route.[4] No biological activity has been reported on this compound (4).

Compounds **3a** and **3b** seem to elicit their antidepressant activity by inhibiting the reuptake of norepinephrine into terminal neuronal granules as the tricyclic antidepressants, amitriptyline and imipramine, do. This was demonstrated by the test involving ^{3}H–NE uptake by the rat heart[5] widely employed in the evaluation of antidepressants in which **3a** was more, and **3b** less, active than imipramine. At the same time it was established that they do not cause release of norepinephrine. Also, in the amine pressor response study in the dogs,[1] another test used to characterize antidepressants, **3a** was more potent than amitriptyline and imipramine in potentiating the effect of norepinephrine and about as potent as the latter in antagonizing the effect of phenethylamine.

Compound **3a** thus seems to be a potential potent antidepressant possessing an unusual structure.

Acknowledgment. I thank Drs. M. Cohen, D. H. Smith, J. M. Stump, J. Jainchill, R. Clark, and C. Smith for the biological data.

Registry No. 1, 52003-32-4; **2**, 90269-35-5; **3a**, 90269-36-6; **3a**·HCl, 90269-37-7; **3b**, 90269-38-8; **3b**·HCl, 90269-39-9; anthracene, 120-12-7.

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Articles

Preparation and Antibacterial Activities of New 1,2,3-Diazaborine Derivatives and Analogues

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1,2-Dihydro-1-hydroxy-2-(organosulfonyl)areno[*d*][1,2,3]diazaborines **2** (arene = benzene, naphthalene, thiophene, furan, pyrrole) were synthesized by reaction of (organosulfonyl)hydrazones of arene aldehydes or ketones with tribromoborane in the presence of ferric chloride. The activities of **2** against bacteria in vitro and in vivo (*Escherichia coli*) were determined and structure–activity relationships are discussed. Included in this study are 2,3-dihydro-1-hydroxy-2-(*p*-tolylsulfonyl)-1*H*-2,1-benzazaborole (**3**) and 1-hydroxy-1,2,3,4-tetrahydro-2-(*p*-tolylsulfonyl)-2,1-benzazaborine (**4**) as well as the carbacyclic benzodiazaborine analogue 4-hydroxy-3-(*p*-tolylsulfonyl)isoquinoline (**7**). The nature of the active species is briefly discussed.

The antibacterial activities of 1,2-dihydro-1-hydroxy-2-(organosulfonyl)benzo-, furo-, and -thieno[*d*][1,2,3]diazaborines are well-documented in the literature.[1-12] In the 2,3,1-benzodiazaborine series the known structural variation is almost exclusively restricted to the organosulfonyl side chain. Apart from compounds unsubstituted on the benzene ring,[1-3,10,13] only a few 5-substituted derivatives

Scheme I

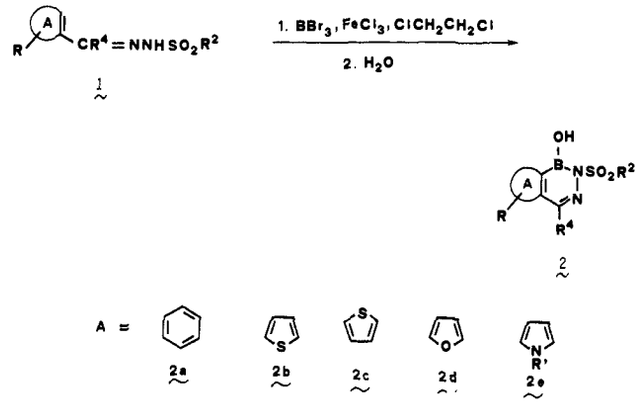

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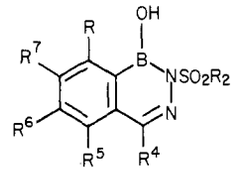
Table I. 2-(Organosulfonyl)-1,2-dihydro-1-hydroxy-2,3,1-benzodiazaborines **2a**



