Antibacterial N-[ω,ω'-Bis(alicyclic and aryl)-sec-alkyl]poly(methylene)triamine and -tetramine Hydrochloride Salts

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A series of antibacterial N-[ω,ω'-(cycloalkyl, bicyclo[2.2.1]heptyl, and alkyl-substituted phenyl)-sec-alkyl]poly(methylene)triamine and -tetramine hydrochloride salts were synthesized in an effort to develop efficient, nonsystemic inhibitors, particularly for *Pseudomonas aeruginosa*. In the 1,5,9-triazanonane group, 3 of 16 compounds were effective at 8–10 μg/mL against pseudomonads. Efficiency appeared more dependent upon lipophilicity of the nitrogen substituent than other characteristics represented by the three types of rings. A parabolic relationship was observed for the entire set between the hydrophobic parameter, π, of the lipoidal moiety and minimal inhibitory concentration. One of 16 tetramines, 1-[1,5-bis(3,3-dimethyl-2-norbornyl)-3-pentyl]-1,5,9,13-tetraazatridecane tetrahydrochloride (**26f**), ranked similarly. An additional two compounds in each series were superior to several commercial cationic detergents in the control of the Gram-negative bacteria. None was inhibitory at up to 200 μg/mL for *Proteus vulgaris*.

Some poly(methylene)polyamines, including naturally occurring spermine, are minimally active broad-spectrum antibacterials[1,2] but, as with triethylenetetramine, can potentiate diverse antibiotics, apparently by alteration of cellular permeability.[3a,b] The gain in biophase solubility obtained with N-(long-chain alkyl)polyamine substitution has provided useful nonsystemic microbial inhibitors and algistats.[4-6] However, such cationic agents have generally appeared less effective against Gram-negative bacteria, which are additionally difficult to penetrate because of a unique outer membrane. This barrier contains in an aqueous milieu anionic lipopolysaccharides and proteins (porins) held responsible for establishing size-dependent permeability channels.[7] Further, the cell-envelope content of total lipids is up to 20% by weight, about tenfold greater than that found in the wall of Gram-positive bacteria. *Pseudomonas aeruginosa* remains particularly troublesome. In this study, to develop disinfectants and antiseptics triamine and tetramine hydrochloride salts were synthesized which contained an N-*sec*-alkyl group symmetrically substituted on end carbon atoms with alicyclic or aryl moieties. These variants introduced lipoidal properties, together with spatial factors such as folding of the aralkyl type, when linked to a terminal polar function and surfaces with proton or electron enrichment.[8,9] The 1,5,9-triazanonane series provided highest inhibitory potencies when the nitrogen-modifying group independent of ring type supplied a calculated Hansch hydrophobic parameter, π,[8,9] in the approximate range of 7–9.

Chemistry.[10a-c] The compounds of Tables I and II, except for 1-[1,5-bis(3,3-dimethyl-2-norbornyl)-3-pentyl]-1,4,7,11-tetraazaundecane tetrahydrochloride (**26b**), were prepared by condensation between an ω,ω'-bis(ring-substituted)alkanone and a dialkylenetriamine or a trialkylenetetramine, reduction of the imine with hydrogen and platinum catalyst or $NaBH_4$ in 2-propanol for 1-[1,7-bis(cyclohexen-3-yl)-4-heptyl]-1,5,9-triazanonane trihydrochloride (**9**), and conversion to tri- or tetrahydrochloride salts. Compound **26b** was synthesized by cyanoethylation of 1-[1,5-bis(3,3-dimethyl-2-norbornyl)-3-pentyl]-1,4,7-triazaheptane (**25a**) [for **29**, by 1-amino-3-[(1,5-dicyclohexyl-3-pentyl)amino]-2-propanol (**30**)] and then catalytic reduction. Preferential primary amine–olefin addition was established by ^{13}C NMR spectra. No changes in chemical shifts were observed for carbon atoms linked to secondary amino groups of the triamine **25a** upon conversion to the tetramine **26b** or for the diamino alcohol derivative **30** and the resultant hydroxytriamine **29**. In contrast, for example, the carbon atom of the primary amino group in **30** moved downfield from 42.00 to 49.86 ppm (Me_2SO-d_6, Me_4Si) in **29**. Also, neither **26b** nor **29** exhibited in its spectrum a carbon atom attached to a tertiary amino group.

Most of the ketone intermediates (Table III) were obtained in yields of 50–90% by the thermal intermolecular decarboxylation of ω-ring-substituted alkanoic acid iron salts.[11] Purification by redistillation or column chromatography on silica gel afforded analytical samples. The known acids, not commercially available, were synthesized and included 4-(cyclohexen-3-yl)butanoic acid,[12] 3-[4-(1-methylethyl)cyclohexenyl]propanoic acid,[13] 3-(3,3-dimethyl-2-norbornyl)propanoic acid,[14] and 4-arylbutanoic acid.[15] 1,5-Diaryl-3-pentanones were readily accessible from the catalytic reduction of the doubly unsaturated araldehyde–acetone condensation product.

