Synthesis and Antiallergic Activity of Dimethyl-2-(phenylcarbamoyl)ethylsulfonium *p*-Toluenesulfonate Derivatives

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The derivatives of dimethyl-2-(phenylcarbamoyl)ethylsulfonium *p*-toluenesulfonates were synthesized and evaluated for antiallergic activity. The 2,3-dihydroxyethoxy group was introduced to the phenyl ring from the standpoint of lipophilicity and electronic effects of substituent. The IgE-induced rat passive cutaneous anaphylaxis (PCA) was inhibited by oral administration of several substituted 2-[(4-propoxyphenyl)carbamoyl]ethyldimethylsulfonium *p*-toluenesulfonate derivatives. Among them (±)-2-[*N*-[4-(3-ethoxy-2-hydroxypropoxy)phenyl]-carbamoyl]ethyldimethylsulfonium *p*-toluenesulfonate (**1a**, IPD-1151T) was found to possess considerable activity in the PCA test, and it was launched as Suplatast tosilate in Japan.

Introduction

The β_2-agonists and steroids have been used as antiallergy drugs for the treatment of bronchi asthma, allergic nose catarrh, and nettle rash. Recently, the release inhibitors of allergic chemical mediators have come to be widely used. Disodium cromoglycate (DSCG)[1] was developed as this type of drug for the first time, but it is ineffective in oral administration, since it is poorly absorbed by the gastrointestinal tract.[2] Tranilast,[3] Ketotifen,[4] and Azelastine[5] are utilized in the oral treatment of allergic diseases (Chart 1). These drugs are considered to inhibit the degranulation of the mast cell induced by the antigen.

Type I allergic reaction is caused by the IgE antibody. Therefore, the drug that specifically inhibits IgE antibody formation will be expected to be efficacious for the fundamental treatment of type I allergic diseases.

We have studied the chemical and biological properties of sulfonium compounds. The sulfonium moiety has been mainly considered to mimic the quaternary ammonium salt in the medical field; however, *S*-methylmethionine was found to have the antiulcer activity as a novel biological activity of sulfonium compounds for the first time. Furthermore, when *S*-methylmethionine was given to guinea pigs, it appeared to increase the formation of antibodies to allergen from horse serum.[6] Therefore, we expected sulfonium compounds to have some immunological activities, and we synthesized various kinds of sulfonium compounds to find a suitable clinical candidate for the treatment of allergic disorders. In this paper we describe the syntheses of a series of dimethyl-2-(phenylcarbamoyl)ethylsulfonium *p*-toluenesulfonates and their evaluation in IgE antibody-mediated passive cutaneous anaphylaxis (PCA) in rats.

Chemistry

The N-substituted 2-carbamoylethyldimethylsulfonium *p*-toluenesulfonate derivatives (**2**, **3**, **4a**−**m**) listed in Tables 1 and 2 were prepared by the general procedures outlined in Scheme 1. Treatment of methyl 3-(methylthio)propionate (**7**) with 25% aqueous NH_3[7] gave 2-carbamoylethyl methyl sulfide (**8**). Cyclohexylamine (**9**) was condensed with 3-(methylthio)propionyl chloride in the presence of triethylamine to give 2-(cyclohexylcarbamoyl)ethyl methyl sulfide (**10**). Other N-substituted carbamoylethyl methyl sulfides (**12a**−**m**) were similarly prepared from aniline derivatives (**11a**−**m**). Methylation of these sulfides (**8**, **10**, **12a**−**m**) with methyl *p*-toluenesulfonate[8] afforded N-substituted 2-carbamoylethyldimethylsulfonium *p*-toluenesulfonate derivatives (**2**, **3**, **4a**−**m**) in good yields. Dimethyl 2-[*N*-(4-substituted propoxyphenyl)carbamoyl]ethylsulfonium *p*-toluenesulfonate derivatives (**1a**−**f**, **5a**,**b**, **6a**−**c**) listed in Table 3 were prepared by a variety of synthetic pathways depicted in Schemes 2 and 3. Nitrobenzene compounds (**15a**−**f**, **19a**,**b**) were prepared from epichlorohydrins (**13**, **18b**,**f**). Condensation of epichlorohydrin (**13**) with *p*-nitrophenol in the presence of pyridine as a catalyst followed by treatment with 5 N KOH gave glycidyl *p*-nitrophenyl ether (**14a**). Compound **14a** was converted into the 4-(3-alkoxy-2-hydroxypropoxy)nitrobenzene compounds (**15a**,**c**−**e**) by treatment with appropriate kinds of alcohol. 4-(3-Phenoxy-2-hydroxypropoxy)nitrobenzene (**15b**) and 4-(3-methoxy-2-hydroxypropoxy)nitrobenzene (**15f**) were similarly prepared from phenyl glycidyl ether (**18b**) or methyl glycidyl ether (**18f**),[9] respectively. 4-(2,3-Dialkoxypropoxy)nitrobenzene compounds (**19a**,**b**) were readily prepared from **15a**,**b** by treatment with sodium hydride followed by alkylation with the appropriate alkyl iodide. Reduction of the nitro compounds (**15a**−**f**, **19a**,**b**) with 10% Pd−C[10] in ethanol afforded aniline compounds (**16a**−**f**, **20a**,**b**). Compounds **16a**−**f** and **20a**,**b** were condensed with 3-(methylthio)propionyl chloride in the presence

