dichloride 3. Reaction with sodium methoxide in methanol as before gave the dimethyl ester, mp 144 °C (MeOH). Anal. ($C_8H_{11}N_2O_5P$) C, H, N.

Dimethyl (4-Aminobenzyl)phosphonate (18a). Reaction of freshly distilled benzyl bromide with trimethyl phosphite gave dimethyl benzylphosphonate, which was treated with HNO_3/H_2SO_4 to give the known 4-nitro compound.[10] Hydrogenation (Pd/C) gave the 4-amino derivative (18a), mp 103 °C (benzene–petroleum ether). Anal. ($C_9H_{14}NO_3P$) C, H, N.

Methyl 4-Nitrobenzyl Sulfone (19a). Reaction of benzyl bromide with aqueous sodium sulfite gave sodium benzylsulfonate, which was converted to the sulfonyl chloride with PCl_5 and reduced to the sulfinite with Zn powder. Alkylation with dimethyl sulfate then gave benzyl methyl sulfone, which was converted to the 4-nitro derivative with HNO_3/H_2SO_4.[11]

Dimethyl *N*-(4-Nitrobenzoyl)phosphoramidate (20a). Reaction of 4-nitrobenzamide with PCl_5, followed by treatment with sodium methoxide in methanol, gave a 65% yield of compound **20a**, mp 154–155 °C (lit.[12] mp 153–154 °C).

Dimethyl *N*-[4-(Benzyloxycarboxamido)-3-methoxyphenyl]phosphoramidate (21a). Reaction of benzyl *N*-(4-amino-2-methoxyphenyl)carbamate (**4b**) (10 g, 3.6 mmol) with an excess (2 equiv) of freshly prepared dimethyl phosphorobromidate in pyridine at 0 °C gave, after normal workup, an oil, which was purified by chromatography on silica (CH_2Cl_2-MeOH, 25:1): yield 5.68 g (41%); mp 115 °C (acetone–petroleum ether).

Anal. ($C_{17}H_{21}N_2O_6P$) C, H, N, P.

Antitumor Testing. F1 hybrid (DBA/2J × C57B/J) mice (19–21 g) of either sex were inoculated with 10^6 P-388 murine leukemia cells on day 0. Drugs, normally as solutions but at the highest doses as suspensions (sonicated) in 30% aqueous ethanol, were administered intraperitoneally in a volume of 0.1 mL on days 1, 5, and 9. Average survival times were measured for each group of six mice, and the percentage increase life span was calculated with respect to the control animals (20–30 mice). Control animals survived 11.0 days on average. Drug doses ranged from a toxic level downwards at 0.67-fold intervals. No long-term survivors were recorded.

Cultures of P-388 leukemia cells and L1210 leukemia cells were used to test drug cytotoxicity over a 3-day incubation time. Conditions for cell culture and drug addition were identical with those previously described.[13]

Imidodisulfamides. 2.[1] Substituted 1,2,3,4-Tetrahydroisoquinolinylsulfonic Imides as Antagonists of Slow-Reacting Substance of Anaphylaxis

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As part of a study of the influence of structural modifications of N',N''-bis(aralkyl)imidodisulfamides on their ability to selectively antagonize SRS-A activity, a few conformationally constrained structures were examined. Among these derivatives having a conformationally restricted alkylene side chain, substituted 1,2,3,4-tetrahydroisoquinolinylsulfonic imides produced optimum SRS-A antagonist activity and selectivity. These compounds were tested for antagonism of partially purified SRS-A induced contractions of isolated guinea pig ileum. In this series of tetrahydroisoquinolines, the effect of aromatic ring substitution, as well as substitution and variation of the size of the heterocyclic ring on SRS-A antagonist activity and selectivity, was studied.

The important roles of SRS-A and the leukotrienes in inducing bronchospasm in human allergic asthma and in anaphylactic shock in animals are well established.[2,3] The search for a potent and selective SRS-A antagonist as an agent for the therapy or prophylaxis of human asthma has intensified recently, especially after the chemical structures of SRS-A and the leukotrienes were elucidated.[4,5] A potent and specific SRS-A antagonist is the chromonecarboxylic acid **1** (FPL-55712).[6] This is of considerable


1 (FPL-55712), X = H
2, X = I
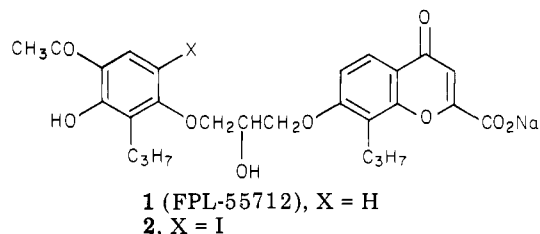
value as a pharmacological tool for the identification of the SRS-A site(s) of action. Recently, the 6-iodo derivative of **1**, i.e., **2** has been disclosed to be a more potent SRS-A antagonist than **1** with longer duration of action and antihistaminic properties.[7] Other structurally unrelated compounds with anti-SRS-A activity have also been described recently.[8]

(1) For part 1, see F. E. Ali, P. A. Dandridge, J. G. Gleason, R. D. Krell, C. H. Kruse, P. G. Lavanchy, and K. M. Sander, *J. Med. Chem.*, 25, 947 (1982).

