O-3-Amino-2,3-dideoxy-α-D-glucopyranosyl-(1→6)-O-[2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl-(1→4)]-2-deoxy-D-streptamine (12). A solution of 1.6 g (1.23 mmol) of aminoglycoside 11 and 940 mg (23.5 mmol) NaOH in 16 mL of CH_3OH and 16 mL of H_2O was heated at reflux for 10 min. The mixture was diluted with 50 mL of ice–water and 12.1 mL of 1 N HCl was added. The aqueous solution was passed over 65 mL of Amberlite resin CG-50 (NH_4^+). The column was eluted with 100 mL of H_2O, followed by a gradient of 275 mL of H_2O and 275 mL of 0.5 N NH_4OH. Fractions were monitored by TLC using a system of $CHCl_3/CH_3OH/NH_4OH$ (3:4:2). A fraction containing 330 mg (57.5%) of aminoglycoside 12 was obtained: FDMS, m/z calcd 467; observed, 468 ($M^+ + 1$). ^{13}C NMR (D_2O) δ 29.6 (C-2), 34.9 (C-2″), 41.9 (C-6′), 49.8, 50.2, and 51.0 (C-3, -1, and -3″), 55.2 (C-2′), 61.9 (C-6″), 68.4, 69.8, 70.8, 72.3, 75.1, 75.8, and 79.6 (C-4″, -4′, -5″, -3′, -5′, -5, and -4), 84.1 (C-6), 97.7 (C-1′), 99.3 (C-1″).

O-4,6-Diacetyl-2,3-dideoxy-3-[(trifluoroacetyl)amino]-α-D-glucopyranosyl-(1→6)-O-[2,6-bis[(trifluoroacetyl)amino]-2,3,4,6-tetradeoxy-α-D-glucopyranosyl-(1→4)]-2-deoxy-1,3-bis-N-(trifluoroacetyl)-D-streptamine (13). In the manner described above, 1.01 g (1.5 mmol) of diol 9 and 500 mg (1.54 mmol) of glycal 15 were reacted and chromatographed to give 391 mg (26.1%) of aminoglycoside 13. ^{13}C NMR (Me_2CO-d_6) δ 20.6 (CH_3), 23.7 and 27.0 (C-3′ and -4′), 32.6, 35.8, 44.2 (3-CH_2), 47.7, 49.8, 50.2, 51.6 (4-CHN), 63.3, 68.0, 70.2, 70.4, 74.1, 77.3, and 86.2 (7-CHO), 95.8 (C-1′), 99.0 (C-1″), 95, 109.9, 124.4, and 139 (CF_3), 156–161 ($COCF_3$), 170.7 and 170.9 (C=O).

O-3-Amino-2,3-dideoxy-α-D-glucopyranosyl-(1→6)-O-[2,6-diamino-2,3,4,6-tetradeoxy-α-D-glucopyranosyl-(1→4)]-2-deoxy-D-streptamine (14). Hydroxylsis of 345 mg (0.35 mmol) of 13 with 196 mg (4.9 mmol) of NaOH in dilute MeOH, followed by passage through 20 mL of Amberlite resin CG-50 (NH_4^+), led to the isolation of 132 mg (86.5%) of aminoglycoside 14: FDMS, m/z calcd 435; observed, 436 ($M^+ + 1$). ^{13}C NMR (D_2O) δ 27.3 (C-4′), 28.8 (C-3′), 37.0 (C-2), 38.2 (C-2″), 46.3 (C-6′), 49.8, 50.9, and 51.3 (2) (C-3, -1, -3″, and -2′), 62.0 (C-6″), 71.6, 73.0, 74.5, and 76.2 (C-4″, -5″, -5′, and -5), 88.2 and 88.7 (C-4 and -6); 100.0 (C-1′), 102.4 (C-1″).

Synthesis and in Vitro Antimicrobial Property of *o*-Carborane Derivatives

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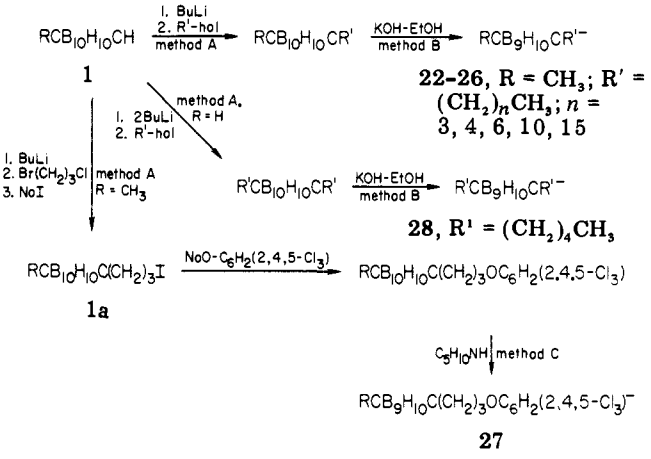
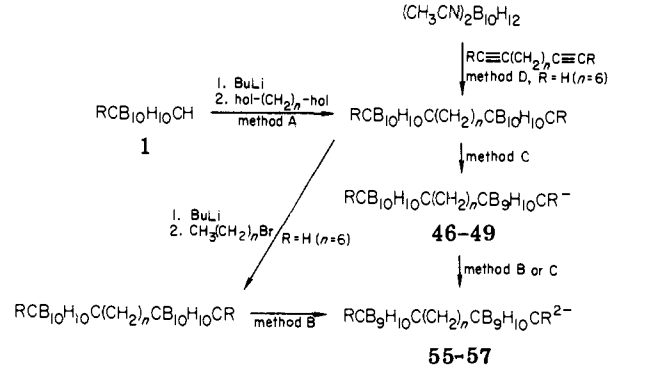
Various *o*-carboranes and nido-type dicarbollide anions have been synthesized and tested for antimicrobial activity. Nearly all of the dicarbollide monoanions investigated were active in vitro against fungi such as *Candida albicans*, *Aspergillus fumigatus*, and *Tricophyton asteroides*, as well as against Gram-positive bacteria. From a consideration of the structure–activity relationships, it seems most reasonable to conclude that the introduction of lipophilic alkyl or *o*-carboranyl groups to the hydrophilic dicarbollide anions leads to the antimicrobial activity.

Pharmacological action of the substances involving the *o*-carborane cage has been little known except for the papers on the application of these to boron-10 neutron-capture therapy.[1] However, there are some instances where the biological effects of the carboranes have been noted. These include the inhibition of certain liver microsomal enzymes by *o*- and *m*-carboranes.[2] Also, the neurotropic property of nitrogen-containing *o*-carborane derivatives[3] and the new findings of carboranylalanine as a chymotrypsin inhibitor[4] are regarded as a development of carboranes in the domain of pharmacology. Since bactericidal and fungicidal properties of 1-(aminoalkyl)-1,2-dicarba-*closo*-dodecaboranes and related compounds were reported in the Japanese patent literature from this company,[5] we describe here the synthesis and antimicrobial property of various types of *o*-carborane derivatives.

