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Influence of Stereochemistry and Lipophilicity on Biological Activity of Some Ganglionic Blocking Agents

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Numerous diverse compounds exhibit ganglionic blocking activity. It is possible that this might involve a nonspecific drug–receptor interaction based on drug lipophilicity. To test this proposal, the rigid analogs of hexamethonium 2(e),6(e)-bis(dimethylamino)-*cis*-decalin dimethiodide (**10**), 2(a),6(e)-bis(dimethylamino)-*cis*-decalin dimethiodide (**11**), and 2(a),6(e)-bis(dimethylamino)-*trans*-decalin dimethiodide (**12**) were synthesized. These were found to be more lipophilic than hexamethonium. Preliminary biological results on the cat nictitating membrane–superior cervical ganglion preparation indicated that they were less efficient ganglionic blocking agents than hexamethonium. However, the synthesis of 2-methyl-6-dimethylaminomethyl-2-azabicyclo[2.2.2]octane dimethiodide (**16**) provided a very active ganglionic blocker with lipophilicity comparable to that of hexamethonium.

Among ganglionic blocking agents,[1] bisquaternary ammonium salts represent a chemical group where the changes in activity which result from relatively minor alterations in molecular structure have been thoroughly investigated. Studies by Barlow and Ing[2] and Paton and Zaimis[3] indicated that among polymethylene α,ω-bis(trimethylammonium) compounds with chain lengths of C_2 to C_{12} a sharp peak of ganglionic blocking potency appeared with chain length of C_5 and C_6. The dependence of activity on chain length in the polymethylene bisoniums was interpreted by assuming that the blocking agent made simultaneous contact with 2 anionic receptor groups and that the C chain length of the most active compounds was a measure of the interreceptor distance.[4-6] The validity of the 2-point contact hypothesis has been questioned by a number of investigators.[7-9]

It is the purpose of this study to examine the possibility that the biological potency of these bisquaternary ammonium compounds, maximum in hexamethonium, is actually a nonspecific drug–receptor interaction based on drug lipophilicity rather than the previously postulated specific spatial arrangement of the drug at the ganglionic receptor. To test this proposal it was thought that if one could freeze hexamethonium into relatively rigid conformations maintaining a 6-C separation between the 2 onium heads, one could examine the contribution of the stereochemistry of the C skeleton and the orientation of the onium heads to the lipophilicity and ganglionic blocking potency of these compounds. For this purpose the decalin system was chosen in its cis (**10**, **11**) and trans (**12**) forms.

Furthermore, if the ganglionic blocking activity of bisquaternary ammonium compounds were truly a function of their lipophilicity, it should be possible to design a biologically active compound structurally different from hexamethonium but having comparable lipophilicity to it. The design of such a compound was achieved in the synthesis of 2-methyl-6-dimethylaminomethyl-2-azabicyclo[2.2.2]-octane dimethiodide (**16**).

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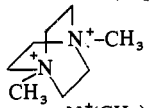
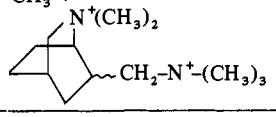
Lipophilicity. Partition coefficients, which provide a convenient measure of lipophilicity, have been used by many investigators to correlate biological activity within drug families with lipid solubility. In the case of saturated bisquaternary ammonium compounds it was necessary first to develop a method for measuring their partition coefficients. A modified procedure of Higuchi and coworkers[10] was applied which involved the conversion of bisquaternary ammonium halides to their picrate salts. The picrate salts, apparently because they form tight ion pairs in organic solvents, were sufficiently lipophilic that their relative partitioning behavior between H_2O and $CHCl_3$ could be measured.

The measured partition coefficients and calcd π values for **1** to **16** are shown in Table I. In the case of the decalin system, it was observed that rigidity of the C chain contributed to an increase in drug lipophilicity. This effect was more pronounced in 2(e)-dimethylamino-*trans*-decalin methiodide (**14**), where the ring juncture is trans and the onium head in an equatorial position. Thus **10**, **11**, **12**, **13**, and **14** were more lipophilic than both hexamethonium and decamethonium. However, the introduction of a bicyclic system resulted in an increase in the polarity of the molecule. For example, **15**[11] was found to be less lipophilic than hexamethonium but had a π value comparable to that of the trimethylene bis(trimethylammonium) salt **2**. Similarly, **16** was less lipophilic than octamethylene bis(trimethylammonium) salt (**7**) but had a π value comparable to that of hexamethonium. The significance of this will be discussed in the biological section.

Chemistry. Catalytic reduction of 2,6-dihydroxynaphthalene (**17**) under two different conditions afforded stereospecifically the cis or trans decalin system. Hydrogenation of **17** in 1% AcOH–MeOH over 5% Rh/Al_2O_3 by a modified procedure of Meyers and coworkers[12] gave 2(e),6(a)-dihydroxy-*cis*-decalin (**18**) and 2(e),6(e)-dihydroxy-*cis*-decalin (**19**). On the other hand, hydrogenation of **17** in MeOH over Raney Ni gave 2(a),6(e)-dihydroxy-*trans*-decalin (**24**) and 2(e),6(e)-dihydroxy-*trans*-decalin (**25**,Scheme I).