Microbiological Studies and Discussion. The in vitro antibacterial assays were run using Gram-positive and -negative bacteria with methods outlined under the Experimental Section.

High inhibitory potency was obtained against two pseudomonad strains (Tables I and II) and other Gram-negative bacteria (Table IV) among the 1,5,9-triazanonane salts with the cyclohexyl, substituted phenyl, or bicyclo derivatives **3**, **14**, and **25b**. The lipid substituent π values ranged from 8.1 to 9.0, and, apparently, the effects on efficiency of variations in steric and surface electronic factors or overall geometry were less significant than lipophilicity. An evaluation of the minimal inhibitory concentration (MIC, μg/mL) of the 16 1,5,9-triazanonane salts and calculated hydrophobic parameter, π, for the substituent $[R(CH_2)_x]_2$ also indicated that for inhibition of *Pseudomonas aeruginosa* the partitioning ratio appeared dominant as compared to other properties of the ring-type substituent. All of the compounds were superior to benzalkonium chloride and cetylpyridinium bromide which, in a previously reported study[16] using the same assay system, were found ineffective at 200 μg/mL against the two strains. The lower activity of the 2-naphthyl compound **24** appeared to reflect more of an unfavorable partition capability, which worsened when the anomaly of extra lipoidal contributions by the fused ring carbons (2 × 0.28) was included.[17]

A parabolic relationship between the N-substituent π and MIC for the cited compounds was evident, which did not differ significantly if log $1/C$ (C = molar inhibitory concentration) was substituted for MIC, μg/mL. Regression analysis using the least-squares method, within 95% confidence limits, provided the predicted curves: MIC (μg/mL) = 974.25 (±118.49) − 235.62 (±29.48)π + 14.28 (±1.79)π^2, n = 16, r = 0.912, and s = 11.102 for strain MB418; MIC (μg/mL) = 708.63 (±156.89) − 177.05 (±39.03)π + 11.16 (±2.37)π^2 for strain MB2245 (Figure 1),

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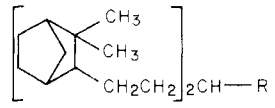
Table I. *N*-(Substituted alkyl)poly(methylene)triamine and -tetramine Hydrochloride Salts: Physicochemical and Antipseudomonad Screening Data

$[R(CH_2)_x]_2CH[NH(CH_2)_y]_zNH(CH_2)_yNH_2 \cdot (2+z)HCl$

compd	R	x	y	z	mp, °C	formula[a,b]	M_r	$[R\text{-}(CH_2)_x]_2$,[c] π	antibact. act.: MIC, μg/mL P.a.[h] MB-418	P.a.[h] MB-2245
1	c-C_6H_{11}	1	3	1	256-257	$C_{21}H_{46}Cl_3N_3$	447.0	6.1	60	40
2	c-C_6H_{11}	2	3	1	243-246	$C_{23}H_{50}Cl_3N_3$	475.1	7.1	30	15
3	c-C_6H_{11}	3	3	1	260-261	$C_{25}H_{54}Cl_3N_3$	503.1	8.1	8	8
4	c-C_6H_{11}	4	3	1	256-257	$C_{27}H_{58}Cl_3N_3$	531.1	9.2	10	15
5	c-C_6H_{11}	2	2	1	280-281	$C_{21}H_{46}Cl_3N_3$	447.0	7.1	100	100
6	c-C_6H_{11}	2	2	2	277-279	$C_{23}H_{52}Cl_4N_4$	526.5	7.1	40	30
7	c-C_6H_{11}	3	2	2	268-269	$C_{25}H_{56}Cl_4N_4$	554.6	8.1	30	30
8[d]	c-C_6H_{11}	2	3	1	247-249	$C_{24}H_{52}Cl_3N_3$	489.1	7.1	8	20
9	Δ^3-c-C_6H_9	3	3	1	222-223	$C_{25}H_{50}Cl_3N_3$	499.1	7.7	20	15
10	c-C_6H_{10}-4-$CH(CH_3)_2$	2	3	1	244-245	$C_{29}H_{62}Cl_3N_3$	559.2	10.1	60	60
11	c-C_5H_9	2	3	1	260-261	$C_{21}H_{46}Cl_3N_3$	447.0	6.3	60	30
12	2-bic-C_7H_{11}[e]	2	3	1	257-258	$C_{25}H_{50}Cl_3N_3$	499.1	7.0	15	10
13	C_6H_4-4-CH_3	2	3	1	225-226	$C_{25}H_{42}Cl_3N_3$	491.3	6.4	60	40
14	C_6H_4-4-$CH(CH_3)_2$	2	3	1	265-267	$C_{29}H_{50}Cl_3N_3$	547.1	8.4	10	10
15	C_6H_4-4-$CH(CH_3)_2$	3	3	1	237-239	$C_{31}H_{54}Cl_3N_3$	575.2	9.4	15	40
16	C_6H_4-4-$CH(CH_3)_2$	2	2	2	269-270	$C_{29}H_{52}Cl_4N_4$	598.6	8.4	40	60
17	C_6H_4-4-$CH(CH_3)_2$	3	2	2	250-252	$C_{31}H_{56}Cl_4N_4$	626.7	9.4	8	80
18	C_6H_4-4-$C(CH_3)_3$	2	3	1	274-275	$C_{31}H_{54}Cl_3N_3$	575.2	9.3	8	15
19	C_6H_4-4-$C(CH_3)_3$	3	3	1	246-247	$C_{33}H_{58}Cl_3N_3$	603.2	10.3	80	40
20	C_6H_4-4-$C(CH_3)_3$	3	2	2	275-276	$C_{33}H_{60}Cl_4N_4$	654.7	10.3	100	100
21	C_6H_4-4-$C(CH_3)_3$	3	3	2	258-259	$C_{36}H_{66}Cl_4N_4$	692.8	10.3	80	100
22	C_6H_3-2-CH_3-5-$C(CH_3)_3$	3	2	2	272-274	$C_{35}H_{64}Cl_4N_4$	682.7	11.4	50	80
23	C_6H_3-2-CH_3-5-$C(CH_3)_3$	3	3	2	259-260	$C_{38}H_{70}Cl_4N_4$	724.8	11.4	40	50
24	2-$C_{10}H_7$[g]	2	3	1	232-235	$C_{31}H_{42}Cl_3N_3$	563.1	9.6	40	100
tetracycline									20	30