Scheme I



Scheme II



Chemistry. Mono- and dicage *o*-carborane derivatives were synthesized by known methods.[6,7] A reaction of

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(5) (a) Nakagawa, T.; Watanabe, H.; Yoshizaki, T. *Jpn. Kokai Tokkyo Koho* **1970**, 31940. (b) Nakagawa, T.; Yoshizaki, T.; Watanbe, H. *Ibid.* **1971**, 21395. (c) Yoshizaki, T.; Shiro, M.; Nakagawa, Y.; Watanabe, H. *Inorg. Chem.* **1969**, *8*, 698.

0022-2623/81/1824-1492$01.25/0

Scheme III

$RCB_{10}H_{10}C—X—CB_{10}H_{10}CR \xrightarrow{\text{method B or C}}$

8–10, X = N=N
11, X = NH—NH
12, X = NR'-NH
13–15, X = NR'-NR''
16, X = S-S

$RCB_{10}H_{10}C—X—CB_9H_{10}CR^- \longrightarrow RCB_9H_{10}C—X—CB_9H_{10}CR^{2-}$

33–35, X = N=N (method B)
36, X = NH-NH (method C)
37–41, X = NR'-NH (method C)
42–45, X = NR'-NR'' (method C)
50, X = S-S (method C)

53, X = N=N (method B)
54, X = S-S (method C)

1-lithio-2-methyl-*o*-carborane (Scheme I) with haloalkanes gave 1-alkyl-2-methyl-*o*-carborane[7] (method A), which was converted to *nido*-dicarbollide anions **22–26** on treatment with a base (method B; KOH–EtOH system[8]). **27** was analogously prepared as shown in Scheme I (method C; piperidine–benzene system[9]). Reaction of 1,2-dilithio-*o*-carborane with *n*-pentyl bromide, followed by degradation (method B), gave **28**. Several 1,*n*-bis(*o*-carboranyl)alkanes (n = 1–3 or 6) were prepared and on base degradation (method B or C) gave the corresponding closo–nido monoanions **46–49** and nido–nido dianions **55–57** (Scheme II). Closo–closo azo- and hydrazo-*o*-carboranes **8–11** were prepared by the method previously reported;[10] azocarboranes **8–10** were transformed to closo–nido monoanions **33–35** and nido–nido dianion **53** by method B.[11] Alkyl- and aryl-substituted hydrazino-*o*-carboranes **12–15** were synthesized[11] and converted to closo–nido monoanions **36–45** in order to investigate their antimicrobial property (Scheme III). Unlike azo-*o*-carboranes, hydrazo-*o*-carboranes did not give the dianion-type compound under conditions similar to those applied in the degradation for the *closo*-azo-*o*-carboranes.[11] *closo*-Carboranyl disulfide **16**[12] was also converted to the corresponding closo–nido monoanion **50** and nido–nido dianion **54** by method C. As demonstrated in Scheme IV, 2-aminobis(*o*-carborane) **6** was converted to 2-chlorobis(*o*-corborane) **7** by treatment with NOCl. Oxidation of the tetraanion of **6** with $KMnO_4$ in liquid NH_3 gave **17**.[11] These *closo*-bis(*o*-carborane)s were transformed to the corresponding nido-compounds **30**, **31**, and **51** using method C. All the dicarbollide anions listed in Table I were finally changed

Scheme IV

$H_2NCB_{10}H_{10}CCB_9H_{10}CH^-$ (**30**) $\qquad HCB_{10}H_{10}CCB_9H_{10}CCl^-$ (**31**)

↑ method C $\qquad$ ↑ method C

$HCB_{10}H_{10}CCB_{10}H_{10}CNH_2$ (**6**) $\xrightarrow{NOCl}$ $HCB_{10}H_{10}CCB_{10}H_{10}CCl$ (**7**)

↓ liq NH_3, 1. Na, 2. $KMnO_4$

$HCB_{10}H_{10}CCB_{10}H_{10}CNHNHCB_{10}H_{10}CCB_{10}H_{10}CH$ (**17**)

↓ method C

$(HCB_9H_{10}CCB_{10}H_{10}CNHNHCB_{10}H_{10}CCB_9H_{10}CH)^{2-}$ (**51**)

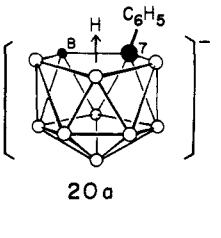
to the water-soluble potassium salts for antimicrobial testing using Amberlite IR-120 ion-exchange resins. The dicarbollide ions in Table III, therefore, are in the form of potassium salts. The reaction conditions of the degradation and ^1H NMR data for compounds **30**, **31**, **46–48**, **50**, **51**, and **54–56**, which do not appear under Experimental Section, are summarized in Table II.

Biological Results and Discussion

In vitro antimicrobial activity of the mono-, di- and tetracage carboranes are summarized in Table III. None of these closo compounds **1–17** showed significant antifungal activity, with the exception that **3** was active against *Tricophyton asteroides*. Some of the compounds in the series were active against Gram-positive bacteria (e.g., **6**, **7**, and **11**). Most of monocage dicarbollide anions **22–28** that have a nido structure exhibited significant in vitro activity against Gram-positive bacteria and especially against fungi (e.g., **25–28**), while innersalt **18**, although only one example for this type of compound, was inactive.

Closo–nido dicage compounds **29–50** were quite active against fungi as shown in Table III; in bis(*o*-carborane) series **29–32**, **31** recorded the highest activity against *Candida albicans* (1.6 μg/mL) and *Aspergillus* fumigatus (1.6 μg/mL). All of the azo- and hydrazocarborane monoanions **33–45** similarly possessed fairly high activity (3.1–25 μg/mL) against fungi. It is noteworthy that closo–nido compound **51** having tetracage carborane stands out as the only one that is superior to clotrimazole and amphotericin B against *Candida albicans*.