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(5) B. Samuelsson, *Trends Pharmacol.*, 1, 227 (1980).

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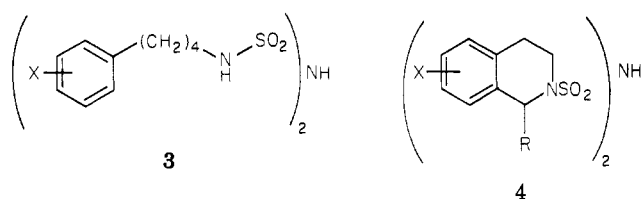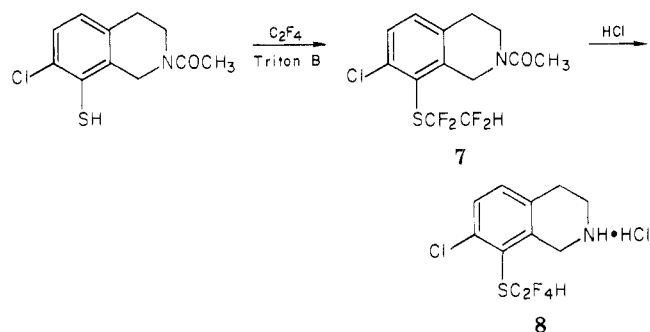
Scheme I
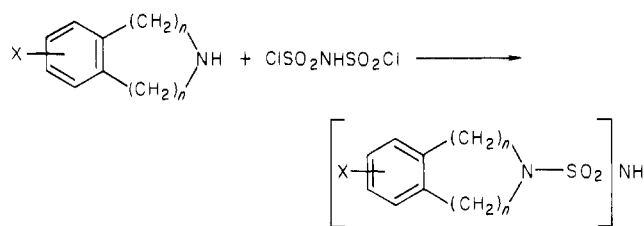
Scheme II
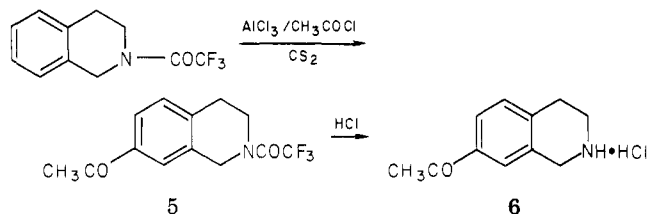
We reported previously[1] that a series of N',N''-bis(aralkyl)imidodisulfamides (3), displayed moderately potent


SRS-A antagonist activities as evaluated by their ability to prevent SRS-A induced contractions of guinea pig ileum. In order for us to assess the influence of some aspects of conformation on SRS-A antagonist potency, the alkylene side chain was modified by incorporation into carbocyclic or fused heterocyclic ring systems. Among the cyclic structures studied, the tetrahydroisoquinoline series 4 afforded the most potent and selective antagonists of SRS-A. In this paper, we describe the synthesis and biological activity of some of the cyclic structures studied and the results of structure–activity relationship studies in a series of substituted 1,2,3,4-tetrahydroisoquinolinylsulfonic imides (4). Particular emphasis was afforded to an investigation of the effect of substitution in the aromatic and heterocyclic rings of 4 on SRS-A antagonist potency and selectivity.

Chemistry. N',N''-Bis(arylcycloalkyl)imidodisulfamides (Table I), substituted tetrahydroisoquinolinylsulfonic imides (Tables II–IV and VI), and other heterocyclic sulfonic imides (Table V) were prepared by the general route described earlier for the N',N''-bis(aralkyl)imidodisulfamides.[1] This sequence involves condensation of appropriate primary or secondary amines with imidodisulfuryl chloride[9] in acetonitrile and in the presence of triethylamine, as shown in Scheme I. Generally, the products obtained were purified via recrystallization from suitable solvent(s). Requisite arylcyclopropyl- and arylcyclohexylamines were prepared according to literature procedures.[10] Most substituted 1,2,3,4-tetrahydroisoquinolines were prepared according to published procedures.[11–14]

Scheme III

Scheme IV
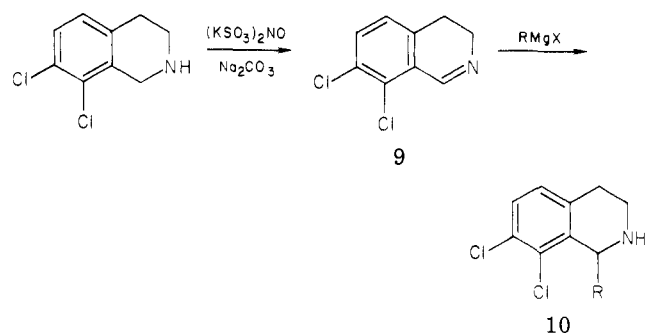
7-Acetyl-1,2,3,4-tetrahydroisoquinoline (6) was prepared by Friedel–Crafts acylation of 2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline as shown in Scheme II.