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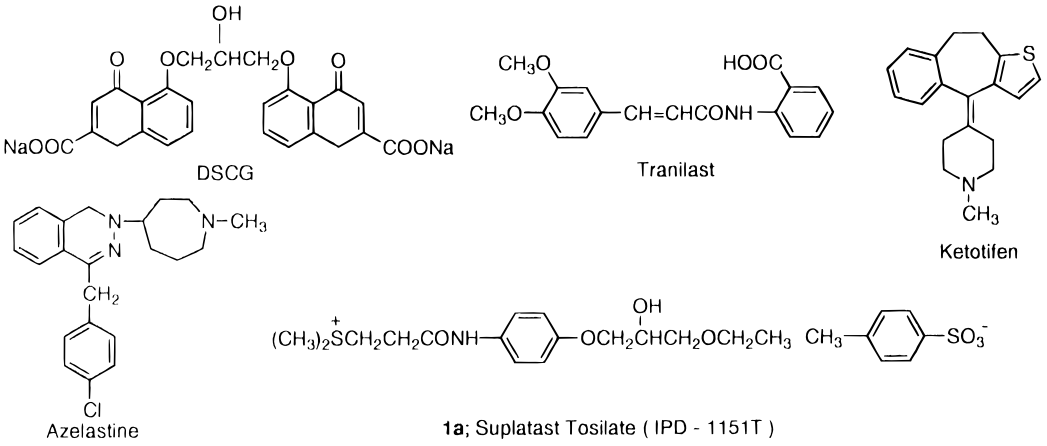
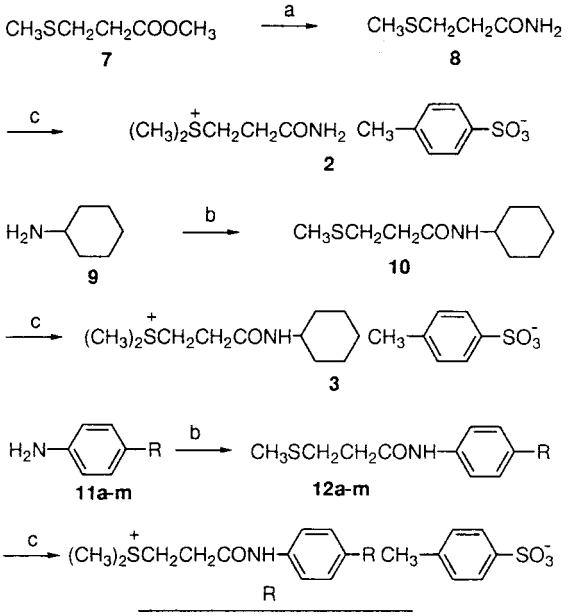
Chart 1



Scheme 1[a]



[a] (a) 25% aq NH_3, rt, 12 h; (b) 3-(methylthio)propionyl chloride, triethylamine, ether, rt, 3 h; (c) methyl *p*-toluenesulfonate, CH_2Cl_2, rt, 5 days.

of triethylamine to give 2-[*N*-(4-substituted propoxyphenyl)carbamoyl]ethyl methyl sulfides **17a**−**f** and **21a**,**b**, respectively. Methylation of sulfides (**17a**−**f**, **21a**,**b**) with methyl *p*-toluenesulfonate finally afforded dimethyl-2-[(substituted 4-propoxyphenyl)carbamoyl]ethylsulfonium *p*-toluenesulfonates (**1a**−**f**, **5a**,**b**) in appropriate yields (Scheme 2).

2-Acetoxy-3-ethoxypropoxy derivatives (**6a**−**c**) were prepared according to the outlined procedures in Scheme 3. Sulfides (**17g**,**h**) were also similarly prepared from epichlorohydrin (**13**) by condensation with *o*-nitrophenol and *m*-nitrophenol, respectively, followed by treatment with EtOH, the reduction of nitro group, and condensation with 3-(methythio)propionyl chloride. Sulfides (**17a**,**g**,**h**) were converted to the 2-acetyl compounds (**22a**−**c**) with acetyl chloride, followed by methylation with methyl *p*-toluenesulfonate to afford 2-[*N*-[(2-acetoxy-3-ethoxypropoxy)phenyl]carbamoyl]ethyldimethyl *p*-toluenesulfonates (**6a**−**c**).

Results and Discussion

Dimethyl-2-(phenylcarbamoyl)ethylsulfonium *p*-toluenesulfonate derivatives were tested for their ability to inhibit the PCA reaction in rats.[11] Among some carbamoylethyldimethylsulfonium derivatives (**2**, **3**, **4a**), phenylcarbamoyl compound **4a** was most effective at 100 mg/kg, (ip) in the PCA test (Table 1). Therefore, compound **4a** was chosen as a lead compound.