Hydrophilic phenyldicarbaundecaborane(1–) **20** is known as a membrane-permeable anion (e.g., **20a**) and is



20a

used as a tool for determining the electric potential of the biological membrane system.[13] In our biological assay, **20** did not exhibit significant antifungal activity. Introduction of an electrophilic nitro group at the para position of the

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Table I. *o*-Carborane Derivatives

no.	compound[a]	yield (method), %	mp, °C	formula	anal.[b]
1	$HCB_{10}H_{10}CH$[c]				
2	$CH_3CB_{10}H_{10}CCOONa$[c]				
3	$CH_3CB_{10}H_{10}C(CH_2)_3N(C_2H_5)_2 \cdot HCl$	77	142–143	$C_{10}H_{30}NB_{10}Cl$	C, H, N, Cl
4	$CH_3CB_{10}H_{10}C(CH_2)_3OC_6H_2(2,4,5\text{-}Cl_3)$	50 (A), 84	124	$C_{12}H_{21}B_{10}Cl_3O$	C, H, Cl
5	$HCB_{10}H_{10}CCB_{10}H_{10}CH$[d]				
6	$HCB_{10}H_{10}CCB_{10}H_{10}CNH_2$	87	sublimes	$C_4H_{23}NB_{20}$	C, H, N, B
7	$HCB_{10}H_{10}CCB_{10}H_{10}CCl$	73	sublimes	$C_4H_{21}B_{20}Cl$	C, H, Cl
8	$HCB_{10}H_{10}CN{=}NCB_{10}H_{10}CH$[e]				
9	$CH_3CB_{10}H_{10}CN{=}NCB_{10}H_{10}CCH_3$[e]				
10	$C_6H_5CB_{10}H_{10}CN{=}NCB_{10}H_{10}CC_6H_5$[e]				
11	$CH_3CB_{10}H_{10}CNHNHCB_{10}H_{10}CCH_3$[f]	65	233–237	$C_6H_{28}N_2B_{20}$	C, H, N
12	$CH_3CB_{10}H_{10}CNHNC_6H_5CB_{10}H_{10}CCH_3$[f]	95	187–189	$C_{12}H_{32}N_2B_{20}$	C, H, N
13	$CH_3CB_{10}H_{10}CNCH_3NCH_3CB_{10}H_{10}CCH_3$[f]	95	257	$C_8H_{32}N_2B_{20}$	C, H, N, B
14	$CH_3CB_{10}H_{10}CNCH_3NC_6H_5CB_{10}H_{10}CCH_3$[f]	95	192–193	$C_{13}H_{34}N_2B_{20}$	C, H, N
15	$CH_3CB_{10}H_{10}CNCH_3N(SO_2CH_3)CB_{10}H_{10}CCH_3$[f]	45	175	$C_8H_{32}N_2B_{20}O_2S$	C, H, N, S
16	$CH_3CB_{10}H_{10}CSSCB_{10}H_{10}CCH_3$[g]	>30	250	$C_6H_{26}B_{20}S_2$	C, H, S
17	$(HCB_{10}H_{10}CCB_{10}H_{10}CNH)_2$–[f]	58	>300	$C_8H_{44}N_2B_{40}$	C, H, N
18	$CH_3CB_9H_{10}^-C(CH_2)_3NH^+(C_2H_5)_2$[h]	29	255–260	$C_{10}H_{30}NB_9$	C, H, N
19	$HCB_9H_{10}CH \cdot TMA$[i]				
20	$HCB_9H_{10}CC_6H_5 \cdot TMA$[i]				
21	$HCB_9H_{10}CC_6H_5(4\text{-}NO_2) \cdot TMA$	50 (C)	>300	$C_{12}H_{28}N_2B_9O_2$	C, H, N
22	$CH_3CB_9H_{10}CC_4H_9 \cdot TMA$	96 (A), 83 (B)	93–97 dec	$C_{11}H_{34}NB_9$	C, H, N
23	$CH_3CB_9H_{10}CC_5H_{11} \cdot TMA$	77 (A), 71 (B)	150–151	$C_{12}H_{36}NB_9$	C, H, N
24	$CH_3CB_9H_{10}CC_7H_{15} \cdot TMA$	76 (A), 76 (B)	179–181	$C_{14}H_{40}NB_9$	C, H, N
25	$CH_3CB_9H_{10}CC_{11}H_{23} \cdot TMA$	53 (A), 89 (B)	190	$C_{18}H_{48}NB_9$	C, H, N
26	$CH_3CB_9H_{10}CC_{16}H_{33} \cdot TMA$	65 (A), 88 (B)	205–210 dec	$C_{23}H_{58}NB_9$	C, H, N
27	$CH_3CB_9H_{10}C(CH_2)_3OC_6H_2(2,4,5\text{-}Cl_3) \cdot TMA$	65 (C)	182–186	$C_{16}H_{33}NB_9Cl_3O$	C, H, N, Cl
28	$C_5H_{11}CB_9H_{10}CC_5H_{11} \cdot TMA$	92 (A), 70 (B)	223–228	$C_{16}H_{44}NB_9$	C, H, N
29	$HCB_{10}H_{10}CCB_9H_{10}CH \cdot TMA$[j]				
30	$H_2NCB_{10}H_{10}CCB_9H_{10}CH \cdot P$	88 (C)	254–255	$C_9H_{35}N_2B_{19}$	C, H, N
31	$HCB_{10}H_{10}CCB_9H_{10}CCl \cdot TMA$	63 (C)	>300	$C_8H_{33}NB_{19}Cl$	C, H, N, Cl
32	$CH_3CB_{10}H_{10}CCB_9H_{10}CCH_3 \cdot TMA$	82 (B)	>300	$C_{10}H_{38}NB_{19}$	C, H, N
33	$HCB_{10}H_{10}CN{=}NCB_9H_{10}CH \cdot TMA$[f]	80 (B)	>300	$C_8H_{34}N_3B_{19}$	C, H, N, B
34	$CH_3CB_{10}H_{10}CN{=}NCB_9H_{10}CCH_3 \cdot TMA$[f]	88 (B)	>300	$C_{10}H_{38}N_3B_{19}$	C, H, N, B
35	$C_6H_5CB_{10}H_{10}CN{=}NCB_9H_{10}CC_6H_5 \cdot TMA$[f]	88 (B)	245–246	$C_{20}H_{42}N_3B_{19}$	C, H, N, B
36	$CH_3CB_{10}H_{10}CNHNHCB_9H_{10}CCH_3 \cdot P$[f]	69 (C)	199–201	$C_{11}H_{40}N_3B_{19}$	C, H, N
37	$CH_3CB_{10}H_{10}CNCH_3NHCB_9H_{10}CCH_3 \cdot TMA$	54 (B)	not measured	$C_{11}H_{42}N_3B_{19}$	C, H, N
38	$CH_3CB_{10}H_{10}CNC_4H_9NHCB_9H_{10}CCH_3 \cdot TMA$	40 (C)	225–228 dec	$C_{14}H_{48}N_3B_{19}$	C, H, N
39	$CH_3CB_{10}H_{10}CNHNC_6H_5CB_9H_{10}CCH_3 \cdot TMA$	55 (C)	120–130 dec	$C_{16}H_{44}N_3B_{19}$	C, H, N
40	$CH_3CB_{10}H_{10}CNHNC_6H_4(4\text{-}NMe_2)CB_9H_{10}CCH_3 \cdot TMA$	29 (C)	130–140 dec	$C_{18}H_{49}N_4B_{19}$	C, H, N
41	$CH_3CB_{10}H_{10}CNHNC_6H_4(4\text{-}Cl)CB_9H_{10}CCH_3 \cdot P$	91 (C)	133–136 dec	$C_{17}H_{43}N_3ClB_{19}$	C, H, N
42	$CH_3CB_{10}H_{10}CNCH_3NC_6H_5CB_9H_{10}CCH_3 \cdot TMA$	49 (C)	149–153 dec	$C_{17}H_{46}N_3B_{19}$	C, H, N
43	$CH_3CB_{10}H_{10}CNCH_3NC_6H_4(4\text{-}Cl)CB_9H_{10}CCH_3 \cdot P$	73 (C)	213–214 dec	$C_{18}H_{43}N_3B_{19}Cl$	C, H, N, Cl
44	$CH_3CB_{10}H_{10}CNCH_3NCH_3CB_9H_{10}CCH_3 \cdot TMA$[f]	90 (C)	>300	$C_{12}H_{44}N_3B_{19}$	C, H, N