7-Chloro-8-[(1,1,2,2-tetrafluoroethyl)thio]-1,2,3,4-tetrahydroisoquinoline (8) was prepared by the reaction of tetrafluoroethylene and 2-acetyl-7-chloro-8-mercapto-tetrahydroisoquinoline[13] in the presence of a quaternary ammonium base as shown in Scheme III.

7,8-Dichloro-1-substituted-tetrahydroisoquinolines (10), requisite intermediates for sulfonic imide derivatives (Table VI), were prepared by the reaction of the appropriate Grignard reagent with 7,8-dichloro-3,4-dihydroisoquinoline (9), which was obtained from Fremy's salt oxidation of the 7,8-dichloro-1,2,3,4-tetrahydroisoquinoline as shown in Scheme IV. 5-Chloroindoline and 2,3,4,5-tetrahydro-1H-3-benzazepine intermediates were also prepared according to known procedures.[15,16]

Results and Discussion

Following the discovery of the SRS-A antagonist activity of N',N''-bis(aralkyl)imidodisulfamides 3 and the observation of the importance of overall hydrophobicity on SRS-A antagonist activity,[1] the present study was initiated to investigate the significance of the conformation of the alkylene side chain on the SRS-A antagonist potency. A few examples were studied in which the flexibility of the alkylene side chain was constrained by incorporation into carbocyclic (Table I) and fused heterocyclic rings (Tables II–VI). Somewhat more detailed studies were focused on the tetrahydroisoquinolines (Table II–IV and VI), which were found to be more potent and selective antagonists.

Incorporation of the alkylene side chain of N',N''-bis-(phenylethyl)imidodisulfamide into a less flexible, conformationally constrained cyclopropyl ring structures 11

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(13) W. E. Bondinell and R. G. Pendleton, U.S. Patent 4 228 170 (1980).
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Table I. N',N''-Bis(arylcycloalkyl)imidodisulfamides

$$RNHSO_2NHSO_2NHR$$

no.	R	yield, %	mp, °C	recrystn solvent	formula	anal.	concn, μM	anti-SRS-A % inhibn [a]
11	C_6H_5	45	139–141	$CHCl_3$-n-C_6H_{14}	$C_{18}H_{21}N_3O_4S_2$	C, H, N, S	5	17 [b]
12	3,4-$Cl_2C_6H_3$	55	170–172	$MeOH$-H_2O	$C_{18}H_{17}Cl_4N_3O_4S_2$	C, H, N, S, Cl	5	42 [c] (61 SRS-A, 19 KCl)
13	C_6H_5	76	178–181	$MeOH$-H_2O	$C_{24}H_{33}N_3O_4S_2$	C, H, N	50	41 [d] (86 SRS-A, 45 KCl)
14		79	199–201	$CHCl_3$-$MeOH$	$C_{18}H_{21}N_3O_4S_2$	C, H, N	50	11 [e]

[a] Calculated as percent inhibition of SRS-A induced contractions minus percent inhibition of 25 mM KCl induced contractions at identical concentration of tested compound. When significant inhibition of both SRS-A and KCl was observed, these data are included in parentheses. For comparison, FPL-55712 exhibited 40% inhibition at 1 μM with no significant inhibition of KCl-induced contractions. [b] For comparison, the acyclic analogue of 11, i.e., the phenylethylimidodisulfamide, inhibited SRS-A induced contractions by 7% at 20 μM. [c] For comparison, the 3,4-dichlorophenylethyl analogue inhibited SRS-A induced contractions by 63% and KCl-induced contractions by 20% at 10 μM. [d] For comparison, the 6-phenylhexyl analogue inhibited SRS-A induced contractions by 49% and KCl-induced contractions by 34% at 10 μM. [e] Not statistically significant.