2a	R^2	R^4	R^5	R^6	R^7	R^8	% yield	mp, °C
1	4-$CH_3C_6H_4$	H	H	H	H	H	78	162–4
2	4-$CH_3C_6H_4$	CH_3	H	H	H	H	28	179–180
3	4-$CH_3C_6H_4$	H	CH_3	H	H	H	70	145–6
4	4-$CH_3C_6H_4$	H	H	CH_3	H	H	78	150–2
5	4-$CH_3C_6H_4$	H	CH_3	H	H	CH_3	83	161–3
6	4-$CH_3C_6H_4$	H	F	H	H	H	76	173
7	4-$CH_3C_6H_4$	H	H	F	H	H	81	168–9
8	4-$CH_3C_6H_4$	H	H	H	F	H	63	168
9	4-$CH_3C_6H_4$	H	Cl	H	H	H	26	182–4
10	4-$CH_3C_6H_4$	H	H	Cl	H	H	71	150–1
11	4-$CH_3C_6H_4$	H	H	H	Cl	H	52	173
12	4-$CH_3C_6H_4$	H	Cl	H	Cl	H	39	185
13	4-$CH_3C_6H_4$	H	H	Cl	Cl	H	71	225
14	4-$CH_3C_6H_4$	H	Br	H	H	H	35	198–201
15	4-$CH_3C_6H_4$	H	H	Br	H	H	82	162–4
16	4-$CH_3C_6H_4$	H	H	H	Br	H	76	180
17	4-$CH_3C_6H_4$	H	H	H	OH	H	69	158
18	4-$CH_3C_6H_4$	H	H	NH_2	H	H	25	188–190
19	4-$CH_3C_6H_4$	H	H	$N(CH_3)_2$	H	H	37	173–6
20	4-$CH_3C_6H_4$	H	H	H	$N(CH_3)_2$	H	68	182
21	4-$CH_3C_6H_4$	H	H	H	$NHCOCH_3$	H	31	198–205
22	4-$CH_3C_6H_4$	H	H	$\overline{NCH_2CH_2CH_2CH_2}$	H	H	43	186–190
23	4-$CH_3C_6H_4$	H	Cl	H	$N(CH_3)_2$	H	30	190–3
24	4-$CH_3C_6H_4$	H	H	H	COOH	H	6	259–261
25	4-$CH_3C_6H_4$	C_6H_5	H	H	H	H	50	209–210
26	C_6H_5	H	H	H	OH	H	48	207–210
27	2,4,6-$(CH_3)_3C_6H_2$	H	F	H	H	H	18	162–5
28	2,4,5-$Cl_3C_6H_2$	H	F	H	H	H	74	225–230
29	2,4,5-$Cl_3C_6H_2$	H	H	Br	H	H	32	260–4
30	4-$H_2NC_6H_4$[a]	H	F	H	H	H	84	216–7
31	4-$H_2NC_6H_4$[a]	H	H	Br	H	H	67	210–5
32	4-$H_2NC_6H_4$[a]	H	H	CH_3	H	H	71	185–8
33	2-Cl-4-$H_2NC_6H_3$[b]	H	H	CH_3	H	H	60	215–7
34	2-Cl-4-$CH_3CONHC_6H_3$	H	H	CH_3	H	H	67	250–5
35	2-Cl-4-$CH_3CONHC_6H_3$	H	H	Br	H	H	16	235–240
36	4-$O_2NC_6H_4$	H	F	H	H	H	59	201–3
37	4-$O_2NC_6H_4$	H	H	Br	H	H	67	214–6
38	CH_3	H	H	H	H	H	40	124–6
39	CH_3	H	H	CH_3	H	H	63	127–8
40	*n*-C_3H_7	H	H	CH_3	H	H	64	109–112
41	*n*-C_3H_7	H	H	Cl	H	H	52	109–113
42	$(CH_3)_2N$	H	H	H	H	H	45	125–6
43	$(CH_3)_2N$	H	H	CH_3	H	H	38	137–140

[a] From the nitro derivative by reduction with Fe/HOAc. [b] From the *N*-acetyl derivative by hydrolysis.

are described,[2] without referring to their biological activities.

One major goal of our work was therefore to synthesize 2,3,1-benzodiazaborines with various substituents on the benzene ring and to evaluate their influence on the antibacterial activities. For that purpose a new synthetic route to arenodiazaborines had to be developed.

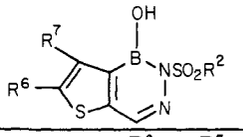
A second point of interest was the question whether the arenodiazaborines themselves are the active species or if hydrolytic cleavage at the BN bond to give the corresponding (dihydroxyboryl)arenes is necessary for biological activities.

Chemistry. At the beginning of our study, the only method described in the literature for the preparation of 2,3,1-benzodiazaborines was the reaction of *o*-formylbenzeneboronic acids with hydrazine or hydrazine derivatives.[14] Since substituted *o*-formylbenzeneboronic acids are difficult to obtain, an alternative approach that would be more suitable for our purpose was investigated. We and B. W. Mueller independently found that (organosulfonyl)hydrazones of many aromatic and heteroaromatic aldehydes and ketones can easily be converted to the corresponding diazaborines with trihaloborane in a Friedel–Crafts type reaction (Scheme I).[13,15] Although the reaction could also be carried out without catalysts, the addition of Lewis acids like $AlCl_3$ was preferable. It led not only to substantially shorter reaction times but also to higher yields. In our hands $FeCl_3$ in boiling 1,2-dichloroethane gave the best results. $AlCl_3$, $ZnCl_2$, and $SnCl_4$ could be used as well, whereas no effect was observed with $TiCl_4$.

As can be seen from the Tables I–VI, alkyl, halogen (F, Cl, Br), amino, alkylamino, and acylamino are tolerated as substituents R on the aromatic ring. With R = alkoxy

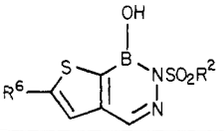
(14) M. J. S. Dewar, *Adv. Chem. Ser.*, *42*, 227 (1964).

Table II. 2-(Organosulfonyl)-1,2-dihyro-1-hydroxythieno-[3,2-*d*][1,2,3]diazaborines **2b**



2b	R^2	R^6	R^7	% yield	mp, °C
1	4-$CH_3C_6H_4$	Br	H	90	170–2
2	4-$CH_3C_6H_4$	H	Br	87	153–5
3	C_6H_5	Br	H	66	190–4
4	2-$CH_3C_6H_4$	Br	H	47	162–4
5	2-$CH_3C_6H_4$	CH_3	H	78	171–4
6	2-ClC_6H_4	Br	H	59	194–8
7	2-ClC_6H_4	CH_3	H	69	200–3
8	2-ClC_6H_4	C_2H_5	H	76	173–5
9	2-Cl-4-$CH_3C_6H_3$	Br	H	68	196–8
10	2-Cl-4-$CH_3C_6H_3$	CH_3	H	74	203–4
11	4-$CH_3C_6H_4$	Cl	H	81	178–180
12	2,4,6-$(CH_3)_3C_6H_2$	Br	H	64	183–4
13	4-$CH_3CONHC_6H_4$	Br	H	60	~217 dec
14	2-Cl-4-$CH_3CONHC_6H_3$	Br	H	44	~256 dec
15	CH_3	H	H	39	132–4
16	C_2H_5	Br	H	7	95
17	*n*-C_3H_7	H	H	58	133–7
18	*n*-C_3H_7	CH_3	H	51	85–6
19	$(CH_3)_2CHCH_2$	Br	H	51	113–5

