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N-(Acyloxyalkyl)pyridinium Salts as Soluble Prodrugs of a Potent Platelet Activating Factor Antagonist

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Pyrrolothiazole **4** is a potent antagonist of platelet activating factor-mediated effects in a variety of in vitro and in vivo assays. Despite its positive activity in models of inflammation and septic shock, **4** lacks the aqueous solubility necessary for intravenous administration. This deficit was overcome by conversion of **4** to water-soluble pyridinium prodrugs. A two-step procedure was used to prepare a series of *N*-(acyloxyalkyl)pyridinium salts, all of which exhibited aqueous solubility of greater than 20 mg/mL. The rate of conversion of these prodrugs to **4** was faster in human plasma than in pH 7 aqueous buffer. This rate difference was shown to be due to serum enzymes since the conversion in plasma was significantly slower in the presence of a serine esterase inhibitor. A strong correlation between prodrug structure and buffer/plasma half-life was established. The *N*-(acetyloxymethyl)pyridinium prodrug **11** (ABT-299) is currently undergoing clinical evaluation for the treatment of sepsis.

Introduction

Platelet activating factor (PAF) is a highly potent phospholipid mediator of inflammation. The pro-inflammatory activities exhibited by PAF can be attributed to its interaction with specific membrane receptors found on a variety of cell types.[1] This interaction gives rise to an increase in vascular permeability, hypotension, and bronchoconstriction.[2] While the precise role of PAF in specific diseases remains equivocal, it has been implicated as an important mediator in a number of life-threatening conditions including septic shock[3] and asthma.[4] Our objective was to discover PAF antagonists which might provide therapeutic benefit for these diseases. This goal was realized upon the identification of **4** as one of the most potent PAF antagonists yet disclosed. Despite its impressive biological activity, **4** lacks the aqueous solubility necessary for intravenous administration. This article describes the preparation and stability of soluble prodrugs of **4** and illustrates an unappreciated technique used to solubilize pyridine-containing drugs.

Results and Discussion

The synthesis of **4** is shown in Scheme 1. 6-(4-Fluorophenyl)indole (**2**) was prepared by palladium-catalyzed cross-coupling of 6-bromoindole[5] with (4-fluorophenyl)boronic acid in 90% yield according to the procedure of Carrera and Sheppard.[6] Indole **2** was acylated at the 3-position by treatment of its zinc salt[7] with the known acid chloride **3**.[8] Carbamoylation of the indole nitrogen gave **4** in 45% overall yield from **2**.

Indole pyrrolothiazole **4** is a highly effective inhibitor of PAF-mediated effects in a variety of in vitro and in vivo assays. For example, **4** is a competitive and reversible inhibitor of [^{3}H]PAF binding to rabbit platelet membranes (K_i = 3.8 nM) and blocks PAF-induced serotonin release from rabbit platelets (K_b = 1.1 nM).[9] The in vivo potency (ED_{50}) of **4** for inhibition of PAF-induced cutaneous vascular permeability in the rat is 0.006 mg/kg after intravenous administration. A 0.1

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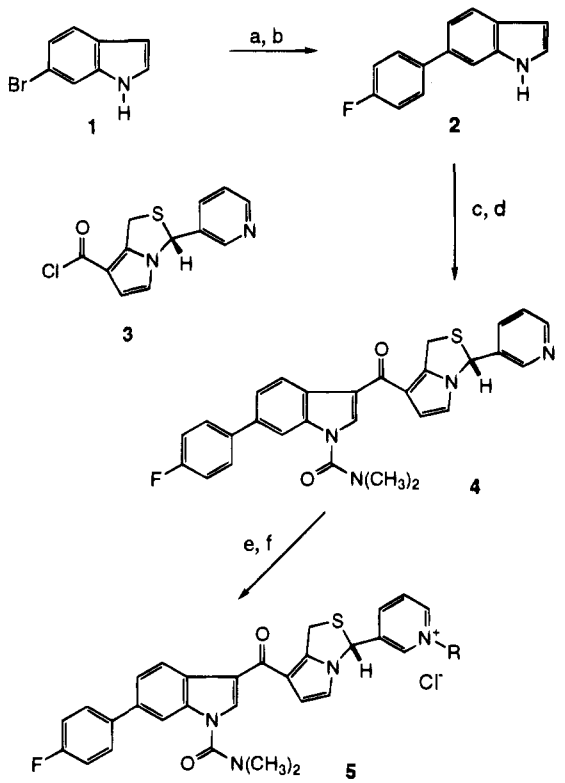
Scheme 1[a]



[a] Reagents: (a) $Pd(PPh_3)_4$, toluene; (b) 4-$FC_6H_4B(OH)_2$, aqueous $NaHCO_3$, EtOH; (c) EtMgBr, $ZnCl_2$, Et_2O then **3**, CH_2Cl_2; (d) $ClCONMe_2$, KOH, THF; (e) RX, $NaBPh_4$, CH_3CN, 82 °C; (f) Dowex 1-chloride, CH_3CN:iPA.

mg/kg dose produces nearly maximal inhibition in this assay for more than 8 h. This antagonist is also effective in animal models of septic shock. It inhibits LPS-induced hypotension in the rat (ED_{50} = 0.01 mg/kg, i.a.) and a 0.1 mg/kg intravenous dose completely inhibits LPS-induced intestinal damage.[10]

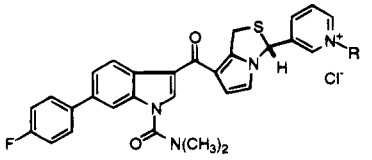
The impressive biological activity exhibited by **4** is consistent with its selection for clinical evaluation. However, with aqueous solubility of less than 1 μg/mL (pH 7), it could not be formulated for intravenous administration. Initial attempts to improve aqueous solubility by using cosolvents and excipients were unsuccessful. Another approach involved the design of analogs which incorporate a water-solubilizing handle into **4**. Substitutents bearing polar or charged groups were attached to the indole nitrogen, fluorophenyl ring, and carbonyl of **4**. Some improvement in aqueous solubility was observed; however, this was usually at the expense of intrinsic and/or in vivo potency. A significant improvement in solubility was achieved by converting **4** to the corresponding *N*-methylpyridinium salt (**8**, Table 1, solubility in pH 3 buffer ≥ 20 mg/mL). While this modification substantially lowered binding and in vitro potency, we reasoned that the pyridinium functionality might be incorporated into prodrugs of **4** to produce highly soluble compounds which rapidly release **4** in vivo.