45	$CH_3CB_{10}H_{10}CN\text{—}(CH_2)_3\text{—}NCB_9H_{10}CCH_3\cdot TMA$	29 (A), (C)	94–98 dec	$C_{13}H_{44}N_3B_{19}$	C, H, N
46	$HCB_{10}H_{10}C(CH_2)CB_9H_{10}CH\cdot TMA$	96 (C)	>300	$C_9H_{36}NB_{19}$	C, H, N
47	$HCB_{10}H_{10}C(CH_2)_2CB_9H_{10}CH\cdot TMA$	(A), 35 (C)	>300	$C_{10}H_{38}NB_{19}$	C, H, N
48	$CH_3CB_{10}H_{10}C(CH_2)_3CB_9H_{10}CCH_3\cdot TMA$	9 (A), 49 (C)	>300	$C_{13}H_{44}NB_{19}$	C, H, N
49	$HCB_{10}H_{10}C(CH_2)_6CB_9H_{10}CH\cdot TMA$	28 (D), 59 (C)	>300	$C_{14}H_{46}NB_{19}$	C, H, N, S
50	$CH_3CB_{10}H_{10}CSSCB_9H_{10}CCH_3\cdot TMA$	95 (C)	224–226	$C_{10}H_{38}NB_{19}S_2$	C, H, N, S
51	$(HCB_9H_{10}CCB_{10}H_{10}CNH)_2\text{—}(TMA)_2$	69 (C)	>300	$C_{16}H_{68}N_4B_{38}$	C, H, N
52	$HCB_9H_{10}CCB_9H_{10}CH\cdot(TMA)_2$ [i]				
53	$HCB_9H_{10}CN{=}NCB_9H_{10}CH\cdot(TMA)_2$ [f]	72 (B)	>300	$C_{12}H_{46}N_4B_{18}$	C, H, N, B
54	$CH_3CB_9H_{10}CSSCB_9H_{10}CCH_3\cdot(TMA)_2$	72 (C)	>300	$C_{14}H_{50}N_2B_{18}S_2$	C, H, N, S
55	$HCB_9H_{10}C(CH_2)CB_9B_{10}CH\cdot(TMA)_2$	84 (B)	>300	$C_{13}H_{48}N_2B_{18}$	
56	$HCB_9H_{10}C(CH_2)_2CB_9H_{10}CH\cdot(TMA)_2$	77 (C)	>300	$C_{14}H_{50}N_2B_{18}$	C, H, N
57	$[CH_3(CH_2)_6CB_9H_{10}C(CH_2)_3]_2\text{—}(TMA)_2$	79 (B)	162–164 dec	$C_{32}H_{86}N_2B_{18}$	C, H, N, B

[a] TMA = tetramethylammonium salt; P = piperidinium salt. [b] Unless otherwise stated, the analyses were within ±0.4% of the theoretical values. [c] Described in ref 7. [d] Described in ref 6. [e] Described in ref 10. [f] Described in ref 11. [g] Described in ref 12. [h] Described in ref 3. [i] Described in ref 8. [j] Described in ref 15.

phenyl substituent of **20** also yielded no antifungal property (compound **21**).

For the alkylated dicrabollide monoanions **22–26**, antifungal activity was enhanced with an increase in alkyl size. The best MIC value was observed for compound **25**, in which an undecyl group bonds to the carbon atom of the dicarbollide anion as seen in **25a**. Based on the above

results, an empirical rule can be drawn which states that the hydrophilic dicarbollide anion and the lipophilic alkyl groups (C_5–C_{17}) bonded to the dicarbollide carbon atom lead to the antimicrobial activity.

There also seems to be a similar relation between the structure of closo–nido dicage carboranes and their high activity (e.g., **29–32**); contrary to the hydrophilicity of the dicarbollide anion, *o*-carborane is thought to be a lipophilic moiety that is soluble in various nonpolar organic solvents. Accordingly, a combination of the dicarbollide anion and the *o*-carboranyl group as illustrated in **32a** would yield the antifungal activity.

Remarkable activity change was not observed in the closo–nido substituted hydrazino derivatives (e.g., **36–45**); in this series, each hydrogen atom that was bonded to the hydrazino group of compound **36** was substituted with alkyl (e.g., **37**, **38**, **44**, and **45**) or aryl (e.g., **39–43**) groups. In spite of our attempts to introduce different size substituents with different electronic properties, we failed to find any marked activity change. Hence, hydrophobicity appears predominant, in contrast with electronic and steric factors, in determining the activity of the carborane derivatives.

Poor antifungal activity of the aryl-substitued dicarbollide anion, **20** (C_6) or **21** (C_6) (*Candida albicans* >100; *Aspergillus fumigatus*, 100; *Tricophyton asteroides*, 25–50 μg/mL), compared with its alkyl-substituted congener **23** (C_6) (*Candida albicans* 50; *Aspergillus fumigatus*, 25; *Tricophyton asteroides*, 6.2 μg/mL) is probably because of π-electron delocalization where electrons on the phenyl ring conjugate with those in the *nido*-carborane cage.

Compounds **27**, **28** and **25** demonstrated comparable antifungal activity. This may be interpreted by the lipophilicity of the substituents bonded to dicarbollide anion; since these monocage dicarbollide anions showed the same MIC values (*Candida albicans* 3.1; *Aspergillus fumigatus*, 3.1; *Tricophyton asteroides*, 6.2 μg/mL), we have presumed that the substituents of these compounds probably have nearly equal lipophilic properties. Actually, the hydrophobic parameter π values for **25**, **27**, and **28** have been

