eral times with ether. The combined extracts were dried (Na_2SO_4) and filtered. The solvent was removed from the filtrate, leaving an oily residue which was treated with ethereal HCl. The solid which separated was taken up in pentane–anhydrous ethanol (2:1) and upon cooling, 0.90 g (72%) of product separated: mp 187–189°; nmr ($CDCl_3$) δ 2.73 [s, 6 H, $N(CH_3)_2$], 2.83–3.40 (broadened m, 8 H, aliphatic H), 3.67 and 3.90 (2 s, 6 H, OCH_3), 6.70–8.17 (m, 4 H, ArH), 8.20–8.47 (m, 1 H, ArH). *Anal.* ($C_{20}H_{26}ClNO_2$) C, H, N.

***dl*-1-Vinyl-3,4-dimethoxy-10-dimethylamino-9,10-dihydrophenanthrene Hydrochloride (11a).** Compound **5** (1.34 g, 0.0032 mol) was refluxed for 6 hr in a solution of 0.955 g (0.024 g-atom) of K in freshly distilled triethylcarbinol (Eastman, white label). The cooled mixture was treated with excess 10% HCl and was extracted with ether. The aqueous layer was treated with excess $NaHCO_3$ and the resulting mixture was extracted several times with ether. The pooled extracts were dried (Na_2SO_4) and filtered, and the ether was removed from the filtrate under reduced pressure. The residual oil was chromatographed on silica gel and eluted with ether. Evaporation of the eluate afforded an oily residue which was treated with ethereal HCl to give 0.40 g (53%) of a solid: mp 182–184°; nmr ($CDCl_3$) δ 2.02 [s, 6 H, $N(CH_3)_2$], 3.62 and 3.88 (2 s, 6 H, OCH_3), 5.15–5.85 (m, 2 H, vinyl H), 7.00–8.00 (m, 5 H, ArH + vinyl H), 8.28–8.55 (m, 1 H, ArH). *Anal.* ($C_{20}H_{24}ClNO_2$) C, H, N.

***(R)*-1,2-Dimethoxyaporphine (Nuciferine, 9).** This was isolated from *Nelumbo lutea* (yellow water lily, collected from a lily pond in the Amana Colonies in eastern Iowa, by an isolation procedure reported by Kupchan, *et al.*[13] nmr ($CDCl_3$) δ 2.53 (s, 3 H, NCH_3), 3.67 and 3.86 (s, 6 H, OCH_3), 6.63 (s, 1 H, ArH), 7.17–7.37 (m, 3 H, ArH), 8.27–8.50 (m, 1 H, ArH).

***(R)*-1-Vinyl-3,4-dimethoxy-10-dimethylamino-9,10-dihydrophenanthrene Hydrochloride (11a).** *(R)*-**5**, prepared from *(R)*-**9** as described for (±)-**5**, was treated as described for *dl*-**11a**: $[\alpha]^{32}D$ −97.70° (*c* 0.174, ethanol).

***dl*-1,2-Dihydroxyaporphine Hydrobromide (*dl*-6).** Compound *dl*-**9** (1.0 g, 0.003 mol) was heated at 110–125° under N_2 with 16 ml of 48% HBr for 4 hr. After removal of volatiles, the solid residue was recrystallized from ethanol to yield 0.60 g (57%) of product, mp 226–228° (Neumeyer, *et al.*,[4] characterized this base as its HI salt). *Anal.* ($C_{17}H_{18}BrNO_2$) C, H, N.

***(R)*-1,2-Dihydroxyaporphine Hydrobromide [(*R*)-6].** This was prepared from *(R)*-**9** as described for *dl*-**6**: $[\alpha]^{32}D$ −272° (*c* 0.500, water).

1-(2-Dimethylaminoethyl)-3,4-dihydroxy-9,10-dihydrophenanthrene Hydrobromide (12b). Compound **12a** (0.60 g, 0.002 mol) was treated as described for *dl*-**6**, and the crude product was recrystallized from ethanol–ether (2:1) to give 0.45 g (72%) of product, mp 180–183°. *Anal.* ($C_{18}H_{22}BrNO_2$) C, H, N.