Table II. Monosubstituted Tetrahydroisoquinolinylsulfonic Imides

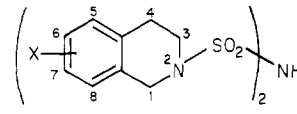| no.	X	yield, %	mp, °C	recrystn solvent	formula	anal.	concn, μM	anti SRS-A % inhibn [a]
15	H	47	138–140	MeOH	$C_{18}H_{21}N_3O_4S_2$	C, H, N, S	50	10 [b]
16	5-Cl	33	176–178	EtOAc-n-C_6H_{14}	$C_{18}H_{19}Cl_2N_3O_4S_2$	C, H, N, S	5	8 [b]
17	6-Cl	71	171–173	MeOH-H_2O	$C_{18}H_{19}Cl_2N_3O_4S_2$	C, H, N, S, Cl	5 50	1.0 84
18	7-Cl	46	186–188	MeOH-H_2O	$C_{18}H_{19}Cl_2N_3O_4S_2$	C, H, N, S, Cl	5	18
19	8-Cl	25	161–162	MeOH	$C_{18}H_{19}Cl_2N_3O_4S_2$	C, H, N, S	5	16 [b]
20	5-Br	61	195–196	MeOH-H_2O	$C_{18}H_{19}Br_2N_3O_4S_2$	C, H, N	5	29
21	7-Br	57	185–188	MeOH [c]	$C_{18}H_{19}Br_2N_3O_4S_2$	C, H, N, S	5	26
22	7-OCH_3	56	156–158	MeOH-EtOH	$C_{20}H_{25}N_3O_6S_2$	C, H, N	5	6 [d]
23	7-$COCH_3$	53	184–185	$CHCl_3$-MeOH-n-C_6H_{14}	$C_{22}H_{25}N_3O_6S_2$ [e]	C, H, N, S	5	4 [b]
24	7-$SOCCl_3$	46	144–146	EtOAc-n-C_6H_{14}	$C_{20}H_{19}Cl_6N_3O_6S_2$	C, H, N, S	5	28
25	5-Ph	37	96–97	MeOH	$C_{30}H_{29}N_3O_4S_2$ [f]	C, H, N, S	5	13

[a] See footnote a in Table I. [b] Not statistically significant. [c] Triturated. [d] Percent enhancement of tissue contractions compared with control. [e] Analysis for $0.25H_2O$. [f] Analysis for $1.0H_2O$.

Table III. Disubstituted Tetrahydroisoquinolinylsulfonic Imides

no.	X	yield, %	mp, °C	recrystn solvent	formula	anal.	concn, μM	anti SRS-A % inhibn [a]
26	7,8-Cl_2	52	143–145	$CHCl_3$-n-C_6H_{14}	$C_{18}H_{17}Cl_4N_3O_4S_2$	C, H, N	5	42
27	6,7-Cl_2	43	201–204	MeOH [b]	$C_{18}H_{17}Cl_4N_3O_4S_2$ [c]	C, H, N, Cl [d]	5	40
28	7,8-$(OCH_3)_2$	53	185–187	MeOH-EtOH	$C_{22}H_{29}N_3O_8S_2$	C, H, N	5	5 [e]
29	7-CH_3, 8-Cl	78	158–160	MeOH-EtOH	$C_{20}H_{23}Cl_2N_3O_4S_2$	C, H, N, S, Cl	5	34
30	7-OCH_3, 8-Cl	21	164–166	MeOH-H_2O	$C_{20}H_{23}Cl_2N_3O_6S_2$	C, H, N	5	20
31	7-SCH_3, 8-Cl	21	181–184	CH_2Cl_2 [d]	$C_{20}H_{23}Cl_2N_3O_4S_4$	C, H, N	5	25
32	7,8-$(CF_3)_2$	51	157–158	EtOH	$C_{22}H_{17}F_{12}N_3O_4S_2$	C, H, N, S	5	27 (45 SRS-A, 18 KCl)
33	7-Cl, 8-SC_2F_4H	44	185–189	MeOH	$C_{22}H_{19}Cl_2F_8N_3O_4S_4$	C, H, N, S	5	22 (36 SRS-A, 14 KCl)
34	5,8-$(OCH_3)_2$	54	189–190	CH_3CN	$C_{22}H_{29}N_3O_8S_2$	C, H, N	5	12
35	5,8-Br_2	49	177–180	$CHCl_3$-PE [f]	$C_{18}H_{17}Br_4N_3O_4S_2$ [g]	C, H, N	5	50

[a] See footnote a in Table I. [b] Triturated. [c] Analysis for $1.0H_2O$. [d] Cl: calcd, 25.17; found, 23.35. [e] See footnote d in Table II. [f] PE = petroleum ether. [g] Analysis for $0.75H_2O$.

Table IV. Multiply Substituted Tetrahydroisoquinolinylsulfonic Imides

no.	X	yield, %	mp, °C	recrystn solvent	formula	anal.	concn, μM	anti SRS-A % inhibn [a]
36	6,7,8-Cl$_3$	41	202-205	EtOAC-n-C$_6$H$_{14}$	C$_{18}$H$_{15}$Cl$_6$N$_3$O$_4$S$_2$	C, H, N, S	5	11
37	5,7,8-Br$_3$	24	206-208	toluene-n-C$_6$H$_{14}$	C$_{18}$H$_{15}$Br$_6$N$_3$O$_4$S$_2$	C, H, N, S	5	7 [b]
38	5,6,7,8-Cl$_4$	52	204 dec	CHCl$_3$-CH$_2$Cl$_2$	C$_{18}$H$_{13}$Cl$_8$N$_3$O$_4$S$_2$	C, H, N	5	14 [b]
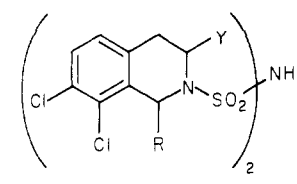
[a] See footnote a in Table I. [b] Not statistically significant.