[a] Analyzed for C, H, and N; also Cl for 2, 8, 12, 13, and 19-21. [b] All salts recrystallized from MeOH, except 8 (MeOH-Et_2O) and 10 and 16 (MeOH-*i*-PrOH). [c] See ref. 8. [d] $[NCH_3(CH_2)_y]_z$. [e] Bicyclo[2.2.1]heptyl. [f] C: calcd, 62.06; found, 62.52. [g] Naphthyl. [h] *P.a.* = *Pseudomonas aeruginosa*.

Table II. 1-[1,5-Bis(3,3-dimethyl-2-norbornyl)-3-pentyl]poly(methylene)triamine and -tetramine Hydrochloride Salts: Physicochemical and Antipseudomonad Screening Data



25, R = $NH(CH_2)_xNH(CH_2)_yNH_2 \cdot 3HCl$

26, R = $NH(CH_2)_xNH(CH_2)_yNH(CH_2)_zNH_2 \cdot 4HCl$

27, R = $NH(CH_2)_xN\langle (CH_2)_yNH_2, (CH_2)_yNH_2 \rangle \cdot 4HCl$

compd	x	y	z	mp, °C	formula[a,b]	M_r	polyamine moiety, π[c]	antibact. act.: MIC, μg/mL P.a.[g] MB418	P.a.[g] MB2245
25a	2	2		274-276	$C_{27}H_{54}Cl_3N_3$	527.1	−0.90	200	>200
25b	3	3		262-263	$C_{29}H_{58}Cl_3N_3$	555.2	−1.74	8	10
26a	2	2	2	267-268	$C_{29}H_{60}Cl_4N_4$	606.6	−0.97	50	30
26b	2	2	3	270-272	$C_{30}H_{62}Cl_4N_4$	602.7	−1.39	60	60
26c	2	3	2	261-262	$C_{30}H_{62}Cl_4N_4$	620.7	−1.55	30	15
26d	3	2	3	262-265	$C_{31}H_{64}Cl_4N_4$	634.7	−1.81	30	15
26e	3	*d*	3	257-259	$C_{33}H_{66}Cl_4N_4$	660.7	−1.37	200	200
26f	3	3	3	262-265	$C_{32}H_{66}Cl_4N_4$	648.7	−2.39	8	8
27a	2	2		247-249	$C_{29}H_{60}Cl_4N_4$	606.7	+0.64	50	8
27b	3	3		255-256	$C_{32}H_{66}Cl_4N_4$	648.7	−2.18	50	30
tetracycline								20	30

[a] Analyzed for C, H, and N; also Cl for 25b, 26e, and 27b. [b] All salts recrystallized from MeOH, except 25b (*i*-PrOH-MeOH) and 26a (*i*-PrOH). [c] Calculated; see ref 8. [d] $-NH(CH_2)_yNH-$ is replaced by $-N(CH_2CH_2)_2N-$. [e] H: calcd, 9.99; found, 10.49. [f] See ref 25 for synthesis of *N,N*-bis(3-aminopropyl)-1,3-propanediamine. [g] *P.a.* = *Pseudomonas aeruginosa*.