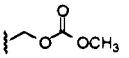
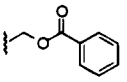
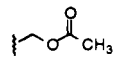
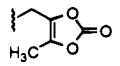
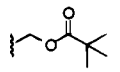
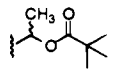
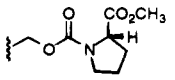
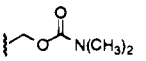
A general strategy for improving the aqueous solubility of tertiary nitrogen or unsaturated nitrogen-containing compounds by converting them to labile ammonium prodrugs was described in 1977 by Bodor.[11] This approach is outlined in Scheme 2 and involves reaction of, in this case, a tertiary nitrogen with an α-halo ester.[12] The charged character of the resulting (acyloxyalkyl)ammonium salt (**6**) imparts enhanced water solubility relative to the starting amine. Hydrolytic degradation of **6** occurs by attack of water at either the ester carbonyl or the aminal carbon and ultimately generates an aldehyde (R^1CHO), an acid (R^2CO_2H), and the starting amine. Enzymatic hydrolysis of **6** produces the unstable (hydroxymethyl)ammonium salt **7**, which can also liberate an aldehyde to regenerate the starting amine. Regardless of the mode of decay, the rate of production of the starting amine will be influenced by the substituents R^1 and R^2 of **6**. Bodor used such a "soft quaternary salt" approach[13] to increase the water solubility of antimalarial agents[14] and to improve the delivery of tertiary amine-containing drugs such as pilocarpine[15] and erythromycin.[16] A vinylogous version of ammonium salt **6** using quinone methides was described by Bogardus,[17] and Vinogradova has studied the hydrolysis of (acyloxymethyl)ammonium salts of several antimuscarinic drugs.[18] Despite its potential general applicability, this approach has not gained wide recognition. We now report the use of *N*-(acyloxyalkyl)-pyridinium prodrugs to improve the aqueous solubility of **4**.

Initial attempts to prepare compounds of the general structure **5** by heating **4** in the presence of an α-halo ester were complicated by incomplete reaction and/or decomposition of **5** under the reactions conditions (Scheme 1). This problem was overcome by running the reaction in the presence of tetraphenylboron sodium which presumably drives the reaction to completion by precipitation of sodium halide.[19] The resulting pyridinium tetraphenylborate salts were then converted to the corresponding chloride by ion exchange chromatography using acetonitrile/2-propanol as the eluting solvent. Yields for this two step procedure are shown in Table 1 which illustrates that the process is compatible with a variety of functional groups.

The pyridinium salts listed in Table **1** are all completely soluble in pH 3 aqueous buffer at concentrations of 20 mg/mL or greater. Thus, a substantial boost in aqueous solubility is achieved regardless of the structure of the prodrug moiety. In contrast, the hydrolytic stabilities of these prodrugs are strongly tied to the nature of R^1 and R^2 of **6**. The carbamate analogs (**15** and **16**) are much more resistant to hydrolysis than either of the pivalate-derived prodrugs (**13** and **14**) which in turn are more stable than the simple alkyl (**11**), aryl (**10**), or carbonate-derived (**9** and **12**) compounds. This general trend is reflected in the plasma half-lives which again exhibit a strong dependence on R^2 in **6**. Comparing stabilities of the pivalate analogs **13** and **14** in pH 7 buffer and in human plasma illustrates the influence of R^1 in **6**. An alkyl branch (**6**: $R^1 = CH_3$) appears to increase susceptibility to hydrolytic cleavage in buffer, but suppresses attack by esterases in human plasma. That the mechanism of cleavage of these prodrugs in plasma bears an enzymatic component is demonstrated by inspection of Figure 1. When **11** was incubated in protein-free pH 7 buffer at 37 °C, its half-life was substantially longer than in human plasma. Preincubation of human plasma with the serine esterase inhibitor diisopropylfluorophosphate extended the half-life of **11** to that obtained with the protein-free buffer. This indicates that serine esterases are likely to catalyze

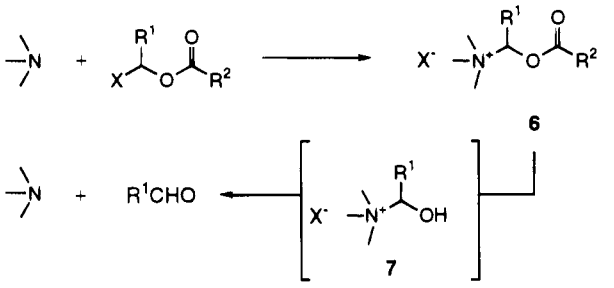
Table 1. Stability of Pyridinium Prodrugs



Compound	R	Yield (%)[a]	Buffer $t_{1/2}$ (min)[b]	Plasma $t_{1/2}$ (min)[c]	Formula[d]
4	-	-	-	-	$C_{29}H_{23}N_4O_2SF$
8		72	-	-	$C_{30}H_{26}N_4O_2SFCl$ 2.00 H_2O
9		71	96 ± 6	1.0 ± 0.1	$C_{32}N_{28}N_4O_5SFCl$ 1.75 H_2O
10		70	510 ± 42	1.0 ± 0.1	$C_{37}H_{30}N_4O_4SFCl$ 2.25 H_2O
11		93	540 ± 12	2.6 ± 0.5	$C_{32}H_{28}N_4O_4SFCl$ 1.00 H_2O
12		69	246 ± 30	2.8 ± 0.2	$C_{34}H_{28}N_4O_5SFCl$ 1.00 H_2O
13		76	2,718 ± 66	20.8 ± 0.7	$C_{35}H_{34}N_4O_4SFCl$ 2.00 H_2O
14		59	1,056 ± 30	31.1 ± 1.3	$C_{36}H_{36}N_4O_4SFCl$ 3.00 H_2O
15		84	7,650 ± 846	160 ± 15	$C_{37}H_{35}N_5O_6SFCl$ 2.00 H_2O
16		84	>10,000	> 600	$C_{33}H_{31}N_5O_4SFCl$ 2.50 H_2O

[a] Yields are for the two-step procedure from **4**. [b] Buffer half-life at pH 7 ± standard error. [c] Human plasma half-life at pH 7 ± standard error. [d] Elemental analysis (C, H, N) were within 0.4% of the theoretical values for the indicated formulas.

Scheme 2



the conversion of **11** to **4** in plasma, although the exact nature of this enzymatic activity remains to be established.

