Imidodisulfamides. 1. A Novel Class of Antagonists of Slow-Reacting Substance of Anaphylaxis[1a]

Fadia El-Fehail Ali,* Penelope A. Dandridge, John G. Gleason, Robert D. Krell, Carolyn H. Kruse, Patricia G. Lavanchy, and Kenneth M. Snader

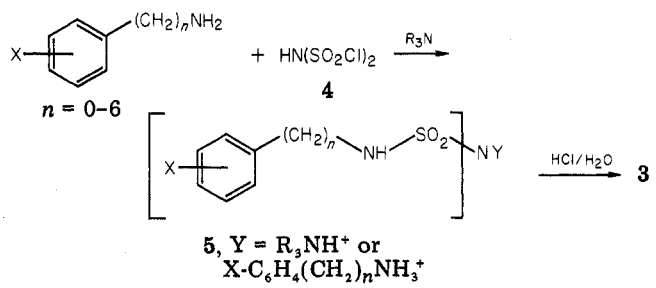
Research and Development Division, Smith Kline & French Laboratories, Philadelphia, Pennsylvania 19101.
Received October 26, 1981

A series of *N',N''*-bis(aryl)- and *N',N''*-(aralkyl)imidodisulfamides was prepared and evalutated as antagonists of slow-reacting substance of anaphylaxis (SRS-A) induced contractions of isolated guinea pig ileum. Some of these compounds, notably *N',N''*-bis(4-phenylbutyl)-, *N',N''*-bis[2-(4-chlorophenyl)ethyl]-, and *N',N''*-bis[2-(4-bromophenyl)ethyl]imidodisulfamides (**16**, **22**, and **26**), were moderately potent and selective antagonists of SRS-A. The influence of lipophilic (π) and electronic (σ) factors on SRS-A antagonist activity appears to be of considerable importance to the derivation of potent and selective SRS-A antagonists.

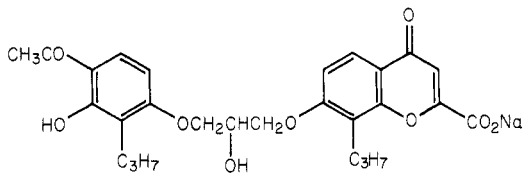
In human allergic asthma and anaphylactic reactions in animals, several mediators apparently are released from the lung tissue to induce bronchoconstriction and other allergic reactions.[1b] These mediators include histamine, slow-reacting substance of anaphylaxis (SRS-A), prostaglandins (PGs), and possibly other humoral factors. There is evidence that at least histamine and SRS-A play an important role in allergic reactions in both man and animals. Histamine and SRS-A are released from guinea pig[2] and human[3] lung tissue after antigen challenge. The role of histamine is important in the guinea pig anaphylactic reaction but not in human asthma.[4,5] This and other indirect evidence suggested an important role for SRS-A in inducing bronchospasm in human allergic asthma.[6] An agent capable of inhibiting the release of SRS-A or selectively antagonizing its effect at the end organ, i.e., bronchial smooth muscle, therefore might be of therapeutic value in treatment of allergic asthma.

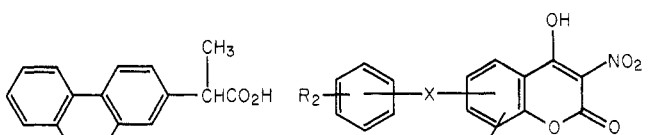
SRS-A was discovered and characterized some 40 years ago;[7,8] however, its structure elucidation and chemical synthesis have been reported only recently. SRS-A[9-11] consists of a mixture of leukotrienes.[12,13] The main components of this mixture, i.e., LTC_4 and LTD_4, are potent constrictors of human bronchi.[14] Guinea pig lung SRS-A and leukotrienes are also similar in structure.[15,16]

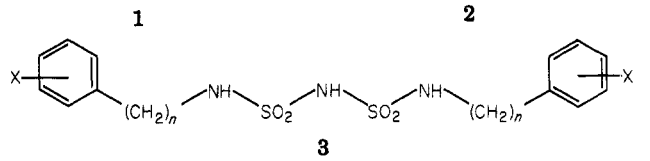
Scheme I



The most potent and selective antagonist of SRS-A known to date is the chromone-2carboxylic acid,[17] FPL-55712. Its clinical and therapeutic use is limited because of its short biological half-life of 0.6 min.[18] A related compound of unknown structure, FPL-59257, apparently has activity similar to that of FPL-55712 but with longer duration of action in animals.[19] Other nonselective antagonists have also been reported. These include a series of substituted hydratropic acids **1**[20] and a series of 4-hydroxy-3-nitrocoumarins **2**.[21]