Table I. Measured Partition Coefficients, Calculated π Values, Ganglionic and Neuromuscular Blocking Activities

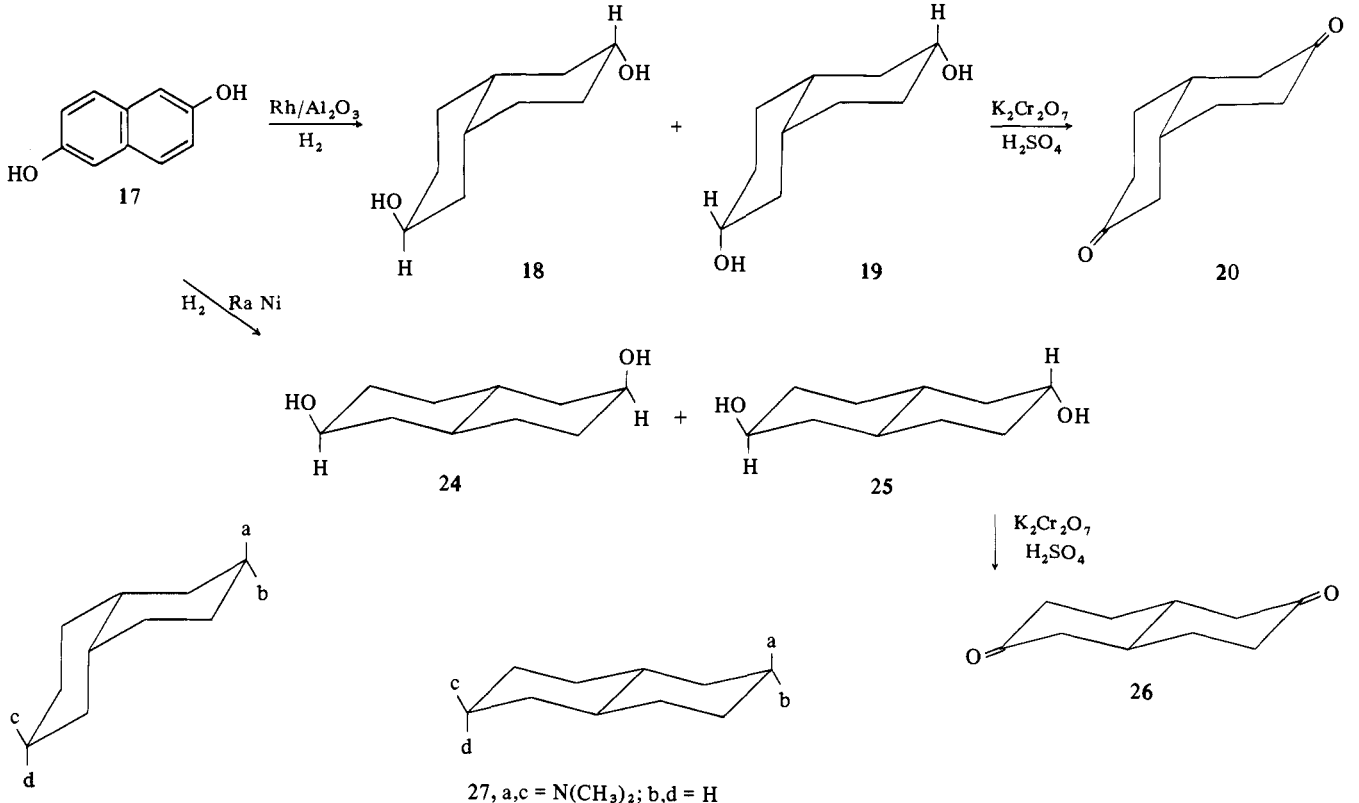
No.	Compd	PC	π	Ganglionic blocking activity, equipotent dose, mg/kg	Neuromuscular blocking activity, equipotent concn, *M*
1	$(CH_3)_3N^+(CH_2)_2N^+(CH_3)_3$	0.001		>5	
2	$(CH_3)_3N^+(CH_2)_3N^+(CH_3)_3$	0.002	0.30	2.5–4	$>10^{-3}$
3	$(CH_3)_3N^+(CH_2)_4N^+(CH_3)_3$	0.0026	0.41	2–3	$>10^{-3}$
4	$(CH_3)_3N^+(CH_2)_5N^+(CH_3)_3$	0.0031	0.54	1–2	1.3×10^{-4}
5	$(CH_3)_3N^+(CH_2)_6N^+(CH_3)_3$	0.0047	0.67	0.5	1.3×10^{-4}
6	$(CH_3)_3N^+(CH_2)_7N^+(CH_3)_3$	0.0051	0.70	1–2	3×10^{-6}
7	$(CH_3)_3N^+(CH_2)_8N^+(CH_3)_3$	0.0059	0.77	2–3	6×10^{-7}
8	$(CH_3)_3N^+(CH_2)_9N^+(CH_3)_3$	0.0071	0.84	2–3	1.3×10^{-7}
9	$(CH_3)_3N^+(CH_2)_{10}N^+(CH_3)_3$	0.0078	0.89	2–3	10^{-7}
10	*cis*-Decalin, *cis*-2,6-$[(CH_3)_3]N^+$	0.031	1.43	2	10^{-4}
11	*cis*-Decalin, *trans*-2,6-$[(CH_3)_3]N^+$	0.0085	0.94	2	10^{-4}
12	*trans*-Decalin, *cis*-2,6-$[(CH_3)_3]N^+$	0.056	1.72	2	10^{-4}
13	*trans*-Decalin, axial $(CH_3)_3N^+$	0.130	2.11	2.5	3×10^{-4}
14	*trans*-Decalin, eq $(CH_3)_3N^+$	0.220	2.34	2.5	3×10^{-4}
15		0.002	0.30	2	$>10^{-3}$
16		0.0045	0.65	0.25	Not tested