Clearly, application of Bodor's quaternary salt prodrug technique to this class of pyridine-containing PAF antagonists results in highly water soluble compounds. The proper choice of R^1 and R^2 in **6** provides a handle by which the desired buffer and plasma stability may be controlled. Having prepared and evaluated these and other pyridinium prodrugs, we focused our attention on the acetyl-substituted analog, **11** (ABT-299), now in clinical trials for the treatment of sepsis. Of the prodrugs with short plasma half-lives, this compound has the greatest buffer stability and is most amenable to large-scale synthesis. As indicated in Figure 1, this compound is rapidly converted to **4** upon incubation with human plasma. Similar results are obtained using plasma from patients diagnosed with septic shock. Pharmacokinetic evaluation of **11** in a number of species indicates that this conversion also occurs in vivo. Nonenzymatic conversion of **11** to **4** proceeds much more

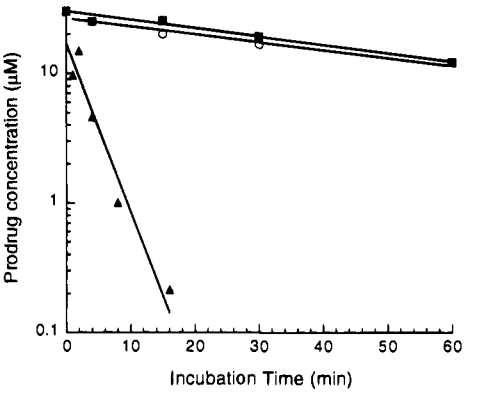


Figure 1. Rate of conversion of **11** to **4**. Prodrug **11** was incubated at pH 7, 37 °C with protein-free buffer (○), human plasma (▲), and with human plasma pretreated with diisopropylfluorophosphate (■). Results are individual values from one experiment.

slowly. Less than 5% of **11** is converted to **4** at 5 °C in pH 3 glycine buffer over 1 week. Most significantly, **11** produces all of the potent in vivo characteristics displayed by **4** with substantially greater aqueous solubility.

Conclusion

In summary, we have identified indole pyrrolothiazole **4** as a very potent PAF antagonist which lacks aqueous solubility. Application of Bodor's technique to solubilize unsaturated amine-containing compounds gives rise to prodrugs with much greater water solubility. The buffer and plasma stability of these prodrugs may be adjusted by variations of R^1 and R^2 in **6**. The *N*-(acetyloxymethyl)pyridinium analog **11** is rapidly converted to **4** in human plasma and possess all of the in vivo characteristics of **4**. This compound is currently undergoing clinical evaluation for the treatment of sepsis.

Experimental Section

Chemistry. Melting points were determined using a Electrothermal digital melting point apparatus, and are uncorrected. Infrared spectra were recorded with a Nicolet 5SXC FT-IR spectrometer, and are reported in wavenumbers (cm^{-1}). ^1H NMR spectra were recorded on a GE QE300 spectrometer, and chemical shifts are reported in parts per million (ppm, δ) relative to tetramethylsilane as an internal standard. Coupling constants are reported in hertz. Mass spectra were obtained on a Kratos MS-50 instrument. Elemental analyses were performed by Robertson Microlit Laboratories, Inc., of Madison, NJ. Optical rotations were obtained using a Perkin-Elmer 241 spectrometer. Acetonitrile, 2-propanol, and ethyl acetate were HPLC grade and were used without further purification. Ethyl ether was purchased as "anhydrous" and used as received. 4-Fluorobenzeneboronic acid, tetraphenylboron sodium, bromomethyl acetate, chloromethyl chloroformate, and chloromethyl pivalate were obtained commercially and used without further purification. 6-Bromoindole was prepared according to the procedure described by Rapoport.[5] 6-(4-Fluorophenyl)indole was prepared according to the procedure of Carrera and Sheppard.[6] 3-(Pyridin-3-yl)-1*H*,3*H*-pyrrolo[1,2-c]thiazole-7-carboxylic acid (**3**)[8] was prepared as described in United States Patent 4,529,728. The electophile used for compound **12** (4-(bromomethyl)-5-methyl-2-oxo-1,3-dioxolene) was prepared as described by Sakamoto.[20]

Synthesis of (*R*)-7-[1-(*N*,*N*-Dimethylcarbamoyl)-6-(4-fluorophenyl)indol-3-oyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole (4). To a heterogeneous mixture of 6-(4-fluorophenyl)indole (**2**; 14.8 g; 0.07 mol; 200 mol %) in Et_2O (350 mL) at room temperature under a nitrogen atmosphere was added ethereal ethylmagnesium bromide (23 mL of a 3.0 M solution; 0.07 mol), and the resulting mixture was stirred for 15 min. A solution of ethereal $ZnCl_2$ (70 mL of a 1.0 M soln; 0.07 mol) was then added, and the heterogeneous mixture was stirred under these conditions over 25 min. In a separate flask, a solution of 3-(pyridin-3-yl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-7-carboxylic acid (8.65 g; 0.035 mol) in methylene chloride (350 mL) at room temperature under a nitrogen atmosphere was treated with sodium hydride (1.54 g of 60% oil dispersion; 110 mol %). This solution was stirred for 15 min followed by the addition of oxalyl chloride (3.37 mL; 110 mol %), after which the solution was stirred for an additional 25 min. The above indole anion mixture was added to the acid chloride solution via an addition funnel, and the resulting reddish-brown mixture was stirred under these conditions for 4 h. Saturated aqueous NH_4Cl (500 mL) was then added and stirring continued over 10 min. The reaction mixture was poured into a flask containing THF/EtOAc (750 mL of 1:1 v/v) and water (500 mL). This mixture was extracted with EtOAc (1 × 750 mL), and the combined organic phase was washed with saturated aqueous $NaHCO_3$ (750 mL) and dried ($MgSO_4$). Filtration and removal of solvent gave a tan solid which was recrystallized from THF/Et_2O to give 8.54 g of a tan solid. This material was suspended in THF (194 mL) and treated with KOH (5.4 g; powdered; 500 mol %) at room temperature. The resulting dark red solution was stirred for 15 min, then dimethylcarbamyl chloride (2.67 mL; 150 mol %) was added, and this solution was stirred under these conditions for 2 h. Saturated aqueous NH_4Cl (200 mL) was added, and this mixture was extracted with THF/EtOAc (500 mL of 2:1 v/v). The organic phase was dried (MgSO4), filtered, and concentrated. The resulting tan solid was recrystallized from THF/Et_2O, which gave **4** (8.1g; 45% from 3-(pyridin-3-yl)-1*H*,3*H*-pyrrolo[1,2-c]thiazole-7-carboxylic acid) as a tan solid: mp 186–188 °C; ^1H NMR (DMSO-d_6, 300 MHz) δ 3.08 (s, 6H), 4.50 (d, 1H, J = 15.0), 4.68 (dd, 1H, J = 1.0, 15.0), 6.73 (d, 1H, J = 3.0), 6.80 (d, 1H, J = 1.0), 6.92 (d, 1H, J = 3.0), 7.31 (t, 2H, J = 8.0), 7.44 (dd, 1H, J = 4.5, 7.5), 7.61 (dd, 1H, J = 1.0, 8.0), 7.69 (dt, 1H, J = 1.0, 7.5), 7.77 (dd, 2H, J = 4.5, 9.0), 7.81 (d, 1H, J = 1.0), 8.31 (d, 1H, J = 9.0), 8.37 (s, 1H), 8.57 (bs, 1H); IR ($CDCl_3$) 1690, 1605, 1540, 1515, 1480; mass spectrum (DCI/NH_3) 511 $(M + H)^+$; $[\alpha]^{25}_D$ = +51.6° (c = 0.24, $CHCl_3$). Anal. ($C_{29}H_{23}N_4O_2SF$) C, H, N.

