Table I. Inhibition of PNMT by Ring-Substituted Amphetamines

Substituent	E_{S-2}[a]	$\Sigma\pi_{-2,3}$[b]	$\Sigma\sigma$	D	pI_{50} Obsd[c]	pI_{50} Calcd[d]	$\lvert\Delta pI_{50}\rvert$
3,4-Cl_2	1.24	0.71	0.60	0.00	5.10	4.70	0.40
3-Cl	1.24	0.71	0.37	0.00	4.23	4.38	0.15
4-CF_3	1.24	0.00	0.54	0.00	4.00	3.91	0.09
3,4-F_2	1.24	0.14	0.40	0.00	3.85	3.85	0.00
3-F	1.24	0.14	0.34	0.00	3.75	3.77	0.02
4-Cl	1.24	0.00	0.23	0.00	3.60	3.48	0.12
4-*i*-Pr	1.24	0.00	−0.15	0.00	3.30	2.94	0.36
3-Me	1.24	0.50	−0.07	0.00	3.17	3.55	0.38
4-Me	1.24	0.00	−0.17	0.00	3.14	2.91	0.23
4-F	1.24	0.00	0.06	0.00	3.01	3.24	0.23
H	1.24	0.00	0.00	0.00	2.89	3.15	0.26
3,4-Me_2	1.24	0.50	−0.24	0.00	2.85	3.31	0.46
4-OC_6H_5	1.24	0.00	−0.32	0.00	2.76	2.70	0.06
4-OMe	1.24	0.00	−0.27	0.00	2.57	2.77	0.20
3-OMe	1.24	−0.02	0.12	1.00	2.07	2.29	0.22
3-OMe, 4-OEt	1.24	−0.02	−0.12	1.00	2.06	1.95	0.11
3,4-$(OMe)_2$	1.24	−0.02	−0.15	1.00	2.00	1.91	0.09
3-Br, 4-OH	1.24	0.86	0.02	0.00	4.15	4.03	0.12
3-Cl, 4-OH	1.24	0.71	0.00	0.00	4.15	3.86	0.29
3,4-$(OH)_2$[e]	1.24	−0.67	−0.25	0.00	3.30	2.14	1.16
4-OH	1.24	0.00	−0.37	0.00	3.12	2.63	0.49
3-OH	1.24	−0.67	0.12	0.00	2.77	2.66	0.11
2,4-Cl_2	0.27	0.71	0.45	0.00	4.02	4.02	0.00
2,5-F_2	0.78	0.14	0.40	0.00	3.48	3.63	0.15
2,6-Cl_2	−0.70	0.71	0.45	0.00	3.47	3.55	0.08
2-Me	0.00	0.50	−0.17	0.00	3.25	2.81	0.44
2-Cl	0.27	0.71	0.23	0.00	3.24	3.71	0.47
2-F	0.78	0.14	0.06	0.00	3.17	3.15	0.02
2,4-F_2	0.78	0.14	0.12	0.00	3.08	3.24	0.16
2,4-Me_2	0.00	0.50	−0.34	0.00	2.85	2.57	0.28
2,5-Me_2	0.00	0.50	−0.24	0.00	2.83	2.71	0.12
2,3-$(OMe)_2$	0.69	−0.04	−0.15	1.00	1.65	1.62	0.03
2,4-$(OMe)_2$	0.69	−0.02	−0.54	0.00	1.51	2.11	0.60

[a]See reference 3. [b]π values are from the benzene system; see reference 4. [c]From reference 2. [d]Calcd using eq 3. [e]This point not used in deriving eq 3.

Baker's bulk tolerance principle[5]) should then be placed in the 3 position. For example, if bulk tolerance would allow the use of a 3-Bu function, the 4-NO_2-3-Bu derivative would be more potent than any of the inhibitors of Table I. The predicted pI_{50} is 6.1. If a group as large as hexyl could be accommodated in the 3 position, pI_{50} would be 7.1.

For *in vivo* work $\log P_o$ would set a lower limit on total lipophilic character. Under these conditions the 4-SO_2CH_3 function could be used to balance a 3-Bu or 3-Hex function.

