Effect of Charge Shielding by Nonpolar Groups on the Partitioning of Quaternized Amines

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Abstract □ The methiodide salts of a number of tertiary organic bases were examined for their distribution properties between chloroform and water. An attempt was made to demonstrate whether the screening of ionic charge by nonpolar groups would substantially increase the lipid solubility of the methiodides. Comparison of a series of 2,6- *versus* 3,5-methyl-substituted *N*-methylpiperidine methiodides revealed little difference in their partition coefficients. Syntheses are described for some previously unreported substituted piperidines.

Keyphrases □ Amines, quaternized—partitioning □ Charge shielding, nonpolar groups, effect—quaternized amine partitioning □ Partition coefficients—quaternized amines □ Tertiary bases—synthesis

In recent years considerable effort has been directed toward the development and study of drugs which affect the central nervous system (CNS). Both qualitative and quantitative aspects of central *versus* peripheral activity depend not only upon the "intrinsic activity" and "receptor affinity" of a given drug, but also upon its rate and extent of distribution to specific sites within the CNS. Although knowledge is still incomplete, numerous studies have served to emphasize the lipid nature of the blood-brain barrier membrane. Two physicochemical parameters become of prime importance in determining rate and degree of penetration of this barrier by a drug (1). These are the lipid/water partition coefficient (K) and the degree of ionization at physiological pH with rate of penetration being directly related to the former and inversely to the latter. Therefore it is generally assumed that there is little or no penetration by charged quaternary ammonium compounds. This is supported by pharmacological experience in that such compounds generally do not elicit effects attributable to central actions.

In the initial phase of a program designed to evaluate the membrane permeability of quaternary ammonium compounds, the effect of structural variations in some quaternized bases have been investigated with regard to the partition coefficient in chloroform–water. Specifically, an attempt has been made to assess the importance of the steric relationship of hydrophobic, charge-insulating moieties to the locus of positive coulombic charge in a series of methyl-substituted piperidine methiodides. In addition, a few other quaternary salts of similar hydrocarbon content, but of a caged nature, were evaluated. The physical data and partition coefficients for all of the methiodides are listed in Table I.

It can be seen from the data in Table I that the major factor which determined the ability of the quaternary compounds to partition more favorably into the organic phase was the amount of hydrocarbon residue. If one allows that a change of about tenfold in the K value is significant, then the compounds of similar hydrocarbon content are not sufficiently different from one another to construct a case for enhancement of partitioning due to charge shielding. Indeed, the results seem to be to the contrary when one compares the 2,6-dimethyl *versus* 3,5-dimethylpiperidines (6 *versus* 7; 10 *versus* 11) and the 2,2,6,6-tetramethyl *versus* 3,3,5,5-tetramethylpiperidines (8 *versus* 9; 12 *versus* 13). These comparisons are between compounds of equal hydrocarbon content, but with differences in proximity of the methyls to the coulombic charge. In each case the more distant 3,5-substituted methiodides have a K about equal to or greater than the corresponding 2,6-substituted compounds. The authors had originally intended to study only the acetoxy amine methiodides but were suspicious that the acetoxy groups were somehow distorting the results. However, comparison of the simple piperidine methiodides (10–13) did not alter their conclusions based on the acetoxy compounds.

It would be premature to say that these results concerning partition coefficient could be extrapolated to a biological situation involving membrane permeability. However, the speculation of Friess *et al.* (2) to explain the similarity in functional acceptance of a quaternary and tertiary amine in the tropine series would seem to be affected by the authors' data. Their hypothesis that the "tropine ring structure may obscure the classic differentiation between quaternary and tertiary amine structure in terms of preferential penetration to and adsorption at certain peripheral and central chemoreceptor surfaces" does not seem to be tenable when based on the concept of charge shielding. Such shielding, as expressed in partition coefficients, is similar in most of the compounds and is certainly not uniquely enhanced for the tropine esters. Again, one must be cautious in this interpretation when comparing chemical *versus* biological systems. The authors hope to report on the degree and rate of penetration of the quaternary compounds through the blood-brain barrier as the second phase of this work.