Synthesis of (*R*)-1-Methyl-3-[7-[1-(*N*,*N*-dimethylcarbamoyl)-6-(4-fluorophenyl)indol-3-oyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazol-3-yl]pyridinium Chloride (8). To a solution of **4** (200 mg; 0.39 mM) in acetonitrile (4 mL; 0.1 M) under a nitrogen atmosphere was added tetraphenylboron sodium (161 mg; 120 mol %) followed by methyl iodide (67 mg; 120 mol %). The resulting mixture was heated at reflux for 4 h, then cooled to room temperature, and filtered through a Celite pad. The filtrate was concentrated to a foam which was triturated in methanol, and the solid was collected and dried in vacuo to give the pyridinium tetraphenylborate salt (308 mg) as a white solid. This material was dissolved in acetonitrile–2-propanol (20 mL; 1:1 v/v) and passed over an ion-exchange column (1 × 10 cm of Dowex 1 × 2 chloride, 50–100 mesh) at ca. 1 mL/min. The eluent was concentrated, and the resulting foam was dried in vacuo and triturated in ethyl acetate. The resulting solid was collected by suction filtration which gave pyridinium chloride **8** (158 mg; 72% from **4**) as a tan solid: mp 185–192 °C; ^1H NMR (DMSO-d_6, 300 MHz) δ 3.09 (s, 6H), 4.39 (s, 3H), 4.55 (d, 1H, J = 15.0), 4.79 (d, 1H, J = 15.0), 4.79 (d, 1H, J = 15.0), 6.86 (d, 1H, J = 3.0), 6.99 (s, 1H), 7.00 (d, 1H, J = 3.0), 7.31 (t, 2H, J = 9.0), 7.61 (d, 1H, J = 9.0), 7.77 (dd, 2H, J = 6.0, 8.0), 7.81 (s, 1H), 8.19 (t, 1H, J = 6.0), 8.32 (d, 1H, J = 8.0), 8.40 (s, 1H), 8.51 (d, 1H, J = 9.0), 9.02 (d, 1H, J = 6.0), 9.11 (s, 1H); IR ($CDCl_3$) 1690; mass spectrum (DCI/NH_3) 511 $(M + H)^+$; $[\alpha]^{25}_D$ = +60.0° (c = 0.41, $CHCl_3$). Anal. ($C_{30}H_{26}N_4O_2$-$SFCl{\cdot}2.00H_2O$) C, H, N.

Synthesis of Chloromethyl Methyl Carbonate.[21] Chloromethyl chloroformate (18.4 g; 0.144 mol) was dissolved in CH_2Cl_2 (150 mL) and cooled to −10 °C. A CH_2Cl_2 (50 mL) solution of methanol (4.4 mL; 0.137 mol) and triethylamine (20 mL; 0.144 mol) was added via an addition funnel over 1 h which produced a white precipitate. Stirring was continued at −10 °C for 15 min and then at 0 °C over 2 h. The solid was then removed by filtration, and the resulting solution washed with saturated aqueous $NaHCO_3$ (200 mL) and water (200 mL) and then dried ($MgSO_4$). Filtration and removal of solvent gave a colorless oil which was purified by distillation and gave chloromethyl methyl carbonate (5.6 g; 33%) as a colorless oil: bp (30 mmHg) = 58–60 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.88, (s, 3H), 5.75 (s, 2H).

Synthesis of (*R*)-1-[[(Methoxycarbonyl)oxy]methyl]-3-[7-[1-(*N*,*N*-dimethylcarbamoyl)-6-(4-fluorophenyl)indol-3-oyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazol-3-yl]pyridinium Chloride (9). The compound was prepared by the procedure described for the preparation of **8** using **4** (200 mg; 0.39 mM), tetraphenylboron sodium (161 mg; 120 mol %), sodium iodide (71 mg, 120 mol %), and chloromethyl methyl carbonate (58 mg; 120 mol %), which gave the pyridinium tetraphenylborate salt (269 mg) as a light yellow solid. Ion-exchange chromatography gave **9** (176 mg; 71% from **4**) as a tan solid: mp 142–147 °C; ^1H NMR (DMSO-d_6, 300 MHz) δ 3.09 (s, 6H), 3.81 (s, 3H), 4.55 (d, 1H, J = 15.0), 4.75 (d, 1H, J = 15.0), 6.48 (s, 2H), 6.88 (d, 1H, J = 2.5), 7.00 (d, 1H, J = 2.5), 7.02 (s, 1H), 7.31 (t, 2H, J = 9.0), 7.61 (d, 1H, J = 9.0), 7.76 (dd, 2H, J =

6.0, 8.0), 7.80 (s, 1H), 8.28 (m, 1H), 8.31 (d, 1H, J = 9.0), 8.38 (s, 1H), 8.65 (d, 1H, J = 8.0), 9.22 (d, 1H, J = 6.0), 9.28 (s, 1H); IR ($CDCl_3$) 1770, 1695; mass spectrum (DCI/NH_3) 511 (M + H)$^+$; $[\alpha]^{25}_D$ = +44.6° (c = 0.17, $CHCl_3$). Anal. ($C_{32}H_{28}N_4O_5SFCl\cdot1.75H_2O$) C, H, N.

Synthesis of Chloromethyl Benzoate.[22] To paraformaldehyde (2.13 g; 71 mmol) and $ZnCl_2$ (75 mg) was added benzoyl chloride (8.3 mL; 71 mmol). The mixture was heated at 80 °C for 2 h, and then distilled under reduced pressure, which gave chloromethyl benzoate (5.6 g; 46%) as a colorless oil: bp (5 mmHg) = 75–85 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.98 (s, 3H), 7.41–7.50 (c, 3H), 7.62 (m, 1H), 8.09 (m, 2H).