$n = 16$, $r = 0.827$, and $s = 14.700$. Where n is the number of assayed compounds used, r is the correlation coefficient, and s the standard deviation from the regression line. Several hundred examples of a similar correspondence between biochemically and biologically active chemicals, including antimicrobials, and their lipophilic properties have been analyzed.[18] More recently, a bilinear model appeared to supply a still better fit for the bacteriostatic potencies of a homologous series of benzyldimethylalkylammonium compounds with *S. aureus*.[19a] However,

Table III. Ketone Intermediates[a]

no.	R	$[R(CH_2)_n]_2C=O$ n	mp or bp (mm), °C	formula[b]	IR (C=O), cm^{-1}	n_D^{20}
31	c-C_6H_{11}[c]	1	38-39	$C_{15}H_{26}O$	1700	
32	c-C_6H_{11}[c]	2	26.5-27.5, 143-145 (1.0)	$C_{17}H_{30}O$	1705	
33	c-C_6H_{11}[c]	3	154-155 (0.5)	$C_{19}H_{34}O$	1700	1.4474
34	c-C_6H_{11}	4	26-28	$C_{21}H_{38}O$	1705	
35	3-c-C_6H_9[d]	3	157-158 (0.2)	$C_{19}H_{30}O$	1705	1.4943
36	c-C_6H_{10}-4-$CH(CH_3)_2$	2	190-195 (0.2)	$C_{23}H_{42}O$	1720	1.4795
37	2-bic-C_7H_{11}[c]	2	168-170 (0.1)	$C_{19}H_{30}O$	1705	1.5045
38	3,3-$(CH_3)_2$-2-bic-C_7H_9	2	172-173 (0.1)	$C_{23}H_{38}O$	1705	1.4986
39	C_6H_4-4-$CH(CH_3)_2$	2	189-190 (0.1)	$C_{23}H_{30}O$	1700	1.5313
40	C_6H_4-4-$CH(CH_3)_2$[c]	3	191-193 (0.05)	$C_{25}H_{34}O$	1705	1.5272
41	C_6H_4-4-$C(CH_3)_3$	2	89-90[e]	$C_{25}H_{34}O$	1700	
42	C_6H_4-4-$C(CH_3)_3$	3	208-210 (0.2)	$C_{27}H_{38}O$	1705	1.5246
43	C_6H_3-2-CH_3-5-$C(CH_3)_3$	3	228-230 (0.6)	$C_{29}H_{42}O$	1700	1.5306
44	2-$C_{10}H_7$	2	117-118[e]	$C_{25}H_{22}O$	1690	

[a] Known ketones, R = c-C_5H_9, n = 2 [bp 132 °C (11 mm); F. E. King, *J. Chem. Soc.*, 982 (1932)], and R = C_6H_4-4-CH_3, n = 2 [mp 53.5-54 °C; N. J. DeStefano, D. K. Johnson, R. M. Lane, and L. M. Venanzi, *Helv. Chim. Acta*, 59, 2674 (1976)], were not analyzed. [b] Analyzed for C and H. [c] Purified by column chromatography (Et_2O-petroleum ether, silica gel). [d] Purified by column chromatography (hexane-EtOAc, silica gel). [e] Recrystallized from EtOH.

Table IV. In Vitro Activity against Bacteria[a]

compd	MIC, μg/mL *S.a.* MB108	*S.a.* MB2865	*B.s.* MB964	*S.s.* MB2837	*E.c.* MB2884	*K.a.* MB1503	*B.b.* MB3551	*B.b.* MB905
1	30	40	10	4	40	8	6	4
2	2	10	2	2	15	6	2	2
3	4	8	4	4	8	4	4	4
4	10	20	8	6	20	20	4	4
5	4	15	4	2	10	8	4	4
6	6	30	6	4	20	15	4	6
7	6	15	4	6	10	6	4	6
8	10	30	4	1	8	4	4	6
9	6	10	4	4	10	6	4	2
10	20	40	6	20	50	50	10	10
11	20	15	6	8	30	15	4	4
12	10	8	4	2	4	4	4	4
13	30	50	4	10	50	15	6	4
14	8	8	4	4	8		4	4
15	20	20	6	10	40	20	10	10
16	6	30	6	4	30	40	15	8
17	6	20	4	10	15	60	30	30
18	6	15	2	4	6	15	4	4
19	20	10	8	8	40	40	8	8
20	20	30	15	8	60	50	60	8
21	30	20	10	15	>200	>200	30	20
22	15	60	4	10	60	10	10	15
23	20	8	6	8	100	200	8	8
24	6	8	8	8	15	20	4	4
25a	6	6	6	50	4	10	4	4
25b	4	10	4	4	8	4	4	4
26a	4	30	4	4	8	8	10	4
26b	20	6	6	6	10	10	30	6
26c	6	6	6	6	8	10	6	8
26d	4	8	4	4	30	15	4	4
26e	6	20	8	6	20	4	8	4
26f	15	8	2	6	10	30	2	2
27a	4	8	4	4	8	8	4	4
27b	6	4	4	4	50	30	2	4
29[b]	8	15	4	4	8	6	4	4
tetracycline	2	2	2	2	30	2	2	2

[a] See Experimental Section for abbreviations. [b] MIC: *P.a.* MB418, 20 μg/mL; *P.a.* MB2245, 8 μg/mL.

a linear relationship was obtained with pseudomonads and a similar homologue series;[19b,c] the investigators proposed that many of the previously reported antibacterial activity–lipophilicity parabolic findings were artifactual, and with test systems that minimized inhibitor colloidal association and complexation caused in part by nutrient media, the linear could prevail. Alternatively, for agents with action sites beyond the outer membrane, the differential possibilities in uptake, diffusion through outer-membrane pores, and micelle formation in the periplasmic space can contribute to nonlinearity. These factors and possible assay medium-imposed changes in compound monomer availability may be reflected in our data as well.