Table II. Reaction Conditions of Degradation and ^{1}H NMR Data

no.	starting material	base[a] KOH	base[a] piperidine	temp,[b] °C	time, h	^{1}H NMR
30	6		4.5	RT	2	CD_3COCD_3: δ 2.08 (br s, 1 H, CH), 4.53 (br s, 2 H, NH_2)
31	7		3.6	RT	0.7	CD_3OD: δ 3.20 (s, 12 H, ME_4N^+), 4.35 (br s, 1 H, $B_{10}CH$)
46	BCM[c]		3.3	RT	12	CD_3CN: δ 1.90 (br s, 1 H, B_9CH), 2.60 (br s, 2 H, CH_2), 4.49 (br s, 1 H, $B_{10}CH$), K^+ salt
47	BCE[d]		3.3	RT	10	CD_3COCD_3: δ 1.67 (m, 2 H, B_9CCH_2), 2.40 (m, 2 H, $B_{10}CCH_2$), 3.43 (s, 12 H, Me_4N^+), 4.78 (br s, 1 H, $B_{10}CH$)
48	BMCP[e]		10	80	25	CD_3COCD_3: δ 1.40 (s, 3 H, B_9CCH_3), 1.72 (m, 4 H, $B_9CCH_2CH_2$), 2.15 (s, 3 H, $B_{10}CCH_3$), 2.17 (m, 2 H, $B_{10}CCH_2$), 3.45 (s, 12 H, Me_4N^+)
50	BMCS[f]		3.3	RT	1	CD_3COCD_3: δ 1.52 (s, 3 H, B_9CCH_3), 2.23 (s, 3 H, $B_{10}CCH_3$), 3.45 (s, 12 H, Me_4N^+)
51	HBC[g]		8.8	80	2	CD_3OD: δ 2.27 (br s, 2 H, B_9CH), 3.20 (s, 24 H, Me_4N^+)
54	BMCS[f]		8.8	RT	1.5	CD_3COCD_3: δ 1.70 and 1.80 (2 s, 6 H, B_9CCH_3), 3.45 (s, 24 H, Me_4N^+)
55	BCM[c]	5		78	24	CD_3CN: δ 3.10 (s, 24 H, Me_4N^+), 3.10 (overlapped with Me_4N^+; CH_2), 1.87 (br s, 2 H, B_9CH)
56	BCE[d]		6.5	80	8	CD_3COCD_3: δ 1.58 (br s, 2 H, B_9CH), 1.72 (s, 4 H, CH_2CH_2), 3.45 (s, 24 H, Me_4N^+)

[a] Amount of base (moles) per starting material (moles). [b] RT denotes room temperature (20–25 °C). [c] BCM = bis(*o*-carboranyl)methane.[16] [d] BCE = 1,2-bis(*o*-carboranyl)ethane.[17] [e] BMCP = 1,3-bis(1-methyl-*o*-carboranyl)propane, prepared by method D.[7] [f] BMCS = bis(2-methyl-*o*-carboranyl)disulfide.[12] [g] HBC = hydrazobis(*o*-carborane).[11]

estimated to have comparable values (e.g., π = 4.8–6.1),[14] as would be expected.

In the case of nido–nido dicage dianions (e.g., **52–56**), antimicrobial activity was very low compared with that of the above-mentioned closo–nido dicage monoanions (e.g., **29–50**). From a consideration similar to the hydrophile–lipophile balance, the reason for the low activity against fungi could be attributed to too much hydrophilic property caused by a couple of the nido cages. Compound **57**, although it is a nido–nido dianion, exhibited high antifungal activity. This compound, having much more lipophilic property compared with that of compounds **52–56**, is probably in appropriate hydrophile–lipophile balance to yield the activity.

From these results we conclude that introduction of lipophilic alkyl or *o*-carboranyl groups to the hydrophilic dicarbollide anions leads to antimicrobial activities.

Experimental Section

All of the reactions involving dicarbollide ions or lithium reagents were carried out under a nitrogen atmosphere. Benzene, ether, and toluene were dried over molecular sieves. Piperidine was distilled before use. Other solvents and chemicals were reagent grade and used without further purification.

Infrared spectra were recorded on a Hitachi 215 spectrometer. NMR spectra were obtained on a Varian T-60 spectrometer. Most compounds involving 7,8-$C_2B_9H_{12}^-$ dicarbollide ions were isolated and purfied in the form of Me_4N^+ or $C_5H_{10}NH_2^+$ salts. Regardless of the form of the compounds isolated, they were always converted to water-soluble K^+ salts in order to investigate antimicrobial activity. Conversion to the K^+ salt was achieved by passage through a potassium cation exchanger, Amberlite IR-120 (K^+).

Preparation of 1,3-Bis(2-methyl-*o*-carboranyl)propane [$MeCB_{10}H_{10}C(CH_2)_3CB_{10}H_{10}CMe$] and 1-Methyl-2-(γ-iodopropyl)-*o*-carborane [$MeCB_{10}H_{10}C(CH_2)_3I$ (1a)]. To an ice-cold solution of 1-lithio-2-methyl-*o*-carborane ($MeCB_{10}H_{10}CLi$) prepared from $MeCB_{10}H_{10}CH$ (1.58 g, 10 mmol)[7] in benzene (15 mL) and *n*-BuLi (10 mmol) in ether (5 mL) was added 1-bromo-3-chloropropane (5 mL); then the mixture was allowed to warm to room temperature and kept for 4 h, followed by reflux for 1 h. After the solvent and volatiles were removed under reduced pressure, to the residue was added hexane (10 mL), the mixture was cooled on an ice bath, and a white solid was filtered off. The solid was recrystallized from hexane to give 180 mg of $MeCB_{10}H_{10}C(CH_2)_3CB_{10}H_{10}CMe$: mp 258–260 °C; NMR ($CDCl_3$) δ 1.7–2.5 (m, 6 H, $CH_2CH_2CH_2$), 2.03 (s, 6H, Me). Anal. ($C_9H_{32}B_{20}$) C, H, B.

The filtrate (10 mL of hexane solution) containing $MeCB_{10}H_{10}C(CH_2)_3Cl$ as a major product was evaporated to leave an oil. The oily residue was dissolved in acetone (15 mL), NaI (1.0 g) was added, and the mixtue was refluxed for 1 h. After the solvent was removed, the residue was recrystallized from hexane to give 2.37 g (73%) of **1a**, mp 33 °C. Anal. ($C_6H_{19}IB_{10}$) C, H, I, B.

1-Methyl-2-[(2,4,5-trichlorophenoxy)propyl]-*o*-carborane (4). A mixture of 1a (490 mg, 1.5 mmol) and 2,4,5-trichlorophenol sodium salt (1.7 mmol) in acetone (10 mL) was refluxed for 3 h and cooled. After the solvent was removed, the residue was extracted with hot hexane (40 mL), and the extract was concentrated to ~5 mL, which crystallized 530 mg of **4**.

2-Aminobis(*o*-carborane) (6). To a solution of 2-lithiobis(*o*-carborane) ($HCB_{10}H_{10}CCB_{10}H_{10}CLi$) prepared from bis(*o*-carborane) ($HCB_{10}H_{10}CCB_{10}H_{10}CH$) 5.7 g, 20 mmol)[6] in benzene (100 mL) and *n*-BuLi (20 mmol) in ether (30 mL) was added with stirring PhN_3 (2.4 g, 20 mmol) in benzene (50 mL) at room temperature. The temperature of the mixture was raised gradually and kept at 55–60 °C for 2 h. After the mixture was cooled on an ice bath, water (50 mL) was added to the mixture with care.