Synthesis of (*R*)-1-[(Benzoyloxy)methyl]-3-[7-[1-(*N*,*N*-dimethylcarbamoyl)-6-(4-fluorophenyl)indol-3-oyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazol-3-yl]pyridinium Chloride (10). The compound was prepared by the procedure described for the preparation of **9** using **4** (200 mg) and chloromethyl benzoate (67 mg; 120 mol %) which gave the pyridinium tetraphenylborate salt (214 mg) as a yellowish solid. Ion-exchange chromatography gave **10** (187 mg; 70% from **4**): mp 116–118 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.09 (s, 6H), 4.55 (d, 1H, J = 15.0), 4.76 (dd, 1H, J = 1.0, 15.0), 6.71 (s, 1H), 6.88 (dd, 1H, J = 1.0, 15.0), 7.00 (d, 1H, J = 3.0), 7.03 (s, 1H), 7.31 (t, 2H, J = 9.0), 7.60 (dd, 2H, J = 7.0, 8.0), 7.62 (m, 1H), 7.76 (m, 2H), 7.82 (s, 1H), 8.04 (d, 1H, J = 8.0), 8.30 (m, 1H), 8.31 (d, 1H, J = 8.0), 8.39 (s, 1H), 8.66 (d, 1H, J = 6.0), 9.37 (d, 1H, J = 6.0), 9.38 (s, 1H); IR ($CDCl_3$) 1735, 1695; mass spectrum (DCI/NH_3) 511 (M + H)$^+$; $[\alpha]^{25}_D$ = +45.7° (c = 0.35, $CHCl_3$). Anal. ($C_{37}H_{30}N_4O_4SFCl\cdot2.25H_2O$) C, H, N.

Synthesis of (*R*)-1-[(Acetyloxy)methyl]-3-[7-[1-(*N*,*N*-dimethylcarbamoyl)-6-(4-fluorophenyl)indol-3-oyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazol-3-yl]pyridinium Chloride (11). The compound was prepared by the procedure described for **8** using **4** (3.37 g; 6.6 mM), sodium tetraphenylborate (2.71 g; 120 mol %), and bromomethyl acetate (1.28 g of 95%; 120 mol %), which gave the pyridinium tetraphenyborate salt (5.60 g) as a yellow solid. Ion-exchange chromatography gave pyridinium chloride **11** (3.80 g; 93% from **4**) as a tan solid: mp 172–180 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.18 (s, 3H), 3.09 (s, 6H), 4.55 (d, 1H, J = 15.0), 4.75 (dd, 1H, J = 1.0, 15.0), 6.41 (s, 2H), 6.86 (d, 1H, J = 3.0), 7.00 (d, 1H, J = 3.0), 7.01 (s, 1H), 7.32 (t, 2H, J = 8.5), 7.62 (dd, 1H, J = 1.0, 8.5), 7.77 (m, 2H), 7.81 (bs, 1H), 8.26 (dd, 1H, J = 6.0, 8.5), 8.32 (d, 1H, J = 8.5), 8.39 (s, 1H), 8.62 (bd, 1H, J = 8.5), 9.21 (d, 1H, J = 6.0), 9.25 (bs, 1H); IR ($CDCl_3$) 1765, 1690, 1600, 1475; mass spectrum (DCI/NH_3) 511 (M + H)$^+$; $[\alpha]^{25}_D$ = +49.5° (c = 0.22, $CHCl_3$). Anal. ($C_{32}H_{28}N_4O_4SFCl\cdot1.00H_2O$) C, H, N.

Synthesis of (*R*)-1-[(5-Methyl-2-oxo-1,3-dioxolen-4-yl)methyl]-3-[7-[1-(*N*,*N*-dimethylcarbamoyl)-6-(4-fluorophenyl)indol-3-oyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazol-3-yl]pyridinium Chloride (12). The compound was prepared by the procedure described for the preparation of **11** using **4** (200 mg) and 4-(bromomethyl)-5-methyl-2-oxo-1,3-dioxolene (91 mg; 120 mol %), which gave the pyridinium tetraphenylborate salt (325 mg) as a tan solid. Ion-exchange chromatography gave **12** (178 mg; 69% from **4**) as a tan solid: mp 170–177 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.31 (s, 6H), 3.09 (s, 6H), 4.55 (d, 1H, J = 15.0), 4.75 (d, 1H, J = 15.0), 5.90 (s, 2H), 6.85 (d, 1H, J = 3.0), 7.01 (s, 1H), 7.02 (d, 1H, J = 3.0), 7.31 (t, 2H, J = 9.0), 7.61 (dd, 1H, J = 1.0, 9.0), 7.77 (dd, 2H, J = 6.0, 8.0), 7.81 (s, 1H), 8.23 (dd, 1H, J = 6.0, 8.0), 8.32 (d, 1H, J = 9.0), 8.39 (s, 1H), 8.52 (d, 1H, J = 9.0), 9.06 (s, 1H), 9.11 (d, 1H, J = 6.0); IR ($CDCl_3$) 1825, 1810, 1695; mass spectrum (DCI/NH_3) 511 (M + H)$^+$; $[\alpha]^{25}_D$ = +34.3° (c = 0.52, $CHCl_3$). Anal. ($C_{34}H_{28}N_4O_5SFCl\cdot1.00H_2O$) C, H, N.

Synthesis of (*R*)-1-[(Pivaloyloxy)methyl]-3-[7-[1-(*N*,*N*-dimethylcarbamoyl)-6-(4-fluorophenyl)indol-3-oyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazol-3-yl]pyridinium Chloride (13). The compound was prepared by the procedure described for the preparation of **9** using **4** (200 mg) and chloromethyl pivalate (71 mg; 120 mol %), which gave the pyridinium tetraphenylborate salt (311 mg) as a yellowish solid. Ion-exchange chromatography gave **13** (197 mg; 76% from **4**): mp 132–138 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.18 (s, 9H), 3.09 (s, 6H), 4.54 (d, 1H, J = 15.0), 4.75 (dd, 1H, J = 1.0, 15.0), 6.46 (s, 2H), 6.89 (d, 1H, J = 3.0), 7.00 (d, 1H, J = 3.00), 7.03 (d, 1H, J = 1.0), 7.31 (t, 2H, J = 9.0), 7.61 (dd, 1H, J = 1.0, 9.0), 7.77 (dd, J = 6.0, 8.0), 7.81 (s, 1H), 8.29 (m, 1H), 8.31 (d, 1H, J = 9.0), 8.39 (s, 1H), 8.69 (d, 1H, J = 8.0), 9.17 (s, 1H), 9.24 (d, 1H, J = 6.0); IR ($CDCl_3$) 1750, 1690; mass spectrum (DCI/NH_3) 511 (M + H)$^+$; $[\alpha]^{25}_D$ = +56.5° (c = 0.27, $CHCl_3$). Anal. ($C_{35}H_{34}N_4O_4SFCl\cdot2.00H_2O$) C, H, N.

Synthesis of 1-Chloroethyl Pivalate.[22] To acetaldehyde (5.00 mL; 89 mmol) and $ZnCl_2$ (75 mg) was added pivaloyl chloride (11.0 mL; 89 mmol). The mixture was heated at 80 °C for 2 h and then distilled under reduced pressure which gave 1-chloroethyl pivalate (10.2 g; 69%) as a colorless oil: bp (20 mmHg) = 63–64 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.22, (s, 9H), 1.80 (d, 3H, J = 5.5), 6.53 (q, 1H, J = 5.5).