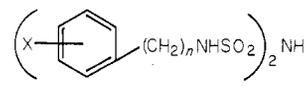




(1) (a) This paper has been presented; see "Abstracts of Papers", 183rd National Meeting of the American Chemical Society, Las Vegas, NE, Mar 28–Apr 2, 1982, American Chemical Society, Washington, DC, 1982, Abstr MEDI 48. (b) K. F. Austen and R. P. Orange, *Am. Rev. Respir. Dis.*, **112**, 423 (1975); J. C. Foreman, *Annu. Rev. Pharmacol. Toxicol.*, **21**, 63 (1981).
(2) W. E. Brocklehurst, *J. Physiol. (London)*, **151**, 416 (1960).
(3) P. Sheard, P. Killingsback, and A. M. J. N. Blaire, *Nature (London)*, **216**, 283 (1967).
(4) P. A. Armitage, H. Herxheimer, and L. Rosa, *Br. J. Pharmacol.*, **7**, 625 (1952).
(5) L. S. Goodman and A. Gilman, "The Pharmacological Basis of Therapeutics", 4th ed., Macmillan, New York, 1970, p 635.
(6) P. Sheard and A. M. J. N. Blair, *Int. Arch. Allergy*, **38**, 217 (1970).
(7) C. H. Kellaway and E. R. Trethewie, *Q. J. Exp. Physiol.*, **30**, 121 (1940).
(8) (a) W. E. Brocklehurst, *J. Physiol.*, **120**, 16P (1953). (b) W. E. Brocklehurst, *Prog. Allergy*, **6**, 539 (1962).
(9) B. Samuelsson, *Trends Pharmacol. Sci.*, **1**, 227 (1980); B. Samuelsson, S. Hammarstrom, R. C. Murphy, and P. Borgeat, *J. Allergy*, **35**, 370 (1980).
(10) W. Dawson, *Nature (London)*, **285**, 68 (1980).
(11) P. Borgeat, *J. Med. Chem.*, **24**, 121 (1981).
(12) R. A. Lewis, K. F. Austen, J. M. Drazen, D. A. Clark, A. Marfat, and E. J. Corey, *Proc. Natl. Acad. Sci. U.S.A.*, **77**, 3710 (1980).
(13) M. K. Bach, J. R. Brashler, S. Hammarstrom, and B. Samuelsson, *J. Immunol.*, **125**, 115 (1980).
(14) S. E. Dahlen, P. Hedqvist, S. Hammarstrom, and B. Samuelsson, *Nature (London)*, **288**, 484 (1980).
(15) G. P. Lewis, *Trends Pharmacol. Sci.*, **2**, 7 (1981).
(16) J. Morris, G. Taylor, D. Piper, and J. Tippins, *Nature (London)*, **285**, 104 (1980).
(17) (a) R. A. Appelton, J. R. Bontick, T. R. Chamberlain, D. N. Hardern, T. B. Lee, and A. D. Pratt, *J. Med. Chem.*, **20**, 371 (1977). (b) J. Angstein, J. B. Farmer, T. B. Lee, P. Sheard, and M. L. Tattersall, *Nature (London), New Biol.*, **245**, 215 (1973).
(18) N. Chand, *Agents Actions*, **9**, 133 (1979).
(19) Scrip: *World Pharm. News*, **557**, 14 (1981).
(20) M. E. Greig and R. L. Griffin, *J. Med. Chem.*, **18**, 112 (1975).
(21) D. R. Buckler, D. J. Outred, J. W. Ross, H. Smith, R. J. Smith, A. Spicer, and B. C. Gasson, *J. Med. Chem.*, **22**, 158 (1979).

0022-2623/82/1825-0947$01.25/0

Table I. *N',N''*-Bis(aralkyl)imidodisulfamides



no.	n	X	yield,[a] %	mp, °C	recrystn solvent	formula	anal.	concn, μM	anti-SRS-A inhibn,[b] %
12	0	H	54	167-168[c]	PhH-$CHCl_3$	$C_{12}H_{13}N_3O_4S_2$	C, H, N, S	20	6.0 (NS)[d]
13	1	H	73	194-196	MeOH	$C_{14}H_{17}N_3O_4S_2$	C, H, N, S	10	0.2 (NS)
14	2	H	56	151-152	CH_2Cl_2	$C_{16}H_{21}N_3O_4S_2$	C, H, N, S	20	7 (NS)
15	3	H	61	174-175	PhH-CH_2Cl_2	$C_{18}H_{25}N_3O_4S_2$	C, H, N, S	20	15 (NS)
16	4	H	60	133-134	MeOH	$C_{20}H_{29}N_3O_4S_2$	C, H, N, S	10	40
17	5	H	43	157-159	MeOH	$C_{22}H_{33}N_3O_4S_2$	C, H, N, S	10	8 (43 SRS-A, 35 KCl)
18	6	H	61	134-135	EtOH	$C_{24}H_{37}N_3O_4S_2$	C, H, N, S	10	15 (49 SRS-A, 34 KCl)
19	4	4-Cl	62	124-125.5	CH_2Cl_2-hex	$C_{20}H_{27}Cl_2N_3O_4S_2$	C, H, N, S, Cl	10	22 (55 SRS-A, 33 KCl)

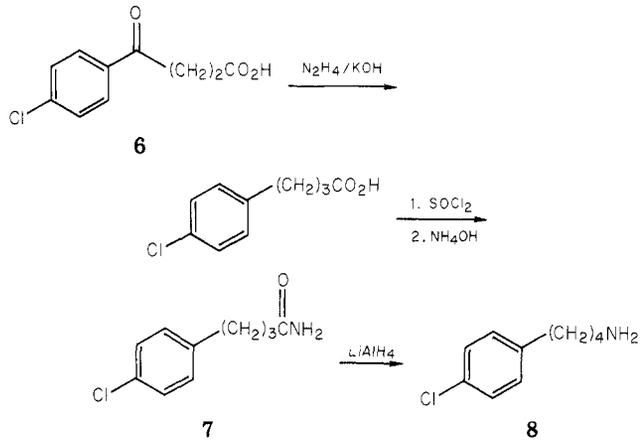
[a] Yields reported for purified first crop only. [b] Calculated as percent inhibition of SRS-A induced contractions minus percent inhibition of 25 mM KCl induced contractions at identical concentration of tested compound where significant inhibition of both SRS-A and KCl was observed; these data are included in parentheses. For comparison, FPL 55712 typically exhibited 40% inhibition at 1 μM with no significant inhibition of KCl-induced contractions. [c] Literature mp 163-165 °C: A. V. Kirsanov and I. U. M. Zolotov, *Zh. Obshch. Khim.*, **28**, 343 (1958). [d] Not statistically significant.