1-(2-Dimethylaminoethyl)-3,4-dihydroxyphenanthrene Hydrobromide (10b). Compound **10a** (0.60 g, 0.002 mol) was treated as described for *dl*-**6**, and the crude product was recrystallized from ethanol to give 0.34 g (44%) of product, mp 258° dec. *Anal.* ($C_{18}H_{20}BrNO_2$) C, H, N.

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Antagonism of Slow Reacting Substance in Anaphylaxis (SRS-A) and Other Spasmogens on the Guinea Pig Tracheal Chain by Hydratropic Acids and Their Effects on Anaphylaxis

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The anaphylactic reaction in the guinea pig is accompanied by the release of histamine,[1,2] slow reacting substance in anaphylaxis (SRS-A),[3-7] bradykinin,[8] and prostaglandins (PG) E_2 and $F_{2\alpha}$[9] and possibly other humoral factors which may or may not contribute to the pathological effect.[10,11] There is evidence that at least histamine, SRS-A, and bradykinin contribute to the anaphylactic bronchospasm in the guinea pig[7,8,12] and that the last two mediators but not histamine are involved in anaphylaxis in cattle.[13] Proof of participation of specific mediators in human asthma is much more difficult but it has been shown that human lung is exquisitely sensitive to SRS-A[14] responding with a prolonged, intense contraction and that SRS-A as well as histamine is released from sensitized human lung when challenged.[15,16]

While the pharmacological properties of histamine and bradykinin are well known, those of SRS-A may be less generally appreciated. SRS-A was first identified as a mediator in anaphylaxis in 1940 by Kellaway and Trethewie[3] but its structure is still unknown. It may be that the SRS released by 48/80 and the SRS-A released during various anaphylactic procedures are not identical but pharmacologically they are very similar.[17,18] Strandberg and Uvnas[19] have shown that SRS from cat paw is a carboxylic acid with hydroxyl groups and one or more double bonds but is probably not a prostaglandin.

SRS-A causes a slowly developing contraction in a limited number of smooth muscles including guinea pig and human bronchial muscle and guinea pig ileum.[20] Antihistamines abolish the bronchoconstrictor response to histamine in the guinea pig but have no effect on that induced by SRS-A or bradykinin. On the other hand, aspirin, sodium flufenamate, sodium mefenamate, and certain other antipyretics antagonize the response to both kinins and SRS-A without affecting the response to histamine.[21]

Antihistamines are of relatively little use in human asthma although they offer limited benefit when administered prophylactically especially in mild cases. They are also of little benefit in human systemic anaphylaxis. It is possible that other autacoids are more important than histamine as mediators in this reaction. Antipyretic

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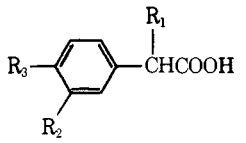
Table I. Antagonism of SRS-A^{rat} by Hydratropic Acid Analogs



Compd no.	Generic name or other identification	R_1	R_2	R_3	No. of expt, n	Potency estimate[a]	Confidence interval
I	Flurbiprofen[b]	CH_3	F	C_6H_5	20	1	
II	(+) isomer of I				4	7.9	1.3–49.0
III	(−) isomer of I				3	0.009	0.001–0.078
IV		CH_3	H	C_6H_5	1	0.29	0.007–11.3
V		CH_3	Cl	C_6H_{11}	1	4.00	0.30–53.0
VI	Fluprofen	CH_3	H	2-F-C_6H_4	1	5.0	0.13–195.0
VII	Ibuprofen	CH_3	H	$(CH_3)_2CHCH_2$	4	0.14	0.022–0.85
VIII		$CH_3CH{=}CHCH_2$	H	C_6H_{11}	7	0.1–0.5	
IX		$CH_2{=}$	H	C_6H_{11}	7	0.01–0.02	
X	Ibufenac	H	H	$(CH_3)_2CHCH_2$	2	No effect at 10–50 μg	
XI	Fenoprofen	CH_3	C_6H_5O	H	6	0.1–0.2	