Synthesis of (*R*)-1-[(*R*,*S*)-Methyl(pivaloyloxy)methyl]-3-[7-[1-(*N*,*N*-dimethylcarbamoyl)-6-(4-fluorophenyl)indol-3-oyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazol-3-yl]pyridinium Chloride (14). The compound was prepared by the procedure described for the preparation of **9** using **4** (200 mg) and 1-chloroethyl pivalate (77 mg; 120 mol %). Trituration in diethyl ether gave the pyridinium tetraphenylborate salt (239 mg) as a yellowish solid. Ion-exchange chromatography gave a tan foam which was triturated in diethyl ether and gave **14** (156 mg; 59% from **4**) as a tan solid: mp 143–149 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.18 (s, 4.5H), 1.19 (s, 4.5H), 1.90 (m, 1H), 3.09 (s, 6H), 4.54 (dd, 1H, J = 2.5, 15.0), 4.75 (d, 1H, J = 15.0), 6.86 (d, 1.5H, J = 3.0), 6.90 (d, 1.5H, J = 3.0), 7.00 (t, 1H, J = 3.0), 7.03 (s, 1H), 7.10 (dd, 1H, J = 6.0, 8.0), 7.31 (t, 2H, J = 9.0), 7.61 (dd, 1H, J = 1.0, 9.0), 7.76 (dd, 2H, J = 6.0, 8.0), 7.81 (s, 1H), 8.29 (m, 1H), 8.31 (d, 1H, J = 8.0), 8.39 (d, 1H, J = 3.0), 8.50 (d, 0.5H, J = 8.0), 8.61 (d, 0.5H, J = 8.0), 9.37 (m, 1.5H), 9.43 (s, 0.5H); IR ($CDCl_3$) 1755, 1695; mass spectrum (DCI/NH_3) 511 (M + H)$^+$; $[\alpha]^{25}_D$ = +88.0° (c = 0.32, $CHCl_3$). Anal. ($C_{36}H_{38}N_4O_4SFCl\cdot3.00H_2O$) C, H, N.

Synthesis of *N*-[[(Chloromethyl)oxy]carbonyl]-L-proline Methyl Ester.[23] To a solution of chloromethyl chloroformate (0.95 mL g; 10.8 mmol) in dichloroethane (25 mL) at −10 °C was added a solution of L-proline methyl ester (2.8 g; 21.6 mmol) in dichloroethane (20 mL) over 25 min. The resulting heterogeneous mixture was allowed to warm to room temperature over 75 min, then the precipitate was removed by filtration, and the filtrate was washed with water (50 mL) and brine (50 mL) and dried ($MgSO_4$). Filtration and concentration gave *N*-[[(chloromethyl)oxy]carbonyl]-L-proline methyl ester (2.24 g) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.88–2.35 (c, 4H), 3.50–3.71 (c, 2H), 3.75 (s, 1.5H), 3.76 (s, 1.5H), 4.41 (m, 1H), 5.66 (d, 0.5H, J = 6.0), 5.75 (d, 1H, J = 3.0), 5.90 (d, 0.5H, J = 6.0); mass spectrum (DCI/NH_3) 239 (M + H)$^+$.

Synthesis of (*R*)-1-[[[(*R*)-(2-Carbomethoxypyrrolidin-1-yl)carbonyl]oxy]methyl]-3-[7-[1-(*N*,*N*-dimethylcarbamoyl)-6-(4-fluorophenyl)indol-3-oyl]-1*H*,3*H*-pyrrolo[1,2-*c*]-thiazol-3-yl]pyridinium Chloride (15). The compound was prepared by the procedure described for the preparation of **9** using **4** (200 mg) and *N*-[[(chloromethyl)oxy]carbonyl]-L-proline methyl ester (104 mg; 120 mol %), which gave the pyridinium tetraphenylborate salt (387 mg) as a yellowish solid. Ion-exchange chromatography gave **15** (241 mg; 84% from **4**): mp 137–150 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.81–1.93 (c, 4H), 2.21 (m, 1H), 3.09 (s, 6H), 3.38 (m, 1H), 3.51 (m, 1H), 3.61 (s, 1.5H), 3.62 (s, 1.5H), 4.55 (d, 1H, J = 15.0), 4.75 (d, 1H, J = 15.0), 6.35–6.52 (c, 2H), 6.86 (d, 1H, J = 3.0), 7.00 (t, 1H, J = 1.5), 7.02 (s, 1H), 7.31 (t, 2H, J = 9.0), 7.61 (d, 1H, J = 9.0), 7.78 (dd, 1H, J = 6.0, 8.0), 7.82 (s, 1H), 8.28 (m, 1H), 8.32 (d, 1H, J = 9.0), 8.39 (s, 1H), 8.65 (t, 1H, J = 8.0), 9.11–9.25 (c, 2H); IR ($CDCl_3$) 1740, 1725, 1695; mass spectrum (DCI/NH_3) 511 (M + H)$^+$; $[\alpha]^{25}_D$ = +22.3° (*c* = 0.32, $CHCl_3$). Anal. ($C_{37}H_{35}N_5O_6SFCl\cdot2.00H_2O$) C, H, N.

Synthesis of Chloromethyl (Dimethylamino)formate.[23] To a solution of chloromethyl chloroformate (20 g; 0.16 mol) in dichloroethane (100 mL) at 0 °C was added a solution of dimethylamine (21 g; 0.46 mol) in dichloroethane (50 mL) over 15 min. The resulting heterogeneous mixture was allowed to warm to room temperature over 45 min, then the precipitate was filtered, and filtrate was concentrated. Diethyl ether (50 mL) was added to the residue, and the resulting solid was again removed by filtration. Concentration of this solution

gave a colorless oil that was distilled under reduced pressure and gave chloromethyl (dimethylamino)formate (6.7 g; 30%) as a colorless oil: bp (4 mmHg) = 65–67 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.96 (s, 3H), 2.99 (s, 3H), 5.79 (s, 2H).