The coefficient with the $\pi_{-2,3}$ term is not uncommon for enzymic hydrophobic bonding.[6,7] The rather large coefficient with the σ term indicates that activity is highly dependent on electron withdrawal by substituents. This might well indicate that an electron-deficient inhibitor benzene ring is interacting with an electron-rich site in the enzyme. The high negative coefficient with D indicates an inexplicable deleterious effect of a 3-MeO function.

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N^1,N^1-Dialkyl-N^4,N^4-dialkylaminoacetylsulfanilamide as Potent Surface Anesthetics

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In a previous communication,[1] we reported the synthesis and potent local anesthetic activity of sulfamoylbenzoic acid ester derivatives of low toxicity. In the present work, we report the synthesis and surface anesthetic activity of a new series of compounds: N^1,N^1-dialkyl-N^4,N^4-dialkylaminoacetylsulfanilamide.

Scheme I

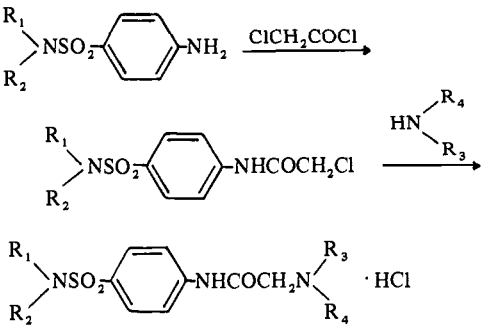
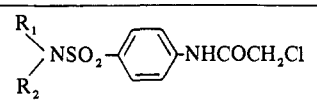


Table I



R_1	R_2	Yield, %	Mp, °C	Formula[a]
CH_3	CH_3	78	120[b]	$C_{10}H_{13}ClN_2O_3S$
C_2H_5	C_2H_5	76	113[c]	$C_{12}H_{17}ClN_2O_3S$
n-C_3H_7	n-C_3H_7	82	119[b]	$C_{14}H_{21}ClN_2O_3S$
n-C_4H_9	n-C_4H_9	73	123[b]	$C_{16}H_{25}ClN_2O_3S$
$(CH_2)_4$		86	157[b]	$C_{12}H_{15}ClN_2O_3S$
$(CH_2)_5$		71	136[c]	$C_{13}H_{17}ClN_2O_3S$
$O(CH_2CH_2)_2$		80	147[b]	$C_{12}H_{15}ClN_2O_4S$

[a] All compds were anlyzed for C, H, and the results were satisfactory. Similarly ir and nmr spectra were as expected. [b] Recrystd from EtOAc. [c] Recrystd from EtOAc–petr ether.

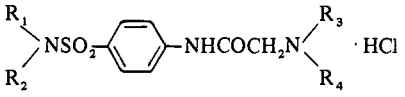
tivity. However, the same compounds with a morpholine residue on the acetamide group were not active. In guinea pigs, as contrasted with rabbits, **14** and **19** were ineffective. All potent compounds caused conjunctival congestion in the first hour, and slight opalescence of the cornea, especially in guinea pigs, was present 48 hr after instillation.

Experimental Section†

N^1,N^1-Dialkyl-N^4,N^4-chloroacetamidosulfanilamide. To a soln of 0.1 mole of N^1,N^1-dialkylsulfanilamides, prepd by known methods, in 50 ml of glacial AcOH, was added dropwise 12.43 g (0.11 mole) of $ClCH_2COCl$ at room temp during 1 hr. The mixt was stirred for an addl 1 hr and then was poured into cold H_2O. The ppt was filtered, dried, and recrystd from AcOEt or AcOEt–petr ether (see Table I).

N^1,N^1-Dialkyl-N^4,N^4-dialkylaminoacetylsulfanilamide. A soln of 0.01 mole of N^1,N^1-dialkyl-N^4,N^4-chloroacetamidosulfanilamide and 0.025 mole of the appropriate amine in 10 ml of dry C_6H_6, was refluxed for 2 hr. The ppt formed was filtered and proved to be the starting dialkylamine · HCl. The filtrate was evapd and the residue was crystd (see Table II). The free amine, dissolved in EtOH, was converted to the corresponding hydrochloride in Et_2O soln (see Table II).