[a]For compounds I–VII the n relative potency estimates for each compound were transformed to logarithms. The means were obtained along with a pooled estimate of the standard deviation based on 16 degrees of freedom. The 95% confidence intervals were computed. The calculated means and end points of the confidence intervals were transformed back to potency values and were entered in the table. For compounds VIII–XI the potency is based on relative effects of single doses of the drug compared with either the same dose of compound I or of a dose of compound I producing a similar degree of contraction. Since these drugs had low activity compared with compound I no statistical analysis was calculated. Similar experiments were also carried out for compounds I–VII, and results were comparable to potency estimates taken from dose–response curves. The statistical analysis of results of compounds I–VII was done by Dr. Mark Johnson of The Upjohn Co. [b]Flufenasil was about 0.1 as active as compound I and phenylbutazone was 0.01–0.1 as active.

drugs, which as mentioned above can antagonize SRS-A and bradykinin, have been claimed to have a beneficial effect in asthma especially in certain patients.[22,23]

This paper is concerned with the antagonism of SRS-A on the guinea pig tracheal chain by a group of hydratropic acid analogs and the action of a few of these in guinea pig anaphylaxis.

Experimental Section

The hydratropic acid analogs were obtained from The Boots Co. Ltd., flufenisal from Merck Sharp & Dohme, and phenylbutazone from Geigy.

Tracheal Chain Assay. The tracheal chain was prepared by the method of Castillo and DeBeer.[24] The guinea pig trachea was sectioned into rings of approximately equal width; the rings were opened on the ventral side of the trachea (opposite the smooth muscle bundle) and were connected by means of short loops of silk thread. A chain usually consisted of five rings. Isotonic contractions were recorded on a Grass polygraph using linear motion transducers (Phipps & Bird, Model ST-2).

SRS-A was prepared by the method of Rapp[25] as modified by Orange, *et al.*[26]

Upjohn pathogen-free male Sprague-Dawley rats were used both for preparation of hyperimmune serum and for peritoneal release of SRS-A by passive anaphylaxis. The perfusate containing the SRS-A was heated at 100° for 5 min to destroy any enzyme activity and was stored in 1-ml aliquots at −60°. The amount of SRS-A required to cause optimum contraction of the tracheal chain in a bath volume of 3 ml was usually 0.01–0.02 ml.

Compounds were dissolved directly in Tyrode's solution or in ethyl alcohol and diluted with Tyrode's solution. The final concentration of alcohol in the muscle bath was never over 0.1%.

The compounds were added to the muscle bath when maximum contraction by SRS-A was reached and the degree of reversal of contraction or relaxation was measured. It was more difficult to obtain consistent results when reversal of contraction was measured instead of prevention (addition of drug before agonist). However, it was thought that reversal might correlate better with clinical effectiveness.

In a few experiments histamine (0.032–0.1 μg/3 ml bath), bradykinin (0.1–0.32 μg/3 ml), arachidonic acid (1.0–2.25 μg/3 ml), linolenic acid (2.25–4.45 μg/3 ml), or $PGF_{2\alpha}$ (0.05–1.0 μg/3 ml) was used as agonist. Concentrations of these agonists were chosen to cause contractions of a degree similar to those produced by 0.01–0.02 ml of SRS-A and which were within the range measurable with the equipment described above. Thus, effectiveness of compounds in reversing the same or a similar degree of contraction was assumed to be comparable.