Table III. 2-(Organosulfonyl)-1,2-dihydro-1-hydroxythieno-[2,3-*d*][1,2,3]diazaborines **2c**



2c	R^2	R^6	% yield	mp, °C
1	4-$CH_3C_6H_4$	Br	66	140–6
2	4-$CH_3C_6H_4$	C_2H_5	36[a]	110
3	2-ClC_6H_4	Br	79	197–202
4	2-ClC_6H_4	C_2H_5	35[a]	177–8
5	2-Cl-4-$CH_3C_6H_3$	CH_3	73[a]	185–6
6	*n*-C_3H_7	CH_3	40[a]	75–6
7	*n*-C_3H_7	C_2H_5	35[a]	60
8	$(CH_3)_2CHCH_2$	CH_3	67[a]	75–6

[a] From the corresponding 3-formylthiophene-2-boronic acid with (organosulfonyl)hydrazine.

the corresponding hydroxy derivatives were obtained as a consequence of concomitant ether cleavage (e.g., **2a–26**).

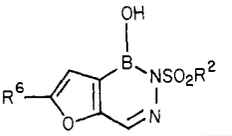
Electron-withdrawing substituents (R = CN or COOH) led to low yields in the cyclization step (e.g., **2a–24**). Likewise no cyclization was observed with tosylhydrazones of aldehydes such as pyridine-2-carboxaldehyde, 1-methylimidazole-2-carboxaldehyde, or 3-methylisothiazole-4-carboxaldehyde. With derivatives of "electron-rich" heterocycles, such as thiophene or furan, good yields of diazaborines were obtained.

Generally, (arylsulfonyl)- and (alkylsulfonyl)hydrazones are equally good substrates for the cyclization reaction. Only the reaction with (alkylsulfonyl)hydrazones of thiophene-3-carboxaldehydes failed, probably due to decomposition of the formed diazaborine under the reaction conditions. 2-(Alkylsulfonyl)-1,2-dihydrothieno[2,3-*d*]-[1,2,3]diazaborines (**2c**) were therefore prepared from 3-formylthiopheneboronic acids with (alkylsulfonyl)-hydrazines as described in the literature.[5]

2,3-Dihydro-1-hydroxy-2-(*p*-tolylsulfonyl)-1*H*-2,1-benzazaborole (**3**) and 1-hydroxy-1,2,3,4-tetrahydro-2-(*p*-tolylsulfonyl)-2,1-benzazaborine (**4**) are close analogues of

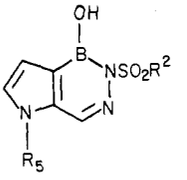
(15) M. Grassberger, Ger. Offen. 2750878, 1978.

Table IV. 2-(Organosulfonyl)-1,2-dihydro-1-hydroxyfuro-[3,2-*d*][1,2,3]diazaborine **2d**



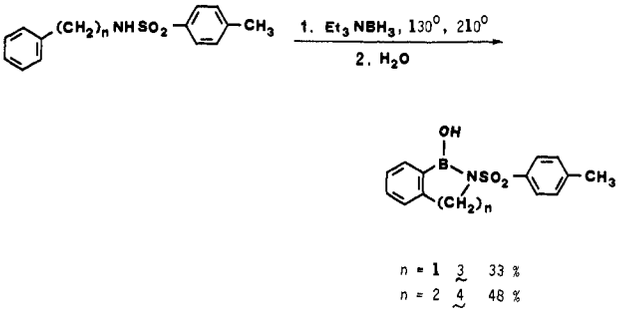
2d	R^2	R^6	% yield	mp, °C
1	4-$CH_3C_6H_4$	CH_3	66	169
2	4-$CH_3C_6H_4$	Br	25	168–170
3	2,4,5-$Cl_3C_6H_2$	Br	84	164–5

Table V. 2-(Organosulfonyl)-1,2-dihydro-1-hydroxypyrrolo-[3,2-*d*][1,2,3]diazaborines **2e**



2e	R^2	R^5	% yield	mp, °C
1	C_3H_7	CH_3	35	125
2	4-$CH_3C_6H_4$	CH_3	45	155–8
3	4-$CH_3C_6H_4$	$C_6H_5CH_2$	12	147–9

Scheme II



the corresponding 2,3,1-benzodiazaborine derivative **2a–l**. They were prepared from *N*-tosylbenzylamine and *N*-tosyl-2-phenylethylamine, respectively, with triethylamine–borane via pyrolytic ring closure[19] (Scheme II).

For biological comparison with the 2,3,1-benzodiazaborine **2a–l**, the boron-free analogue 4-hydroxy-3-(*p*-tolylsulfonyl)isoquinoline (**7**) was prepared in four steps from phthalic acid anhydride (Scheme III).