The assignment of the stereochemistry of the ring juncture was based on the conversion of the cis isomers (**18**, **19**) and the trans isomers (**24**, **25**) by a modified procedure of Johnson and coworkers[13] to the respective diketones, *cis*-decalin-2,6-dione (**20**) and *trans*-decalin-2,6-dione (**26**).[14]

In addition, the authenticity of a trans ring juncture in reductions with Ni catalyst is well documented.[15,16]

Reductive amination of **20** and **26** with 25% aq Me_2NH over 5% Pd/C at 3.8 kg/cm^2 H_2 pressure yielded **21** and **27**, respectively. Treatment of **21** and **27** with MeI afforded 2(e),6(e)-bis(dimethylamino)-*cis*-decalin dimethiodide (**10**) and 2(a),6(e)-bis(dimethylamino)-*trans*-decalin dimethiodide (**12**). The nmr spectrum of **10** showed CH absorption at δ 3.4 ($W_{1/2}$ = 17 cps) indicative of an axial orientation of the C-2 and C-6 methine protons.[17] However the nmr spectrum of **12** showed CH absorptions at δ 3.9 ($W_{1/2}$ = 6 cps)

Scheme I



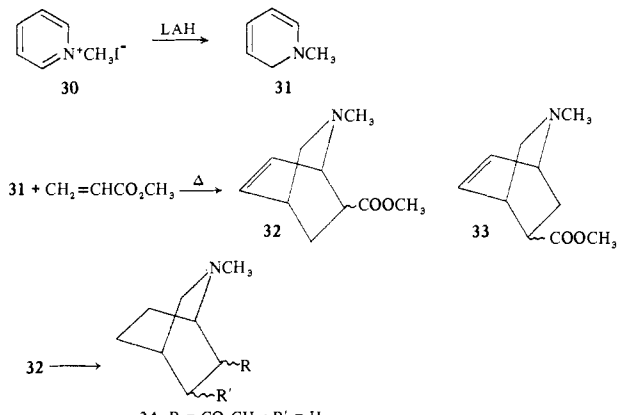
21, a,c = H; b,d = $N(CH_3)_2$
22, a,d = H; b,c = *p*-$O_2SC_6H_4CH_3$
23, a,d = $N(CH_3)_2$; b,c = H
10, a,c = H; b,d = $N^+(CH_3)_3$
11, a,d = $N^+(CH_3)_3$; b,d = H

27, a,c = $N(CH_3)_2$; b,d = H
28, a,c = *p*-$O_2SC_6H_4CH_3$; b,d = H
29, a,c = H; b,d = $N(CH_3)_2$
12, a,c = $N^+(CH_3)_3$; b,d = H

and 3.5 ($W_{1/2}$ = 16 cps) indicative of equatorial and axial orientations of the C-2 and C-6 methine protons, respectively. Treatment of **18** and **24** with *p*-TsCl in pyridine yielded the corresponding tosylates **22** and **28**. Displacement of the tosylate groups using anhyd Me_2NH in DMF yielded **23** and **29** which upon quaternization with MeI gave 2(a),6(e)-bis-(dimethylamino)-*cis*-decalin dimethiodide (**11**), together with **12**. The nmr spectrum of **11** exhibited CH absorptions at δ 3.9 ($W_{1/2}$ = 6 cps) and 3.6 ($W_{1/2}$ = 16 cps) indicative of equatorial and axial protons at C-2 and C-6, respectively.