Guinea Pig Anaphylaxis. Male guinea pigs weighing 200–300 g were sensitized by the injection of 1 ml sc and 1 ml ip of a solution containing egg albumin, 100 mg/ml in 0.9% NaCl. They were challenged at the times after sensitization indicated in the tables by subjecting them to an aerosol containing 1.0% egg albumin delivered through a DeVilbiss atomizer at a pressure of 5.0 lb/in.^{2}. The chamber in which the spraying was done was an inverted battery jar of about 12-l. capacity placed on a platform in which holes were bored to accommodate the atomizer and a delivery tube for the antigen solution. Compounds were administered ip 30 min before challenge.

The time for collapse of the guinea pig was measured with a stop watch. If the guinea pig had not collapsed in 6 min it was considered to be protected and was removed from the jar. Those which did collapse were removed immediately and treated with oxygen until dyspnea was reduced.

Histamine Shock. Normal guinea pigs were exposed to an aerosol containing 0.125% histamine delivered through a DeVilbiss atomizer at a pressure of 5.0 lb/in.^{2}. The procedure was the same as that described above for guinea pig anaphylaxis.

Results and Discussion

Table I shows the relative ability of compounds to relax the tracheal chain stimulated with SRS-A^{rat}. Compound I was arbitrarily assigned a value of 1. Potency estimates for compounds II–VII and for flufenasil and phenylbutazone were taken from dose–response curves as described in the caption to Table I. Other results were from paired single dose experiments where either the effects of the same dose were compared or doses causing the same degree of reversal of contraction were compared. Compounds I, II, IV, V, and VI were the most active of those tested. Compound II, the (+) isomer of I, was unexpectedly many fold more active than the racemic mixture (compound I). In the dose–response estimate it was eightfold more active; in single dose comparisons it was an average of 30-fold more active (range 1–100, $n = 9$, $p < 0.01$). Since it was

Table II. Comparison of Hydratropic Acid Analogs as Antagonists of Various Agonists on the Guinea Pig Tracheal Chain

Expt[a]	Agonist	Concn of agonist, μg/3 ml	Antagonist compd	Concn of antagonist, μg/3 ml	% reversal
1	SRS-A		VI	0.001	100
			VI	0.00056	31
			I	0.001	27
2	SRS-A		I	0.0032	100
			I	0.0018	0
			VI	0.00056	40
	Histamine	0.01	I	0.112	19
	Histamine	0.01	VI	0.592	0
3	Histamine	0.01	I	0.064	7
	Histamine	0.01	VI	0.164	0
	Arachidonic acid	1.2	I	0.018	26
	Arachidonic acid	1.2	I	1.0	100
4	Arachidonic acid	1.0	I	0.18	100
	Arachidonic acid	1.0	I	0.032	48
5	Arachidonic acid	1.0	I	0.01	16
	Arachidonic acid	1.0	VII	0.1	39
6	Arachidonic acid	1.0	I	0.01	52
	Arachidonic acid	1.0	VII	0.056	54
7	Linolenic acid	4.45	I	0.056	45
	Linolenic acid	4.45	I	0.32	100
	Linolenic acid	4.45	I	0.1	100
8	$PGF_{2\alpha}$	0.01	I	0.0056	100
		0.01	I	0.001	29
9	$PGF_{2\alpha}$	0.01	I	0.0032	100
		0.01	I	0.00056	24
10	$PGF_{2\alpha}$	0.05	I	0.0018	70
		0.05	I	0.00056	0
11	SRS-A	0.01 ml	I	0.0056	100
	$PGF_{2\alpha}$	0.1	I	0.0056	70
12	Bradykinin	0.32	I	0.018	81
		0.32	VI	0.032	85
13	Bradykinin	0.32	VI	0.1	100
		0.32	VI	0.032	85
14	Bradykinin	0.32	VI	0.032	66
		0.32	I	0.018	81

[a] Each experiment was performed on the same tracheal chain preparation (results of single experiments).

more than twice as active it was assumed that, in the racemate, the (−) isomer (compound III) was inhibiting the effect of the (+) isomer. This indeed proved to be the case, as when an equal amount of compound III was added to the muscle bath simultaneously with an amount of compound II which alone caused 100% reversal, the result was only 5–10% reversal.