Biological Results and Discussion

As observed earlier with other diazaborine derivatives,[1,4,5,11] the antibacterial activity is almost exclusively confined to Gram-negative bacteria, including *Neisseria gonorrhoea*. This specificity has been explained on the basis of the mode of action of these derivatives which have been shown to inhibit the biosynthesis of the lipopolysaccharide of Gram-negative bacteria.[12]

Particularly good activity is shown against *Proteus*, *Klebsiella*, and *Salmonella* and a somewhat lower activity against *Escherichia coli* and *Enterobacter* (compare Tables

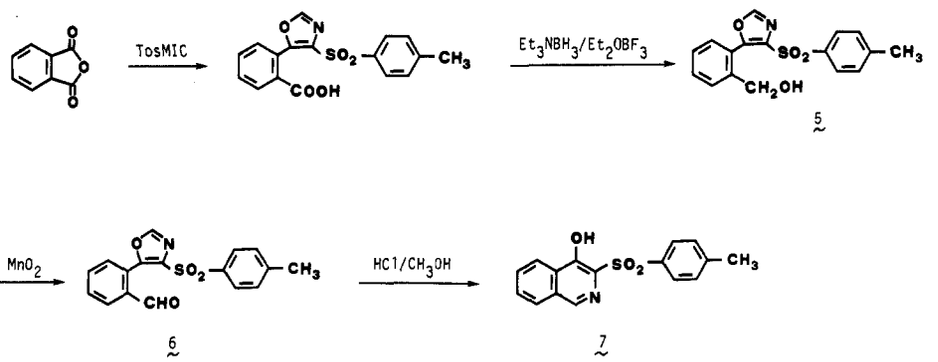
(16) M. J. S. Dewar in "Progress in Boron Chemistry", H. Steinberg and A. L. McCloskey, Ed., Macmillan, New York, 1964, Vol. 1.
(17) M. J. Cook, A. R. Katritzky, and P. Linda, *Adv. Heterocycl. Chem.*, 17, 255 (1974).
(18) S. Gronowitz, *J. Heterocycl. Chem., Suppl.* 3, S-17 (1976).
(19) Compare: R. Koester, K. Iwasaki, S. Hattori, and Y. Morita, *Justus Liebigs Ann. Chem.*, **720**, 23 (1968).

Table VI. Antibacterial Activity of **2a**[a]

		MIC values, μg/mL						
		E. coli	*E. aerogenes*	*S. typhimurium*	*K. pneumoniae*	*P. mirabilis*	*N. gonorrhoeae*	
no.	ED_{50}, mg/kg	Δ120	Δ220	Δ119	Δ217	Δ89	AS 7720	W 2
1	~25	25	>50	6.25	3.12	12.5	2	8
2	~100	>50		>50				
3	>100	>50	>50	50	10	5	2	8
4	~15	12.5	50	3.12	1.56	3.12	1	8
5	>600	>50	>50	>50	>50	>50		
6	~5	>50	>50	25	25	3.12	2	8
7	~25	25	>50	6.25	6.25	6.25	2	8
8	~250	>50		>50				
9	~100	>50		>50				
10	~20	25	>50	3.12	6.25	3.12	1	2
11	~50	>50	>50	12.5	12.5	25	1	>8
12	>100	>50		>50				
13	>100	>50		>50				
14	>100	>50		>50				
15	~40	25	>50	6.25	6925	1.56	1	2
16	~30	50	>50	6.25	6.25	12.5	2	8
17	~300	>50		>50				
18	>300	>50	>50	>50	50	50		
19	>300	>50		>50				
20	~100	>50		>50				
21	>300	>50		>50				
22	>300[b]	>50	>50	>50	>50	>50		
23	>300	>50		>50				
24		>50		>50				
25	>300	>50		>50				
26	~100	50	>50	12.5	50	50	>8	>8
27	>100	>50	>50	>50	50	10		
28	>300	>50	>50	>50	>50	25		
29	>300	>50	>50	>50	50	6.25	1	8
30	65	25	50	10	10	6.25	8	8
31	16	10	25	3.12	1.56	0.78	1	2
32	5	6.25	25	3.12	1.56	0.39	2	8
33	14	10	10	3.12	0.78	0.39	1	1
34	16	25	25	6.25	1.25	1.25	0.5	1
35	83	50	50	12.5	3.12	1.56	1	2
36	~100	>50		50				
37	~25	6.25	>50	3.12	0.78	3.12	1	8
38		>50		>50				
39	42	25	>50	12.5	6.25	25	>8	>8
40	73	6.25	10	2.5	1.25	1.56	2	2
41	14	10	25	3.12	1.56	2.5	2	2
42	57	>50	>50	50	12.5	50	>8	>8
43		>50	>50	12.5	6.25	6.25	8	8

[a] The minimum inhibitory concentrations (MICs) were determined by serial broth dilutions in trypticase soy broth after incubation for 16 h at 37 °C. The inocula were 10^4–10^5 colony forming units. The MIC values for *Neisseria gonorrhoeae* were determined by the agar dilution test (Kellogg agar) with 10^5 colony forming units after incubation at 36 °C in 5% CO_2 for 20 h. The MIC is defined as the lowest concentration that inhibited visible growth. The ED_{50} values were determined in NMRI mice infected intraperitoneally with *E. coli* 120 and treated po immediately and 5 h after the infection. [b] Subcutaneous application.

Scheme III



5 6 7

VI–IX). *Pseudomonas aeruginosa* was not found to be susceptible to diazaborine compounds.