The synthesis of 2-methyl-6-dimethylaminomethyl-2-azabicyclo[2.2.2]octane dimethiodide (**16**, Scheme II) was

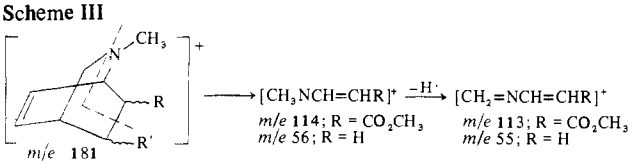
Scheme II



34, R = CO_2CH_3; R' = H
35, R = CH_2OH; R' = H
36, R = SO_2CH_3; R' = H
37, R = $CH_2N(CH_3)_2$; R' = H
16, R = $CH_2N^+(CH_3)_3$; R' = H

achieved according to a modified method of Schenker and Druey.[18] This involved a heterocyclic Diels–Alder reaction between *N*-methyl-1,2-dihydropyridine (**31**),[19] obtained by LAH reduction[20,21] of **30**,[22] and methyl acrylate, yielding as a product a mixture of 2-methyl-6-carbomethoxy-2-azabicyclo[2.2.2]oct-7-ene (**32**) and 2-methyl-6-carbomethoxy-2-azabicyclo[2.2.2]oct-7-ene (**33**). Compounds **32** and **33** were separated on an alumina column. Their structural identity was based on their nmr, ir, and mass spectral data. Both showed almost identical nmr and ir spectra, but characteristic differences in their mass spectra allowed structural assignment. The mass spectra of **32** and **33** were generally similar and are recorded in the Experimental Section. However, characteristically different fragments at *m/e* 114, 113 and 56, 55 were observed in the spectra of **32** and **33**, respectively. These, as shown in Scheme III, allowed posi-

Scheme III



32, R = CO_2CH_3; R' = H
33, R = H; R' = CO_2CH_3

tion of the carbomethoxy in **32** and **33** to be assigned. Such a fragmentation arises from rearrangements similar to that of other azabicyclic compounds.[23] An attempt to separate **32** into its endo and exo isomers was unsuccessful. Based on the rule of endo addition[24-26] in Diels–Alder reactions, the endo product probably represents the major product. Hydrogenation of **32** over 10% Pd/C gave **34**, which upon reduction with LAH afforded **35**. The corresponding mesylate **36** was prepared by treatment of **35** with NaH and MesCl in C_6H_6. Nucleophilic displacement of the mesylate function from **36** with anhyd Me_2NH in DMF at elevated temp and pressure gave **37**. Treatment of **37** with MeI afforded the corresponding dimethiodide salt **16**.

Biology. Ganglionic blocking potency of hexamethonium rigid analogs **10**, **11**, and **12**, whose synthesis has been described, the rigid monoquaternary ammonium conformers **13** and **14**, prepared in these laboratories by E. E. Smissman and R. T. Borchardt, and azabicyclic analogs **15** and **16** were determined according to Trendelenburg[27] on a standard cat nictitating membrane-superior cervical ganglion preparation. These preliminary data (Table I) indicate that among the bisquaternary and monoquaternary ammonium compounds, **10**, **11**, **12**, **13**, and **14**, differences in the stereochemistry of the carbon chain and in the orientation of the onium heads did not produce a noticeable change in ganglionic blocking activity. Furthermore, **10**, **11**, **12**, **13**, and **14** showed less blood pressure lowering than hexamethonium but exhibited respiratory inhibition, which may have resulted from a neuromuscular blocking effect. Therefore, the neuromuscular blocking effects of **10**, **11**, **12**, **13**, and **14** were determined on isolated chick biventer cervices nerve muscle.[28] These materials were found to be effective neuromuscular blocking agents, although they were slighly less potent than decamethonium. This lowered neuromuscular blocking activity may result from the fact that all these compounds are more lipophilic even than decamethonium (Table I). Among the azabicyclic analogs, **16** was found to be twice as effective as hexamethonium as a ganglionic blocking agent.

These results indicate that, among the compounds studied, those whose lipophilicity is greater than hexamethonium behave biologically more like decamethonium despite the fact that in the bisquaternary ammonium series the 2 onium heads are separated by 6 C. However, **16**, which is structurally different from hexamethonium but has comparable lipophilicity to it, blocks ganglionic transmission in a manner apparently analogous to hexamethonium.

Thus, although many of the complexities inherent in *in vivo* drug activity are not involved, these studies indicate a need to seriously examine the hypothesis that ganglionic blocking potency among a homologous series of compounds is a function primarily of their lipophilic character. Furthermore, it is conceivable that a similar situation exists among neuromuscular blocking agents, in which case lipophilicity of a different order of magnitude may be required.

Experimental Section

Melting points, obtained on a Thomas-Hoover Uni-Melt apparatus, are corrected. Ir spectra were recorded on a Beckman IR 10 spectrophotometer, nmr spectra on Varian Associates Model A-60A and T-60 spectrometers, visible spectra on a Beckman DB and mass spectra on a Varian-MAT CH5 mass spectrometer.

Microanalyses were performed on the F and M Model 185 C, H, N analyzer, University of Kansas, Lawrence, Kan. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical value.

2,6-Dihydroxy-*cis*-decalin. 2,6-Dihydroxynaphthalene‡ (**17**) (4 g, 0.025 mole) was dissolved in 1% AcOH–MeOH (40 ml) and hydrogenated over 5% Rh/Al_2O_3 (2 g) at room temp at an initial H_2 pressure of 4.2 kg/cm². After H_2 absorption had ceased the catalyst was removed by filtration, solvent removed *in vacuo*, and residue dissolved in $CHCl_3$. The resulting soln was washed with 10% NaOH

‡2,6-Dihydroxynaphthalene was purchased commercially from Aldrich Chemical Company.

and then with H_2O. The $CHCl_3$ soln was dried (Na_2SO_4) and concd giving 1.4 g of a thick yellow oil.