Table II



Compd	R_1	R_2	R_3	R_4	Yield, %	Mp, °C Base	Mp, °C HCl	Formula[a]
1	CH_3	CH_3	CH_3	CH_3	76	107	251	$C_{12}H_{20}ClN_3O_3S$
2	CH_3	CH_3	C_2H_5	C_2H_5	82	84	219	$C_{14}H_{24}ClN_3O_3S$
3	CH_3	CH_3	$(CH_2)_4$		79	151	260	$C_{14}H_{22}ClN_3O_3S$
4	CH_3	CH_3	$(CH_2)_5$		69		249	$C_{15}H_{24}ClN_3O_3S$
5	CH_3	CH_3	$O(CH_2CH_2)_2$		85	194	223	$C_{14}H_{22}ClN_3O_4S$
6	C_2H_5	C_2H_5	CH_3	CH_3	81	102	209	$C_{14}H_{24}ClN_3O_3S$
7	C_2H_5	C_2H_5	C_2H_5	C_2H_5	82	77	203	$C_{16}H_{28}ClN_3O_3S$
8	C_2H_5	C_2H_5	$(CH_2)_4$		79	104	202	$C_{16}H_{26}ClN_3O_3S$
9	C_2H_5	C_2H_5	$(CH_2)_5$		80	120	179	$C_{17}H_{28}ClN_3O_3S$
10	C_2H_5	C_2H_5	$O(CH_2CH_2)_2$		73	97	212	$C_{16}H_{26}ClN_3O_4S$
11	n-C_3H_7	n-C_3H_7	CH_3	CH_3	77		217	$C_{16}H_{28}ClN_3O_3S$
12	n-C_3H_7	n-C_3H_7	C_2H_5	C_2H_5	81		191	$C_{18}H_{32}ClN_3O_3S$
13	n-C_3H_7	n-C_3H_7	$(CH_2)_4$		79	69	182	$C_{18}H_{30}ClN_3O_3S$
14	n-C_3H_7	n-C_3H_7	$(CH_2)_5$		68	99	189	$C_{19}H_{32}ClN_3O_3S$
15	n-C_3H_7	n-C_3H_7	$O(CH_2CH_2)_2$		80	120	181	$C_{18}H_{30}ClN_3O_4S$
16	n-C_4H_9	n-C_4H_9	CH_3	CH_3	86		226	$C_{18}H_{32}ClN_3O_3S$
17	n-C_4H_9	n-C_4H_9	C_2H_5	C_2H_5	83		173	$C_{20}H_{36}ClN_3O_3S$
18	n-C_4H_9	n-C_4H_9	$(CH_2)_4$		79		178	$C_{20}H_{34}ClN_3O_3S$
19	n-C_4H_9	n-C_4H_9	$(CH_2)_5$		71		163	$C_{21}H_{36}ClN_3O_3S$
20	n-C_4H_9	n-C_4H_9	$O(CH_2CH_2)_2$		80	93	125	$C_{20}H_{34}ClN_3O_4S$
21	$(CH_2)_4$		CH_3	CH_3	79	102	265	$C_{14}H_{22}ClN_3O_3S$
22	$(CH_2)_4$		C_2H_5	C_2H_5	85	132	234	$C_{16}H_{26}ClN_3O_3S$
23	$(CH_2)_4$		$(CH_2)_4$		79	150	260	$C_{16}H_{24}ClN_3O_3S$
24	$(CH_2)_4$		$(CH_2)_5$		75	152	249	$C_{17}H_{26}ClN_3O_3S$
25	$(CH_2)_4$		$O(CH_2CH_2)_2$		72		262	$C_{16}H_{24}ClN_3O_4S$
26	$(CH_2)_5$		CH_3	CH_3	77	113	217	$C_{15}H_{24}ClN_3O_3S$
27	$(CH_2)_5$		C_2H_5	C_2H_5	69	110	205	$C_{17}H_{28}ClN_3O_3S$
28	$(CH_2)_5$		$(CH_2)_4$		72	150	235	$C_{17}H_{26}ClN_3O_3S$
29	$(CH_2)_5$		$(CH_2)_5$		77	149	145	$C_{18}H_{28}ClN_3O_3S$
30	$(CH_2)_5$		$O(CH_2CH_2)_2$		68	187	226	$C_{17}H_{26}ClN_3O_4S$
31	$O(CH_2CH_2)_2$		CH_3	CH_3	70	116	229	$C_{14}H_{22}ClN_3O_4S$
32	$O(CH_2CH_2)_2$		C_2H_5	C_2H_5	71	98	218	$C_{16}H_{26}ClN_3O_4S$
33	$O(CH_2CH_2)_2$		$(CH_2)_4$		82	139	247	$C_{16}H_{24}ClN_3O_4S$
34	$O(CH_2CH_2)_2$		$(CH_2)_5$		66	160	210	$C_{17}H_{26}ClN_3O_4S$
35	$O(CH_2CH_2)_2$		$O(CH_2CH_2)_2$		73	201	224	$C_{16}H_{24}ClN_3O_5S$