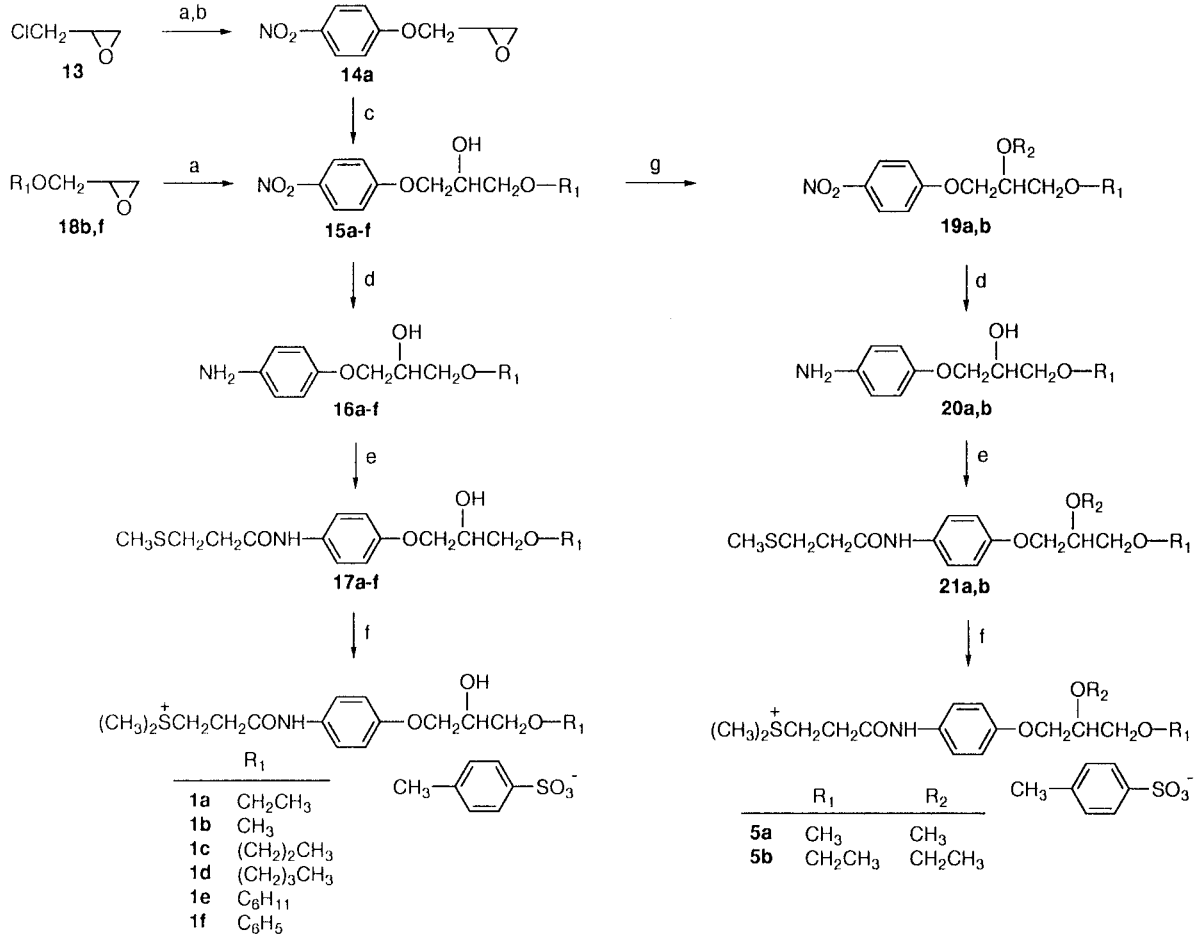
Table 2 shows the data on various substituted phenylcarbamoyl derivatives designed to investigate electronic effects of the aryl group.[12] At 50 mg/kg, (ip) in the PCA test, trifluoromethyl (**4b**), chloro (**4d**), and fluoro (**4e**) compounds were inactive. On the other hand, acetyl (**4c**), carboxymethyl (**4f**), methyl (**4g**), methoxy (**4h**), and hydroxy (**4i**) compounds were more active than **4a**. Compounds with electron-donating groups such as methyl, methoxy, and hydroxy substituents were preferable for inhibition of the PCA reaction compared to those with electron-withdrawing groups such as trifluoromethyl, chloro, and fluoro except for the acetyl substituent.

On the other hand, compounds with hydrophilic groups such as carboxymethyl, acetyl, hydroxy, and methoxy substituents were more effective than those with hydrophobic groups such as chloro, fluoro, and trifluoromethyl except for the methyl substituent.

Consequently, the alkoxy substituent was chosen for further studies; therefore we synthesized the propoxy (**4j**) and 2,3-dihydroxypropoxy (**4k**) compounds. The 2,3-dihydroxypropoxy substituent is the important moiety of DSCG. Both compounds **4j**,**k** were active, and compound **4k** was more active than **4j** at doses of 20 and 50 mg/kg (ip).

To ascertain the biological effects of the hydroxy substituent attached to the propoxy moiety, the toxicity of compounds **4j**−**m** was tested. Compound **4j** bearing no hydroxy group had high toxicity, a 2- or 3-hydroxypropoxy moiety (**4l**, **4m**) had reduced toxicity, and a 2,3-

Scheme 2[a]



[a] (a) *p*-Nitrophenol, pyridine, 90 °C, 5 h; (b) KOH, actone−H_2O, rt, 2 h; (c) R_1OH, H_2SO_4, 80 °C, 6 h; (d) 10% Pd−C, H_2, EtOH, 8 h; (e) 3-(methylthio)propionyl chloride, triethylamine, CH_2Cl_2, 10 °C, 3 h; (f) methyl *p*-toluenesulfonate, CH_2Cl_2, rt, 5 days; (g) R_2I, NaH, DMF, rt, 12 h.

dihydroxypropoxy moiety (**4k**) had the lowest toxicity according to the value of LD_{50}[13] (Table 4). These results suggested that the hydroxy moiety of the propoxy substituent may have an effect of reducing toxicity.

Although compound **4k** had potent activity at intraperitoneal administration, it had no suitable activity after oral administration (Table 2). The sulfonium moiety and 2,3-dihydroxypropoxy substituent are hydrophilic; consequently the low lipophilicity of compound **4k** may result in poor absorption. Therefore, lipophilic groups were introduced into compound **4k** on the 2- or 3-hydroxy moiety of propoxy substituent.

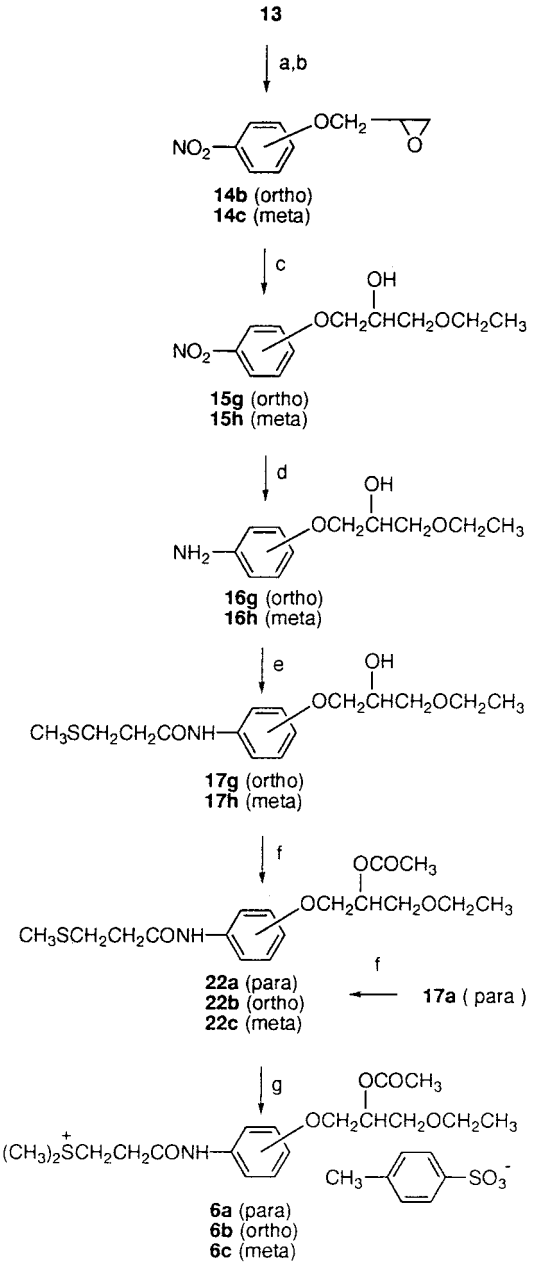
Table 3 shows the physical and biological data of **4k** derivatives prepared for the optimization of oral potency. As a measure of the lipophilicity, the substituent lipophilicity of the substituted propoxy group (π_{calcd}) was calculated by CLOGP[14] (Table 5). The activity of ethoxy (**1a**) and methoxy (**1b**) compounds improved with the increase in lipophilicity, but more lipophilic propoxy (**1c**) and butoxy (**1d**) compounds reduced their activity. To confirm these results, more lipophilic cyclohexyloxy (**1e**) and phenoxy (**1f**) derivatives were tested and had little activity as expected (Figure 1).