Separation of 2(e),6(a)-Dihydroxy-*cis*-decalin (18) and 2(e),6(e)-Dihydroxy-*cis*-decalin (19). The mixt of isomers (1.4 g) was chromatogd on a silica gel column (70 g) and eluted (50% $CHCl_3$–EtOAc), affording 2 major fractions. The first fraction contd after recrystn (Skelly B–$CHCl_3$) 0.6 g (14%) of **18**: mp 111–113°; ir (KBr) 3300, 2940, 1440, 1000, 1050 cm^{-1}; nmr ($CDCl_3$) δ 4.10 (m, 1 H, $W_{1/2}$ = 7 cps, C-6 CH), 3.7 (m, 1 H, $W_{1/2}$ = 18 cps, C-2 CH). *Anal.* ($C_{10}H_{18}O_2$) C, H. The second fraction contd after recrystn (hexane–$CHCl_3$), 0.2 g (5%) of **19**: mp 125–126°; ir (KBr) 3250, 1450, 1040, 1070 cm^{-}; nmr ($CDCl_3$) δ 3.7 (m, 2 H, $W_{1/2}$ = 17 cps, C-2 and C-6 CH). *Anal.* ($C_{10}H_{18}O_2$) C, H.

cis-Decalin-2,6-dione (20). A suspension of **18** and **19** (8 g, 0.049 mole) in C_6H_6 (120 ml) was cooled to 6° and to this was added dropwise with stirring a cold soln of 12 g of $Na_2Cr_2O_7$, in 9.0 ml of AcOH, 16.2 ml of concd H_2SO_4, and 52.7 ml of H_2O. During the addn, which required about 4 hr, the temp of the reaction mixt was not allowed to exceed 6°. After the addn was complete the mixt was stirred for an addl 2.5 hr at ice bath temp and allowed to stand at room temp overnight. The aq layer was sepd and extd with C_6H_6. The combined C_6H_6 fractions were washed with satd $NaHCO_3$ and H_2O. The C_6H_6 was dried ($MgSO_4$) and removed *in vacuo* to give 1.3 g (16%) of **20**: mp 72°, (lit.[14] mp 73–75°).

2(e),6(e)-Bis(dimethylamino)-*cis*-decalin (21). To **20** (1.3 g, 0.0078 mole) in EtOH (50 ml) was added 25% aq Me_2NH (35 ml). The mixt was hydrogenated over 5% Pd/C (1 g) at initial H_2 pressure of 3.8 kg/cm^2. After H_2 absorption had ceased the solvent was removed *in vacuo*, and the residue was acidified (3 *N* HCl) and washed (Et_2O). The aq layer was then made basic (concd NH_4OH) and extd (Et_2O). The Et_2O soln was washed (satd NaCl) and dried (Na_2SO_4) and the solvent removed *in vacuo* to give 0.3 g (17%) of a yellow oil. Chromatography on a prep tlc plate (50% Skelly B–Et_2O) afforded as a major fraction 0.2 g (11%) of light yellow oil: ir (neat) 2950, 2790, 1450 cm^{-1}; nmr ($CDCl_3$) δ 2.2 (s, 14 H), 1.5 (m, 14 H).

2(e),6(e)-Bis(dimethylamino)-*cis*-decalin Dimethiodide (10). A soln of **21** (0.3 g, 0.0013 mole) in *i*-PrOH (30 ml) was heated under reflux for 12 hr with a 4-fold excess of MeI. After cooling, a white solid was filtered, washed with Et_2O, and, after recrystn (50% Et_2O–anhyd EtOH), afforded 0.5 g (75%) of **10**: mp 220–222°; ir (KBr) 2950, 2700, 2800, 1450 cm^{-1}; nmr (D_2O) δ 3.4 (m, 2 H, $W_{1/2}$ = 17 cps, C-2 and C-6 CH), 3.1 (s, 18 H, N^+CH_3). *Anal.* ($C_{16}H_{34}I_2N_2$) C, H, N.

2(e),6(e)-Bis(tosyloxy)-*cis*-decalin (22). To a soln of **18** (0.4 g, 0.0024 mole) in dry pyridine (8 ml) was added at 0° *p*-TsCl (1.2 g, 0.0058 mole). The mixt was kept cold for 48 hr after which it was poured into 100 ml of cold H_2O. The resulting crystals were removed by filtration and recrystn (Et_2O–hexane) to afford 0.9 g (80%) of **22**: mp 142°; ir (KBr) 2930, 1450, 1180, 1190 cm^{-1}; nmr ($CDCl_3$) δ 7.2–7.8 (m, 8 H, arom), 4.8 (m, 1 H; $W_{1/2}$ = 7 cps, 6-C CH), 4.4 (m, 1 H, $W_{1/2}$ = 18 cps, C-2 CH), 2.45 (s, 6 H, aryl CH_3). *Anal.* ($C_{24}H_{30}O_6S_2$) C, H.