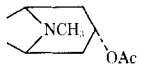
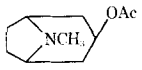
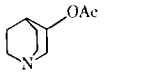
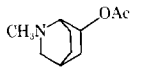
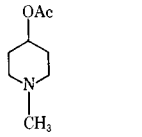
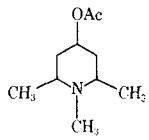
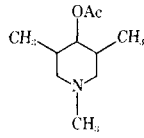
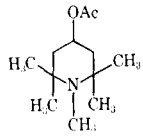
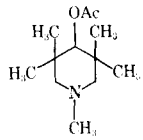
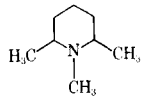
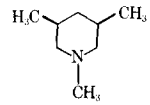
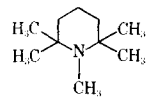
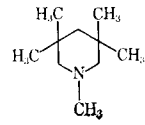
CHEMISTRY

With the exception of the 1,3,3,5,5-pentamethylpiperidine compounds, synthesis of the various tertiary bases proceeded in a straightforward manner. All of the bases were liquids and characterization was achieved *via* methiodide or picrate salts. The Reformatsky reaction of ethyl formate, amalgamated zinc, and two equivalents of ethyl 2-bromoisobutyrate afforded diethyl 3-hydroxy-2,2,4,4-tetramethylglutarate in a 75% yield. Acid hydrolysis yielded the glutaric acid (3) which was converted to the *N*-methyl-4-acetoxy-3,3,5,5-tetramethylglutarimide by the general procedure of Hall (4). Reduction of the acetoxy imide with diborane in tetrahydrofuran afforded 1,3,3,5,5-pentamethyl-4-piperidinol. 1,3,3,5,5-Pentamethylpiperidine was also prepared by Hall's procedure.

EXPERIMENTAL

Melting points are uncorrected and were taken in evacuated capillaries in the case of the methiodide salts.

Table I—Physical Data for Tertiary Amines and Methiodides

No.	Amines: Structure	Amines: B.p., °C. /mm.Hg	Methiodides: M.p., °C.	Methiodides: Formula	Methiodides: Calcd.	Methiodides: Found	$K \times 10^4$ ($CHCl_3/H_2O$)
1		64/0.65	279–280	$C_{11}H_{20}INO_2$	C, 40.6 H, 6.20 N, 4.31	C, 40.8 H, 6.28 N, 4.31	2.3, 1.8
2		60/0.65	189–190	$C_{11}H_{20}INO_2$	C, 40.6 H, 6.20 N, 4.31	C, 40.8 H, 6.22 N, 4.16	8.1
3		70/0.5	163–164	$C_{10}H_{18}INO_2$	C, 38.7 H, 5.84 N, 4.50	C, 38.7 H, 5.85 N, 4.31	2.0, 2.3
4		(Ref. 5)		$C_{11}H_{20}INO_2$			6.3
5		35/0.65	166–167	$C_9H_{18}INO_2$	C, 36.1 H, 6.07 N, 4.68	C, 36.1 H, 6.12 N, 4.66	1.5, 2.0
6		48/0.4	160–161.5	$C_{11}H_{22}INO_2$	C, 40.4 H, 6.77 N, 4.28	C, 40.5 H, 6.65 N, 4.42	5.3
7		52/0.75	210–211	$C_{11}H_{22}INO_2$	C, 40.4 H, 6.77 N, 4.28	C, 40.4 H, 6.84 N, 4.40	8.1
8		70/0.3	170–172	$C_{13}H_{26}INO_2$	C, 44.0 H, 7.37 N, 3.94	C, 43.9 H, 7.28 N, 3.98	14.0
9			260–263	$C_{13}H_{26}INO_2$	C, 44.0 H, 7.37 N, 3.94	C, 44.5 H, 7.40 N, 4.01	99.0
10		(Ref. 6, 7)		$C_9H_{20}IN$			9.0
11			280–281.5	$C_9H_{20}IN$	C, 40.2 H, 7.49 N, 5.20	C, 40.4 H, 7.61 N, 5.14	11.6
12		119/116	203–204	$C_{11}H_{24}IN$	C, 44.5 H, 8.14 N, 4.71	C, 44.6 H, 8.39 N, 4.41	20.0
13		80/65	310	$C_{11}H_{24}IN$	C, 44.5 H, 8.14 N, 4.71	C, 44.2 H, 8.05 N, 4.79	30.0

1,3,5-Trimethyl-4-piperidinol—A mixture of 0.30 g. of lithium aluminum hydride, 1.0 g. of 1,3,5-trimethyl-4-piperidone hydrochloride (8) and 20 ml. of dioxane was stirred at reflux for 5 hr. The solvent was removed *in vacuo* and the residue was suspended in ether and decomposed with ice water. The ether was decanted from the aqueous sludge and three additional ether extractions were made. The ether was dried over magnesium sulfate and evaporated to leave 0.60 g. (74%) of syrup; λ^{film} 3.0 μ (OH), no ketone remained at 5.8 μ. Vapor-phase chromatography showed a single peak. The oil was characterized as the methiodide salt, m.p. 226–230°.