Correlations between variation in the relatively polar polyamine moiety of compounds having the identical N substituent and antimicrobial potency were not obtained.

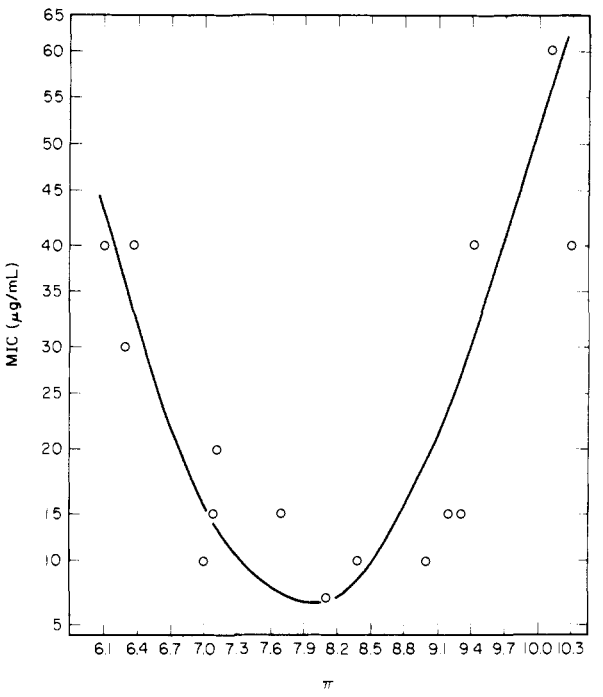


Figure 1. (O) Plot of the calculated Hansch hydrophobic parameter for the lipoidal substituent, $[R(CH_2)_x]_2$ (Table I), of 1-substituted 1,5,9-triazanonane trihydrochlorides and in vitro minimal inhibitory concentration; (—) regression-analysis predicted curve: *Pseudomonas aeruginosa* MB2245.

A similar difficulty was previously reported by others for long-chain aliphatic monoamines; activity correlated better with the substituent contribution, π, for the "tail" or length of chain alone rather than when combined with π for the amine "head", which was varied from primary to secondary and tertiary.[20]

Calculation of the π parameter for nonprotonated polyamine moieties (Table II) by the fragment and factor constant method was modeled with *N,N'*-bis(2-aminoethyl)-1,2-ethanediamine, log P = −1.34 and measured log P = −0.82.[21] The difference was arbitrarily corrected by 0.6, which approximates a hydrogen bond, and log P = −0.74 was then converted to π = −0.97, by subtracting f_H = 0.23. The compounds are predominantly protonated at pH 7.4, that of the antimicrobial assay system. The problem of relating partition coefficient and protonation of amines to antibacterial action, especially on membranes, needs further resolution.[22a,b]

The more hydrophilic linear triamine and tetramines with a 1-[1,5-bis(3,3-dimethyl-2-norbornyl-3-pentyl] substituent (**25b**, **26b**, and **26f**) were among the better inhibitors. Interestingly, metal chelate stability constants for the unsubstituted polyamines, which range from log K = 14.2 for *N*-(3-aminopropyl)-1,3-propanediamine to log K = 23.9 for *N,N'*-bis(2-aminoethyl)-1,3-propanediamine based upon a 1:1 complex with Cu^{2+},[23] did not align with the potencies of the alkylated polyamines and, apparently, were not an overriding factor. One mechanism proposed for the action of polyamines in altering microbial cell-wall permeability is the ability to chelate metal-ion structural components analogous to ethylenediaminetetraacetic acid.[3a,b]

The broad-spectrum antimicrobial screen (Table IV) generally reflected activities for Gram-negative bacteria, which paralleled that with *Pseudomonas aeruginosa*. The 1,5,9-triazanonane salt derivatives **3**, **9**, **12**, **14**, and **25b** and the tetramines **26c**, **26f**, and **27a** were effective at 2–10 μg mL for the six microorganisms. This potency level against the Gram-negative bacteria appeared significantly higher than that previously reported for a number of commercial N-(long-chain alkyl)polyamines, wherein benzalkonium chloride also served as a reference activity standard.[4]

Additional test data indicated all compounds of Tables I and II at 2–8 μg/mL inhibited *Streptococcus pyogenes*, *Pasturella multocida*, and, with one exception, *Corynebacterium pseudodiphtheritium*; **21** required 15 μg/mL. None blocked *Proteus vulgaris* at the highest level assayed, 200 μg/mL.