In the case of 2,3-dialkoxy-substituted compounds, 2,3-dimethoxy (**5a**) and more lipophilic 2,3-diethoxy (**5b**) compounds were less active than **1a**. 2-Acetoxy-3-ethoxy compound (**6a**) had almost the same activity as **1a**, but the structural isomers of **6a**, ortho derivative **6b** and meta derivative **6c**, had less activity than compounds **6a** and **1a**. Therfore, the para position is considered to be most favorable for substitution on the phenyl ring. Consequently, we selected **1a** as the candidate compound for clinical trial, considering **1a** was synthesized easier than **6a**.

Compound **1a** (IPD-1151T) is a new type of antiallergic agent and suppressed IgE synthesis without having a direct effect on B cells,[15,16] the synthesis of interleukin-4 and interleukin-5 in Th2 cells, the expression of local eosinophilia that is regulated by Th2 cells,[18] and the induction of mast cells.[19] Therefore compound **1a** will be used for the fundamental treatment of type I allergic diseases.

Compound **1a** contains a chiral center, the physicochemical properties and biological profile of the individual enantiomers were investigated, and **1a** was classified into a mixture of racemic compound crystals.[18] There were no remarkable differences between **1a** and enantiomers in suppression of the synthesis of interleukin-4 in mouse helper T cells and acute toxicity.[20] Therefore compound **1a** was selected as an agent for the treatment of bronchial asthma, atopic dermatitis, and allergic rhinitis, and it was launched as Suplatast tosilate in 1995 in Japan.

Scheme 3[a]



[a] (a) *o,m,p*-Nitrophenol, pyridine, 90 °C, 5 h; (b) KOH, acetone−H_2O, rt, 2 h; (c) EtOH, H_2SO_4, 80 °C, 6 h; (d) 10% Pd−C, H_2, EtOH, 8 h; (e) 3-(methylthio)propionyl chloride, triethylamine, CH_2Cl_2, 10 °C, 3 h; (f) acetyl chloride, pyridine, benzene, 10 °C, 3 h; (g) methyl *p*-toluenesulfonate, CH_2Cl_2, rt, 5 days.

Experimental Section

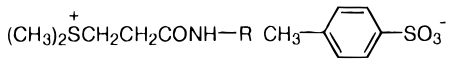
Melting points were determined with a Yamagimoto MP-3 micromelting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained in DMSO-d_6 with Me_4Si as internal standard on a JEOL LMN-FX 100 spectrometer. Analytical results for compounds followed by elemental symbols are within ±0.4% of theory and were determined on a Perkin-Elmer model 240 CHN analyzer. Column chromatography was performed with Merck silica gel 60.

Method A. Synthesis of 2-Carbamoylethyldimethylsulfonium *p*-Toluenesulfonate (2). Methyl 3-(methylthio)propionate (**7**) (33.5 g, 0.25 mol) was added to a 25% aqueous NH_3 solution (900 mL), and the mixture was stirred for 12 h at room temperature. The reaction mixture was extracted with $CHCl_3$ (500 mL). The extracts were washed with water, dried ($MgSO_4$), and concentrated. The residue was dissolved in CH_2Cl_2 (100 mL) and added to methyl *p*-toluenesulfonate (23.3 g, 0.125 mol). The mixture was stirred for 5 days at room temperature, and then ether (200 mL) was added. A crystallized solid was collected by filtration and recrystallized from ethanol−ether to give 36.6 g (29.3%) of **2**: mp 114−116 °C; ^{1}H NMR (DMSO-d_6) δ 10.13 (2H, s, NH_2), 7.43 (2H, d, J = 7.8 Hz, tosyl $H_{3,5}$), 7.04 (2H, d, J = 7.8 Hz, tosyl $H_{2,6}$), 3.35 (2H, t, J = 6.2 Hz, S^+CH_2), 2.82 (6H, s, $(CH_3)_2S^+$), 2.62 (2H, t, J = 6.2 Hz, $S^+CH_2CH_2$), 2.22 (3H, s, tosyl CH_3). Anal. ($C_{12}H_{19}NO_4S_2 \cdot {}^1/_4H_2O$) C, H, N.

