90412-50-3; (±)-*trans*-17, 90390-84-4; (±)-*trans*-17·fum, 90390-86-6; (±)-*cis*-18, 90390-66-2; (±)-*cis*-18·HBr, 90390-81-1; (±)-*trans*-18, 90390-85-5; (±)-*trans*-18·HBr, 90390-87-7; DA, 51-61-6; NE, 51-41-2; 5-HT, 50-67-9; (±)-2-phenylpyrrolidine, 56586-11-9; (±)-*m*-trifluoromethylstyrene oxide, 53631-36-0; (±)-*p*-chloromandelic acid, 7138-34-3.

Supplementary Material Available: Table I, 95% confidence limits for the data presented (1 page). Ordering information is given on any current masthead page.

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Synthetic CNS Agents. 1. (±)-1,2,3,4,4a,5,10,10a-Octahydro-5,10[1′,2′]-benzenobenz[*g*]isoquinoline Hydrochloride. A New, Highly Potent, Potential Antidepressant

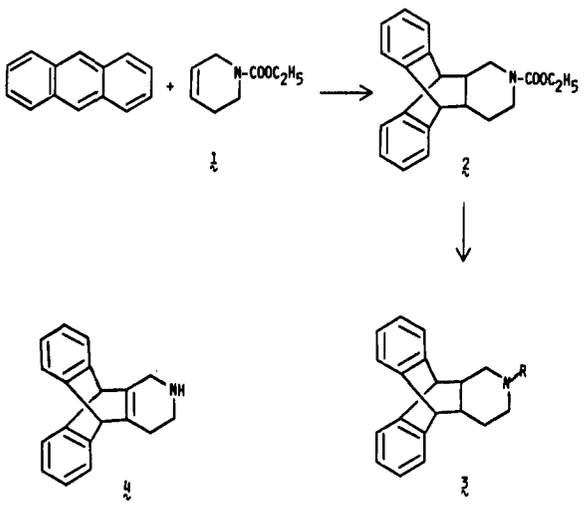
Sir:

In our search for new types of antidepressants, we had occasion to synthesize the title compound (**3a**), which, on the basis of tests with animals, seems to possess potent antidepressant-like properties.

The biological data on **3a**, and its *N*-methyl derivative (**3b**), are listed in Table I along with those of amitriptyline and imipramine, two tricyclic antidepressants in clinical practice.

As is evident from the table, **3a** is thrice as potent in mice and several times as potent in rats as amitriptyline and imipramine in reversing the ptosis induced by tetrabenazine (TBZ)[1] in these species. It exhibits neither stimulation nor dose-induced depression in mice and rats[1] and is not a monoamine oxidase inhibitor in vitro or in vivo. The outstanding feature of its profile is that it lacks both peripheral and central anticholinergic activity as borne out by the oxotremorine antagonism test[2] in mice in which it is inactive in contrast to both amitriptyline and imipramine. In a 12-day subacute toxicity study with rats, **3a** was well tolerated up to a dose of 50 mg/kg po, which represents 100 times the ED_{50} value.[3]

The *N*-methyl derivative (**3b**) of **3a**, while equipotent to amitriptyline and imipramine in mice, is however less active than **3a**. Besides, it is fairly potent in the oxotremorine antagonism test[2] indicative of undesirable anticholinergic side effects and is, therefore, less interesting than **3a**.



(a) R = H (hydrochloride)
(b) R = CH_3 (hydrochloride)

Compound **3a** was synthesized by the Diels–Alder reaction of anthracene with 1-(ethoxycarbonyl)-1,2,3,6-tetrahydropyridine (**1**) to yield **2**, the best condition for which was the use of a large excess of **1** as the solvent and heating the mixture at reflux for 18 h under nitrogen. Removal of the excess of **1** under reduced pressure furnished, in an almost quantitative yield, **2**, which, on hydrolysis with KOH in boiling *t*-butyl alcohol with concomitant loss of CO_2, afforded **3** (R = H) as a colorless crystalline solid (mp 161–162 °C, from hexane). It was converted to its hydrochloride **3a** (mp 339–340 °C dec, from methanol) for screening purposes. Reduction of **2** with lithium aluminum hydride yielded **3** (R = CH_3), which was isolated as its hydrochloride, **3b** (mp 173–175 °C, from THF). The structures of **3a** and **3b** were confirmed by elemental analysis and by the NMR and mass spectra of the corresponding bases.

At the time the compounds **3a** and **3b** were synthesized, the parent heterocyclic ring system was unknown. The synthesis of **4**, a dehydro derivative of **3** (R = H), has recently been described and follows an entirely different

Table I. Biological Evaluation of Compounds **3a** and **3b**

compd	TBZ antagonism[a]		MAO inhibition		oxotremorine antagonism[a]		pressor response (dog)[d]		acute toxicity[f] (mouse)
	mouse	rat	in vitro[b]	in vivo[c]	tremors	lacrimation	↑NE	↓PE	
3a	0.41 (0.26–0.65)	0.5 (0.21–1.21)	$>1 \times 10^{-3}$	>81	>243	>243	0.22	1.2	320
3b	1.0	*e*	*e*	*e*	100[g]	36 (22.9–56.7)	*e*	*e*	126
amitriptyline	1.3 (0.59–2.86)	12 (6.2–23.4)	$>1 \times 10^{-3}$	>135	21 (12.2–36.2)	27 (18.5–40.3)	1.0	1.1	177
imipramine	1.3 (0.96–1.8)	4.12 (2.78–6.11)	$>1 \times 10^{-3}$	>135	70 (43.1–113)	130	3.0	1.5	300

[a] ED_{50}, mg/kg po. [b] KI_{50}, mol/L, with 5-HT as substrate (mouse brain). [c] ED_{50}, mg/kg po, tryptamine potentiation test (mouse).[1] [d] ED_{50}, mg/kg iv; ↑NE refers to potentiation of the response to norepinephrine; ↓PE refers to inhibition of the response to phenethylamine.[1] Confidence limits not determined. [e] Not determined. [f] 24 h LD_{50}, mg/kg po. Confidence limits not determined. [g] Extrapolated value.

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(3) Unpublished results.

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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Received February 13, 1984

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Articles

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

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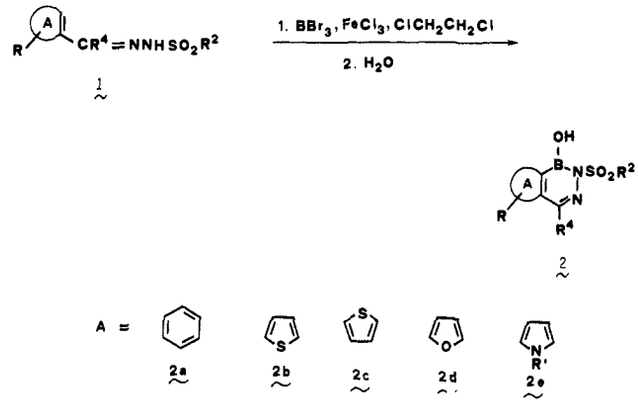
1,2-Dihydro-1-hydroxy-2-(organosulfonyl)areno[*d*][1,2,3]diazaborines **2** (arene = benzene, naphthalene, thiophene, furan, pyrrole) were synthesized by reaction of (organosulfonyl)hydrazones of arene aldehydes or ketones with tribromoborane in the presence of ferric chloride. The activities of **2** 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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