Halogen substitution on R_2 had little effect on activity (compare compound I with compound IV). Saturation of the ring on R_3 had little effect (compare compound I with compound V). Halogen substitution on the ring on R_3 increased activity (compare compound VI with compound IV). Changing the phenyl group to an aliphatic group at R_3 decreased activity (compare compound VII with compound IV). Substitution of a CH_3 group on R_1 resulted in better activity than substitution with other groups (compare compounds IV and V with VIII and IX).

While compound I antagonized the effect of SRS-A on the tracheal chain, it had little or no effect on the stimulating action of SRS-A on the guinea pig ileum. Likewise, while it antagonized the effect of bradykinin on the tracheal chain it did not affect the increase in vascular permeability caused by bradykinin in the rat skin. These compounds thus appear to indicate that receptor sites for SRS-A and bradykinin are different in different organs.

The compounds most active against SRS-A were effective in concentrations of 1–10 ng/ml (Tables I and II). The concentration of compound I necessary to produce 50% inhibition was 1–3 ng/ml. Table II shows the antagonizing effects of compound I (flurbiprofen), compound VI (fluprofen), and compound VII (ibuprofen) against various agonists. Results for each experiment were obtained on the same tracheal chain with similar degrees of contraction for each agonist. While SRS-A and $PGF_{2\alpha}$ were antagonized by 0.5–5 ng of compound, concentrations required to antagonize arachidonic and linolenic acids were 5–10 times higher.

Compounds which antagonized SRS-A also antagonized bradykinin but the concentrations required were usually higher. Histamine was only slightly antagonized by concentrations of drug 50–100 times those which were effective against SRS-A.

Jaques[27] has shown that arachidonic acid causes slow contractions of the guinea pig ileum which are antagonized by analgesics and local anesthetics.

Dakhil and Vogt[28] postulate that linoleic, linolenic, and arachidonic acids have no gut-contracting action until they are oxidized. They conclude that the intestine-stimulating effect is due to formation of hydroperoxides which is independent of the formation of prostaglandin.

Table III. Effects of Several Antagonists on Guinea Pig Anaphylaxis Induced at Various Times after Sensitization

Expt no.	Time after sensitization, weeks	Compd	Dose, mg/kg ip	No. protected/ total no. tested
1	4	I (flurbiprofen)	0.5	0/3
		I	1.0	4/5
		VII (ibuprofen)	2.0	0/2
		Phenylbutazone	3.5	0/4
			23.0	2/2
2	8	I (flurbiprofen)	1	0/3
			2	0/1
			3	0/1
			4	0/1
			5	0/1
		Mepyramine	0.5	1/1
			1	2/2
3	3	I (flurbiprofen)	1	3/6[a]
			2	5/5
		Mepyramine	0.25	1/1
			0.5	3/3
			1	1/1
4	5	I (flurbiprofen)	1	0/4
		Mepyramine	0.25	4/4
5	4	I (flurbiprofen)	6	7/8 ($p < 0.001$)
			4	2/2
			3	2/4
			2	0/2
			1.5	2/5
		II [(+) isomer of I]	6	5/7
			3	4/4
			1.5	3/3
			0.75	4/5
		III [(−) isomer of I]	12	2/2
			6	0/4
		VI (fluprofen)	2	2/2
			1.5	2/3
			1.0	3/3

[a] +2 more partially protected.

Vane[29] has shown that arachidonic acid is metabolized by lung tissue to PGE_2 and $PGF_{2\alpha}$ and that certain anti-inflammatory compounds inhibit this reaction. Since $PGF_{2\alpha}$ stimulates tracheal muscle to contract it is possible that the effect of certain hydratropic acid derivatives in antagonizing arachidonic acid lies in their inhibition of formation of $PGF_{2\alpha}$. As mentioned above the concentrations required to antagonize the effect of arachidonic acid (or perhaps inhibit its metabolism) are very much higher than those required to antagonize effects of SRS-A or $PGF_{2\alpha}$ on the target organ. The similarity in the concentrations of antagonist required to reverse effects of SRS-A and $PGF_{2\alpha}$ may indicate a similarity in structure of these agonists.