(14) Roughly estimated π values for the substituents of **25**, **27**, and **28** are 5.7, 6.1, and 4.8, respectively. Hydrophobic parameters (π) were cited from Hansch, C.; Leo, A.; Unger, S. H.; Kim, K.-H.; Nikaitani, D.; Lein, E. J. *J. Med. Chem.* **1973**, *16*, 1207.

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Table III. Antifungal and Antibacterial Activities of *closo*-*o*-Carborane Derivatives (1–17) and Nido Potassium Salts (18–57)

	minimum inhibitory concn, μg/mL									minimum inhibitory concn, μg/mL							
compd	*C.a.*[a]	*A.f.*[a]	*T.a.*[a]	*S.a.*[b]	*S.p.*[b]	*E.c.*[b]	*K.p.*[b]	*P.a.*[b]	compd	*C.a.*[a]	*A.f.*[a]	*T.a.*[a]	*S.a.*[b]	*S.p.*[b]	*E.c.*[b]	*K.p.*[b]	*P.a.*[b]
1	>100	>100	>100	>100	>100	>100	>100	>100	31·K	1.6	1.6	6.2	6.2	6.2	>100	>100	>100
2	>100	>100	>100	>100	>100	>100	>100	>100	32·K	3.1	3.1	6.2	6.2	6.2	>100	>100	>100
3	>100	>100	1.6	50	6.2	100	100	>100	33·K	6.2	50	12.5	6.2	0.8	>100	100	>100
4	>100	>100	>100	>100	>100	>100	>100	>100	34·K	3.1	12.5	6.2	3.1	0.4	>100	>100	>100
5	>100	>100	>100	>100	>100	>100	>100	>100	35·K	3.1	12.5	12.5	6.2	0.4	>100	>100	>100
6	>100	>100	>100	12.5	6.2	>100	>100	>100	36·K	6.2	6.2	12.5	3.1	3.1	>100	>100	>100
7	25	12.5	50	6.2	1.6	>100	>100	>100	37·K	3.1	3.1	25	6.2	6.2	>100	>100	>100
8	>100	>100	>100	>100	>100	>100	>100	>100	38·K	3.1	6.2	12.5	6.2	6.2	>100	>100	>100
9	100	>100	>100	100	>100	>100	>100	>100	39·K	6.2	6.2	12.5	1.6	0.8	>100	>100	>100
10	50	100	>100	50	100	>100	>100	>100	40·K	12.5	50	12.5	6.2	0.8	>100	>100	>100
11	>100	>100	>100	6.2	6.2	>100	>100	>100	41·K	6.2	6.2	25	3.1	0.8	>100	>100	>100
12	>100	>100	>100	>100	>100	>100	>100	>100	42·K	6.2	1.6	12.5	6.2	6.2	>100	>100	>100
13	>100	>100	>100	>100	>100	>100	>100	>100	43·K	3.1	3.1	25	3.1	0.4	>100	>100	>100
14	>100	>100	>100	>100	>100	>100	>100	>100	44·K	3.1	3.1	12.5	3.1	1.6	100	100	100
15	>100	>100	>100	>100	>100	>100	>100	>100	45·K	3.1	6.2	6.2	6.2	6.2	>100	>100	>100
16	>100	>100	>100	>100	>100	>100	>100	>100	46·K	6.2	3.1	3.1	3.1	1.6	>100	100	>100
17	>100	>100	50	50	50	>100	>100	>100	47·K	6.2	6.2	6.2	6.2	0.4	100	100	100
18	>100	>100	>100	>100	>100	>100	>100	>100	48·K	6.2	3.1	25	1.6	0.4	100	100	100
19·K	>100	>100	>100	>100	12.5	100	100	>100	49·K	1.6	3.1	12.5	1.6	0.8	50	50	50
20·K	>100	>100	50	100	6.2	>100	>100	>100	50·K	1.6	3.1	12.5	3.1	1.6	100	100	100
21·K	>100	>100	25	25	0.8	>100	>100	>100	51·2K	0.8	1.6	6.2	0.8	0.8	100	100	50
22·K	50	25	12.5	12.5	0.8	>100	>100	>100	52·2K	>100	>100	>100	100	12.5	>100	>100	>100
23·K	50	25	6.2	12.5	0.4	>100	>100	>100	53·2K	>100	>100	>100	100	1.6	>100	>100	>100
24·K	12.5	12.5	6.2	6.2	0.8	100	100	>100	54·2K	>100	>100	50	100	1.6	>100	>100	>100
25·K	3.1	3.1	6.2	1.6	0.4	50	50	50	55·2K	>100	>100	>100	>100	6.2	>100	>100	>100
26·K	6.2	6.2	25	3.1	1.6	>100	>100	100	56·2K	>100	>100	100	>100	1.6	>100	>100	>100
27·K	3.1	3.1	6.2	0.8	0.4	50	25	50	57·2K	6.2	6.2	25	3.1	1.6	50	50	25
28·K	3.1	3.1	6.2	1.6	1.6	25	25	50	clotrimazole	3.1	3.1	<0.1					
29·K	3.1	3.1	6.2	12.5	6.2	>100	>100	100	amphotericin B	1.6	3.1	3.1					
30·K	12.5	12.5	12.5	25	6.2	>100	>100	>100									

[a] Fungi: *C.a.* = *Candida albicans*; *A.f.* = *Aspergillus fumigatus*; *T.a.* = *Tricophyton asteroides*. [b] Bacteria: *S.a.* = *Staphylococcus aureus*; *S.p.* = *Streptococcus pyogenes*; *E.c.* = *Escherichia coli*; *K.p.* = *Klebsiella pneumoniae*; *P.a.* = *Pseudomonas aeruginosa*.

The organic layer was separated, washed with water, dried over Na_2SO_4, and concentrated. The residue was extracted with hot hexane (500 mL), and the extract was concentrated to crystallize 5.9 g (73%) of 2-phenyltriazenylbis(*o*-carborane) [$HCB_{10}H_{10}CCB_{10}H_{10}CN_3(H)C_6H_5$]: mp 141–143 °C dec. Anal. ($C_{10}H_{27}N_3B_{20}$) C, H, N, B. A mixture of the triazene derivative (5.7 g, 14 mmol) and glacial acetic acid (120 mL) was heated at 90 °C for 1 h. After the acid was evaporated under reduced pressure, the residue was extracted with hot benzene (100 mL × 2). The combined extracts were evaporated, and the residue was crystallized from ether–hexane to give 3.7 g (87%) of **6**.

2-Chlorobis(*o*-carborane) (7). To a solution of compound **6** (600 mg, 2.0 mmol) in chloroform (10 mL) was added NOCl (400 mg, 6 mmol), and the mixture was stirred at room temperature for 4 h. After the solvent and excess NOCl were removed under reduced pressure, the residue was chromatographed on silica gel 60 using methylene chloride–hexane (1:9) as an eluant and recrystallized from hexane to give 470 mg (73%) of **7**.