Experimental Section

Melting points were determined in open capillary tubes in a Thomas-Hoover melting point apparatus and are uncorrected. NMR spectra were obtained in $CDCl_3$ or Me_2SO-d_6 on a Varian A-60 spectrometer or in Me_2SO-d_6 on a Varian CFT-20 spectrometer with Me_4Si as an internal standard for both. IR spectra were run neat for liquids or as mulls with solids in mineral oil on a Perkin-Elmer 137 spectrophotometer. Spectral data for all reported compounds appeared consistent with assigned structures. Refractive-index measurements were made with a Bausch and Lomb Abbe 3L refractometer. TLC was performed on Analtech Inc. precoated silica gel GF glass plates (250 μm), using NH_4OH–EtOH (1:4) as the developing solvent, iodine staining for amine hydrochloride salts, and Et_2O–PE or hexane–EtOAc mixtures for ketones. Elemental analyses are within ±0.4%, unless otherwise indicated; hydrochloride salts were usually hydrated and required drying for 4 h at 80 °C (0.05 mm) before analysis. All hydrogenations were run at 20–25 °C and 40 psi until theoretical hydrogen uptake, usually requiring from 1 to 4 h. After catalyst removal by filtration, the solvent was distilled in vacuo.

Microbiological Assays. An in vitro chemotherapy screen[16] was run with Gram-positive and Gram-negative bacteria: *Staphylococcus aureus* (*S.a.*), *Bacillus subtilis* (*B.s.*), *Streptococcus pyogenes*, *Corynebacterium pseudodiphtheritium*, *Escherichia coli* (*E.c.*), *Klebsiella aerogenes* (*K.a.*), *Pseudomonas aeruginosa*, *Bordetella bronchiseptica*, *Salmonella schottmuelleri* (Merck Bacteria 2837) (*S.s.*), *Proteus vulgaris* (MB838), and *Pasturella multocida* (MB7). See Tables I, II, and IV for the other microbial strains.

Compounds were assayed at concentrations of 0, 1, 2, 4, 6, 8, 10, 15, 20, 30, 40, 50, 60, 80, 100, and 200 μg/mL; all were run in duplicate. Tetracycline was routinely tested as a check on medium, incubation conditions, and inoculum virility.

General Procedures. Synthesis of Ketones from Alkanoic Acids.[10,11] All of the required ketones, except 1,5-bis(aryl)-3-pentanones for **13**, **14**, **16**, **18**, and **24**, were obtained by the iron–carboxylic acid process, and the following examples illustrate both methods.

1,5-Bis[4-(1-methylethyl)cyclohexyl]-3-pentanone (36). A mixture of 3-[4-(1-methylethyl)cyclohexyl]propanoic acid (**28**; 39.7 g, 0.20 mol) and iron powder (6.2 g, 0.11 g-atom, H_2 reduced) was heated gradually under N_2 and mechanically stirred. H_2 evolution began at 165–170 °C, and the mixture was heated at 190–195 °C for 2 h; during this period, visible gas bubbling stopped. The internal temperature was raised to 280 °C and maintained for 1.5 h. The reaction was then cooled to 20 °C, and the fluid mixture was extracted with Et_2O (2–500 mL). The combined organic liquors were washed (5% $NaHCO_3$) and dried (Na_2SO_4), the solvent was evaporated in vacuo, and the resulting oil was distilled to give 17.3 g (51.5%) of faintly yellow oil. Anal. ($C_{23}H_{42}O$) C, H.

1,5-Bis[4-(1-methylethyl)phenyl]-3-pentanone (39). A solution of 1,5-bis[4-(1-methylethyl)phenyl]-3-pentadienone (21.2 g, 0.07 mol) in CH_2ClCH_2Cl (200 mL) was mixed with Raney nickel (50 g) and hydrogenated. The liquid residue was distilled to give 18 g (84%) of faintly yellow oil. Anal. ($C_{23}H_{30}O$) C, H.

General Procedures. Alkylation of Polyamines and Hydrochloride Salt Preparation. Ketone–polyamine condensation, reduction, and workup is typified by the preparation of **25a**. Final solvent removal provided practically pure alkylated base, which was dissolved in dry MeOH or *i*-PrOH; the solution was cooled in an ice bath and treated with excess dry HCl. The resultant hydrochloride salt isolated by filtration was, if required,

further purified by recrystallization.

1-[1,7-Bis(cyclohexen-3-yl)-4-heptyl]-1,5,9-triazanonane Trihydrochloride (9). 1,7-Bis(cyclohexen-3-yl)-4-heptanone (5.5 g, 0.02 mol) and *N*-(3-aminopropyl)-1,3-propanediamine (13.1 g, 0.10 mol) in toluene (150 mL) were condensed, the solution was concentrated in vacuo, and the residual oil after solution in *i*-PrOH (25 mL) was then added dropwise to a stirred suspension of $NaBH_4$ (1.9 g, 0.05 mol) in *i*-PrOH (50 mL). The mixture was heated at reflux for 1 h after complete addition and cooled to 25 °C gradually, and the solvent was removed under reduced pressure. The residue was treated with H_2O (250 mL) and extracted with Et_2O (2 × 75 mL), and the organic solution was dried (Na_2SO_4) and concentrated to leave a near colorless oil, 6.55 g (85%). The oil was dissolved in MeOH (30 mL), cooled in an ice bath, and treated with dry HCl for 15 min. The colorless solid which precipitated was removed by filtration, after the mixture was kept at 5 °C overnight, washed with Et_2O, and dried in vacuo to yield 6.20 g (74%) of **9**.