Anal.—Calcd. for $C_9H_{20}INO$: C, 37.9; H, 7.08; N, 4.91. Found: C, 38.0; H, 6.99; N, 5.01.

1,2,2,6,6-Pentamethyl-4-piperidinol—To a solution of 9.2 g. (0.059 mole) of 2,2,6,6-tetramethyl-4-piperidone (free base) in 55

ml. of toluene was added 3.0 ml. (0.025 mole) of methyl chloroformate and the mixture was stirred at reflux for 45 hr. The toluene solution was washed with dilute acid, dried over magnesium sulfate, and evaporated *in vacuo* to leave 3.15 g. (59%) of the *N*-carbomethoxy compound as a syrup; λ^{film} 5.80 μ (ketone, C=O), 5.92 (urethan, C=O).

A mixture of 3.1 g. of the crude urethan, 3.1 g. of lithium aluminum hydride, and 50 ml. of dioxane was stirred at reflux for 30 hr. The mixture was cooled in ice and cautiously decomposed with ice water. The dioxane was removed *in vacuo* and the white, pasty residue was extracted with several portions of ether. The ether was dried over magnesium sulfate and evaporated to leave 2.1 g. (84%) of the pentamethyl alcohol as a viscous syrup; λ^{film} 3.0 μ (OH), no carbonyl remained. Picrate, m.p. 244–246° (from ethanol).

Anal.—Calcd. for $C_{16}H_{24}N_4O_8$: C, 48.0; H, 6.04; N, 14.0. Found: C, 48.0; H, 5.95; N, 14.0.

3-Hydroxy-2,2,4,4-tetramethylglutaric Acid—A stirred mixture of 13.3 ml. (0.165 mole) of ethyl formate, 39 g. (0.60 g. atom) of 20-mesh zinc amalgam, 30 g. of ethyl 2-bromoisobutyrate, and a catalytic amount of iodine was heated to boiling. Reaction commenced immediately and an additional 64.7 g. (total of 0.49 mole) of bromo ester was added dropwise over 15 min. The mixture was refluxed for 4 hr., cooled in ice, and decomposed by the addition of 250 ml. of 3 *N* hydrochloric acid. The benzene layer was separated and the aqueous portion extracted twice with 150-ml. portions of benzene. The combined benzene extracts were washed with water, dried over magnesium sulfate, and evaporated *in vacuo*. Distillation of the residual liquid through a short Vigreux condenser afforded 31.5 g. (75%) of diethyl 3-hydroxy-2,2,4,4-tetramethylglutarate at b.p. 86–93° (0.35 mm.).

Hydrolysis of the ester (30.4 g.) was accomplished by refluxing with 620 ml. of 6 *N* hydrochloric acid for 6 hr. The solution was chilled to afford 14.1 g. (60%) of white crystals, m.p. 170–171°; lit. (3) m.p. 169–170°.

***N*-Methyl-4-hydroxy-3,3,5,5-tetramethylglutarimide**—The hydroxy diacid above (14.1 g.) was refluxed for 16 hr. with 113 ml. of acetyl chloride, followed by evaporation of the reagent and distillation of the residue under vacuum (100° at 0.2 mm.) to afford 15.6 g. (98%) of 4-acetoxy-3,3,5,5-tetramethylglutaric anhydride. This material was immediately added to an ice-cold mixture of 60 ml. of 40% methylamine and 100 ml. of 75% acetone (4). After 20 min. the acetone was removed and the aqueous residue was acidified and extracted with chloroform to give 17.0 g. of a syrup regarded as the 4-acetoxy-3,3,5,5-tetramethylglutaric acid mono *N*-methylamide. The amino acid (16 g.) was treated with 25 ml. of acetic anhydride and 75 ml. of pyridine at reflux for 5 min. followed by standing at room temperature for 40 hr. The solvent was removed *in vacuo* and the residue treated with ice water and concentrated hydrochloric acid to precipitate *N*-methyl-4-acetoxy-3,3,5,5-tetramethylglutarimide (12.6 g., 85%). Recrystallization of a portion from water afforded white crystals, m.p. 53–55°.