Synthesis of (*R*)-1-[[[(Dimethylamino)carbonyl]oxy]-methyl]-3-[7-[1-(*N*,*N*-dimethylcarbamoyl)-6-(4-fluorophenyl)indol-3-oyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazol-3-yl]pyridinium Chloride (16). The compound was prepared by the procedure described for the preparation of **9** using **4** (200 mg) and chloromethyl (dimethylamino)formate (64 mg; 120 mol %), which gave the pyridinium tetraphenylborate salt (360 mg) as a yellowish solid. Ion-exchange chromatography gave **16** (213 mg; 84% from **4**): mp 149–153 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.86 (s, 3H), 2.92 (s, 3H), 3.09 (s, 6H), 4.53 (d, 1H, J = 15.0), 4.75 (dd, 1H, J = 1.0, 15.0), 6.41 (s, 2H), 6.89 (d, 1H, J = 3.0), 7.00 (d, 1H, J = 3.0), 7.03 (d, 1H, J = 1.0), 7.31 (t, 2H, J = 9.0), 7.61 (dd, 1H, J = 1.0, 8.0), 7.76 (dd, 2H, J = 6.0, 8.0), 7.81 (s, 1H), 8.25 (dd, 1H, J = 6.0, 8.0), 8.32 (d, 1H, J = 8.0), 8.40 (s, 1H), 8.60 (d, 1H, J = 6.0), 9.20–9.25 (c, 2H); IR ($CDCl_3$) 1725, 1695; mass spectrum (DCI/NH_3) 511 (M + H)$^+$; $[\alpha]^{25}_D$ = +46.0° (c = 0.30, $CHCl_3$). Anal. ($C_{33}H_{31}N_5O_4$·SFCl·2.50H_2O) C, H, N.

Solubility and Stability Measurements. The aqueous solubility of prodrugs **8**–**16** was assessed in buffer containing 100 mM glycine hydrochloride and 8% lactose at pH 3. Compounds were dispersed in the buffer with sonication, and the resulting solution was passed through a 0.2 μm nylon membrane by centrifugation (4000*g*, 5 min). Compound concentration in the filtrate was determined by high-performance liquid chromatography (HPLC) with a C18 reverse-phase column (5 × 0.46 cm, 3 μm Spherisorb S30DS2, Regis, Morton Grove, IL) eluted with a linear gradient of 0.1% TFA in 10 mM trimethylammonium perchlorate and 10% methanol in acetonitrile (40:60–60:40) over 20 min. Elution was monitored at 250 nm and the concentration determined by comparison of peak areas to an external calibration curve. For analysis of stability in buffer, compounds (20 μM) were incubated in K_2PO_4 buffer (25 mM, pH 7) at room temperature. Aliquots were removed at various times and assayed by HPLC as described above. Half-life values ($t_{1/2}$) were derived from the decay rate constant (k) by fitting the concentration and time values to the exponential decay function: $C = C_0e^{-kt}$, where C = concentration at time t, C_0 = initial concentration, and $t_{1/2} = \ln(2)/k$. The rate of hydrolytic cleavage in plasma was assessed by incubating compounds (30 μM) at 37 °C with human plasma adjusted to pH 7 with K_2PO_4 buffer (50 mM final). Aliquots were removed at various times, quenched with 2 volumes of acidified acetonitrile to halt further conversion, and centrifuged to remove precipitated materials. Compound concentrations in the supernatants and half-life values were determined as described above. The effect of an esterase inhibitor on plasma hydrolysis of 11 was studied by preincubating plasma with 0.29 M diisopropyl fluorophosphate for 10 min at 37 °C. At the end of the preincubation, aliquots of the treated plasma were incubated with 11 and rate of conversion determined as above.

Biological Assays. Methods for the [^{3}H]PAF rabbit platelet membrane binding assay, PAF-induced serotonin release assay, and the PAF-induced cutaneous vascular permeability assay have been previously described.[9] The LPS-induced hypotension assay was conducted in the rat according to the following procedure. The carotid artery of anesthetized male, Sprague–Dawley rats (190–220 g) was cannulated with PE-50 tubing. The tubing was tunneled subcutaneously to the posterior neck, exteriorized, and connected to a pressure transducer and polygraph (Model MI^2, Modular Instruments Inc., Southeastern, PA) for monitoring arterial pressure. Animals were allowed to recover from surgery for at least 1 h. After the recovery period, baseline values for arterial pressure were determined and normalized to 100 mmHg. Animals were pretreated with **4** or vehicle by intraarterial administration. Pretreatment time was 15 min prior to agonist challenge unless otherwise stated. Compound **4** was prepared for dosing by the stepwise addition of DMSO, PEG 400, 45% (hydroxypropyl)-β-cyclodextrin, and 0.9% saline (2.5:20:30:47.5, vol/vol) and **4** to final concentration. Following pretreatments, animals were challenged with LPS (*E. coli* endotoxin, serotype 0111:B4, Sigma Chemical Co., St. Louis, MO, 25 mg/kg) in phosphate-buffered saline (pH 7.4) administered as an intraarterial bolus. Measurements of arterial pressure were taken at 1 min intervals until the conclusion of the experiment. Response to LPS challenge and drug was measured by calculating the area under the curve of blood pressure vs time for the response to the challenge over the experimental period. From these areas, percent inhibition of the agonist-induced response was calculated as (drug − agonist)/(vehicle − agonist). The LPS-induced gastrointestinal bleeding assay was conducted in the rat according to the following procedure. Intestinal bleeding was determined by measuring hemoglobin which leaked into the gastrointestinal lumen of Sprague–Dawley rats (200–225 g). Compound **4** or vehicle (25 mM sodium acetate, pH 4) was injected intravenously via the tail vein followed by LPS (25 mg/kg) 30 min later. The rats were sacrificed 30 min after LPS challenge, and a 15 cm segment of intestine, starting from the duodenum, was collected from each rat. Luminal content was collected by rinsing the intestine segment. Hemoglobin concentration in the rinse was measured with a hemoglobinometer (Coulter Electronic Inc., Hialeah, FL) by comparison to a calibration curve obtained with standard hemoglobin solutions.

References

(1) Snyder, F., Ed. *Platelet-Activating Factor and Related Lipid Mediators*; Plenum Press: New York, 1987.

(2) (a) Summers, J. B.; Albert, D. H. Platelet Activating Factor Antagonists. In *Advances in Pharmacology*; Murad, F., Ed.; Academic Press: New York, 1995; Vol. 32, pp 67–168. (b) Venabe, M. E.; Zimmerman, G. A.; McIntyre, T. M.; Prescott, S. M. Platelet-Activating Factor: A Phospholipid Autacoid with Diverse Actions. *J. Lipid. Res.* **1993**, *6*, 78–87.

(3) Sanchez-Crespo, M. Potential of PAF Receptor Antagonists in the Treatment of Septic Shock. *Drug News Perspect.* **1993**, *6*, 78–87.

(4) Parsons, W. H.; Chabala, J. C. Platelet-Activating Factor, Hyperreactivity and Asthma. In *Airways Hyperresponsiveness: Is it really Important for Asthma?*; Page, C., Gardiner, P., Eds.; Blackwell Scientific Publications: Oxford, 1991.

(5) Moyer, M. P.; Shiurba, J. F.; Rapoport, H. Metal-Halogen Exchange of Bromoindoles. A Route to Substituted Indoles. *J. Org. Chem.* **1986**, *51*, 5106–5110.

