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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

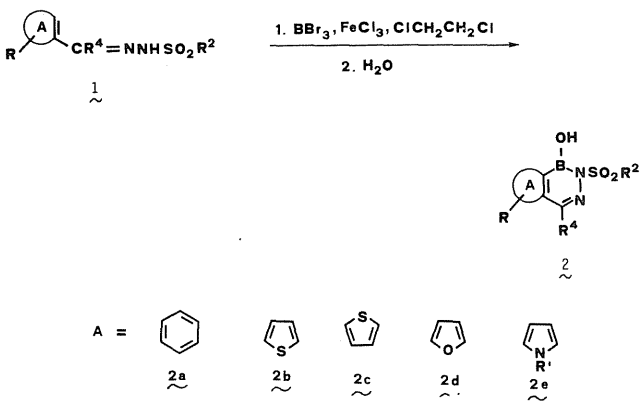

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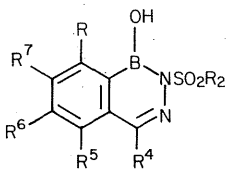
Table I. 2-(Organosulfonyl)-1,2-dihydro-1-hydroxy-2,3,1-benzodiazaborines **2a**



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	$NCH_2CH_2CH_2CH_2$	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.

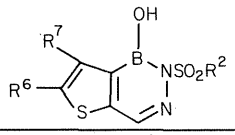
One major goal of our work was therefore to synthesize 2,3,1-benzodiazaborines with various substituents on the benzene ring and to evaluate their influence on the antibacterial activities. For that purpose a new synthetic route to arenodiazaborines had to be developed.

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*-formylbe 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 $TiCl_4$.

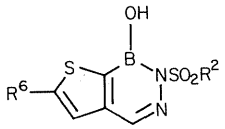
As can be seen from the Tables I–VI, alkyl, halogen (F, Cl, Br), amino, alkylamino, and acylamino are tolerated

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.

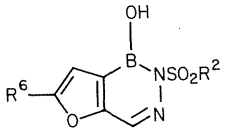
the corresponding hydroxy derivatives were obtained as a consequence of concomitant ether cleavage (e.g., **2a–26**).

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]

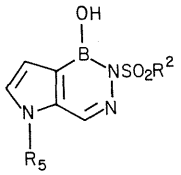
2,3-Dihydro-1-hydroxy-2-(*p*-tolylsulfonyl)-1*H*-2,1-benzazaborole (**3**) and 1-hydroxy-1,2,3,4-tetrahydro-2-(*p*-tolylsulfonyl)-2,1-benzazaborine (**4**) are close analogues of

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



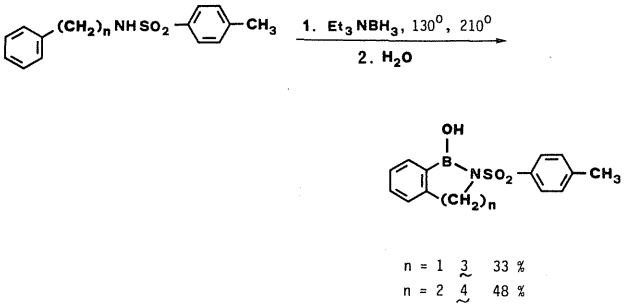
2d	R^2	R^6	% yield	mp, °C
1	4-$CH_3C_6H_4$	CH_3	66	169
2	4-$CH_3C_6H_4$	Br	25	168–170
3	2,4,5-$Cl_3C_6H_2$	Br	84	164–5

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

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