In vivo compound I was active in protecting sensitized guinea pigs against anaphylactic shock when they were challenged 3-4 weeks after sensitization but was ineffective when challenge was 5-8 weeks after sensitization (Table III). This would indicate that SRS-A and/or bradykinin may be involved early but not later in the development of the immune response. A similar phenomenon was observed by Dawson, *et al.*,[30] who found that a combination of ascorbic acid with mepyramine protected rats against anaphylactic shock at 10 days after sensitization but not at 20 days. They proposed that bradykinin was the mediator in the early phase but not in the later phase. In our experiments mepyramine was effective both early and later after sensitization.

Table IV. Effect of Compound I (Flurbiprofen) on Guinea Pigs Exposed to a Histamine Aerosol

Treatment	Dose, mg/kg ip	No. of guinea pigs	Av time for collapse, sec (range)	p value
Control		4	66 (60–75)	
Compound I (flurbiprofen)	1	3	205 (200–215)	<0.001
Control		2	60 (55, 65)	
Mepyramine	0.5	2	>360 (no collapse)	

When guinea pigs were exposed to a histamine aerosol (Table IV) compound I prolonged the time of exposure before collapse but did not confer complete protection as was the case with mepyramine.

When tested 4 weeks after guinea pigs were sensitized, the antianaphylactic effects of compounds I (flurbiprofen), II [(+) isomer of I], and III [(−) isomer of I] correlated well with *in vitro* activity against SRS-A on the tracheal chain. Compound II was the most active, compound III was the least. *In vivo* compound II showed a greater than twofold effect over compound I when tested in guinea pig anaphylaxis (Table III, experiment 5). At 80% protection compound II was five- to sevenfold more active than I. The *in vitro* and *in vivo* effects of these three drugs also correlated when histamine was the agonist, little effect being produced either in the animal or on the tracheal chain.

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Antifertility Effects of Chlorine-Substituted Dioxolanes, Dithiolanes, and Dithianes in Male Rats

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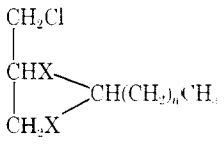
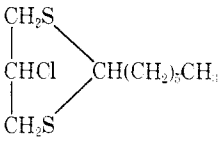
Interest in male antifertility agents was renewed by the disclosure that 1-chloro-2,3-propanediol (1) exerted a posttesticular antifertility effect in male rats.[1,2] Subsequent findings indicated similar effectiveness in monkeys,[3] guinea pigs,[4] rams,[5] and swine.[6] Recently, Banik, *et al.*,[7] have shown that 4-(chloromethyl)-2-methyl-2-pentyl-1,3-dioxolane induced sterility in adult male rats with no interference with mating nor any apparent irreversible effects. This report describes the synthesis and biological activity of two acetals **2** and **3** of 1-chloro-2,3-propanediol and two thioacetals **4** and **5** of 1-chloro- and 2-chlorodimercaptopropane.

The compounds were prepared by reaction of the glycol or dithiol,[8] *p*-TsOH, and the corresponding aldehyde in benzene. We were able to isolate 2-pentyl-2-nonenal, presumably formed *via* aldol condensation of heptanal, during the preparation of **5**.



2, $n = 5$; X = O
3, $n = 16$; X = O
4, $n = 5$; X = S



5

Biological Activity. The antifertility activity was evaluated in adult male Wistar and Sprague-Dawley rats (250–300 g). The compounds were dissolved or suspended in propylene glycol and administered either orally or subcutaneously for 14 consecutive days with controls receiving an equal quantity of the vehicle only. On the last day of treatment, each male was individually cohabited with a proestrus female. Vaginal washings were checked the following morning for evidence of positive mating and those males failing to mate were given another opportunity the following night. After the mating, all males were autopsied for examination of the testes, epididymides, and accessory sex organs. All females were autopsied and examined for pregnancy (implantation sites) 14 days after cohabitation.