In this paper is reported a series of novel compounds, *N',N''*-bis(aryl)- and *N',N''*-bis(aralkyl)imidodisulfamides **3**. These compounds were evaluated as antagonists of partially purified SRS-A, obtained from guinea pig lung tissue, on the isolated guinea pig ileum. The effect of structural variation of the alkylene side chain and ring substitution of some imidodisulfamide derivatives on SRS-A antagonist activity is reported here. Subsequent papers will describe the effect of other structural variations on this action.

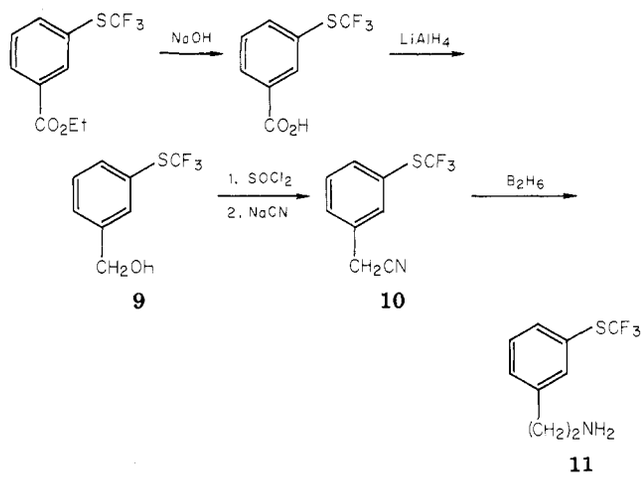
Chemistry. *N',N''*-Bis(substituted)imidodisulfamides[22] were easily prepared by condensing an appropriately substituted primary aromatic or aralkylamine with imidodisulfuryl chloride (**4**)[23] in an inert organic solvent, such as acetonitrile, and in the presence of a tertiary nitrogenous base, such as triethylamine, or pyridine as shown in Scheme I. Generally, treating the reaction products **5**, which were usually obtained as an ammonium salt, with aqueous acid in methanolic solution precipitated the desired products **3** (Tables I–III) as colorless crystals. Recrystallization from suitable solvent(s) gave moderate to good yields of the product. Another convenient way to isolate the desired product involved partitioning **5** between an organic solvent and 2 N HCl. The product was separated from the solvent and purified by recrystallization. In some cases, ion-exchange chromatography, followed by recrystallization, was required for purification.

Most of the required primary amines are available commercially. 5-Phenylpentylamine[24] and 6-phenylhexylamine[25a] were obtained according to literature directions. 4-(4-Chlorophenyl)butylamine (**8**) was derived from 4-(4-chlorophenyl)-4-oxobutanoic acid (**6**) (Scheme II). Wolff–Kishner reduction of **6** gave 4-(4-chlorophenyl)butanoic acid free from any dehydrated product, which was obtained as a byproduct from the modified Clemmensen reduction.[25b] 2-[3-[(Trifluoromethyl)thio]-phenyl]ethylamine (**11**) was synthesized from ethyl 3-[(trifluoromethyl)thio]benzoate[26a] via the acid and **9**–**11**

Scheme II



Scheme III



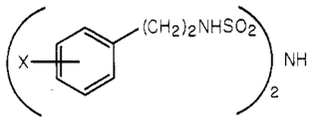
as shown in Scheme III. *N',N''*-Bis-[2-(4-hydroxyphenyl)ethyl]imidodisulfamide (**27**) was prepared from the corresponding methoxy analogue **25** using boron tribromide to cleave the methyl ether.

Results and Discussion

As part of an antiallergic screening program in our laboratories, *N',N''*-bis(4-phenylbutyl)imidodisulfamide

(22) G. Borggrefe and P. Kings, Ger. Offen., 2021680 (1971); R. Appel and R. Helwerth, *Chem. Ber.*, **101**, 1743 (1968).
(23) R. Appel, French Patent 1351486 (1964); R. Appel and G. Eisenhauer, *Ber. Dtsch. Chem. Ges.*, **95**, 1753 (1962); R. Appel, German Patent 1143494 (1963).
(24) W. Shrive and C. Skinner, U.S. Patent 2966488 (1960); N. K. Kochetkov and N. V. Dudykina, *Zh. Obshch. Khim.*, **28**, 2399 (1958).
(25) (a) V. S. Shklyaer and Y. V. S. Chakryshkin, *Zh. Org. Khim.*, **4**, 79 (1968). (b) E. L. Martin, *J. Am. Chem. Soc.*, **58**, 1438 (1936).
(26) (a) D. Remy, K. E. Rittle, C. A. Hunt, and M. B. Freedman, *J. Org. Chem.*, **41** 1644 (1976). (b) Some antagonism of serotonin and prostaglandins E_2 and F_2 was noted.

