature for 20 h and concentrated in vacuo. The residue was chromatographed on silica gel, with *n*-hexane–AcOEt (9:1) as eluent, to give 4.35 g (89%) of **33** as colorless needles: mp 46.5–47.5 °C (from *n*-hexane); NMR (60 MHz, $CDCl_3$) δ 0.93 (3 H, m), 1.23 (32 H, s), 3.15 (2 H, m), 3.43 (3 H, s), 3.55 (3 H, s), 4.18 (2 H, m), 4.53 (2 H, s), 7.28 (5 H, s); IR (neat) 3320, 2930, 2850, 1690, 1540, 1465, 1270, 1110 cm^{-1}; $[\alpha]^{22}_D$ −4.6° (*c* 1, $CHCl_3$). Anal. ($C_{30}H_{53}NO_4$) C, H, N.

In an identical manner, 3-*O*-benzyl-2-*O*-methyl-1-*O*-(octadecylcarbamoyl)-*sn*-glycerol (**32**) was prepared from **30**: mp 47–48 °C (from *n*-hexane); $[\alpha]^{23}_D$ +3.5° (*c* 1, $CHCl_3$). Anal. ($C_{30}H_{53}NO_4$) C, H, N.

2-*O*-Methyl-3-*O*-(octadecylcarbamoyl)-*sn*-glycerol ((*R*)-(+)-10). A solution of **33** (4.25 g, 8.6 mmol) in 80% AcOH–H_2O (50 mL) containing 500 mg of 5% Pd/C catalyst was subjected to hydrogenolysis for 2 h. The catalyst was removed by filtration and the solvent was evaporated. The residue was recrystallized from *n*-hexane to give 3.40 g (98%) of (*R*)-(+)-**10** as colorless needles: mp 62–63 °C (racemic **10**[14]: mp 55–56 °C); $[\alpha]^{26}_D$ +13.8° (*c* 1, $CHCl_3$). Anal. ($C_{23}H_{47}NO_4$) C, H, N. The compound was identical with racemic **10** with respect to IR, NMR, and TLC.

In an identical manner, 2-*O*-methyl-1-*O*-(octadecylcarbamoyl-*sn*-glycerol ((*S*)-(−)-**10**) was prepared from **32**: mp 61–62 °C; $[\alpha]^{22}_D$ −13.6° (*c* 1, $CHCl_3$). Anal. ($C_{23}H_{47}NO_4$) C, H, N. The compound was identical (IR, NMR, TLC) with racemic **10** and (*R*)-(+)-**10**.

Chiral Purity of the Enantiomer of 10. The above enantiomers of **10** were converted to the Mosher's ester derivatives by treatment with (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride and pyridine according to the method described in the literature[16] and were examined by ^{13}C NMR in $CDCl_3$. The best separation of signals was found for the methylene protons at the 3-position of the glycerin backbone, which occurred at 65.01 and 64.63 for (*S*)-(−)-**10** and (*R*)-(+)-**10**, respectively. The chiral purity was determined by integration and estimated to be greater than 97% for each isomers.

Inhibition of Platelet Aggregation in Vitro. Platelet aggregation studies were done by the method of Born,[18] using three channel aggregometer (RIKADENKI, Japan). Blood was collected in 3.15% sodium citrate (1 mL for 9 mL of blood) by cardiac puncture from conscious male white rabbits. The blood was then centrifuged at room temperature at 800 rpm for 10 min to prepare platelet-rich plasma (PRP). The remaining blood was further centrifuged at 3000 rpm to obtain platelet-poor plasma (PPP) to adjust the number of platelets to $4.5 \times 10^5/\mu L$. This PRP (250 μL) was stirred at 37 °C for 3 min, and a test drug was added. After the mixture was stirred for 2 min, PAF (1×10^{-8} M) was added. The extent of aggregation was expressed by the maximum change of light transmission expressed as a percentage, taking the difference between light transmission for PRP and PPP as 100%.

Inhibitory Effect on PAF-Induced Hypotension in Rats. Male Sprague-Dawley (Jcl) rats, 6–9 weeks old, weighing 300–450 g, were anesthetized with sodium pentobarbital (50 mg/kg, ip). An additional dose was administered when required. The right femoral artery and left femoral vein were cannulated for measurement of mean arterial blood pressure and for injection of drugs, respectively. Blood pressure was recorded from the femoral artery through a cannula connected to a pressure transducer (Nihon Kohden). PAF (0.3 μg/kg) and test drugs were given in volumes of 0.2 and 0.4 mL/kg, respectively. Each agent was completely flushed with 0.25 mL of saline for 25 s through the cannula. To determine the inhibitory activity of test drugs, PAF (one dose per rat) was first injected twice at an interval of 20 min. Twenty minutes after the second injection, drugs were given iv and after 5, 60, and 120 min, PAF was injected, and each blood pressure drop was measured. Inhibition was calculated with use of the second PAF-induced blood pressure drop as a control value.

Protective Effects on PAF-Induced Death. Conscious male ICR-Jcl mice, 5–7 weeks old, were used. Saline (control) or drugs dissolved in saline (0.1 mL/10 g) were delivered into the tail vein 8 or 24 h before the injection of PAF. At given times, PAF (50 μg/kg) was injected iv (0.1 mL/10 g). Death was defined by the cessation of respiration, and the survival rates were recorded 60 min after the injection of PAF.