Table V. Other Heterocyclic Sulfonic Imides

R—SO$_2$NHSO$_2$—R

no.	R	yield, %	mp, °C	recrystn solvent	formula	anal.	concn, μM	anti-SRS-A % inhibn [a]
39		42	175-176	MeOH	C$_{16}$H$_{17}$N$_3$O$_4$S$_2$	C, H, N, S	50	13 [b]
10		57	113-116	MeOH-H$_2$O-HCl	C$_{16}$H$_{15}$Cl$_2$N$_3$O$_4$S$_2$ [c]	C, H, N, S, Cl	5	13 [d]
41		67	184-186	MeOH	C$_{20}$H$_{25}$N$_3$O$_4$S$_2$ [e]	C, H, N, S	50	14 (30 SRS, 16 KCl)

[a] See footnote a in Table I. [b] See footnote d in Table II. [c] Analysis for 0.75H$_2$O. [d] Not statistically significant. [e] Analysis for 0.25H$_2$O.

Table VI. 7,8-Dichloroheterocycle-Substituted Tetrahydroisoquinolinylsulfonic Imides

no.	R	Y	yield, %	mp,[a] °C	recrystn solvent	formula	anal.	concn, μM	anti SRS-A % inhibn [b]
42	CH$_3$	H	50	100-150	MeOH-HCl-H$_2$O	C$_{20}$H$_{21}$Cl$_4$N$_3$O$_4$S$_2$	C, H, N	5	48 (65 SRS-A, 17 KCl)
43	n-C$_6$H$_{13}$	H	20	94-106	MeOH	C$_{30}$H$_{41}$Cl$_4$N$_3$O$_4$S$_2$	C, H, N	5	5 [c]
44	Ph	H	44	125-150	MeOH	C$_{30}$H$_{25}$Cl$_4$N$_3$O$_4$S$_2$	C, H, N	5	20
45	CH$_2$Ph	H	76	125-150	MeOH	C$_{32}$H$_{29}$Cl$_4$N$_3$O$_4$S$_2$	C, H, N	5	8 [d]
46	c-C$_5$H$_9$	H	98 [e]	80-120		C$_{28}$H$_{33}$Cl$_4$N$_3$O$_4$S$_2$	C, H, N	5	4.0 [d]
47	c-C$_3$H$_5$	H	34	78-81	CH$_2$Cl$_2$	C$_{24}$H$_{25}$Cl$_4$N$_3$O$_4$S$_2$	C, H, N, Cl	5	47 (60 SRS-A, 13 [d] KCl)
48	H	CH$_3$	65	87-124	MeOH-H$_2$O	C$_{20}$H$_{21}$Cl$_4$N$_3$O$_4$S$_2$	C, H, N	5	18 (36 SRS-A, 18 [d] KCl)

[a] Melting point indicative of a mixture of diastereoisomers. [b] See footnote a in Table I. [c] See footnote d in Table II. [d] Not statistically significant. [e] Crude yield as a foam, analytically pure.

and 12 (Table I), increased the SRS-A antagonist potency as compared with the acyclic analogue.[1] An increase in the conformational flexibility of the cyclic structure through incorporation into a larger ring, i.e., cyclohexyl, has little effect on activity; compound 13 has activity comparable to that of N',N''-bis(6-phenylhexyl)imidodisulfamide.[1] Both compounds were nonselective antagonists. Incorporation of the alkylene side chain into a fused carbocyclic structure as in the 2-indanylimidodisulfamide 14 did not impart SRS-A antagonist activity. In contrast, incorporation of the alkylene side chain into a fused heterocyclic ring, particularly a tetrahydroisoquinoline ring, resulted in potent and selective antagonists provided appropriate hydrophobicity was retained. The dichloro compound 26, which was the first prepared in this series,

was a selective SRS-A antagonist. It failed to shift significantly the dose–response curves of histamine (0.01–10 μM), carbachol (0.01–10 μM), or potassium chloride (1–100 mM) at the same concentrations (5–50 μM) that provided a significant shift in the SRS-A dose–response curve. Some antagonist activity for prostaglandin- and serotonin-induced contractions was observed. The activity and selectivity noted for 26 led to further structure–activity studies in the tetrahydroisoquinoline series (Tables II–IV and VI).

The effect on anti-SRS-A activity of a single substituent in various positions of the aromatic ring was investigated; the results are shown in Table II. Single chlorine substitution in the aromatic ring provided compounds 16–19 that were slightly more active than the unsubstituted

parent 15; however, these were less potent than the dichloro analogues 26 and 27. A comparison of the potencies of 16–19 and 21 suggested that halogen substitution in the 7- and 8-positions of the isoquinoline nucleus was more advantageous than substitution in 5- and 6-positions; however, since the 5-bromo congener 20 was nearly equipotent with the 7-bromo analogue 21, it appeared that halogen substitution, but not location on the aromatic ring, is important for SRS-A antagonist activity. A few other monosubstituted derivatives, 22–25, bearing substituents exhibiting varying electronic, steric, or lipophilic effects were studied. In general, with the exception of compound 24, these compounds, like the parent 15, showed little or no SRS-A antagonist activity.