2(a),6(e)-Bis(dimethylamino)-*cis*-decalin (23). To a suspension of 22 (1.2 g, 0.0025 mole) in DMF (4 ml) was added anhyd Me_2NH (8 ml). The reaction autoclave was sealed and heated at 70° for 16 hr after which it was cooled, the autoclave was opened, and excess Me_2NH was allowed to evap. The residue was dissolved in 4 *N* HCl and the product isolated as described for **21** to yield 0.2 g (20%) of a yellow oil: ir (neat) 2950, 2790, 1450 cm^{-1}; nmr ($CDCl_3$) δ 2.3 (s, 14 H), 1.6 (m, 14 H).

2(a),6(e)-Bis(dimethylamino)-*cis*-decalin dimethiodide (11) was prepd in 45% yield as described for **10**: mp 245–247°; ir (KBr) 2970, 2710, 2798, 1450 cm^{-1}; nmr (D_2O) δ 3.9 (m, 1 H, $W_{1/2}$ = 6 cps, C-2 CH), 3.6 (m, 1 H, $W_{1/2}$ = 16 cps; C-6 CH), 3.2 (s, 18 H, N^+CH_3). *Anal.* ($C_{16}H_{34}I_2N_2$) C, H, N.

2,6-Dihydroxy-*trans*-decalin. 2,6-Dihydroxynaphthalene (**17**) (4 g, 0.025 mole) was dissolved in MeOH (120 ml) and hydrogenated over Raney Ni (W-2,[29] 2 g) at an initial H_2 pressure of 215 kg/cm^2. The reaction vessel was heated to 180° during which time the pressure increased to 250 kg/cm^2. These condns were maintd for 24 hr. After cooling the soln was filtered (Celite) and the solvent removed *in vacuo* to give a residue which was dissolved in $CHCl_3$. The work-up procedure that followed was identical with that of 2,6-dihydroxy-*cis*-decalin and gave 3 g of brown viscous oil.

Separation of 2(a),6(e)-Dihydroxy-*trans*-decalin (24) and 2(e),-6(e)-Dihydroxy-*trans*-decalin (25). The mixt of isomers (3 g) was chromatogd on a silica gel column (150 g) and eluted (50% EtOAc–$CHCl_3$) to afford 2 major fractions.

The first fraction contd after recrystn (Et_2O–$CHCl_3$) 1.5 g (32%) of **24**: mp 100–102°; ir (KBr) 3340, 2920, 1450, 1000, 1050 cm^{-1}; nmr ($CDCl_3$) δ 4.2 (m, 1 H, $W_{1/2}$ = 8 cps, C-2 CH), 3.7 (m, 1 H, $W_{1/2}$ = 19 cps, C-6 CH). *Anal.* ($C_{10}H_{18}O_2$) C, H. The second fraction contained after recrystn (Et_2O–$CHCl_3$) 0.3 g (7%) of **25**: mp 143–145°; ir (KBr) 3300, 2950, 1450, 1010, 1050 cm^{-1}; nmr ($CDCl_3$) δ 3.5 (m, 2 H, $W_{1/2}$ = 17 cps, C-2 and C-6 CH). *Anal.* ($C_{10}H_{18}O_2$) C, H.

trans-Decalin-2,6-dione (26) was prepd in 22% yield as described for **20**: mp 138–139° (lit.[14] mp 139.5–141.5°).

2(a),6(e)-Bis(dimethylamino)-*trans*-decalin (27) was prepd in 13% yield as described for **21**: ir (neat) 2940, 2800, 1450 cm^{-1}; nmr ($CDCl_3$) δ 2.2 (s, 14 H), 1.6 (m, 14 H).

2(a),6(e)-Bis(dimethylamino)-*trans*-decalin dimethiodide (12) was prepd in 36% yield as described for **10**: mp 298–299°; ir (KBr) 3000, 2920, 2700, 2800, 1450 cm^{-1}; nmr (D_2O) δ 3.9 (m, 1 H, $W_{1/2}$ = 6 cps, C-2 CH), 3.5 (m, 1 H, $W_{1/2}$ = 16 cps, C-6 CH), 3.2 (s, 18 H, N^+CH_3). *Anal.* ($C_{16}H_{34}N_2I_2$) C, H, N.

2(a),6(e)-Bis(tosyloxy)-*trans*-decalin (28) was prepd in 81% yield as described for **22**: mp 136–138°; ir (KBr) 2970, 1450, 1181, 1190 cm^{-1}; nmr ($CDCl_3$) δ 7.2–7.8 (m, 8 H, arom), 4.75 (m, 1 H, $W_{1/2}$ = 7 cps, C-2 CH), 4.45 (m, 1 H, $W_{1/2}$ = 18 cps, C-6 CH), 2.4 (s, 6 H, aryl CH_3). *Anal.* ($C_{24}H_{30}O_6S_2$) C, H.