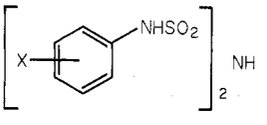
Table II. *N',N''*-Bis[2-(substituted-phenyl)ethyl]imidodisulfamides



no.	X	yield,[a] %	mp, °C	recrystn solvent	formula	anal.	concn, μM	anti-SRS-A inhibn,[b] %
20	2-Cl	63	126-128	CH_2Cl_2	$C_{16}H_{19}Cl_2N_3O_4S_2$[c]	C, H, N, S, Cl	10	8 (NS)[d]
21	3-Cl	67	137-138	MeOH	$C_{16}H_{19}Cl_2N_3O_4S_2$	C, H, N, S, Cl	50	16 (49 SRS-A, 33 KCl)
22	4-Cl	56	148-149	MeOH-CH_2Cl_2	$C_{16}H_{19}Cl_2N_3O_4S_2$	C, H, N, S, Cl	20	62
23	2-OCH_3	57	182-184	MeOH-EtOH	$C_{18}H_{25}N_3O_6S_2$	C, H, N, S	50	0.2 (NS)
24	3-OCH_3	58	100-102	MeOH-H_2O	$C_{18}H_{25}N_3O_6S_2$[c]	C, H, N, S	50	9 (NS)
25	4-OCH_3	65	152-153	MeOH	$C_{18}H_{25}N_3O_6S_2$	C, H, N, S	50	18 (33 SRS-A, 15 KCl)
26	4-Br	52	152-153	EtOAc-hex	$C_{16}H_{19}Br_2N_3O_4S_2$	C, H, N	50	72
27	4-OH	90[e]	180-181	EtOAc-hex	$C_{16}H_{21}N_3O_6S_2$	C, H, N, S	50	7 (NS)
28	4-NO_2	53	155-156	MeOH-H_2O	$C_{16}H_{19}N_5O_8S_2$	C, H, N, S	50	19 (NS)
29	4-CH_3	49	171-172	MeOH	$C_{18}H_{25}N_3O_4S_2$	C, H, N, S	50	1 (NS)
30	3-SCF_3	19	107-108	CH_2Cl_2-hex	$C_{18}H_{19}F_6N_3O_4S_2$	C, H, N, S	5	−6 (35 SRS-A, 41 KCl)
31	3-CF_3	65	139-140	CH_2Cl_2	$C_{18}H_{19}F_6N_3O_4S_2$	C, H, N	50	32 (75 SRS-A, 43 KCl)
32	3,4-$(Cl)_2$	25	110-111	MeOH-Et_2O-hex	$C_{16}H_{17}Cl_4N_3O_4S_2$	C, H, N	10	43 (63 SRS-A, 20 KCl)

[a,b] See corresponding footnotes in Table I. [c] Analysis for $0.25H_2O$. [d] Not statistically significant. [e] Yield from the methoxy analogue.

Table III. *N',N''*-Bis(substituted-phenyl)imidodisulfamide



no.	X	yield,[a] %	mp, °C	recrystn solvent	formula	anal.	concn, μM	anti-SRS-A inhibn,[b] %
33	3-Cl	45	164-166	MeOH-HCl	$C_{12}H_{11}Cl_2N_3O_4S_2$[c]	C, H, N, S, Cl	50	16 (43 SRS-A, 27 KCl)
34	4-Cl	13	157-158	EtOAc-hex	$C_{12}H_{11}Cl_2N_3O_4S_2$	C, H, N	50	2[d] (NS)
35	3-Br	52	178-179	EtOH	$C_{12}H_{11}Br_2N_3O_4S_2$	C, H, N, S, Br	50	38 (79 SRS-A, 41 KCl)
36	4-Br	69	215-222	H_2O	$C_{12}H_{11}Br_2N_3O_4S_2$[e]	C, H, N	50	47
37	3-F	19	142-144	$CHCl_3$-hex	$C_{12}H_{11}F_2N_3O_4S_2$	C, H, N	50	10 (NS)
38	4-F	39	144-146	$CHCl_3$	$C_{12}H_{11}F_2N_3O_4S_2$	C, H, N	50	1 (NS)
39	3-CH_3	59	159-161	MeOH-H_2O	$C_{14}H_{17}N_3O_4S_2$	C, H, N	50	13 (NS)
40	4-*n*-Bu	77	153-154	MeOH-H_2O; PhH-hex	$C_{20}H_{29}N_3O_4S_2$	C, H, N, S	5	5 (NS)
41	3-SCH_3	1.2	107-108	CH_2Cl_2-hex	$C_{14}H_{17}N_3O_4S_4$	C, H, N, S	50	12 (NS)
42	3-CF_3	64	179-180	Et_2O-hex	$C_{14}H_{11}F_6N_3O_4S_2$	C, H, N, S, F	50	34 (41 SRS-A, 7 KCl)
43	4-CF_3	1.7	149-150	$CHCl_3$-hex	$C_{14}H_{11}F_6N_3O_4S_2$	C, H, N, S	10 50	24 86
44	4-CO_2Et	1.8	178-179	MeOH	$C_{18}H_{21}N_3O_8S_2$	C, H, N	5	5[d] (NS)
45	4-$COCH_3$	13	170-180 dec	MeOH-HCl	$C_{16}H_{17}N_3O_6S_2$[f]	C, H, N, S	50	11[d] (NS)
46	4-CN	1.6	201-202	HCl-H_2O	$C_{14}H_{11}N_5O_4S_2$	C, H, N, S	50	8[d] (NS)

[a,b] See footnotes in Table I. [c] Analysis for $0.25H_2O$. [d] Percent enhancement of tissue contractions compared with control; NS = not significant. [e] Analysis for $1.0H_2O$ and 1.0Na. [f] Analysis for $0.2H_2O$.