Compounds **1** and **2** were both effective antifertility agents when given orally or subcutaneously to male rats (Table I). However, **2** appeared to have some therapeutic advantage since its minimum effective oral antifertility dose was similar to that for **1** and no apparent toxic side effects were observed at doses as high as 500 mg/kg whereas compound **1** caused extensive weight loss and deaths at 100 mg/kg. The LD_{50} values (mouse, ip, 48 hr) for compounds **1** and **2** were 73 and >1000 mg/kg, respectively. The longer chain acetal **3** was active orally and subcutaneously but at higher dose levels. Thioacetals **4** and **5** did not exhibit any antifertility activity at the doses tested.

Epididymal cysts and antispermatogenic effects were observed in a few of the rats which received the higher doses of compounds **1** and **2**. This has been previously reported[2,4,7] and appears to occur only in rats. No epididymal cysts or abnormal effects on the testes were observed in males receiving compounds **3**, **4**, and **5**. The sex accessory organs were normal in all animals which is consistent with other reports[2,7] that compounds in this series do not cause androgenic or antiandrogenic effects.

Our findings substantiate the previously reported male antifertility activity of compound **1** and 2-substituted-4-(chloromethyl)-1,3-dioxolanes. We have also found that dithiolane **4** and dithiane **5** are devoid of biological activity at doses comparable to their oxygen analogs.

Experimental Section

Melting points were determined on a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Analytical results are within ±0.4% of the calculated values. Ir spectra were recorded on a Beckman IR-8 as neat samples and nmr spectra were determined on a Varian A-60 spectrometer using $CDCl_3$ as solvent with trimethylsilane as internal standard. The ir and nmr data of all compounds were consistent with the proposed structures.

2-Heptadecyl-4-chloromethyl-1,3-dioxolane (3). A solution of 5.5 g (0.05 mol) of 1-chloro-2,3-propanediol, 13.9 g (0.05 mol) of octadecyl aldehyde (prepared from the bisulfite),[9] and 100 ml of benzene was refluxed in a Dean Stark apparatus for 15 min. Then 200 mg of *p*-TsOH was added and the solution azeotroped for an additional 4 hr. The solution was washed with 10% aqueous Na_2CO_3 and H_2O, dried ($MgSO_4$), and concentrated. Column chromatography of the residue on Silic AR, CC-7, eluting with ethyl acetate–hexane (1:3) and distillation of the crude product gave **3** (9.8 g, 54%): bp 144–150° (0.001 mm). *Anal.* ($C_{21}H_{41}ClO_2$) C, H, Cl.

2-Hexyl-4-chloromethyl-1,3-dioxolane (2). This compound was prepared in the same manner as **3** and afforded **2**: bp 82° (0.4 mm) [lit.[10] 123° (14 mm)].

2-Hexyl-4-chloromethyl-1,3-dithiolane (4). To an azeotropically distilled mixture of 14.4 g (0.1 mol) of heptanal, 100 ml of benzene, and a catalytic amount of *p*-TsOH was added 14.5 ml (0.1 mol) of 1-chloro-2,3-dimercaptopropane.[11] When the theoretical amount of water was collected the solution was washed with saturated aqueous K_2CO_3 and H_2O, dried (K_2CO_3), and concentrated. The residue was purified by an initial distillation (bp 118–121°, 0.1 mm), followed by column chromatography through Silic AR, CC-7, using ethyl acetate–hexane (5:95) as the eluent and a final distillation through a short-path distillation apparatus to afford **4**; 3.0 g (12%). *Anal.* ($C_{10}H_{19}ClS_2$) C, H, Cl, S.