General Procedure for Compounds 22–26. Tetramethylammonium 7-Methyl-8-pentyl-7,8-dicarbollide (23). Starting neutral alkylcarboranes ($MeCB_{10}H_{10}CC_nH_{2n+1}$) were prepared by the reaction of 1-lithio-2-methyl-*o*-carborane and alkyl bromides (method A), which were degraded to the corresponding substituted $7,8\text{-}C_2B_9H_{12}^-$ dicarbollide ions **22–26** with ethanolic potassium hydroxide (method B).

In a typical example, to an ethereal solution (2 mL) of $MeCB_{10}H_{10}CLi$ prepared from 1-methyl-*o*-carborane[7] (140 mg, 0.90 mmol) and *n*-BuLi (0.90 mmol) in situ was added 1-bromopentane (210 mg, 1.4 mmol) in benzene (2 mL), and the mixture was refluxed for 6 h and then cooled. After the mixture was shaken with water (0.2 mL), the organic layer was separated and dried over $MgSO_4$, and the solvent was evaporated. The residue was extracted with hexane (3 mL × 2), and the combined extracts were passed through a silica gel column. The hexane and volatiles were removed (110 °C, 2 mmHg, 1 h) to give 160 mg (77%) of $MeCB_{10}H_{10}CC_5H_{11}$ as a colorless oil, which satisified the elemental analysis. A mixture of the above-obtained $MeCB_{10}H_{10}CC_5H_{11}$ (110 mg, 0.48 mmol) and KOH (56 mg, 1.0 mmol) in ethanol (3 mL) was refluxed for 8 h and cooled. A piece of dry ice was added to the mixture to precipitate the excess of KOH as K_2CO_3. The filtered ethanol solution was evaporated and the residue was crystallized from methylene chloride–hexane to give colorless crystals of the potassium dicarbollide. The potassium salt is very hygroscopic. The tetramethylammonium salt was prepared for analysis by the usual method.[8] The potassium salt was dissolved in water and addition of aqueous tetramethylammonium chloride precipitated the tetramethylammonium salt. It was filtered, washed with water, and dried under reduced pressure. The yield of **23** was 73%.

Tetramethylammonium 7-Methyl-8-[(2,4,5-trichlorophenoxy)propyl]-7,8-dicarbollide (27). A mixture of **4** (260 mg, 0.66 mmol) and piperidine (560 mg, 6.6 mmol) in benzene (5 mL) was refluxed for 16 h. A volume of the mixture was reduced to approximately 1 mL under reduced pressure and then hexane (30 mL) was added to precipitate the crude piperidinum dicarbollide. The salt was dissolved in 80% methanol (10 mL), neutralized with dilute HCl, and passed through a column packed with Amberlite IR-120 (Na^+) resin rinsed with 50% acetonitrile. The effluent containing the sodium salt was concentrated to about 10 mL and filtered. Addition of aqueous Me_4NCl to the filtrate precipitated the tetramethylammonium salt. It was recrystallized from ethanol–water to yield 220 mg (71%) of the pure salt. The potassium salt was prepared by passing the tetramethylammonium salt in 50% acetonitrile through a column packed with Amberlite IR-120 (K^+) resin rinsed with the same solvent. The concentration of the eluted product left hydrated potassium salt. This was dehydrated by drying in vacuo.

Tetramethylammonium 7,8-Dipentyl-7,8-dicarbollide (28). To a ethereal solution (3 mL) of 1,2-dilithio-*o*-carborane prepared from *o*-carborane[7] (100 mg, 0.70 mmol) and *n*-BuLi (1.4 mmol) in situ was added *n*-pentyl bromide (0.3 g) in benzene (3 mL), and the mixture was refluxed for 12 h and then cooled. After the mixture was shaken with water (0.2 mL), the organic layer was separated and concentrated, and the residue was extracted with hexane (5 mL). Removal of hexane and volatiles (100 °C, 2 mmHg) left 185 mg (92%) of $C_5H_{11}CB_{10}H_{10}CC_5H_{11}$ as a colorless oil. It was degraded and purified in the same manner as described for **23** except that the reaction was carried out at reflux for 12 h.

Tetramethylammonium 7-(*o*-Carboran-1′-ylhexyl)-7,8-dicarbollide (49). Starting material 1,6-bis(*o*-carboranyl)hexane ($HCB_{10}H_{10}C(CH_2)_6CB_{10}H_{10}CH$) was prepared by method D as shown in Scheme II.[7] A mixture of bis(acetonitrile)decaborane [$B_{10}H_{12}(MeCN)_2$] (1.4 g, 0.4 mmol) and 1,9-decadiyne (0.38 g, 2.9 mmol) in toluene (10 mL) was heated at 110 °C for 8 h. After the solvent was removed under reduced pressure, the residue was extracted with methylene chloride (10 mL) and recrystallized from methylene chloride–hexane to give 660 mg (28%) of 1,6-bis(*o*-carboranyl)hexane: mp 162–163 °C. Anal. ($C_{10}H_{34}B_{20}$) C, H, B. To a solution of 1,6-bis(*o*-carboranyl)hexane (70 mg, 0.19 mmol) in ethanol (2.5 mL) was added KOH (17 mg, 0.3 mmol), and the mixture was refluxed for 4 h and cooled. After treatment with dry ice, the filtrated solution was concentrated and chromatographed on silica gel. An elution with methylene chloride–acetone (3:1) gave the potassium salt, which was converted to the tetramethylammonium salt for analysis by the same method described before: yield 50 mg (59%); mp >300 °C; NMR (CD_3COCD_3) δ 1.33 [m, 11 H, $(CH_2)_5CB_9CCH$], 2.35 (m, 2 H, $B_{10}CCH_2$), 3.45 (s, 12 H, NMe_4), 4.65 (br s, 1 H, $B_{10}CH$). Anal. ($C_{14}H_{45}NB_{20}$) C, H, N.