1-[1,5-Bis(3,3-dimethyl-2-norbornyl)-3-pentyl]-1,4,7,11-tetraazaundecane Tetrahydrochloride (26b). (a) 1-[1,5-Bis(3,3-dimethyl-2-norbornyl)-3-pentyl]-1,4,7-triazaheptane Trihydrochloride (25a). 1,5-Bis(3,3-dimethylnorborn-2-yl)-3-pentanone (6.6 g, 0.02 mol) and *N*-(2-aminoethyl)-1,2-ethanediamine (10.3 g, 0.10 mol) in toluene (150 mL) were heated at reflux until constant H_2O level in a Dean–Stark trap. The residual oil obtained after solvent removal in vacuo was dissolved in EtOH (150 mL), mixed with PtO_2 (1.2 g), and hydrogenated. The oily residue was dissolved in Et_2O (500 mL), washed with H_2O (3 × 250 mL) and then brine, and dried (Na_2SO_4). Solvent removal in vacuo left 8.1 g (97%) of 1-[1,5-bis(3,3-dimethyl-2-norbornyl)-3-pentyl]-1,4,7-triazaheptane as a colorless oil. Anal. ($C_{27}H_{51}N_3$) H, N; C: calcd, 77.63; found, 78.10. The amine (1.2 g, 0.003 mol) was dissolved in Et_2O (10 mL) and mixed with a solution (1.3 mL) of dry HCl in 2-propanol (29%, w/w). Additional Et_2O was added until no further precipitation occurred, and the product was collected to yield 0.9 g (59%) of **25a**.

(b) Cyanoethylation of Free Base and Reduction. The amine (10.7 g, 0.026 mol) prepared as above in *tert*-butyl alcohol (30 mL) was chilled and mixed with acrylonitrile (1.5 g, 0.026 mol). The solution kept under N_2 was heated at 55 °C for 18 h. The solvent was removed in vacuo, and the residual oil was dissolved in AcOH (100 mL), mixed with PtO_2 (1.0 g), and hydrogenated. The residual oil was taken up in CH_2Cl_2 (150 mL), washed with 2.5 N NaOH and then H_2O, and dried (Na_2SO_4). After removal of solvent, the liquid amine (12 g, 98%) was dissolved in a mixture of MeOH (25 mL) and Et_2O (200 mL) and treated with dry HCl until no further precipitation occurred, and the solids were filtered, washed with Et_2O, and dried to yield 11 g (70%) of **26b**.

1-[1,5-Bis(3,3-dimethylnorborn-2-yl)-3-pentyl]-1,5,8,12-tetraazadodecane Tetrahydrochloride (26d). The alkylated polyamine base from 1,5-bis(3,3-dimethylnorborn-2-yl)-3-pentanone (6.6 g, 0.02 mol) and *N,N'*-1,2-ethanediylbis(1,3-propanediamine)[24] (17.4 g, 0.10 mol), after workup as with **25a**, was obtained in a practically pure state as a light yellow oil, 9.7 g (approximately 100%). It was dissolved in MeOH (50 mL), cooled in an ice bath, and treated with a stream of dry HCl for 15 min; during this period, a gummy precipitate resulted. The solvent was removed in vacuo and the residue crystallized from *i*-PrOH as colorless needles to yield 9.35 g (76%) of **26d**.

3-[4-(1-Methylethyl)cyclohexyl]propanoic Acid (28). 3-[4-(1-Methylethyl)cyclohexenyl]propanoic acid (5 g, 0.026 mol) was dissolved in EtOH (50 mL), mixed with 5% Pd/C (0.5 g), and hydrogenated to yield **28**, a colorless liquid which partially solidified on standing: yield 5 g (97%); bp 112–115 °C (0.05 mm). Its NMR spectrum ($CDCl_3$, Me_4Si) indicated no vinyl proton as in the initial unsaturated acid (δ 5.45 ppm) and the product to be apparently a cis, trans isomer mixture, as noted by a doublet for each isopropyl group: NMR δ 0.79 and 0.81 (CH, d, CH_3CHCH_3); IR (film) 1710 cm^{-1} (C=O); MS (M^+ 198). Anal. ($C_{12}H_{22}O_2$) C, H.

1-(1,5-Dicyclohexyl-3-pentyl)-3-hydroxy-1,5,9-triazanonane Trihydrochloride (29). (a) 1-Amino-3-[(1,5-dicyclohexyl-3-pentyl)amino]-2-propanol Dihydrochloride (30). 1,5-Dicyclohexyl-3-pentanone (20.0 g, 0.08 mol) and 1,3-diamino-2-propanol (36.0 g, 0.40 mol) in toluene (500 mL) were condensed and hydrogenated as in the outlined procedure. The residual liquid was dissolved in CH_2Cl_2 (600 mL), washed with H_2O (4 × 300 mL) and then brine, and dried (Na_2SO_4). Evaporation of the solvent left a near colorless oil, 25.8 g (100%). The oil (0.65 g, 0.002 mol) in MeOH (25 mL) was cooled in an ice bath and treated with dry HCl for 15 min; the solution was concentrated until crystallization, and the product was collected to yield 0.76 g (95%) of **30**, mp 254–255 °C. Anal. ($C_{20}H_{42}Cl_2N_2O$) C, H, N.