Since the dichloro derivative 26 showed greater SRS-A antagonist activity than these compounds having a single aromatic ring substituent, the effects of multiple substitution were investigated. As indicated in Table III, the dichloro and dibromo compounds 26, 27, and 35 had the greatest SRS-A antagonist potency and selectivity. Again, these results suggest that the location of the halogens is of little significance. Replacement of one of the chloro substituents of 26 with substituents with differing physical parameters, e.g., 29–31 and 33, resulted in compounds with no better potency than 26. Decreased potency or selectivity was also observed in 28, 32, and 34, in which the dihalogen substituents in 26 and 35 were replaced by methoxy or trifluoromethyl groups.

Since a slight increase in SRS-A antagonist activity was observed following synthesis of the monohalo congeners (16–21), and further enhancement upon dihalo substitution (26, 27, and 35), tri and tetrahalo substituted analogues (36–38) (Table IV) were examined. As indicated in Table IV, a marked reduction of SRS-A antagonist potency was observed in these compounds as compared with their dihalogenated counterparts 26, 27, and 35. In summary (Tables II–IV), it appears that simple aromatic dihalogen substituents afford the optimal degree of SRS-A antagonist potency and selectivity in the tetrahydroisoquinolinylsulfonic imides.

To study the effect of the heterocycle ring size on activity, we examined some representative structures (Table V). When the heterocyclic ring size was decreased to a five-membered fused ring, as in the indolines 39 and 40, a significant diminution of SRS-A antagonist activity resulted. Increasing the ring size to a fused seven-membered ring, as in 41, was also of little benefit; the compound was nonselective. It appears that homologation of the heterocyclic ring of tetrahydroisoquinolinylsulfonic imides leads to diminished selectivity. Methyl-substituted analogues of 26 were also prepared in order to probe the influence of an additional methylene on anti-SRS-A potency and selectivity. As indicated in Table VI, methyl group substitution at position 1 or 3, i.e., 42 and 48, has no beneficial effects on potency; moreover, some loss of selectivity was noted. These results, together with those obtained in Table V, suggests that the six-membered heterocyclic ring is important for selective anti-SRS-A activity. The relatively small influence of the methyl group on potency suggests that substituents larger than a hydrogen might be tolerated without affecting the overall interaction of the molecule with the site(s) of action. This led to examination of a few examples in which the hydrogen at position 1 of 26 is replaced by relatively bulky groups. As indicated in Table VI, substituents such as phenyl, benzyl, or cyclopentyl led to analogues of diminished potency. Surprisingly, the cyclopropyl analogue 47 retained antagonist activity.

In summary, among a few of the conformationally restricted cyclic structures studied in the aralkylimidodisulfamides series, the tetrahydroisoquinolinylsulfonic imides were found to have optimum SRS-A antagonist activity and selectivity in the guinea pig ileum test. The dichloro (26 and 27) and the dibromo (35) substituted tetrahydroisoquinolinylsulfonic imides are the most potent and selective SRS-A antagonists among the compounds studied. Variation of the heterocyclic ring size or substitution by simple alkyl, cycloalkyl, or phenyl groups generally failed to enhance selective anti-SRS-A potency.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed on Perkin-Elmer 240 apparatus by the Analytical Department of Smith Kline & French Laboratories, and where analyses are indicated by the symbol of the elements, the analytical results obtained for these elements were within ±0.4% of the theoretical values. TLC was taken on Analtech silica Gel GF 1 × 4 in. slides, 250-μm thick, using 20% MeOH–CHCl$_3$. Field-desorption mass spectra were obtained on Varian MAT CH-5 DF spectrometer. IR spectra were obtained on a Perkin-Elmer 137 spectrophotometer as Nujol mulls, and ^{1}H NMR spectra were obtained on a Hitachi Perkin-Elmer R24 and on a Varian EM-360 spectrometer as a solution in a mixture of CDCl$_3$–Me$_2$SO-d_6, with Me$_4$Si as an internal standard. All spectra were consistent with the assigned structures.

N',N''-**Bis-*trans*-[2-(3,4-dichlorophenyl)cyclopropyl]imidodisulfamide (12).** To a stirred solution of 2.1 g (10 mmol) of imidodisulfuryl chloride in acetonitrile was added dropwise 3.0 g (30 mmol) of triethylamine at –40 °C. The reaction was warmed to 0 °C, and a solution of 4.0 g (20 mmol) of *trans*-2-(3,4-dichlorophenyl)cyclopropylamine[10] in acetonitrile was added dropwise. The reaction mixture was stirred at 25 °C for 16 h. Precipitated triethylamine hydrochloride was filtered, and the filtrate was concentrated. The residual oil was acidified with dilute HCl, and the material obtained was recrystallized from aqueous methanol to give 2.95 g (55%) of 12, mp 170–172 °C. Anal. (C$_{18}$H$_{17}$Cl$_4$N$_3$O$_4$S$_2$) C, H, N, S, Cl.