Degradation Products of Hydrazobis(*o*-carborane) (51). To a suspension of hydrazobis(*o*-carborane)[11] (250 mg, 0.41 mmol) in benzene (5 mL) was added with stirring piperidine (310 mg, 3.6 mmol) at room temperature, which separated a red layer (due to dissociation of the hydrazo proton with the base) and a colorless layer. The mxiture was vigorously stirred at 80 °C for 2 h. The red color disappeared within 1 h. After the mixture was cooled, hexane (20 mL) was added and an oil precipitate of the crude piperidinium salt of the product was collected. It was converted to the tetramethylammonium salt in the same manner as described for **27**. The tetramethylammonium salt was dissolved in a minimum amount of acetone, followed by the addition of a large amount of ether. The resulting yellow crystalline product $(Me_4N)_2[HCB_{10}H_{10}CCB_{10}H_{10}CNNHCB_{10}H_{10}CCB_9H_{10}CH]$, was filtered off: yield 60 mg; mp 300 °C dec; NMR (Me_2SO-d_6) δ 1.95 (br s, 1 H, B_9CH), 3.10 (s, 24 H, NMe_4), 4.32 (br s, 1 H, $B_{10}CH$), 8.35 (br s, 1 H, NH). Anal. ($C_{16}H_{67}N_4B_{39}$) C, H, N. Recrystallization of this compound from acetone–water in the presence of dilute HCl gave colorless N-protonated species, (Me_4N)-$[HCB_{10}H_{10}CCB_{10}H_{10}CNHNHCB_{10}H_{10}CCB_9H_{10}CH]$: mp 265–266 °C; NMR ($Me_2SO$-$d_6$) δ 1.97 (br s, 1 H, B_9CH), 3.10 (s, 12 H, NMe_4), 4.42 (br s, 1 H, $B_{10}CH$), 8.35 (br s, 1 H, $NHCB_{10}H_{10}CCB_9$). The N–H proton signal of $NHCB_{10}H_{10}CCB_{10}$ was not observed; a rapid exchange would occur between the hydrogen of the N–H and those of the water molecule in Me_2SO-d_6 solvent. Anal. ($C_{12}H_{56}N_3B_{39}$) C, H, N. The mother liquor was evaporated, the residue was dissolved in a minimum amount of methanol, and a large amount of methylene chloride was added. The solution was left standing at room temperature for several hours, which resulted in colorless crystals of the tetramethylammonium salt **51**: yield 200 mg (69%); ^1H NMR data are shown in Table II.

Preparation of 1,6-Bis(2-heptyl-*o*-carboranyl)hexane and Its Degradation Product (57). Starting material 1,6-bis(2-heptyl-*o*-carboranyl)hexane [$C_7H_{15}CB_{10}H_{10}C(CH_2)_6CB_{10}H_{10}C$-$C_7H_{15}$] was prepared by the method D.[7] To a slurry of $LiCB_{10}$-$H_{10}C(CH_2)_6CB_{10}H_{10}CLi$ prepared from 1,6-bis(*o*-carboranyl)hexane and *n*-butyllithium (1.0 mmol) in ether (4 mL) in situ was added *n*-pentyl bromide (360 mg) in benzene (6 mL). The mixture was refluxed for 6 h. After the mixture was cooled, water was added, and the organic layer was separated, dried over Na_2SO_4, and concentrated to near dryness. The residue was extracted with hot hexane, and the extract was concentrated, which crystallized 195 mg (85%) of 1,6-bis(2-heptyl-*o*-carboranyl)hexane, mp 102–103 °C. Anal. ($C_{24}H_{62}B_{20}$) C, H, N. A mixture of this compound (130 mg, 0.23 mmol) and KOH (62 mg, 1.1 mmol) in absolute ethanol (3 mL) was refluxed for 1, h and cooled. The tetramethylammonium salt was obtained by the same manner as described for **23**. The yield of **57** was 130 mg (81%).

Antimicrobial Activity. Fungal Strains. *Candida albicans*, *Aspergillus fumigatus*, and *Trichophyton asteroides*, originally isolated from clinical specimens, were tested. Before testing, these strains were grown on Sabouraud's dextrose agar slants at 28 °C.

An inoculum of *C. albicans* was prepared by suspending the yeast cells grown for 48 h in Sabouraud's dextrose broth. Inocula of *A. fumigatus* and *T. asteroides* were prepared by suspending the conidia grown for 14 days in the same broth containing Tween 80 at 0.1%.

Bacterial Strains. *Staphylococcus aureus, Streptococcus pyogenes, Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa* were tested. These strains, except *S. pyogenes,* were grown overnight at 37 °C on Heart Infusion agar slants. *S. pyogenes* was grown on a Brain–Heart Infusion agar slant. Inocula were prepared by suspending the growth in Mueller–Hinton broth.

Preparation of Drugs. Stock solutions of *o*-carborane derivatives were prepared at a concentration of 1 mg/mL. Methyl alcohol was used to solubilized the compound, which were insoluble in water.

Determination of MIC. Minimum inhibitory concentrations (MICs) were determined with the microtiter system. Inocula of fungal and bacterial strains were equally adjusted to 1×10^5 colony forming units per milliliter. Sabouraud's dextrose broth was used as the testing medium for fungi, and Mueller–Hinton broth was used for bacteria. The drug concentrations ranged from 100 to 0.01 μg/mL using the automatic twofold serial dilution technique. The final volume in the microtiter well was 0.05 mL. The concentration of methyl alcohol never exceeded 2%, which showed no inhibitory effect on any of the test organisms. After dilution, the microtiter plates were sealed with a cellophane membrane and incubated at 37 °C for 48 h. The MIC was defined as the lowest concentration of drug at which no visible fungal or bacterial growth was observed.

Synthesis of Pyridylallylamines Related to Zimelidine and Their Inhibition of Neuronal Monoamine Uptake

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Analogues of the antidepressant agent zimelidine [**6**, (*Z*)-3-(4-bromophenyl)-*N*,*N*-dimethyl-3-(3-pyridyl)allylamine], a selective inhibitor of neuronal 5-hydroxytryptamine reuptake, were synthesized by several routes with the aim of obtaining compounds having a cis configuration (with respect to pyridyl and allylamine). Two methods utilized suitably substituted benzoylpyridines as starting materials. In two other routes, the bromine in **6** was either directly displaced (CN) or converted via the corresponding lithio derivative to H, Cl, I, Me, $SiMe_3$, and SMe. The configurations were determined by UV, ^1H NMR, and lanthanide-induced shifts in ^1H NMR. The compounds were evaluated as uptake inhibitors by measuring the accumulation of [^3H]noradrenaline and 5-hydroxy[^{14}C]tryptamine in mouse brain slices (in vitro and in vivo). Para substitution favored 5-hydroxytryptamine activity and ortho substitution favored NA activity in the cis series. The in vitro effect on 5-hydroxytryptamine was rather insensitive to variations in the para substituent, whereas pronounced effects in vivo were observed only with Cl, Br (**6**), and I.

The possible involvement of 5-hydroxytryptamine (5-HT) in the etiology of endogenous depression[1-4] has aroused interest in the development of selective inhibitors of neuronal 5-HT reuptake.[5-12] One such compound, zimelidine [**6**, (*Z*)-3-(4-bromophenyl)-*N*,*N*-dimethyl-3-(3-pyridyl)allylamine], has been shown in double blind clinical studies to possess antidepressive action similar to that of tricyclic antidepressant drugs.[13-16] Furthermore, there are indications of a low incidence of adverse effects of zimelidine.[13,14] This might be explained by the negligible action of **6** on most neurotransmitter receptors in the brain and the periphery (α_1-, α_2-, and β-adrenergic; 5-HT; histamine H_1 and H_2; muscarinic).[17,18] The lack of significant interaction with ethanol, barbiturates, and benzodiazepines

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