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Registry No. **3**, 89104-47-2; **3** (phenyl carbonate), 116953-25-4; **4**, 116953-28-7; **4** (2-*O*-benzyl derivative), 116953-26-5; **4** (2-*O*-benzyl derivative)·HCl, 116953-27-6; **5**, 116953-29-8; **5**·HCl, 116953-90-3; **6**, 116953-30-1; **7**, 116953-31-2; **7** (tosylate),

116953-32-3; **8**, 116953-33-4; **8** (2-ol), 116953-34-5; **8** (2-acetate), 116953-35-6; **9**, 116953-36-7; **10**, 93635-31-5; (*R*)-(+)-**10**, 117020-35-6; (*S*)-(−)-**10**, 117020-38-9; **11**, 116953-37-8; **12a**, 116970-37-7; **12b**, 116953-81-2; **13**, 116953-72-1; **14**, 116953-52-7; **15**, 116953-53-8; **16a**, 116953-39-0; **16b**, 116953-73-2; **16c**, 116953-40-3; **16d**, 116953-74-3; **16e**, 116953-41-4; **16f**, 116953-75-4; **16g**, 116953-43-6; **16h**, 116953-76-5; **17a**, 116970-38-8; **17b**, 116953-54-9; **17c**, 116953-55-0; **17d**, 116953-56-1; **17e**, 116953-57-2; **17f**, 116970-39-9; **17g**, 116953-58-3; **17h**, 116953-59-4; **18a**, 116953-82-3; **18b**, 116953-83-4; **18c**, 116953-84-5; **18d**, 116953-85-6; **18e**, 116953-38-9; (*R*)-(−)-**18e**, 117020-36-7; (*S*)-(+)-**18e**, 117020-37-8; **18f**, 116953-45-8; **18g**, 116953-86-7; **19a**, 116953-77-6; **19b**, 116953-78-7; **19c**, 116953-79-8; **19d**, 116953-80-1; **19e**, 116953-44-7; (*R*)-(−)-**19e**, 117020-39-0; (*S*)-(+)-**19e**, 117020-40-3; **19f**, 116953-46-9; **19g**, 116953-47-0; **20a**, 116953-60-7; **20b**, 116953-61-8; **20c**, 116953-62-9; **20d**, 116953-63-0; **20e**, 116953-64-1; **20f**, 116953-69-6; **20g**, 116953-71-0; **21**, 117064-08-1; (*R*)-(−)-**21**, 116953-65-2; (*S*)-(+)-**21**, 116953-66-3; **22**, 116953-67-4; **23**, 116953-68-5; **24**, 116953-70-9; **25**, 116953-49-2; **25** (iodide salt), 116953-48-1; **27**, 70259-44-8; **28**, 116953-87-8; **28** (2-ol), 83526-68-5; **29**, 116953-50-5; **30**, 116953-88-9; **31**, 70259-28-8; **32**, 116953-89-0; **33**, 116953-51-6; ClCOOPh, 1885-14-9; $H_2NCH_2CH_2NMe_2$, 108-00-9; $H_2NCH_2CH_2OH$, 141-43-5; ClCOOMe, 79-22-1; $C_{18}H_{37}NCO$, 112-96-9; 2-(aminomethyl)pyridine, 3731-51-9; 3-*O*-[(*N*-[2-(dimethylamino)ethyl]-*N*-(phenoxycarbonyl)carbamoyl]-2-*O*-methyl-1-*O*-(octadecylcarbamoyl)glycerol, 116953-42-5; pyrrolidine, 123-75-1.

Amine Peroxides as Potential Antimalarials

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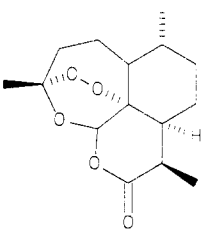
Six model amine peroxides (**4–9**) were synthesized as targeted antimalarial oxidants. They were approximately 1 order of magnitude more potent than *tert*-butyl hydroperoxide (**3**) in vitro against *Plasmodium falciparum*, but like **3**, they were inactive in vivo against *Plasmodium berghei*.

Several peroxides have shown antimalarial activity. The most notable of these is the complex endoperoxide sesquiterpene lactone artemisinin (**1**),[1-3] a clinically useful antimalarial agent. However, simple peroxides such as H_2O_2 (**2**)[4] and *tert*-butyl hydroperoxide (**3**)[5,6] are also antimalarial albeit much less potent than **1**. The efficacy of **1–3** may depend in part on the observation that malaria-infected red cells are selectively damaged by oxidants.



1

This oxidant sensitivity of malaria-infected erythrocytes may arise both from precedent damage by parasite-generated oxidants and from a weakening of oxidant defense mechanisms of the erythrocyte.[7] The inhibition of intraerythrocytic growth of malaria parasites under supraphysiologic concentrations of oxygen[8] and protection against malaria infection by several red blood cell (RBC) disorders that increase the susceptibility of RBCs to oxidative stress exemplify this oxidant sensitivity.[9-16] Numerous articles[7,17-24] have summarized specific mechanisms that may account for the susceptibility of malaria to oxidants.

Structure–activity studies demonstrate that the endoperoxide group in **1** and its analogues is absolutely essential for antimalarial activity,[25] suggestive of an oxidative mode of action. A progressive increase in the potency of **1** with increasing oxygen tensions ranging from 3 to 30% and a significant reduction in the potency of **1** by coadministration of reducing agents[26] support this hypothesis.

Hydrogen peroxide (**2**) has antimalarial properties; micromolar concentrations of **2** kill various murine ma-

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