Method B. Synthesis of 2-[*N*-(4-(Trifluoromethyl)-phenyl)carbamoyl]ethyldimethylsulfonium *p*-Toluenesulfonate (4b). 3-(Methylthio)propionyl chloride (13.9 g, 0.10 mol) was added dropwise to a solution of *p*-(trifluoromethyl)-aniline (**11b**) (16.1 g, 0.10 mol) and triethylamine (15.2 g, 0.15 mol) in ether (150 mL) below 10 °C. The mixture was stirred for 3 h at room temperature and then filtered. The filtrate was washed successively with 1 N HCl (50 mL), saturated $NaHCO_3$ (50 mL), and H_2O (50 mL). The ethereal layer was separated, dried ($MgSO_4$), and evaporated. The residue was dissolved in CH_2Cl_2 (20 mL), and methyl *p*-toluenesulfonate (18.3 g, 0.10 mol) was added to the solution. The mixture was stirred for 5 days at room temperature, and ether (200 mL) was added. A crystallized solid was collected by filtration and recrystallized from ethanol−ether to afford 26.8 g (59.6%) of **4b**: mp 164−165 °C; ^{1}H NMR (DMSO-d_6) δ 10.20 (1H, s, NH), 7.80 (2H, d, J = 9.0 Hz, aromatic $H_{2,6}$), 7.69 (2H, d, J = 9.0 Hz, aromatic $H_{3,5}$), 7.46 (2H, d, J = 7.8 Hz, tosyl $H_{3,5}$), 7.11 (2H, d, J = 7.8 Hz, tosyl $H_{2,6}$), 3.54 (2H, t, J = 6.2 Hz, S^+CH_2), 3.03 (2H, t, J = 6.2 Hz, $S^+CH_2CH_2$), 2.94 (6H, s, $(CH_3)_2S^+$), 2.31 (3H, s, tosyl CH_3). Anal. ($C_{19}H_{22}NO_4S_2F_3$) C, H, N.

Method C. Synthesis of (±)-2-[*N*-[4-(3-Ethoxy-2-hydroxypropoxy)phenyl]carbamoyl]ethyldimethylsulfonium *p*-Toluenesulfonate (1a). A mixture of *p*-nitrophenol (50.0 g, 0.36 mol), epichlorohydrin (**13**) (31.5 g, 0.34 mol), and pyridine (3 drops) was stirred for 6 h at 90 °C. The reaction mixture was concentrated. The residue was dissolved in acetone (200 mL), and 5 N KOH (150 mL) was added to the solution. The mixture was stirred for 2 h at room temperature, and then acetone was removed. The residue was extracted with $CHCl_3$ (500 mL). The extracts were washed with water, dried ($MgSO_4$), and concentrated. The residue was dissolved in EtOH (300 mL), and H_2SO_4 (4 drops) was added to the solution. The reaction mixture was refluxed for 6 h, and then EtOH was removed. The residue was poured into water (200 mL) and extracted with $CHCl_3$ (500 mL). The extracts were washed with water, dried ($MgSO_4$), and concentrated. The residue was distilled under reduced pressure to give 58.9 g of the nitro compound (**15a**) (bp 180−181 °C/2−3 mmHg). A solution of the nitro compound (**15a**) (58.9 g, 0.24 mol) in EtOH (250 mL) along with 10% Pd−C was hydrogenated at room temperature until 1 equiv of hydrogen had been used (8 h). The solution was filtered, and the filtrate was concentrated under reduced pressure to give 47.6 g of aniline compound (**16a**). 3-(Methylthio)propionyl chloride (32.0 g, 0.23 mol) was added dropwise to a solution of the aniline compound (**16a**) (47.6 g, 0.23 mol) and triethylamine (34.8 g, 0.35 mol) in CH_2Cl_2 (350 mL) below 10 °C. The mixture was stirred for 3 h at room temperature and then filtered. The filtrate was washed successively with 1 N HCl (150 mL), saturated $NaHCO_3$ (150 mL), and H_2O (150 mL). The CH_2Cl_2 layer was separated, dried ($MgSO_4$), and evaporated. The residue was dissolved in CH_2Cl_2 (50 mL), and methyl *p*-toluenesulfonate (42.1 g, 0.23 mol) was added to the solution. The mixture was stirred for 5 days at room temperature and was added to ether (500 mL). A crystallized solid was collected by filtration and was recrystallized from ethanol−ether to give 63.4 g (37.4%) of **1a**: mp 86−87 °C; NMR (DMSO-d_6) δ 10.13 (1H, s, NH), 7.51 (2H, d, J = 9.0 Hz, aromatic $H_{2,6}$), 7.50 (2H, d, J = 7.8 Hz, tosyl $H_{3,5}$), 7.16 (2H, d, J = 7.8 Hz, tosyl $H_{2,6}$), 6.89 (2H, d, J = 9.0 Hz, aromatic $H_{3,5}$), 4.43 (1H, broad, OH), 3.88 (3H, broad, OCH_2CH), 3.52 (2H, t, J = 6.2 Hz, S^+CH_2), 3.46 (2H, broad, CH_2OEt), 3.43 (2H, q, J = 7.0 Hz, OCH_2CH_3), 2.93 (6H, s, $(CH_3)_2S^+$), 2.93 (2H, t, J = 6.2 Hz, $S^+CH_2CH_2$), 2.28 (3H, s,

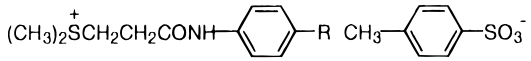
Table 1. Physical Properties and Antiallergic Activity of Dimethyl-2-(*N*-substituted carbamoyl)ethylsulfonium *p*-Toluenesulfonates



compd	R	formula[a]	mp (°C)[b]	method of prep[c]	yield (%)	PCA inhibition (%)[d] 50[e]	100[e]
2	H	$C_{12}H_{19}NO_4S_2$	114−116	A	29	2.4 ± 0.1 (7)	13.7 ± 0.7 (8)
3	C_6H_{11}	$C_{18}H_{29}NO_4S_2$	187−188	B	52	9.0 ± 0.4 (7)	17.0 ± 1.8 (8)
4a	C_6H_5	$C_{18}H_{23}NO_4S_2$	144−146	B	66	−8.3 ± 1.4 (7)	27.1 ± 3.6 (7)

[a] Elemental analyses for C, H, N were within ±0.4% of the calculated values. [b]Recrystallization solvent was EtOH−ether. [c] Letters refer to methods of preparation and are described in the Experimental Section. [d] Inhibition (%) ± SD in homologous PCA in rats. The number of animals is shown in parentheses. [e] Dose (mg/kg, ip).