As can be seen from Table VI (entries 1–16), substitution by methyl or halogen (F, Cl, Br) on the benzene ring of **2a** (R^2 = *p*-tolylsulfonyl, R^4 = H) has no marked influence on the antibacterial activities in vitro. Generally, deriva-

Table VII. Antibacterial Activity of **2b**[a]

		MIC values, μg/mL						
		E. coli	*E. aerogenes*	*S. typhimurium*	*K. pneumoniae*	*P. mirabilis*	*N. gonorrhoeae*	
no.	ED_{50}, mg/kg	Δ120	Δ220	Δ119	Δ217	Δ89	AS 7720	W 2
1	~15	6.25	25	3.12	1.56	1.56	0.5	2
2	>300	>50	>50	>50	>50	50		
3	~20	3.12	12.5	0.78	0.78	1.56	1	2
4	57	25	50	6.25	3.12	1.56	0.5	0.5
5	50	25	50	6.25	0.78	1.56	0.5	0.5
6	39	25	25	3.12	1.56	0.78	0.5	1
7	49	12.5	12.5	1.56	1.56	1.56	0.5	0.5
8	49	3.12	12.5	0.78	0.31	0.39	0.5	1
9	39	50	50	12.5	6.25	3.12	0.25	1
10	32	50	50	12.5	1.56	1.56	0.5	1
11	28	25	50	5	2.5	1.56	1	1
12	>600	>50	>50	>50	25	2.5	1	2
13	55	25	25	3.12	3.12	3.12	1	1
14	208	50	25	3.12	3.12	6.25	1	1
15	113	>50	>50	>50	>50	>50	>8	>8
16		12.5	12.5	3.12	3.12	6.25	2	2
17	28	6.25	25	3.12	1.56	25	8	8
18	4.5	1.56	3.12	0.78	0.39	0.78	1	1
19	73	12.5	12.5	1.56	1.56	6.25	2	2

[a] See footnote *a* of Table VI.

Table VIII. Antibacterial Activity of **2c**[a]

		MIC values, μg/mL						
		E. coli	*E. aerogenes*	*S. typhimurium*	*K. pneumoniae*	*P. mirabilis*	*N. gonorrhoeae*	
no.	ED_{50}, mg/kg	Δ120	Δ220	Δ119	Δ217	Δ89	AS 7720	W 2
1	>300	>50	>50	>50	>50	25	>8	>8
2	9	6.25	25	1.56	1.25	1.25	0.25	0.5
3	>300	>50	>50	>50	>50	>50	>8	>8
4	24	10	25	2.5	1.25	1.56	0.5	1
5	25	50	50	6.25	3.12	1.56	1	1
6	2	1.25	1.56	0.19	0.31	1.56	0.5	1
7	4	2.5	5	0.31	0.31	1.25	0.5	0.5
8	5	6.25	6.25	1.56	0.78	1.56	1	1

[a] See footnote *a* of Table VI.

Table IX. Antibacterial Activity of **2d–h**[a]

		MIC values, μg/mL						
		E. coli	*E. aerogenes*	*S. typhimurium*	*K. pneumoniae*	*P. mirabilis*	*N. gonorrhoeae*	
no.	ED_{50}, mg/kg	Δ120	Δ220	Δ119	Δ217	Δ89	AS 7720	W 2
2d–1	~10	12.5	25	3.12	1.56	3.12	1	8
2d–2	~30	12.5	25	3.12	3.12	3.12	2	8
2d–3	>300	>50	>50	50	50	6.25	0.5	2
2e–1	>300	>50	>50	>50	25	>50	>8	>8
2e–2	>300	>50	nt	>50	nt	nt	nt	nt
2e–3	>600	>50	>50	>50	50	50	nt	nt
2f	>100	>50	>50	>50	25	3.12	2	8
2g	>300	>50	>50	>50	>50	50	>8	>8
2h	>600	>50	>50	>50	>50	50	2	8

[a] See footnote *a* of Table VI.

tives with methyl or halogen in position 5 or 7 are less active than the unsubstituted parent compound **2a–1**. The 7-bromo derivative **2a–16** is the most active compound out of this group and shows the same activity as **2a–1**. Substitution (methyl, halogen) in position 6 has practically no influence on the antibacterial activities.

The in vivo data (*E. coli* septicaemia) follow the same trend. The only exception is the 5-fluoro derivative **2a–6**, for which a surprisingly low ED_{50} value has been determined. We have no explanation so far for this phenomenon. In metabolic studies[20] its main metabolite was isolated from the urine, which, however, exhibited only a slightly better antibacterial activity as compared to the parent compound.

Substitution of **2a** with polar groups (OH, NH_2, NR_2, $NHCOCH_3$, COOH) in position 6 or 7 (Table VI, entries 17–24) generally leads to complete loss of activity. Only the 7-hydroxy derivative **2a–27** is slightly active in vitro.

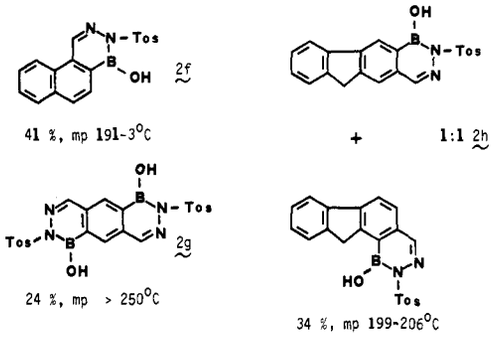
Regarding the organosulfonyl side chain, replacement of *p*-tolylsulfonyl by (4-aminophenyl)sulfonyl enhances the antibacterial activities (Table VI, entries 30–33). The 5-fluoro derivative **2a–30** however, does not show the exceptional increase in the in vivo activity that was observed in the *p*-tolylsulfonyl series (**2a–6**). Against *E. coli* 120 the order of activity in vitro and in vivo is 5-F < 6-Br < 6-Me. Derivatives of **2a** with alkylsulfonyl in position 2 and

(20) F. Battig, unpublished results.

chlorine or methyl in position 6 (Tables VI, entries 39–41) showed surprisingly low MIC and ED_{50} values.