(6) Carrera, G. M. Jr.; Sheppard, G. S. Synthesis of 6- and 7-Arylindoles *via* Palladium-Catalyzed Cross-Coupling of 6- and 7-Bromoindole with Arylboronic Acids. *Synlett* **1994**, 93–94.

(7) Bergman, J.; Venemalm, L. Acylation of the Zinc Salt of Indole. *Tetrahedron* **1990**, *46*, 6061–6066.

(8) (a) Lavé, D.; James, C.; Rajoharison, H.; Bost, P. E.; Cavero, I. Pyrrolo[1,2-*c*]thiazole Derivatives: Potent PAF Receptor Antagonists. *Drugs Future* **1989**, *14*, 891–898. (b) Fabre, J.; Farge, D.; James, C.; Lavé, D. 1*H*,3*H*-Pyrrolo[1,2-*c*]thiazole derivatives having Anti-Allergic and Anti-Inflammatory Activity. U.S. Patent 4 529 728, 1985; *Chem. Abstr.* **1984**, *101*, 230510z.

(9) For assay protocols, see: Sheppard, G. S.; Pireh, D.; Carrera, G. M., Jr.; Bures, M. G.; Heyman, H. R.; Steinman, D. H.; Davidsen, S. K.; Phillips, J. G.; Guinn, D. E.; May, P. D.; Conway, R. G.; Rhein, D. A.; Calhoun, W. C.; Albert, D. H.; Magoc, T. J.; Carter, G. W.; Summers, J. B. 3-(2-(3-Pyridinyl)thiazolidin-4-oyl)indoles, a Novel Series of Platelet Activating Factor Antagonists. *J. Med. Chem.* **1994**, *37*, 2011–2032.

(10) (a) Summers, J. B.; Albert D. H.; Davidsen, S. K.; Conway, R. G.; Holms, J. H.; Magoc, T. J.; Luo, G.; Tapang, P.; Rhein, D. A.; Carter, G. A. ABT-299, A Potent Antagonist of Platelet Activating Factor. In *Advances in Prostaglandin, Thromboxane, and Leukotriene Research*; Samuelsson, B., Paoletti, R., Ramwell, P., Eds.; Raven: New York, 1994, in press. (b) Albert, D. H.; Summers, J. B.; Kleinert, H. D. The Potential Role of PAF Antagonists in the Therapy of Sepsis. In *Novel Therapeutic Strategies in the Treatment of Sepsis*; Morrison, D., Ryan, J., Eds.; Marcel Dekker, Inc: New York, 1994, in press.

(11) Bodor, N. Novel Approaches for the Design of Membrane Transport Properties of Drugs. In *Design of Biopharmaceutical Properties through Prodrugs and Analogs*; Roche, E. B., Ed.; Academy of Pharmaceutical Sciences: Washington, 1977; pp 98–135.

(12) French and Adams first characterized the adducts of pyridine and tertiary amines with α-halo esters in 1921. See: French, H. E.; Adams, R. *J. Am. Chem. Soc.* **1921**, *43*, 651–659.

(13) (a) Bodor, N. The Soft Drug Approach. *ChemTech* **1984**, *14*, 28–38. (b) Bodor, N. Novel Approaches in Prodrug Design. *Drugs Future* **1981**, *6*, 165–182. (c) Bodor, N. Labile, Non-Heterocyclic Quaternary Ammonium Salt/Esters as Transient Derivatives.

U.S. Patent 4 160 099, 1979; *Chem. Abstr.* **1979**, *91*, 157420p. (d) Bodor, N.; Kaminski, J. J.; Selk, S. Soft Drugs. 1. Labile Quaternary Ammonium Salts as Soft Antimicrobials. *J. Med. Chem.* **1980**, *23*, 469–473.

(14) Bodor, N. Prodrugs Versus Soft Drugs. In *Design of Prodrugs*; Bundgaard, H., Ed.; Elsevier Science: Amsterdam, 1985; pp 333–354.

(15) Bodor, N. Selected Quaternary Ammonium Salts of Pilocarpine Useful in Reducing Intraocular Pressure in Warm-Blooded Animals. U.S. Patent 4 061 722, 1977; *Chem. Abstr.* **1978**, *88*, 89917s.

(16) Bodor, N.; Freiberg, L. A. Salts of Erythromycin A Esters. U.S. Patent 4 264 765, 1981; *Chem. Abstr.* **1981**, *95*, 81424c.

(17) Bogardus, J. B. Labile Quaternary Ammonium Derivatives of Tertiary Amines. Pharmaceutical Application for Quinone Methides, Ph.D. Thesis, University of Kansas, 1973; *Chem. Abstr.* **1974**, *81*, 126743k.

(18) Vinogradova, N. D.; Kuznetsov, S. G.; Chigareva, S. M. Quaternary Ammonium Salts with a Labile Nitrogen (N+)-Carbon Bond as Drug Precursors. *Khim.-Farm. Zh.* **1980**, *14*, 41–47.

(19) King, J. A., Jr.; Bryant, G. L., Jr. Preparation and Characterization of Crystalline *N*-Acylammonium Salts *J. Org. Chem.* **1992**, *57*, 5136–5139. In cases for which a chloride electrophile was used, sodium iodide (120 mol %) was added. While salts of the general structure **5** produce **4** upon extended exposure to water, they could be manipulated in alcoholic solvents without decomposition. In addition, pyridinium salts of this type are known to be more stable under acidic conditions. See: Anders, E.; Gassner, T. Synthesis and Properties of *N*-[1-(Arylcarbonyloxy)alkyl]-pyridinium Salts. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 289–290.

(20) Sakamoto, F.; Ikeda, S.; Tsukamoto, G. Studies on Prodrugs. II. Preparation and Characterization of (5-Substituted 2-Oxo-1,3-dioxolen-4-yl)methyl Esters of Ampicillin. *Chem. Pharm. Bull.* **1984**, *32*, 2241–2248.

(21) Patonay, T.; Patonay-Peli, E.; Mogyorodi, F. α-Haloalkyl Haloformates and Related Compounds 1. A Convenient Synthesis of Carbamates *via* Chloromethyl Carbonates. *Synth. Commun.* **1990**, *20*, 2865–2885.

(22) Ulich, L. H.; Adams, R. The Reaction Between Acid Halides and Aldehydes *J. Am. Chem. Soc.* **1921**, *43*, 660–667.

(23) *N*-[[(Chloromethyl)oxy]carbonyl]-L-proline methyl ester and chloromethyl (dimethylamino)formate were prepared by analogy to the procedures described by Schrader, see: Schrader, G.; Hammann, I. *O*-Alkyl-*S*-(carbamoyloxy-methyl)-(thiono) thiolphosphoric (phosphonic) Acid Esters. U.S. Patent 3 862 268, 1975; *Chem. Abstr.* **1973**, *79*, 115723m.