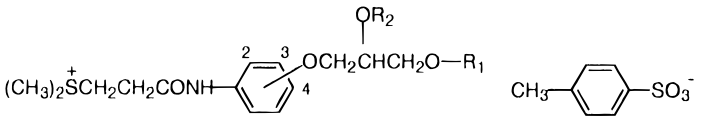
Table 2. Physical Properties and Antiallergic Activity of Dimethyl-2-(*N*-substituted carbamoyl)ethylsulfonium *p*-Toluenesulfonates **4b**−**m**



compd	R	formula[a]	mp (°C)[b]	method of prep[c]	yield (%)	PCA inhibition (%)[d] 20[e]	50[e]
4b	CF_3	$C_{19}H_{22}F_3NO_4S_2$	164−165	B	60	−7.8 ± 0.5 (6)	−10.3 ±0.8 (6)
4c	$COCH_3$	$C_{20}H_{25}NO_5S_2$	149.5−150.5	B	11	9.0 ± 0.5 (7)	25.1 ± 2.9 (7)
4d	Cl	$C_{18}H_{22}ClNO_4S_2$	155−156	B	45	−0.2 ± 0.1 (8)	0.3 ± 0.1 (8)
4e	F	$C_{18}H_{22}FNO_4S_2$	122−123	B	57	4.0 ± 0.6 (7)	1.2 ± 0.1 (7)
4f	CH_2COOH	$C_{20}H_{25}NO_6S_2$	oil	B	51	14.9 ± 0.9 (7)	25.5 ± 1.6 (7)
4g	CH_3	$C_{19}H_{25}NO_4S_2$	169−170	B	48	18.9 ± 2.6 (7)	22.0 ± 2.3 (7)
4h	OCH_3	$C_{19}H_{25}NO_5S_2$	119−123	B	22	−4.4 ± 0.2 (7)	17.4 ± 1.1 (7)
4i	OH	$C_{18}H_{23}NO_5S_2$	178−180	B	23	21.9 ± 3.3 (7)	9.7 ± 0.3 (7)
4j	$OCH_2CH_2CH_3$	$C_{21}H_{29}NO_5S_2$	149−150	B	64	13.8 ± 1.4 (7)	29.8 ± 2.7 (7)
4k	$OCH_2CH(OH)CH_2OH$	$C_{21}H_{29}NO_7S_2$	oil	B	43	38.7 ± 6.1 (7) 1.4 ± 0.1 (7)[f]	34.9 ± 3.9 (7) 18.6 ± 1.4 (7)[f]
4l	$OCH_2CH_2CH_2OH$	$C_{21}H_{29}NO_6S_2$	oil	B	51		
4m	$OCH_2CH(OH)CH_3$	$C_{21}H_{29}NO_6S_2$	oil	B	59		

[a−d] See corresponding footnotes of Table 1. [e] Dose (mg/kg, ip). [f] At po administration.

Table 3. Physical Properties and Antiallergic Activity of 2-[*N*-[(2,3-Disubstituted propoxy)phenyl]carbamoyl]ethyldimethylsulfonium *p*-Toluenesulfonate Derivatives **1a**−**f**, **5a**,**b**, and **6a**−**c**



compd	R_1	R_2	position	formula[a]	mp (°C)[b]	method of prep[c]	yield (%)	PCA inhibition (%)[d] 20[e]	50[e]
1a	CH_2CH_3	H	4	$C_{23}H_{33}NO_7S_2$	86−87	C	37	28.9 ± 4.5 (6)	35.5 ± 7.4 (7)
1b	CH_3	H	4	$C_{22}H_{31}NO_7S_2$	144−146	D	30	17.7 ± 0.9 (7)	24.8 ± 1.6 (8)
1c	$(CH_2)_2CH_3$	H	4	$C_{24}H_{35}NO_7S_2$	oil	C	21	16.3 ± 1.1 (7)	13.8 ± 1.2 (6)
1d	$(CH_2)_3CH_3$	H	4	$C_{25}H_{37}NO_7S_2$	oil	C	35	7.9 ± 0.7 (7)	4.4 ± 0.4 (6)
1e	C_6H_{11}	H	4	$C_{27}H_{39}NO_7S_2$	oil	C	29	10.2 ± 0.2 (7)	−7.4 ± 0.6 (7)
1f	C_6H_5	H	4	$C_{27}H_{33}NO_7S_2$	132−133	D	13	14.4 ± 1.2 (7)	4.6 ± 0.3 (7)
5a	CH_3	CH_3	4	$C_{23}H_{33}NO_7S_2$	88−90	E	33	17.9 ± 1.2 (7)	10.5 ± 1.0 (8)
5b	CH_2CH_3	CH_2CH_3	4	$C_{25}H_{37}NO_7S_2$	107−108	E	33	0.1 ± 0.1 (7)	5.1 ± 0.3 (6)
6a	CH_2CH_3	$COCH_3$	4	$C_{25}H_{35}NO_8S_2$	89−91	F	58	35.1 ± 2.7 (6)	30.2 ± 3.4 (7)
6b	CH_2CH_3	$COCH_3$	2	$C_{25}H_{35}NO_8S_2$	oil	F	45	−2.0 ± 0.1 (7)	20.0 ± 1.6 (7)
6c	CH_2CH_3	$COCH_3$	3	$C_{25}H_{35}NO_8S_2$	oil	F	48	18.2 ± 1.0 (7)	17.7 ± 1.4 (7)

[a−d] See corresponding footnotes of Table 1. [e] Dose (mg/kg, po).

tosyl CH_3), 1.10 (3H, t, J = 7.0 Hz, OCH_2CH_3). Anal. ($C_{23}H_{33}NO_7S_2$) C, H, N.