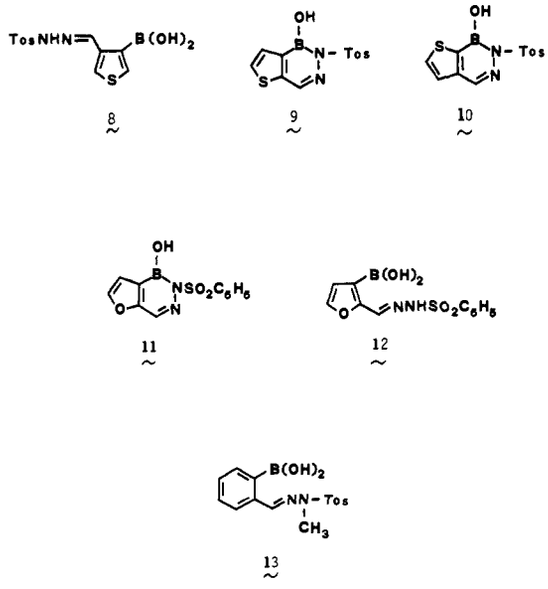
In the thienodiazaborine series, the thieno[2,3-*d*]diazaborines **2b** are generally slightly more active than their thieno[3,2-*d*] counterparts **2c** (Tables VII and VIII) with the exception of the 6-bromo derivatives of **2c** (Table VIII, entries 1, 2), which are inactive. Remarkably good activities in vitro and in vivo were observed with the 2-alkylsulfonyl derivatives of **2b** and **2c**. Compound **2b**–**18** has been selected for further evaluation.

As in the thienodiazaborines (**2b**), substitution of bromine instead of methyl in position 6 of the furodiazaborines **2d** also brings no advantage in biological activity (Table IX). With the oligocyclic diazaborine derivatives **2f**–**2h**, only very low activities in vitro were observed (Table IX). The pyrrolo compounds **2e** are totally inactive (Table IX).



Variation of the diazaborine ring itself led to negative results: the benzazaborole **3** is only slightly active against *Klebsiella* and *Proteus* in vitro. No antibacterial activity was found with the tetrahydrobenzazaborine **4**.

One major problem with the diazaborines is their inherent toxic potential, which is probably due to the



structural element of areneboronic acid amide. When designing boron-free analogues, a very important question has to be considered; either the bicyclic arenodiazaborines themselves are the active species or the BN bond has to be cleaved during or prior to the interaction of the molecule with the biological target. Gronowitz et al.[4] reported that the tosylhydrazone **8** of 4-(dihydroxyboryl)-thiophene-3-carboxaldehyde, which does not readily cyclize to the corresponding diazaborine, has about the same weak activity against Gram-negative bacteria as the cyclic analogues **9** and **10**, although no detailed biological data were given for **8**. Studies[11] with the highly active furodiazaborine **11** showed that the product of hydrolytic cleavage at the BN bond **12**, which is the main metabolite isolated from animals, has only slight antibacterial activities. However, it cannot be excluded that at least partial recyclization might occur under in vivo conditions.

To avoid the problem of potential ring opening and recyclization, we decided to study the biological activities of analogues where such reactions are principally not possible. The isoquinoline **7** was selected as a stable analogue of benzodiazaborine **2a**–**l**, since various studies[14,16–17] have shown that replacement of a C–C unit in aromatic compounds by the isoelectronic BN group leads to heterocycles with similar chemical and physical properties. If **2a**–**l** in its bicyclic form represents the active species, one should expect to find at least some biological activity with the carbacyclic analogue. However, we found that in all test systems **7** was completely inactive.

The *N*-methyl derivative **13** was prepared as a stable ring-opened analogue to **2a**–**l**. This compound inhibited the growth of the *E. coli* strain PL 2 but was at least 10 times less active than the corresponding bicyclic diazaborine **2a**–**l** (data not shown). Benzeneboronic acid had a much lower effect on the growth of the *E. coli* strain. Since neither of our analogues (**7**, **13**) showed activities similar to **2a**–**l**, no conclusion can be drawn from our experiments, although they do support to some extent the hypothesis that ring opening is a necessary event for antibacterial action. The lower activities of **13** as compared to **2a**–**l** might be caused either by a reduced transport of the ring-opened compound to the target or by the additional methyl group in **13**, causing a less favorable interaction between the compound and the target. More detailed studies on the mode of action of these compounds are presently being carried out.

Experimental Section

1,2-Dihydro-5-fluoro-1-hydroxy-2-(*p*-tolylsulfonyl)-2,3,1-benzodiazaborine (2a–6). To 0.4 g (2.5 mmol) of $FeCl_3$ in 200 mL of dry $ClCH_2CH_2Cl$ were added simultaneously from two dropping funnels with intensive stirring under argon atmosphere 10 mL (26 g, 104 mmol) of BBr_3 in 30 mL of $ClCH_2CH_2Cl$ and 10 g (34 mmol) of *o*-fluorobenzaldehyde tosylhydrazone in 500 mL of $ClCH_2CH_2Cl$ within 5 min. The mixture was heated under reflux for 20 min, cooled to 5 °C, and poured into 300 mL of ice water. The organic phase was separated, washed with water (2 × 50 mL), and extracted with 1 N NaOH (3 × 200 mL). After acidification of the water phase (pH 2–3), the product was reextracted with CH_2Cl_2. On evaporation of the dried ($MgSO_4$) CH_2Cl_2 solution, 8.3 g (76%) of **2a–6** was obtained: white crystals, mp 173 °C. Anal. ($C_{14}H_{12}BFN_2O_3S$) C, H, N, S.