(b) Cyanoethylation of 30 Free Base and Reduction. The above amine (13 g, 0.04 mol) was added to a solution of acrylonitrile (2.6 g, 0.05 mol) in $CHCl_3$ (100 mL) and under N_2 and then heated at reflux for 36 h. The liquid obtained after solvent removal was dissolved in AcOH (150 mL), mixed with PtO_2 (0.6 g), and hydrogenated. The residual oil was dissolved in Et_2O (200 mL), washed with 2.5 N NaOH and then H_2O, and dried (Na_2SO_4). Upon solvent removal, the amine (14 g, 86%) was dissolved in a mixture of MeOH (30 mL) and Et_2O (200 mL) and treated with dry HCl until no further precipitation occurred, the solids were collected, washed with Et_2O, and dried in vacuo, affording 14 g (78%) of **29**, mp 267–269 °C. Anal. ($C_{23}H_{50}Cl_3N_3O$) C, H, N.

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Notes

Bufotenine Esters

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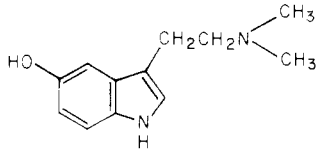
Bufotenine (5-hydroxy-*N*,*N*-dimethyltryptamine) has been reported to be behaviorally inactive or only very weakly active in man and animals; this may be a consequence of its low partition coefficient and resultant inability to penetrate the blood–brain barrier. The acetyl, propionyl, butyryl, isobutyryl, and pivalyl esters of bufotenine were prepared for future pharmacological evaluation. Unexpectedly, it was found that these esters all possess a relatively high affinity for the serotonin receptors of the isolated rat stomach fundus preparation. A semiquantitative chromatographic measurement of ester hydrolysis suggests that extensive hydrolysis of the esters to bufotenine does not occur under the conditions of the affinity assay

Bufotenine (5-hydroxy-*N*,*N*-dimethyltryptamine, 1) has



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been reported to be halucinogenic in man.[2a] This finding has been refuted,[2b] however, and it is now commonly held that the psychotomimetic activity of bufotenine is questionable. It has been suggested that, because of poor lipid solubility, appreciable amounts of administered bufotenine do not penetrate the blood–brain barrier.[3,4] In addition, attempted administration of larger doses of 1 to human subjects produces peripheral effects which may mask or obscure any central effectis.[2b] Indeed, bufotenine is not very lipid soluble, as reflected by its partition coefficient.[5] The inability of 1 to penetrate the blood–brain barrier has also been demonstrated experimentally by measurement of animal brain levels, at various time intervals, following the administration of bufotenine.[3,4]

The question which now arises is whether 1 is intrinsically inactive or whether it is an active compound which simply does not get into the brain. This question is of more than mere academic significance, since enzyme systems which can convert the neurotransmitter serotonin to 1 have now been identified.[6] In addition, though still a subject of controversy,[7,8] bufoteine and other methylated tryptamines have been detected in the urine of schizophrenics.[9-12] To this extent, Sanders and Bush[3] have found that, in rats, only 6% of an administered dose of 1 is excreted unchanged; even detection of small amounts in the urine of schizophenic patients might thus be quite significant.

There is indirect evidence that 1 is behaviorally active. For example, Mandel[13] and Geyer et al.[14] have found 1 to be at least equiactive with the hallucinogen 5-methoxy-*N*,*N*-dimethyltryptamine (5-OMe-DMT) when administered to animals via intraventricular injection, thereby bypassing the blood–brain barrier. Newborn (24–48-h old) chicks possess a poorly developed blood–brain barrier, and Rauzzino and Siefter[15] have noticed that administration of bufotenine to such animals results in responses typical of those of other established hallucinogens, such as *N*,*N*-dimethyltryptamine (DMT). Gessner and Dankova[4] administered the more lipid-soluble 5-acetoxybufotenine to mice, where it is hydrolyzed, presumably by brain tissue esterases, to bufotenine. Measuring LSD-like activity as a function of brain concentration, the order of potency was found to be bufotenine > 5-OMe DMT > DMT. Glennon et al.[16] have recently reported that several potent tryptamine and phenalkylamine hallucinogens possess high affinities for the serotonin receptors of the isolated rat fundus preparation, and Glennon and Gessner[17] had previously reported bufotenine to possess twice the affinity of 5-OMe-DMT.

It was thus of interest to prepare several esters of bufotenine for eventual pharmacological evaluation. We now report a series of five such esters, along with their serotonin receptor binding affinities.

Results and Discussion

The esters **2–6** were prepared by direct acylation of bufotenine and are listed in Table I. Bufotenine itself possesses a high affinity for serotonin receptors. In order to ascertain whether the ester function serves simply as a protecting group or whether the bufotenine esters themselves might possess some affinity, serotonin receptor-binding affinities were determined and are also

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