Method D. Synthesis of (±)-2-[*N*-[4-(3-Methoxy-2-hydroxypropoxy)phenyl]carbamoyl]ethyldimethylsulfonium *p*-Toluenesulfonate (1b). A mixture of *p*-nitrophenol (50 g, 0.36 mol), glycidyl methyl ether (**18b**) (34.8 g, 0.40 mol), and pyridine (3 drops) was stirred for 6 h at 90 °C. The reaction mixture was extracted with $CHCl_3$ (500 mL). The extracts were washed successively with 2 N NaOH and water, dried ($MgSO_4$), and concentrated to give 57.0 g of the nitro compound (**15b**) (bp 182−185 °C/3−4 mmHg). A solution of the nitro compound (**15b**) (57.0 g, 0.25 mol) in EtOH (250 mL) along with 10% Pd−C was hydrogenated at room temperature until 1 equiv of hydrogen had been used (8 h). The solution was filtered, and the filtrate was concentrated under reduced pressure to give 47.5 g of the aniline compound (**16b**). 3-(Methylthio)propionyl chloride (33.4 g, 0.24 mol) was added dropwise to a solution of the aniline compound (**16b**) (47.5 g, 0.24 mol) and triethylamine (35.8 g, 0.36 mol) in CH_2Cl_2 (350 mL) below 10 °C. The mixture was stirred for 2 h at room temperature and then filtered. The filtrate was washed successively with 1 N HCl (150 mL), saturated $NaHCO_3$ (150 mL), and water (150 mL). The CH_2Cl_2 layer was separated, dried ($MgSO_4$), and evaporated. The residue was dissolved in CH_2Cl_2 (50 mL), and methyl *p*-toluenesulfonate (43.9 g, 0.24 mol) was added to the solution. The mixture was stirred for 5 days at room temperature, and then ether (500 mL) was added. A crystallized solid was collected by filtration and was recrystallized from ethanol−ether to give 58.3 g (30%) of **1b**: mp 144−146 °C; NMR (DMSO-d_6) δ 10.13 (1H, s, NH), 7.50

Table 4. LD_{50} (ip) in Mice of Dimethyl-2-[*N*-(4-substituted propoxyphenyl)carbamoyl]ethylsulfonium *p*-Toluenesulfonates

compd	LD_{50} (mg/kg)[a]
4j	97
4k	1040
4l	324
4m	495

[a] The value of LD_{50} was determined in male ddY mice ($n = 5$) by the up−down method described in ref 13.

Table 5. Calculated Lipophilicity (π_{calcd}) of Substituted Propoxy Groups

compd	propoxy group	π_{calcd}[a]
4k	$OCH_2CH(OH)CH_2OH$	−1.78
1a	$OCH_2CH(OH)CH_2OCH_2CH_3$	−0.63
1b	$OCH_2CH(OH)CH_2OCH_3$	−1.16
1c	$OCH_2CH(OH)CH_2O(CH_2)_2CH_3$	−0.10
1d	$OCH_2CH(OH)CH_2O(CH_2)_3CH_3$	0.43
1e	$OCH_2CH(OH)CH_2OC_6H_{11}$	0.87
1f	$OCH_2CH(OH)CH_2OC_6H_5$	0.88
5a	$OCH_2CH(OCH_3)CH_2OCH_3$	0.49
5b	$OCH_2CH(OCH_2CH_3)CH_2OCH_2CH_3$	0.57

[a] Calculated by CLOGP.

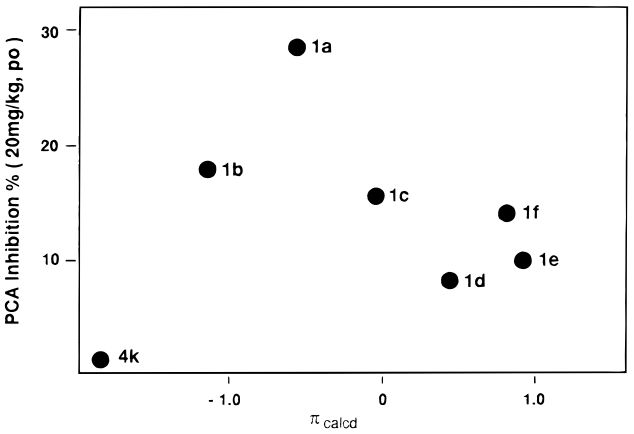


Figure 1. Plot of p_{calcd} versus PCA inhibition (%) (20 mg/kg, po).

(2H, d, $J = 9.0$ Hz, aromatic $H_{2,6}$), 7.49 (2H, d, $J = 7.8$ Hz, tosyl $H_{3,5}$), 7.12 (2H, d, $J = 7.8$ Hz, tosyl $H_{2,6}$), 6.89 (2H, d, $J = 9.0$ Hz, aromatic $H_{3,5}$), 3.88 (3H, broad, OCH_2CH), 3.74 (1H, broad, O*H*), 3.52 (2H, t, $J = 6.2$ Hz, S^+CH_2), 3.40 (2H, broad, CH_2OCH_3), 3.27 (3H, s, OCH_3), 2.93 (6H, s, $(CH_3)_2S^+$), 2.93 (2H, t, $J = 6.2$ Hz, $S^+CH_2CH_2$), 2.29 (3H, s, tosyl CH_3). Anal. ($C_{22}H_{31}NO_7S_2$) C, H, N.