2-[(4-Aminophenyl)sulfonyl]-6-bromo-1,2-dihydro-1-hydroxy-2,3,1-benzodiazaborine (2a–31). To 1.7 g (4.1 mmol) of 6-bromo-1,2-dihydro-1-hydroxy-2-[(4-nitrophenyl)sulfonyl]-2,3,1-benzodiazaborine in 15 mL of acetic acid was added 0.94 g of iron powder at 50–60 °C with intensive stirring. The mixture was heated to 70–80 °C for 45 min. After addition of water and filtration, the crude crystalline product separated from the filtrate on cooling to room temperature. Recrystallization from DMF–water gave 1.08 g (68%): light yellow crystals, mp 210–215 °C. Anal. Calcd for $C_{13}H_{11}BBrN_3O_3S$: C, 41.09; H, 2.92; N, 11.06. Found: C, 40.65; H, 3.00; N, 11.22.

2-[4-Amino-2-chlorophenyl)sulfonyl]-1,2-dihydro-6-methyl-2,3,1-benzodiazaborine (2a–33). 2-[(4-Acetamido-2-chlorophenyl)sulfonyl]-1,2-dihydro-1-hydroxy-6-methyl-2,3,1-benzodiazaborine (2.6 g, 6.6 mmol) in 160 mL of THF and 20 mL of concentrated aqueous HCl were stirred for 7 days at room temperature. The solution was then concentrated in vacuo to a volume of 40 mL, neutralized with 2 N NaOH (pH 6–7), and

extracted with $CHCl_3$. Drying ($MgSO_4$) and evaporation of the $CHCl_3$ solution afforded crude product, which was purified by chromatography on silica gel with $CHCl_3$–CH_3OH–H_2O (75:12:1) to give 1.4 g (60%) of **2a–33**: mp 215–217 °C. Anal. ($C_{14}H_{13}BClN_3O_3S$) C, H, N.

2,3-Dihydro-1-hydroxy-2-(*p*-tolylsulfonyl)-1*H*-2,1-benzazaborole (3). In a Kugelrohr apparatus, a mixture of *N*-(*p*-tolylsulfonyl)benzylamine (5.6 g, 21.5 mmol) and triethylamine–borane (3.7 g, 32 mmol) was heated under argon to 130 °C for 1 h. H_2 was evolved and triethylamine was distilled off. The temperature was raised to 210 °C and maintained until no further gas evolution was observed (ca. 3 h). The residue was dissolved in $CHCl_3$ and the solution extracted with 1 N NaOH. The crude product that was obtained from acidification of the aqueous phase, extraction with $CHCl_3$, drying ($MgSO_4$), and evaporation was purified by chromatography on silica gel with $CHCl_3$–CH_3OH–H_2O (75:12:1) to give 2.05 g (33%) of **3**: white solid, mp 143–145 °C. Anal. ($C_{14}H_{14}BNO_3$) C, N, H.

1-Hydroxy-1,2,3,4-tetrahydro-2-(*p*-tolylsulfonyl)-2,1-benzazaborine (4). The title compound was obtained from *N*-(*p*-tolylsulfonyl)benzeneethanamine in 48% yield as described for the preparation of **3** as an oil. Anal. Calcd for $C_{15}H_{16}BNO_3$: C, 59.82; H, 5.35; N, 4.65. Found: C, 60.43; H, 5.38; N, 4.51.

2-[4-(*p*-Tolylsulfonyl)oxazol-5-yl]benzyl Alcohol (5). To a stirred solution of 4.0 g (11.6 mmol) of 2-[4-(*p*-tolylsulfonyl)-oxazol-5-yl]benzoic acid[21] in 360 mL of THF was added 8.4 g (73 mmol) of triethylamine–borane followed by 10.4 g (73 mmol) of diethyl ether–trifluoroborane under argon. The mixture was stirred for 15 h at 50–60 °C and evaporated subsequently in vacuo. The residue was taken up with water–diethyl ether (150 + 50 mL), and after separation of layers, the water phase was extracted again with ether (2 × 50 mL). The combined ether extracts were dried ($MgSO_4$) and evaporated. Some unreacted triethylamine–borane was removed from the residue in vacuo (10^{-3} mm). On recrystallization of the residue from 2-propanol, 2.1 g of **5** (55%), was obtained, mp 116–121 °C.

2-[4-(*p*-Tolylsulfonyl)oxazol-1-yl]benzaldehyde (6). MnO_2 (10.5 g) and **5** (3.5 g, (10.9 mmol) were stirred in 200 mL of 1,2-dimethoxyethane for 3 h at room temperature. After filtration, the solution was evaporated and the residue triturated with diethyl ether to give 2.9 g (81%) of **6**, mp 131–133 °C.

4-Hydroxy-3-(*p*-tolylsulfonyl)isoquinoline (7). Compound **6** (1.8 g, 5.5 mmol) was stirred in 50 mL of methanol and 10 mL of concentrated aqueous HCl for 3 h at 50 °C. On cooling to room temperature 560 mg (34%) of **7** separated from the solution: white crystals, mp 179–180 °C. From the filtrate further material could be obtained after aqueous workup and chromatographic purification on silica gel with $CHCl_3$–ethanol (100:2). Anal. ($C_{16}H_{13}NO_3S$) C, H, N.

(21) A. M. van Leusen, D. E. Hoogenboom, and H. Siderius, *Tetrahedron Lett.* 2369 (1972).