2(e),6(a)-Bis(dimethylamino)-*trans*-decalin (29) was prepd in 18% yield as described for **23**. The dimethiodide salt was identical with **12**, in all respects based on mp, nmr, and ir data.

***N*-Methylpyridinium Iodide (30).** To a soln of pyridine (79 g, 1 mole) in anhyd Et_2O (700 ml) was added dropwise MeI (142 g, 1 mole). The reaction mixt was stirred for 3 hr at room temp. The pptd salt was filtered, washed with Et_2O, and dried *in vacuo* at 50° to give 160 g of **30**: mp 116–117° (lit.[21] mp 118°).

***N*-Methyl-1,2-dihydropyridine (31).** To a suspension of **30** (20 g, 0.091 mole) in anhyd Et_2O (200 ml) was added LAH (14 g, 0.37 mole) and the mixt stirred under N_2 at room temp for 3 hr. The excess LAH was decomposed (wet Et_3O) and the aq layer was extd several times (Et_2O). The combined Et_2O fractions were washed (H_2O and satd NaCl soln) and dried (Na_2SO_4), and the solvent was removed *in vacuo* to afford 1.7 g (20%) of a very unstable yellow oil: ir (neat) 3040, 2940, 2785, 1650, 1600, 1450 cm^{-1}.

2-Methyl-6-carbomethoxy-2-azabicyclo[2.2.2]oct-7-ene (32) and 2-Methyl-5-carbomethoxy-2-azabicyclo[2.2.2]oct-7-ene (33). Methyl acrylate (24 ml, 0.39 mole) was heated under reflux with **31** (7.1 g, 0.075 mole) for 24 hr. After cooling to room temp, Et_2O (150 ml) was added and the reaction mixt was acidified (4 *N* HCl). The rest of the work-up procedure was the same as in **21** which afforded 8.2 g (60%) of a red viscous oil. Chromatography on Woelm alumina (800 g, neutral, activity II) and eluting with 30% Et_2O–C_6H_6, gave 2 major fractions. The first fraction afforded 0.3 g (3.7%) of **33** as a light yellow oil: ir (neat) 3020, 2960, 2780, 1730, 1450, 1200 cm^{-1}; nmr ($CDCl_3$) δ 5.8 (m, 2 H, vinyl CH), 3.8 (d, 3 H, ester CH_3), 3.25 (m, 2 H, bridgehead CH), 2.3 (m, 5 H, $CHNCH_3$). Its mass spectrum showed peaks at *m/e* 181, 122, 121, 96, 95, 94, 86, 85, 84, 78, 77, 56, and 55. The second fraction afforded 3 g (37%) of **32** as light brown oil which had almost identical nmr and ir spectra with those of **33**. Its mass spectrum showed peaks at *m/e* 181, 122, 121, 114, 113, 96, 95, 94, 86, 85, 84, 78, and 77.

2-Methyl-6-carbomethoxy-2-azabicyclo[2.2.2]octane (34). To a soln of **32** (8 g, 0.044 mole) in 95% EtOH (70 ml) was added 10% Pd/C (4 g) and the mixt hydrogenated at initial H_2 pressure of 3.8 kg/cm^2 at room temp. After H_2 absorption ceased the catalyst was removed; evapn of the solvent yielded 4 g (33.3%) of **34** as orange-yellow oil: ir (neat) 2940, 2800, 1740, 1450, 1200 cm^{-1}; nmr ($CDCl_3$) δ 3.8 (d, 3 H, ester CH_3), 2–3 (m, 7 H), 1–1.8 (m, 7 H). The mass spectrum of **34** showed peaks at *m/e* 183, 130, 114, 113, 97, 96, 87, 86, 74, 59, 44, and 43. *Anal.* ($C_{10}H_{18}ClNO_2$) H, N, C: Calcd: 54.67; Found: 53.50.

2-Methyl-6-hydroxymethyl-2-azabicyclo[2.2.2]octane (35). LAH (0.52 g, 0.0137 mole) in anhyd Et_2O (70 ml) was heated to reflux for 1 hr. To the LAH soln was added a soln of **34** (1 g, 0.0055 mole) in anhyd Et_2O (30 ml) at such a rate as to maintain reflux. The mixt was heated at reflux for 24 hr after which excess LAH was decompd (wet Et_2O). The rest of the work-up was the same as in **31** which afforded 0.4 g (74%) of **35** as light yellow viscous oil: ir (neat) 3400, 2960, 2800, 1450, 1050 cm^{-1}; nmr ($CDCl_3$) δ 3.5 (m, 2 H, CH_2OH), 2–3 (m, 7 H), 1–2 (m, 7 H). The mass spectrum of **35** showed peaks at *m/e* 155, 124, 97, 85, 84, and 58. *Anal.* ($C_9H_{16}ClNO$) H, N, C: Calcd: 56.9; Found: 55.0.