(16) was found to be an antagonist of SRS-A induced contractions of isolated guinea pig ileum. Its action was somewhat selective on the ileum in that it failed to shift significantly the dose–response curve of histamine (0.01–10 μM), carbachol (0.01–10 μM) or potassium chloride (1–100 mM) at the same concentrations (10–50 μM) that provided a significant shift in the SRS-A dose–response curve.[26b] This observation prompted the synthesis of a series of structurally related compounds to permit investigaton of the effect of structural modification on SRS-A antagonist activity. The described study focused on the influence of variation of the alkylene side-chain length and the substitution in the phenyl ring on SRS-A antagonist activity. The compounds prepared and their potencies in a test for antagonism of SRS-A induced contractions of guinea pig ileum in vitro are presented in Tables I–III.

A comparison of activities of compounds **12–18** (Table I) indicated maximum anti-SRS-A potency and selectivity (lack of effect on KCl-induced contractions) with a four-carbon spacing between the aryl ring and the imidodisulfamide moiety, i.e., **16**. Decreasing the length of the side chain, **12–15**, was detrimental to SRS-A antagonist activity. Elongation of the side chain, **17** and **18**, decreased selectivity substantially, since they were potent inhibitors of

both SRS-A and KCl induced contractions.

Several factors, for example, conformational adaptability of the alkylene side chain for interaction of the molecule with the SRS-A receptor site(s) and/or the influence of the bridge on total lipophilicity (hydrophobicity) of the molecule, could account for the preferred four-carbon aryl to imidodisulfamide spacing. Detailed studies concerning the influence of conformation adaptability of the alkylene side chain for receptor interaction will be addressed in a subsequent paper. Primary emphasis in the present study of bissubstituted imidodisulfamides was directed toward the effect of total lipophilicity of the aryl and aralkyl substituent on anti-SRS-A activity and selectivity. This initial approach was suggested by the observation that 4,4'-dichloro derivative **19** was less selective than its unsubstituted counterpart **16**. The decreased selectivity of action of **19** may be a consequence of the contribution of the chloro substitution to increased lipophilicity (π) and perhaps electronic factors which increases the overall lipophilicity of the molecule four times as compared with **16**.

To examine the overall influence of lipophilicity on SRS-A antagonist selectivity, two series of substituted imidodisulfamides were studied. These were ring-substituted *N',N''*-bis[(phenyl)ethyl]imidodisulfamides (Table II), and *N',N''*-bis(phenyl)imidodisulfamides (Table III). The Topliss scheme[27] was employed in an effort to garner maximum structure–activity relationship (SAR) information with a minimum number of compounds. Topliss has utilized Hansch considerations that a particular substituent may modify activity relative to the parent compound by virtue of resulting changes in hydrophobic, electronic, and steric effects. The unsubstituted phenyl derivative **14** was utilized as the parent for application of the Topliss scheme. Since many systems are $+\pi$ dependent, i.e., activity increases with increasing π values, the 4-chloro analogue **22** was selected first. Since the potency of the 4-chloro analogue **22** was greater than that of the parent **14**, it was attributed to a $+\pi$, a $+\sigma$ effect, or a combination of both. The 3,4-dichloro analogue **32** was selected because its π and σ values are larger than for its monochloro counterpart. Although the SRS-A antagonist potency was increased in **32** as compared with **22**, selectivity was decreased as measured by its ability to inhibit KCl-induced contractions of guinea pig ileum. The decreased selectivity of **32** suggested either an unfavorable steric effect of meta substitution, exceeding optimum lipophilicity, or both. To test which factor had a greater influence on SRS-A selectivity, compounds **30** and **31** were prepared. The lipophilicity of the 3-SCF_3 derivative **30** is comparable and the 3-CF_3 derivative **31** is less than that of the 3,4-dichloro analogue **32**. Both metasubstitued compounds **30** and **31** are more lipophilic than the 4-Cl derivative **22**. As indicated in Table II, **30** and **31** were highly nonselective. The decreased selectivity of these compounds may reflect an unfavorable influence of meta substitution but does not preclude the possibility that lipophilicity is exceeded beyond an optimum value. The 4-bromo compound **26** was examined because it is para substituted and less lipophilic than the 3,4-Cl_2 derivative **32** but more lipophilic than the 4-Cl congener **22**. The 4-bromo analogue **26** represents an alternative to the 4-CF_3 compound, since they are of comparable lipophilicity. Compound **26** was indeed a potent and selective SRS-A antagonist, which supports the notion that substitution by an optimum lipophilic group at the para position is favorable for a high degree of potency and selectivity. In order to verify the $+\sigma$ dependency and an optimum π value less than that of Br or CF_3 groups, the 4-nitro compound **28** was selected (low $+\pi$ and high $+\sigma$). The weak activity of **28** supports the suggested importance of an optimum π value for selective anti-SRS-A activity of ring-substituted *N',N''*-bis(2-phenylethyl)imidodisulfamides. In order to probe the importance of $+\sigma$ value, the 4-CH_3 compound **29** ($+\pi$, $-\sigma$) was tested; its biological activity also supported the importance of both $+\pi$ and $+\sigma$ values. To further confirm this, a few compounds carrying substituents with $-\pi$, $-\sigma$ values, namely, **24**, **25** and **27**, were studied. Such substitution had little or no influence on SRS-A antagonist activity (compare **24**, **25**, and **27** vs. **14**). As indicated in Table II, chloro substitution increased anti-SRS-A potency and selectivity in the following order: para (**22**) > meta (**21**) > ortho (**20**). A similar but less decisive order was observed upon substitution with the less lipophilic methoxy group: para (**25**) > meta (**24**) > ortho (**23**).