[a] All compds were analyzed for C, H, and the results were satisfactory. Similarly ir and nmr spectra were as expected.

The general route of the synthesis is shown in Scheme I. In the case of N^1,N^1-dipropyl-N^4,N^4-dialkylaminoacetylsulfanilamide, the starting N^1,N^1-dipropylsulfanilamide was prepared by Curtius rearrangement of the appropriate benzoyl azide. The physical data of all compounds prepared are summarized in Tables I and II.

Pharmacology. All compounds were screened for surface anesthetic activity. The results for potent compounds are summarized in Table III. Among the compounds synthesized, those having di-*n*-propylsulfamoyl, or di-*n*-butylsulfamoyl groups were found to have surface anesthetic ac-

Acknowledgment. The authors are grateful to Dr. M. L. Smith of the Central Treaty Organization for providing

†Melting points were taken on a Kofler hot stage microscope and are uncorrected. The ir spectra were detd with a Leitz Model III spectrograph (KBr). Nmr spectra were obtd on a Varian A60A instrument (Me_4Si).

Table III[a]

Compd	Concn, %	Rabbit cornea		Guinea pig cornea	
		Potency	Duration	Potency	Duration
11	1	0.46 (0.37-0.56)	0-23	0.25 (0.17-0.33)	0-14
12	1	0.96 (0.93-1.00)	24-33	0.92 (0.86-0.97)	16-39
	0.50	0.37 (0.28-0.46)	8-12	0.39 (0.29-0.48)	0-13
13	1	0.99 (0.97-1.00)	11-36	0.97 (0.94-1.00)	15-33
	0.50	0.44 (0.34-0.53)	4-15	0.80 (0.72-0.87)	9-18
14	1	1.00	24-63	0.07 (0.02-0.12)	0-6
	0.50	0.95 (0.91-0.99)	16-30	0.00	
16	1	1.00	18-69	0.90 (0.84-0.96)	16-27
	0.50	0.70 (0.61-0.79)	8-27	0.78 (0.70-0.86)	11-18
	0.25	0.17 (0.09-0.24)	0-9	0.09 (0.04-0.15)	0-4
17	1	0.88 (0.81-0.94)	16-29	0.29 (0.20-0.38)	0-28
18	1	1.00	27-156	0.96 (0.93-1.00)	57-143
	0.50	0.96 (0.92-1.00)	17-51	0.87 (0.81-0.93)	18-63
	0.25	0.50 (0.40-0.60)	0-17	0.12 (0.06-0.18)	0-9
19	1	0.96 (0.93-1.00)	69-111	0.00	
	0.50	0.87 (0.80-0.94)	17-39	0.00	
	0.25	0.13 (0.07-0.20)	0-7	0.00	
Cocaine	1	0.95 (0.92-0.98)	16-24	0.61 (0.52-0.70)	8-21
	0.50	0.54 (0.46-0.62)	7-15	0.55 (0.45-0.64)	4-18
	0.25	0.13 (0.08-0.18)	2-6	0.09 (0.04-0.15)	0-5

[a]Surface anesthesia was tested according to the method of Chance and Lobstein,[2] and the anesthetic potency was calcd for the first 18 min.[3] A potency of 1.00 indicates an onset of anesthesia in 1 min and a duration of at least 18 min.

essential materials. Technical assistance by Miss S. Levtov and Mrs. A. Ramazani is gratefully acknowledged.