(6-Chloro-1,2,3,4-tetrahydroisoquinolinyl)sulfonic Imide (17). To a stirred solution of 0.51 g (2.38 mmol) of imidodisulfuryl chloride[9] in 5 mL of dry acetonitrile was added dropwise 0.72 g (7.14 mmol) of triethylamine at –40 °C. After the addition of the triethylamine was completed, the reaction was warmed to 0 °C, and a solution of 0.9 g (4.77 mmol) of 6-chloro-1,2,3,4-tetrahydroisoquinoline in 10 mL of acetonitrile–methylene chloride was added dropwise. The reaction mixture was stirred at 25 °C for 12 h. It was concentrated to dryness in vacuo, and the residue was partitioned between a mixture of EtOAc and dilute HCl. The organic layer was separated, washed with H$_2$O, dried (MgSO$_4$), and concentrated. The residual oil was crystallized from MeOH–H$_2$O to give a white solid (0.8 g, 71%), mp 171–173 °C. Anal. (C$_{18}$H$_{19}$Cl$_2$N$_3$O$_4$S$_2$) C, H, N, S, Cl.

7-Acetyl-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinolines (5). To 42.08 g (0.2 mol) of trifluoroacetic anhydride was added, with stirring, 13.3 g (0.1 mol) of 1,2,3,4-tetrahydroisoquinoline at a such rate that the temperature was kept below 15 °C. The reaction mixture was stirred at 25 °C for 16 h. Excess trifluoroacetic anhydride was evaporated, and the product was distilled to give 21.6 g (95%) of 2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline, bp 158–167 °C (34–36 torr). To a stirred slurry of 11.4 g (0.05 mol) of 2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline and 40.0 g (0.3 mol) of AlCl$_3$ in 70 mL of CS$_2$ was added dropwise 11.8 g (0.15 mol) of acetyl chloride. Addition was controlled so that gentle reflux was maintained. After the addition of the acetyl chloride was completed, the reaction mixture was refluxed for 1 h. Excess CS$_2$ and acetyl chloride were removed in vacuo, and the residue was decomposed **carefully** with 50 mL of ice-cold 3 N HCl and extracted with CHCl$_3$. The CHCl$_3$ extract was washed successively with H$_2$O, 5% NaHCO$_3$, and H$_2$O and then was dried (MgSO$_4$) and concentrated. The residual solid was triturated with hexane and recrystallized from MeOH–H$_2$O to give 8.9 g (66%) of 5, mp 84–86 °C.

7-Acetyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (6).

A mixture of 8.1 g of **5**, 150 mL of 3 N HCl, and 80 mL of *n*-BuOH was refluxed for 3 h. It was concentrated in vacuo to give a yellow solid, which was recrystallized from EtOH to a white solid (5.3 g, 83%), mp 230–231 °C. Anal. ($C_{11}H_{13}NO\cdot HCl$) C, H, N.

2-Acetyl-7-chloro-8-[(1,1,2,2-tetrafluoroethyl)thio]-1,2,3,4-tetrahydroisoquinoline (7). A glass pressure bomb was charged with 4.5 g (1.86 mmol) of 2-acetyl-7-chloro-8-mercapto-1,2,3,4-tetrahydroisoquinoline, 1.56 g (3.72 mmol) of Triton B, and 35 mL of dry DMF. The solution was magnetically stirred while it was flushed twice with tetrafluoroethylene to 20 psi, charged at 20 psi, and sealed. The pressure bottle was recharged each hour until the pressure stabilized at 20 psi and was then stirred for 16 h. The reaction mixture was poured into 80 mL of cold H_2O and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with H_2O, 5% Na_2CO_3, and then with H_2O, dried (K_2CO_3), and concentrated. The residual oil was crystallized from CCl_4–hexane and then from toluene–hexane to give 4.7 g (74%) of **7**: mp 79–94 °C; TLC (silica, 40% CH_2Cl_2–ether) single spot.

7-Chloro-8-[(1,1,2,2-tetrafluoroethyl)thio]-1,2,3,4-tetrahydroisoquinoline Hydrochloride (8). A mixture of 2.2 g (6.4 mmol) of **7** and 25 mL of concentrated HCl was refluxed at 135–140 °C for 5 h. The reaction mixture was concentrated in vacuo, and the residue was recrystallized from EtOH–ether with decolorizing carbon to give 1.8 g (83%) of **8**, mp 234 °C. Anal. ($C_{11}H_{10}ClF_4N_3\cdot HCl$) C, H, N.