Anal.—Calcd. for $C_{12}H_{19}NO_4$: C, 59.7; H, 7.94; N, 5.81. Found: C, 59.7; H, 7.82; N, 5.58.

1,3,3,5,5-Pentamethyl-4-piperidinol—A mixture of 5.0 g. of the imide, 40 ml. of tetrahydrofuran, and 60 ml. of 1 *M* diborane in tetrahydrofuran was refluxed for 3 hr. An equal charge of diborane solution was added and refluxing was continued for another 3 hr. The solution was cooled in ice and treated with 1 ml. of water and a few drops of 6 *N* hydrochloric acid. A violent reaction caused the loss of approximately one-half of the contents of the flask. The remainder was evaporated *in vacuo* and the residue was treated with 40 ml. of water and 6 *N* hydrochloric acid until strongly acidic. The resulting precipitate was extracted into chloroform, which was dried and evaporated to leave a white crystalline residue which possessed strong B-H bands in the IR at 4.2–4.4 μ. The complex was decomposed by heating with 50 ml. of 2 *N* hydrochloric acid for 15 hr. The resulting solution was made strongly alkaline with 10% sodium hydroxide and extracted with dichloromethane. The extract was dried over magnesium sulfate and evaporated *in vacuo* to leave 1.1 g. of liquid which was directly acetylated and characterized as the methiodide salt.

1,3,5-Trimethylpiperidine—A solution of 9.1 g. of 1,3,5-trimethyl-pyridinium iodide (9) in 100 ml. of 80% methanol was passed through a column of 90 g. of ion-exchange resin [Dowex 2 (chloride)]. The column was further eluted with 80% methanol and the solvent then evaporated *in vacuo* to leave 5.2 g. (91%) of the methochloride salt. The material (4.7 g.) was hydrogenated over 1.0 g. of platinum oxide in glacial acetic acid at 3 atm. After 20 hr. the calculated amount of gas was consumed. The catalyst was removed and the solvent evaporated *in vacuo*. The residue was alkalized with 10% sodium hydroxide and the base was extracted into dichloromethane. Since the amine tended to form a carbonate salt rapidly, it was directly converted to the methiodide salt.

Acetate Esters—The appropriate alcohol, as the free base, was mixed with excess acetic anhydride and the solution was heated 3–5 hr. on the steam bath. Pyridine was added in the case of hydrochloride salts. Excess reagent was removed *in vacuo* and the residue was partitioned between chloroform and 10% potassium carbonate. The chloroform extract was dried over magnesium sulfate, evaporated, and the residual liquid distilled *in vacuo* through a short path apparatus; yields were 50–70%. The boiling points of the bases are listed in Table I. Tropinol, pseudo-tropinol, 3-hydroxyquinuclidine hydrochloride, and 1-methyl-4-piperidinol were obtained from commercial sources; 1,2,6-trimethyl-4-piperidinol hydrochloride (β-epimer, m.p. 266°) was prepared by the hydrogenation of 1,2,6-trimethyl-4-pyridone (10).

Methiodide Salts—An ethereal or acetone solution of the appropriate tertiary base was treated with excess methyl iodide and allowed to stand for 24 hr. For the hindered bases, no cosolvent was used and reaction times were extended to 2 days in the case of 1,2,6-trimethyl-4-acetoxy piperidine and 7 days for 1,2,2,6,6-pentamethyl-4-acetoxypiperidine; 1,2,2,6,6-pentamethylpiperidine was refluxed 20 hr. in methyl iodide solution. The salts were recrystallized from absolute ethanol for analysis. Physical data are listed in Table I. 1,2,2,6,6-Pentamethylpiperidine was prepared by the method of Laboratorios Bonaplata, S.A. (11) and 1,3,3,5-5-pentamethylpiperidine by the procedure of Hall (4).

Determination of Partition Coefficients—Values of *K* were estimated from the distribution of quaternary salts between chloroform and water (10:1 volume ratio). Compounds were dissolved in the aqueous phase (2.0 mg./ml.) and partitioned with shaking over a period of 0.5 hr. The material in the chloroform phase was extracted into water and the quantity determined colorimetrically by the bromophenol blue method of Mitchell and Clark (12). A standard curve was determined for each compound.

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