2-Formylbenzeneboronic Acid Methyl(*p*-tolylsulfonyl)hydrazone (13). To 0.75 g (3.8 mmol) of *N*-methyl-*N*-(*p*-tolylsulfonyl)hydrazine and 0.56 g (3.8 mmol) of 2-formylbenzeneboronic acid in 3.5 mL of ethanol was added two drops of acetic acid and the mixture stirred at room temperature for 30 min. Evaporation and recrystallization from ethanol gave 1.3 g (89.3%) of the diethyl ester of **13**: white needles, mp 98–103 °C; ^1H NMR ($CDCl_3$) δ 7.1–8.0 (m, 9, arom H, CH=N), 3.85 (q, 4, J = 7 Hz, OCH_2), 3.27 (s, 3, NCH_3), 2.45 (s, 3), 1.20 (t, 6, $J \approx$ 7 Hz). The ester was hydrolyzed by stirring with 1 g of wet Dowex 50 W (H^+) in a mixture of 5 mL of THF and 0.5 mL of water for 1.5 h at room temperature. After filtration and evaporation, the residue was triturated with diethyl ether to give 1.0 g of (93.8%) **13**: white crystals, mp 238–239 °C. Anal. Calcd for $C_{15}H_{17}BN_2O_4S$ (acid, 332.19) C, 54.24; H, 5.16; N, 8.43 and for $C_{15}H_{15}BN_2O_3S$ (anhydride, 314.18) C, 57.35; H, 4.81; N, 8.92. Found: C, 55.23; H, 4.82; N, 8.68. ^1H NMR ($CDCl_3$–Me_2SO-d_6) δ 7.0–8.0 (m, 9, arom H, CH=N), 2.97 (s, NCH_3, 3), 2.33 (s, 3).

Registry No. **2a-1**, 22959-81-5; **2a-2**, 90555-01-4; **2a-3**, 67397-80-2; **2a-4**, 67397-59-5; **2a-5**, 67397-81-3; **2a-6**, 67397-61-9; **2a-7**, 67397-83-5; **2a-8**, 67397-63-1; **2a-9**, 67397-62-0; **2a-10**, 67397-78-8; **2a-11**, 65904-09-8; **2a-12**, 67397-60-8; **2a-13**, 67397-66-4; **2a-14**, 67397-68-6; **2a-15**, 67397-65-3; **2a-16**, 67397-64-2; **2a-17**, 67553-13-3; **2a-18**, 67397-84-6; **2a-19**, 67397-77-7; **2a-20**, 67397-69-7; **2a-21**, 67397-67-5; **2a-22**, 90555-02-5; **2a-23**, 67397-72-2; **2a-24**, 67397-74-4; **2a-25**, 90555-03-6; **2a-26**, 67397-96-0; **2a-27**, 67397-91-5; **2a-28**, 67397-95-9; **2a-29**, 67397-94-8; **2a-30**, 67397-97-1; **2a-31**, 67397-98-2; **2a-32**, 67397-99-3; **2a-33**, 67398-04-3; **2a-34**, 67398-06-5; **2a-35**, 90555-04-7; **2a-36**, 67397-90-4; **2a-37**, 67397-89-1; **2a-38**, 67397-75-5; **2a-39**, 67398-05-4; **2a-40**, 67398-02-1; **2a-41**, 67398-01-0; **2a-42**, 90555-05-8; **2a-43**, 90555-06-9; **2b-1**, 67397-82-4; **2b-2**, 67397-86-8; **2b-3**, 67398-08-7; **2b-4**, 90555-07-0; **2b-5**, 90555-08-1; **2b-6**, 90555-09-2; **2b-7**, 90555-10-5; **2b-8**, 90555-11-6; **2b-9**, 90555-12-7; **2b-10**, 90555-13-8; **2b-11**, 67397-88-0; **2b-12**, 67397-92-6; **2b-13**, 90555-14-9; **2b-14**, 90555-15-0; **2b-15**, 67398-09-8; **2b-16**, 90555-16-1; **2b-17**, 67398-10-1; **2b-18**, 67398-03-2; **2b-19**, 90555-17-2; **2c-1**, 90555-18-3; **2c-2**, 90555-19-4; **2c-3**, 90555-20-7; **2c-4**, 90555-21-8; **2c-5**, 90555-22-9; **2c-6**, 90555-23-0; **2c-7**, 90555-24-1; **2c-8**, 90555-25-2; **2d-1**, 49777-46-0; **2d-2**, 67397-79-9; **2d-3**, 90555-26-3; **2e-1**, 67398-00-9; **2e-2**, 67397-73-3; **2e-3**, 67397-87-9; **2f**, 67397-85-7; **2g**, 90555-27-4; **2h**, 90555-28-5; **3**, 90555-30-9; **4**, 90584-11-5; **5**, 90555-31-0; **6**, 90555-32-1; **7**, 90555-33-2; **13**, 90555-34-3; **13** diethyl ester, 90555-35-4; BBr_3, 10294-33-4; 1,2-dihydro-1-hydroxy-2-(*p*-tolylsulfonyl)-1*H*-fluoreno[1,2-*d*][1,2,3]-diazaborine, 90555-29-6; *o*-fluorobenzaldehyde tosylhydrazone, 90555-36-5; borane, 13283-31-3; *N*-(*p*-tolylsulfonyl)benzylamine, 1576-37-0; *N*-(*p*-tolylsulfonyl)-*N*-phenylethylamine, 1821-40-5; 2-[4-(*p*-tolylsulfonyl)oxazol-5-yl]benzoic acid, 37118-21-1; *N*-methyl-*N*-(*p*-tolylsulfonyl)hydrazine, 22547-51-9; 2-formylbenzeneboronic acid, 40138-16-7.