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Synthesis and Antibacterial Activity of 5-Nitro-2-furfurylidene Arylthioacethydrazides and 5-Nitro-2-furfurylidene Arylsulfonylacethydrazides

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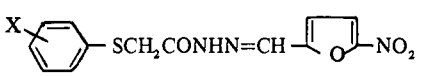
In the course of studies on new antibacterial compounds based on nitrofuran, we have synthesized and screened the title compounds.

Arylthioacetic acid ethyl esters prepared by known methods were treated with hydrazine hydrate to give arylthioacethydrazides. Arylsulfonacethydrazides were prepared similarly from the corresponding arylsulfonylacetic acid ethyl esters. The acethydrazides reacted with 5-nitro-2-furaldehyde afforded the appropriate 5-nitro-2-furfurylidene acethydrazides I and II (see Table II).



I, X_I = H, *m*-F, *p*-CH_3O, *o*-CF_3, *m*-CF_3, *m*-NO_2

II, X_{II} = H, *m*-F, *p*-F, *o*-Cl, *p*-Cl, *o*-CH_3O, *m*-CF_3, *m*-NO_2, *p*-NO_2

New acethydrazides prepared are tabulated in Table I.

Biological Evaluation. Compounds listed in Table II were tested against various Gram-positive and Gram-negative bacteria. Furazolidone was used as a control. The compounds were dissolved in Me_2CO and diluted with H_2O to give a concentration of 250 μ/ml. Paper disks of 9-mm diameter were immersed in the prepared solutions and put on the inoculated penicillin assay seed agar surface.

All compounds were inactive against *Bacillus pyocyaneus* and *Streptococcus β-hemolyticus* at the test concentrations. Compounds **13**, **15**, **20**, and **21** showed slight activities against *Bordetella bronchiseptica* ATCC 4617. Compound **21** showed a hazy inhibition zone with an average value of 12.8 mm against *Proteus vulgaris*. Furazolidone was inactive against the 4 mentioned organisms. The antibacterial activities of the compounds prepared are listed in Table III.

Table I

Compd	Ar	$ArCH_2CONHNH_2$ Mp, °C	Yield, %	Formula[a]
1	$C_6H_5SO_2$	130	68	$C_8H_{10}N_2O_3S$
2	*m*-FC_6H_4S[b]	63	78	$C_8H_9FN_2OS$
3	*m*-$FC_6H_4SO_2$	93	59	$C_8H_9FN_2O_3S$
4	*p*-$FC_6H_4SO_2$	142	61	$C_8H_9FN_2O_3S$
5	*o*-$ClC_6H_4SO_2$	160	64	$C_8H_9ClN_2O_3S$
6	*p*-$ClC_6H_4SO_2$	156	73	$C_8H_9ClN_2O_3S$
7	*m*-$CF_3C_6H_4S$	68	72	$C_9H_9F_3N_2OS$
8	*m*-$CF_3C_6H_4SO_2$	133	61	$C_9H_9F_3N_2O_3S$
9	*m*-$NO_2C_6H_4S$	80	74	$C_8H_9N_3O_3S$
10	*m*-$NO_2C_6H_4SO_2$	155	76	$C_8H_9N_3O_5S$
11	*p*-$NO_2C_6H_4SO_2$	185	66	$C_8H_9N_3O_5S$

[a]All compounds were analyzed for C, H, and the results were satisfactory. Similarly ir, nmr, and mass spectra support the structure assignments. [b]The corresponding ester was prepared according to reference 1.