7,8-Dichloro-3,4-dihydroisoquinoline (9). To a stirred solution of 62.6 g (0.233 mol) of Fremy's salt in 1-L of 5% Na_2CO_3 was added portionwise 21.9 g (0.092 mol) of 7,8-dichloro-1,2,3,4-tetrahydroisoquinoline hydrochloride.[11] The reaction mixture was stirred at 25 °C for 24 h. It was extracted with 3 × 250 mL of CH_2Cl_2, which was washed with a saturated salt solution, dried, and concentrated. The orange residual oil was crystallized upon standing and recrystallized twice from EtOAc to give 9.6 g (52%) of **9**, mp 55–57 °C.

7,8-Dichloro-1-methyl-1,2,3,4-tetrahydroisoquinoline (10, R = Methyl). To flame-dried magnesium turnings (3.7 g, 0.15 g-atom) was added 40 mL of anhydrous Et_2O. A solution of 24.8 g (0.175 mol) of methyl iodide in 125 mL of ether was added dropwise at a rate sufficient to maintain a gentle reflux. After the addition was completed, the Grignard solution was cooled to 25 °C, and a solution of 10.54 g (0.053 mol) of **9** in 40 mL of dry toluene was added dropwise. It was refluxed for 2 h. The reaction mixture was decomposed **cautiously** by adding 90 mL of H_2O and was filtered through Celite, and the residue was washed with EtOAc. The combined organic–EtOAc filtrates were washed with a saturated salt solution, dried, and concentrated. The residual oil was purified by Kughelrohr distillation to give 8.6 g (75%)

of **10** (R = methyl).

Biological Test Procedures. Sections of ileum, proximal to Peyer's patch, are resected from male, albino, Hartley strain, guinea pigs (400–600 g) and placed in 5-mL tissue baths containing modified Tyrode's solution (37.5 °C) of the following composition (mM): NaCl, 137; KCl, 3.4; $CaCl_2$, 1.3: $MgCl_2$, 0.10; NaH_2PO_4, 11.9; atropine, 0.000738; pyrilamine, 0.00249; glucose, 5. In experiments using carbachol and histamine as agonists, atropine and pyrilamine, respectively, are omitted from the Tyrode's solutions. One end of the tissue is fixed to a glass tissue holder and the other is connected to a Grass force-displacement transducer, and the tissue is placed under a tension of 500 mg. Isometric tissue contractions are recorded on a six-channel polygraph. Baths are constantly aerated with 95% O_2–5% CO_2. After a 20-min "stabilization" period, a concentration of the appropriate agonist that provides a contraction height of 60–80% of the maximum obtainable to that agonist (as determined from full sequential concentration-response curves in separate experiments) is added to the tissue bath, and the response is recorded. The procedure is repeated until reproducible responses are obtained. For most agonists, two applications in rapid succession, followed 15 min later by a third, is sufficient to establish reproducibility. Experimental tissues are incubated with the concentration of the test compound indicated in the tables for 15 min. Experimental and control tissues are subjected to five bath changes during the incubation interval. Changes in bath fluid during the incubation period are helpful in ensuring the reproducibility of tissue responses to the agonist. Control tissues are incubated with test compound vehicle (if any). The same concentration of the agonist is reapplied in the presence of the test compounds, and the response is registered and compared with controls. Percent inhibition produced by the test compound is calculated by subtracting the mean percentage change in control tissue from the mean percentage change in tissues exposed to the test compound. Additional compounds are then evaluated as long as the tissue remains reproducibly responsive to the agonist. Six tissues obtained from six animals are used simultaneously—three controls and three experimental. Partially purified guinea pig SRS-A was prepared and purified as described.[17] Compound 1 was used as a reference for each compound tested.

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Synthesis and Spasmolytic Activities of 2-(1,2-Benzisoxazol-3-yl)-3-[[ω-(dialkylamino)alkoxy]phenyl]acrylonitriles[1]

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Several 2-(1,2-benzisoxazol-3-yl)-3-[[ω-(dialkylamino)alkoxy]phenyl]acrylonitrile derivatives were synthesized and screened for potential spasmolytic activity. The effect of structural variation of these molecules on biological activities was systematically examined. Among these compounds, (*Z*)-2-(1,2-benzisoxazol-3-yl)-3-[2-(2-piperidinoethoxy)-phenyl]acrylonitrile (**1d**), (*Z*)-2-(1,2-benzisoxazol-3-yl)-3-[2-(2-morpholinoethoxy)phenyl]acrylonitrile (**1f**), and their analogues (**3c,d**) having a methoxy substituent at C_5 of the benzoisoxazole ring showed potent antispasmodic activities in the in vitro and in vivo studies.

It has been suggested that an agent showing inhibitory action on the release of acetylcholine from the vagus nerve has antispasmodic potency comparable to antimuscarinic

agents on the gastrointestinal system in experimental animals, and such an agent may be attractive for clinical use as a spasmolytic.[2] We have tried to find a novel type of spasmolytic agent having potent antispasmodic activity

(1) Part 8 in the series "Studies on 3-Substituted 1,2-Benzisoxazole Derivatives". For Part 7, see H. Uno and M. Kurokawa, *Chem. Pharm. Bull.*, **30**, 333 (1982).

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