2-Methyl-6-methylsulfonyloxymethyl-2-azabicyclo[2.2.2]octane (36). To a mixt of MesCl (1.4 g, 0.015 mole) and NaH (0.8 g, 0.018 mole) in dry C_6H_6 (50 ml) was added dropwise a soln of **35** (2 g, 0.01 mole) in dry C_6H_6 (30 ml) over 1 hr. The mixt was stirred for an addl 2 hr, and then allowed to stand at room temp overnight. The excess NaH was decompd (wet C_6H_6) and the resulting mixt

acidified (cold 4 *N* HCl). This was washed (C_6H_6) after which the aq layer was made basic at 0° (concd NH_4OH) and extd (C_6H_6). The C_6H_6 fractions were washed (satd NaCl) and dried (Na_2SO_4). Evapn of the solvent *in vacuo* yielded 0.8 g (30%) of **36** as dark yellow oil: ir (neat) 2970, 2800, 1450, 1350, 1180 cm^{-1}; nmr ($CDCl_3$) δ 4.5 (m, 2 H, $CH_2OSO_2CH_3$), 3 (s, 3 H, mesylate CH_3), 2–3 (m, 7 H).

2-Methyl-6-dimethylaminomethyl-2-azabicyclo[2.2.2]octane (37) was prepd in 43% yield as described for **23** and obtd as a yellow oil: ir (neat) 2970, 2780, 1450 cm^{-1}; nmr ($CDCl_3$) δ 3 (m, 2 H), 2.2 (s, 9 H), 1–2 (m, 11 H). Its mass spectrum showed peaks at *m/e* 184, 141, 112, 113, 114, 98, 85, 84, 70, 58, and 44.

2-Methyl-6-dimethylaminomethyl-2-azabicyclo[2.2.2]octane dimethiodide (16) was prepd in 50% yield as described for **10** and analyzed as the dipicrate: mp 180–182°. *Anal.* ($C_{28}H_{30}N_8O_{14}$) C, H, N.

Partition Coefficients. The dipicrate salt (0.005 g) (Table I) was dissolved in H_2O and made up to 250 ml. Two 30-ml aliquots were pipetted into flasks contg 170 ml of $CHCl_3$. The mixt was stirred for 24 hr at 25°. The system was allowed to stand for 20–30 min to assure complete phase sepn. The aqueous phase was transferred to a clean flask with care being taken to assure that no $CHCl_3$ phase contaminated it at this point. The amt of the dipicrate salt which partitioned into the $CHCl_3$ was detd spectrophotometrically at 352 mμ. Calcn of π values was carried out according to the equation[30] $\pi = \log P_X - \log P_{n=2}$ where P_X and $P_{n=2}$ are the measured partition coefficients of quat ammonium compounds with longer C chains and the parent, 2-C chain compd (**1**), respectively.

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Antistaphylococcal and Antifibrinolytic Activities of N^{α}-(ω-Aminoacyl)-L-lysines[1,2,†]

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A series of N^{α}-(ω-aminoacyl)-L-lysines (**1–5**) have been synthesized and tested for antistaphylococcal and antifibrinolytic activities. All of the N^{α}-L-lysine dipeptides had antistaphylococcal activity which was approximately equal to or slightly less than that of γ-aminobutyryl-L-histidine. These compounds were found to be effective antifibrinolytic agents and N^{α}-(ε-aminocaproyl)-L-lysine was the most active of the dipeptides investigated.

In previous publications,[1,3] it was found that a series of ω-amino acids and of ω-aminoacyl-L-histidines protected mice from death by *Staphylococcus aureus* infections. Of the peptides, ε-aminocaproyl-L-histidine possessed the highest antistaphylococcal activity.[1] The present investigation extends these studies to N^{α}-(ω-aminoacyl)-L-lysines which have been synthesized and tested for antistaphylococcal activity in Swiss albino mice. The antifibrinolytic activity of these dipeptides was also tested because of the interest described previously.[1]

The compounds discussed in this paper are: N^{α}-(ω-aminoacyl)-L-lysines, $H_2N(CH_2)_nCONHCH[(CH_2)_4NH_2]COOH$, where $n = 1$, N^{α}-glycyl-L-lysine (**1**); $n = 2$, N^{α}-(β-alanyl)-L-lysine (**2**); $n = 3$, N^{α}-(γ-aminobutyryl)-L-lysine (**3**); $n = 4$, N^{α}-(δ-aminovaleryl)-L-lysine (**4**); $n = 5$, N^{α}-(ε-aminocaproyl)-L-lysine (**5**).

Chemistry. The syntheses of **1**,[4-10] **2**,[11,12] and **3**[13,14] have been reported from several laboratories using the carbobenzoxy method. All of these methods are modifications of that reported by Bergmann, *et al.*,[4] who used N^{ϵ}-carbobenzoxy-L-lysine methyl ester and N^{α}-carbobenzoxyglycine as the starting materials for the N^{α}-glycyl-L-lysine preparation. The same method was employed by us in an endeavor to synthesize the higher ω-amino acid homologs of this N^{α}-L-lysine dipeptide. It was found to be very difficult to obtain pure N^{ϵ}-carbobenzoxy-L-lysine methyl ester by the method described.[4] On tlc the recrystallized product showed

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