Studies on the phenylimidodisulfamide series were directed to substituted derivatives having a wide range of both π and σ values. Appropriate substitutents were selected from the two-dimensional maps described by Graig.[28] Only the meta- and para-substituted derivatives were studied. The results tabulated in Table III indicated that SRS-A antagonist potency is greatest upon addition of lipophilic substituents, such as Cl, Br, and CF_3 ($+\pi$, $+\sigma$), and selectivity is favored by the para substitution. Substituents in the para position selected from the second quadrant of the two-dimensional map (i.e., $+\pi$, $+\sigma$) with a wide range of values are represented in compounds **34**, **36**, **38**, and **43**. Once again, increased potency was observed with optimum $+\pi$, $+\sigma$ [i.e., Br (**36**) and CF_3 (**43**)], while no effect on potency with low $+\pi$, $+\sigma$ [i.e., F (**38**)] was observed. Unexpectedly, the *p*-chloro compound **34** lacked significant activity. Substituents selected from other quadrants [i.e., having $-\pi$, $+\sigma$ (represented in **45** and **46**) and having $+\pi$, $-\sigma$ (represented in **40**)] had no effect on activity. Substitution in the meta position with similar $+\pi$, $+\sigma$ values were generally nonselective (see compounds **33**, **35**, and **42**). These results again suggested that meta substitution is detrimental to anti-SRS-A activity. Substitution with low positive or negative π and σ value substitutients, such as in **37**, **39**, and **41** has no effect on potency.

In summary, among a series of *N',N''*-bis(aryl)- and *N',N''*-bis(aralkyl)imidodisulfamides, selective activity as antagonists of SRS-A induced contractions of isolated guinea pig ileum seems to depend on both lipophilic (π) and electronic (σ) factors. The *N',N''*-[2-(*p*-chlorophenyl)ethyl]- (**22**) and *N',N''*-[2-(*p*-bromophenyl)ethyl]-imidodisulfamide (**26**) were optimum among a number of such compounds selected by the Topliss method[27] and the two-dimensional π, σ maps of Craig.[28]

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer 240 apparatus by the Analytical Department of Smith Kline & French Laboratories, and where analyses are indicated by the symbols of the elements, the analytical results obtained for those elements were within ±0.4% of the theoretical values. TLC was performed on Analtech Silica Gel GF 1 × 4 in. slides, 250 μm thick, using 20% CH_3OH–$CHCl_3$ as an eluent. Field-desorption mass spectra were obtained on Varian MAT CH-5 DF spectromer. IR spectra were obtained on a Perkin-Elmer 137 spectrophotometer as Nujol mulls, and ^1H

(27) J. G. Topliss, *J. Med. Chem.*, **15**, 1006 (1972).

(28) P. N. Craig, *J. Med. Chem.*, **14**, 680 (1971).

NMR spectra were obtained on a Hitachi Perkin-Elmer R-24 as a solution in a mixture of $CDCl_3$–Me_2SO-d_6 using Me_4Si as an internal standard. All spectra were consistent with the assigned structures.

***N',N''*-Bis(4-phenylbutyl)imidodisulfamide (16).** To a solution of 8.56 g (0.04 mol) of imidodisulfuryl chloride[23] in 20 mL of dry acetonitrile was added dropwise 12.1 g (0.12 mol) of dry triethylamine at −40 °C. After the addition was completed, the mixture was allowed to warm to 0 °C and then a solution of 4-phenylbutylamine (13.43 g, 0.09 mol) in 20 mL of acetonitrile was added portionwise. The reaction mixture was stirred at 25 °C for 12 h. Precipitated triethylamine hydrochloride was filtered off, and the filtrate was concentrated. The residual oil was dissolved in aqueous methanol, and the solution was acidified with 2 N HCl to give a white solid. It was recrystallized from CH_3OH to give 10.55 g (60%) of **16**, mp 133–134 °C. Anal. ($C_{20}H_{29}N_3O_4S_2$) C, H, N, S.

***N',N''*-Bis[2-(2-methoxyphenyl)ethyl]imidodisulfamide (23).** To a solution of 5.35 g (0.025 mol) of imidodisulfuryl chloride in 15 mL of acetonitrile was added dropwise 7.58 g (0.075 mol) of triethylamine at −40 °C. After addition of the triethylamine was completed, the reaction was warmed to 0 °C, and a solution of 7.56 g (0.05 mol) of 2-(2-methoxyphenyl)ethylamine in 20 mL of acetonitrile was added dropwise. The mixture was stirred at 25 °C for 12 h. The triethylamine hydrochloride was filtered, and the filtrate was concentrated. The residual oil was partitioned between ethyl acetate and dilute HCl. The ethyl acetate extract was washed twice with water and concentrated to a small volume. A white crystalline solid that separated was recrystallized from a mixture of methanol and ethanol to yield 6.4 g (58%), mp 182–184 °C. Anal. ($C_{18}H_{25}N_3O_6S_2$) C, H, N, S.