Method E. Synthesis of (±)-2-[*N*-[4-(2,3-Dimethoxypropoxy)phenyl]carbamoyl]ethyldimethylsulfonium *p*-Toluenesulfonate (5a). To a solution of 4-(2-hydroxy-3-methoxypropoxy)nitrobenzene (**15b**) (45.4 g, 0.20 mol) in dry DMF (100 mL) was added NaH (5.5 g, 0.23 mol), and the reaction mixture was stirred for 2 h at room temperature. To the mixture was added methyl iodide (28.4 g, 0.20 mol), and the mixture stirred for 12 h at room temperature. The reaction mixture was concentrated and extracted with ether (200 mL). The extracts were washed with water, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography on silica gel with $CHCl_3$−ether (4:1) as an eluent. The appropriate fractions were combined and concentrated to give 34.0 g of 4-(2,3-dimethoxypropoxy)nitrobenzene (**19a**). A solution of the nitro compound (**19a**) (34.0 g, 0.14 mol) in EtOH (100 mL) along with 1.0 g of 10% Pd/C was hydrogenated at room temperature until 1 equiv of hydrogen had been used (8 h). The solution was filtered, and the filtrate was concentrated under reduced pressure to give 28.0 g of the aniline compound (**20a**). 3-(Methylthio)propionyl chloride (18.4 g, 0.13 mol) was added dropwise to a solution of the aniline compound (**20a**) (28.0 g, 0.13 mol) and triethylamine (16.2 g, 0.16 mol) in CH_2Cl_2 (150 mL) below 10 °C. The mixture was stirred for 3 h at room temperature and then filtered. The filtrate was washed successively with 1 N HCl (150 mL), a saturated $NaHCO_3$ solution (150 mL), and water (150 mL). The CH_2Cl_2 layer was separated, dried ($MgSO_4$), and evaporated. The residue was dissolved in CH_2Cl_2 (50 mL), and methyl *p*-toluenesulfonate (24.2 g, 0.13 mol) was added to the solution. The mixture was stirred for 5 days at room temperature, and then ether (500 mL) was added. A crystallized solid was collected by filtration and recrystallized from ethanol−ether to give 33.2 g (33.2%) of **5b**: mp 88−90 °C; NMR (DMSO-d_6) δ 10.16 (1H, s, N*H*), 7.51 (2H, d, $J = 9.0$ Hz, aromatic $H_{2,6}$), 7.50 (2H, d, $J = 7.8$ Hz, tosyl $H_{3,5}$), 7.12 (2H, d, $J = 7.8$ Hz, tosyl $H_{2,6}$), 6.90 (2H, d, $J = 9.0$ Hz, aromatic $H_{3,5}$), 3.96 (2H, broad, OCH_2CH), 3.52 (2H, t, $J = 6.4$ Hz, S^+CH_2), 3.48 (2H, broad, CH_2OCH_3), 3.47 (1H, m, OCH_2CH), 3.36 (3H, s, OCH_3), 3.27 (3H, s, OCH_3), 2.93 (6H, s, $(CH_3)_2S^+$), 2.93 (2H, t, $J = 6.4$ Hz, $S^+CH_2CH_2$), 2.28 (3H, s, tosyl CH_3). Anal. ($C_{23}H_{33}NO_7S_2$) C, H, N.

Method F. Synthesis of (±)-2-[*N*-[4-(3-Ethoxy-2-acetoxypropoxy)phenyl]carbamoyl]ethyldimethylsulfonium *p*-Toluenesulfonate (6a). Acetyl chloride (8.27 g, 0.10 mol) was added dropwise to a solution of 2-[[4-(3-ethoxy-2-hydroxypropoxy)phenyl]carbamoyl]ethyl methyl sulfide (**17a**) (30.0 g, 0.10 mol) and pyridine (0.13 mol) in benzene (300 mL) below 10 °C. The mixture was stirred for 3 h at room temperature. The reaction mixture was filtered, and the filtrate was washed with 3 N HCl (50 mL) twice and water, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography on silica gel with ether as an eluent. The appropriate fractions were combined and concentrated. The residue was recrystallized from petroleum ether−ether to give 4-[[(2-acetoxy-3-ethoxypropoxy)phenyl]carbamoyl]ethyl methyl sulfide (**22c**) (26.0 g, 76.4%). A mixture of **22c** (26.0 g, 0.07 mol) and methyl *p*-toluenesulfonate (54.0 g, 0.29 mol) was stirred for 5 days at room temperature, and ether (200 mL) was added. A crystallized solid was collected by filtration and recrystallized from ethanol−ether to give 23.0 g (58.1%) of **6a**: mp 89−91 °C; NMR (DMSO-d_6) δ 10.13 (1H, s, N*H*), 7.52 (2H, d, $J = 9.0$ Hz, aromatic $H_{2,6}$), 7.51 (2H, d, $J = 7.8$ Hz, tosyl $H_{3,5}$), 7.12 (2H, d, $J = 7.8$ Hz, tosyl $H_{2,6}$), 6.91 (2H, d, $J = 9.0$ Hz, aromatic $H_{3,5}$), 5.18 (1H, m, OCH_2CH), 4.08 (2H, broad, OCH_2CH), 3.59 (2H, broad, CH_2O), 3.52 (2H, d, $J = 6.4$ Hz, S^+CH_2), 3.45 (2H, q, $J = 7.1$ Hz, OCH_2CH_3), 2.94 (6H, s, $(CH_3)_2S^+$), 2.92 (2H, t, $J = 6.4$ Hz, $S^+CH_2CH_2$), 2.28 (3H, s, tosyl CH_3), 2.03 (3H, s, $COCH_3$), 1.02 (3H, t, $J = 7.1$ Hz, OCH_2CH_3). Anal. ($C_{25}H_{35}NO_8S_2$) C, H, N.

Homologous Passive Cutaneous Anaphylaxis (PCA) in Rat. Antiserum containing homocytotropic antibody was obtained from rats that had been immunized with 2,4-dinitrophenyl-coupled ascaris (DNP-As) mixed with killed *Bordetella pertussis* according to Tada et al.[21] The antibody titer of this serum (rat anti-DNP-As serum) was about 1:256 as estimated by the 48-h PCA. The antiserum diluted 20-fold with 0.9% saline was injected intradermally in 0.1-mL dose into three sites on the shaved backs of normal rats. The same dose of physiologic saline was similarly injected into the other side. After 48 h, the animals were given 1.0 mL of 0.25% Evans blue solution containing 2.0 mg of antigen intravenously. Thirty minutes later, the animals were sacrificed by exsanguination, and the skins were removed to measure the PCA bluing lesion. The amount of the dye was then estimated colorimetrically after extraction by the method of Harada et al.[22]

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Supporting Information Available: Physical property data and ^1H NMR spectral data for **1a**−**f**, **2**, **3**, **4a**−**m**, **5a**,**b**, and **6a**−**c** (8 pages). Ordering information is given on any current masthead page.

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