***N',N''*-Bis[2-(4-hydroxyphenyl)ethyl]imidodisulfamide (27).** To a suspension of 7.37 g (0.0166 mol) of *N',N''*-bis[2-(4-methoxyphenyl)ethyl]imidodisulfamide (**25**) in 120 mL of methylene chloride was added a solution of 25.0 g (0.099 mol) of boron tribromide in 150 mL of methylene chloride during 2 h. After being stirred for 3 h, the reaction mixture was cooled by means of an ice–water bath and was quenched **cautiously** with 210 mL of water, followed by addition of 400 mL of ether. The ether layer was separated, and the aqueous layer was extracted three times with ether. The combined ether extracts were extracted with 2.5 N NaOH. The alkaline extract was acidified with 2.5 N HCl, and the mixture was extracted with ether. The ether extract was dried ($MgSO_4$) and concentrated. The residual solid was recrystallized from a mixture of ethyl acetate–*n*-hexane to give 6.2 g (90%) of **27**, mp 180–181 °C. Anal. ($C_{18}H_{21}N_3O_6S_2$) C, H, N, S.

4-(4-Chlorophenyl)butanoic Acid. A mixture of 5.0 g (0.0235 mol) of 4-(4-chlorophenyl)-4-oxobutanoic acid,[30] 3.5 g of KOH, and 2.5 mL of hydrazine hydrate (99–100%) in 25 mL of diethylene glycol was refluxed azeotropically at 120–130 °C for 90 min. Heating under reflux was continued at 190 °C for 3 h. The reaction mixture was cooled to 25 °C, diluted with 25 mL of water, and poured into 30 mL of 2.5 N HCl to give 4.4 g (94%) of a white crystals: mp 54–57; ^1H NMR and IR were considered consistent with the saturated acid.

4-(4-Chlorophenyl)butanamide (7). A mixture of 6.7 g (0.0337 mol) of 4-(4-chlorophenyl)butanoic acid and 10 mL (0.137 mol) of thionyl chloride in 50 mL of chloroform was refluxed for 8 h. Chloroform and excess thionyl chloride were removed in vacuo, and the residue was evaporated twice with 25 mL of toluene to remove traces of thionyl chloride. The residue was taken into 10 mL of toluene and added to 30 mL of cold concentrated amonnium hydroxide to give 5.5 g (83%) of **7**. Recrystallization from $CHCl_3$–*n*-hexane gave white needles, mp 113–115 °C.

4-(4-Chlorophenyl)butylamine (8).[31] To a stirred suspension of 12.6 g (0.33 mol) of $LiAlH_4$ in 340 mL of dry ether was added dropwise at 25 °C a solution of 16.4 g (0.083 mol) of **7** in 150 mL of dry THF. The mixture was stirred at 25 °C for 4 h. The complex was decomposed by adding dropwise, with **caution**, successively 13 mL of water, 10 mL of 5 N NaOH, and 45 mL of water. The organic layer was separated, and the emulsion was extracted three times with 50 mL of ether. The combined organic and ether extracts were dried over sodium hydroxide and concentrated to give a colorless liquid, which was distilled at 75–80 °C (0.2–0.25 torr) to afford 11.0 g (72%) of **8**. A hydrochloride had mp 162–164 °C (from EtOH–EtOAc). Anal. ($C_{10}H_{14}ClN$·HCl) C, H, N, Cl.

3-[(Trifluoromethyl)thio]benzyl Alcohol (9). To a stirred suspension of 1.5 g (0.0426 mol) of $LiAlH_4$ in 50 mL of dry ether was added dropwise a solution of 4.7 g (0.0213 mol) of 3-[(trifluoromethyl)thio]benzoic acid in 100 mL of ether–THF. After the addition was completed, the reaction mixture was refluxed for 6 h. The complex was decomposed by adding dropwise, with **caution**, successively water, 2.5 N NaOH, and then water. The organic layer was separated, and the aqueous phase was extracted with ether. The combined organic and ether extracts were dried ($MgSO_4$) and concentrated to give 2.4 g (55%) of **9**.

[3-[(Trifluoromethyl)thio]phenyl]acetonitrile (10). Thionyl chloride (50 mL, 0.69 mol) was added to **9** (17.0 g, 0.082 mol) while cooling by means of an external ice–water bath. The mixture was stirred at 25 °C for 18 h. Excess thionyl chloride was removed in vacuo, and the residue was evaporated twice with benzene to give 17.0 g (91%) of 3-[(trifluoromethyl)thio]benzyl chloride, which was refluxed with a mixture of 5.14 g of sodium cyanide, 0.68 g of sodium iodide, 63.2 mL of ethanol, and 15.8 mL of water for 90 min. The resulting solution was concentrated in vacuo, and the residue was taken into water and extracted with ether. The ether extract was dried ($MgSO_4$) and concentrated to give 15.9 g (98%) of **10**.

2-[3-[(Trifluoromethyl)thio]phenyl]ethylamine (11). To a stirred solution of 147 mL of 1 M diborane in THF and 100 mL of THF was added dropwise a solution of 15.9 g (0.0733 mol) of **10** in 100 mL of THF at 0–5 °C. The solution was stirred at 0–5 °C for 1 h and at 25 °C for 16 h, and then it was refluxed for 5 h. The complex was decomposed by adding dropwise 60 mL of methanol at 0–10 °C, and then the solution was concentrated in vacuo. The residue was evaporated twice with methanol to remove methyl borate. The residual oil was treated with 2.5 N HCl and then was basified with 10 N NaOH and extracted with ether. The ether extract was washed twice with water, dried, and concentrated. Sausage flask distillation gave 9.3 g (57%) of **11**. A hexamate melted at 157–158 °C. Anal. ($C_9H_{10}F_3NS$·$C_6H_{13}NO_2S$) C, H, N.

Biological Test Procedure. 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 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

(29) D. M. Engineer, V. Niederhauser, P. J. Piper, and P. Sirois, *Br. J. Pharmacol.*, **62**, 61 (1978); H. R. Morris, G. W. Taylor, P. J. Piper, P. Sirois, and J. R. Tippins, *FEBS Lett.*, **87**, 203 (1978); M. O'Donnell, K. Falcone, and R. D. Krell, to be published in *Prostaglandins*.

(30) L. Fieser and A. Seligman, *J. Am. Chem. Soc.*, **60**, 170 (1938).

(31) G. Lambelin, J. Roba, C. Gillet, and R. Roncocci, Ger. Offen. 2651572 (1977); Continental Pharma. Fr. Demande 2370472 (1978).

test compound indicated above 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 reporducibly 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.[29] FPL-55712 was used as a reference for each compound tested.

Acknowledgment. The authors are grateful to Dr. C. Kaiser for advice and encouragement. Our thanks to Ms. I. Uzinskas for preparing 11 and the Analytical and Physical Chemistry staff at Smith Kline & French Laboratories for performing the mass spectra and elemental analyses. We also thank Ms. R. Osborn, Ms. M. Graus, and Mr. E. Poserina (deceased) for the biological screening.

Synthesis and Antitumor Activity of New Platinum Complexes

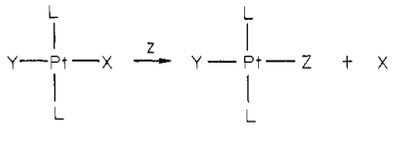
David B. Brown,* A. R. Khokhar, M. P. Hacker, L. Lokys, J. H. Burchenal, R. A. Newman, J. J. McCormack, and David Frost

Vermont Regional Cancer Center and Departments of Chemistry and Pharmacology, University of Vermont, Burlington, Vermont, and Memorial Sloan-Kettering Cancer Center, New York, New York 10021. *Received June 26, 1981*

A new type of antitumor platinum complex has been prepared and examined for antitumor activity against L1210 leukemia both in vitro and in vivo. The coordination environment of platinum in these complexes consists of three anionic chloride ions and a positively charged amine. The positive charge is introduced by monoprotonation or monoalkylation of a diamine. Platinum(IV) derivatives have been prepared for several of the complexes, and a water-soluble sulfate derivative has been prepared for one of them. Several of these complexes exhibit significant in vitro activity, and trichloro(3-aminoquinuclidinium)platinum(II) (QTP) exhibits significant in vivo activity as well. An increase in life span of approximately 40% has been observed using QTP. QTP is toxic at doses slightly in excess of effective doses.

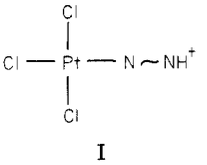
The effectiveness of transition-metal complexes, particularly platinum complexes, as experimental antitumor agents has been demonstrated repeatedly in recent years.[1] *cis*-Dichlorodiammineplatinum(II) (PDD, cisplatin) is the prototype metal complex with antitumor activity and is currently available for clinical use in testicular tumors, ovarian carcinoma, and other tumor types.[2] A large number of platinum complexes have been evaluated in an effort to identify compounds with a broader spectrum of clinical applicability than PDD and lower toxicity than PDD. The vast majority of platinum complexes that have been examined are of the general form *cis*-A_2PtX_2, where X is an anionic ligand, typically chloride, and A is an amine (or A_2 a chelating diamine).

The mechanistic details of the reaction(s) of platinum complexes with cellular macromolecules are still not established satisfactorily, but it is generally agreed that cytostatic activity results from substitution reactions involving displacement of anionic ligands from the metal complex.[3] The rates of substitution reactions at square-planar platinum(II) are dominated by the trans effect.[4] All other factors being comparable, the relative rate of displacement of a particular ligand, X, is dependent on the nature of the ligand, Y, occupying the position trans to it in the complex (eq 1). PDD has a leaving group, the



(1)

chloride ion, that is situated trans to ammonia. Amines are at the lower end of the trans effect series; consequently, the substitution reactions of Cl^- in PDD are relatively sluggish. The reactivity of PDD, and possibly its biological activity, could be enhanced by replacing ammonia with ligands that are higher in the trans-effect series. Replacing ammonia with anionic ligands would produce negatively charged complexes that might not penetrate target cells readily. However, the desired complex neutrality could be obtained if one ammonia were replaced by an anion and the other ammonia were replaced by a cationic ligand. We have chosen to introduce the chloride ion, which lies above ammonia in the trans-effect series, as the new anionic ligand and to use monoprotonated (or monoalkylated) diamines as the cationic ligands. This results in a series of compounds having the general structure I, where N~



I

NH^+ represents a protonated diamine. The trans effect dictates that a chloride ion lying trans to another chloride will be substitutionally labile, and the symmetry of the complex provides two activated chloride ions that can serve as the initial leaving group. This report describes the synthesis and biological activity of a series of complexes of type I.

Discussion

Synthesis and Characterization of Complexes. There have been a few reports of platinum complexes with positively charged amine ligands, but in most instances the complexes were prepared only as precursors for studies of

(1) Cleare, M. J.; Hydes, P. C. *Met. Ions Biol. Syst.* **1980**, *11*, 1-62.
(2) Einhorn, L. H.; Williams, S. D. *N. Engl. J. Med.* **1979**, *300*, 289.
(3) Rosenberg, B. *Cancer Treat. Rep.* **1979**, *63*, 1433.
(4) Hartley, F. R. *Chem. Soc. Rev.* **1973**, *2*, 163.

0022-2623/82/1825-0952$01.25/0