has been determined using liquids to simulate the ointment bases. A reduction of the water/oil ratio of an emulsion base tended to retard diffusion of the sulfonamides. A statistical evaluation of the results was made. In general, the surfactant increased the solubilities of the sulfonamides in the solvents used and in most of the determinations tended to increase diffusion from the ointment bases. The 5% concentration of surfactant appeared to be most effective.

The authors conducted a similar study utilizing the sodium salts of these two sulfonamides. These results will be submitted at a later date.

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Relationships Between the Surface Activity and Cholinesterase Inhibition of Carbamoylpiperidinoalkanes II

Variations in the Amide Function

By RONALD P. QUINTANA

The static surface tension of aqueous solutions of selected mono- and bis(carbamoylpiperidino)ethanes and -decanes has been determined and compared with the ability of these compounds to inhibit human plasma pseudo-cholinesterase. Parallels reported in a preceding communication were confirmed, and other relationships between surface-active properties and biochemical activity were explored.

IN A PREVIOUS communication (1), the relationships between surface activity and cholinesterase inhibition of a series of mono- and bis-[3 - (*N,N* - diethylcarbamoyl)piperidino]alkanes were reported. While a parallel was observed between the ability of mono[3-(*N,N*-diethylcarbamoyl)piperidino]alkanes to lower surface tension and their inhibition of isolated human plasma pseudo-cholinesterase, no such relationship was noted in the case of the corresponding bis-substituted alkanes. Subsequently, the influence of variation in the amide function of mono- and bis(carbamoylpiperidino)ethanes and -decanes upon inhibitory characteristics was studied (2), and a parallel between electric moments of *N*-alkyl substituted nicotinamides and cholinesterase inhibition of identically substituted 1-decylnipecotamides was observed (3).

In the present paper, parallels reported in the preceding paper (1) were confirmed, and additional relationships between surface activity and biochemical response were explored.

EXPERIMENTAL

Materials.—The chemistry and properties of the mono- and bis(carbamoylpiperidino)ethanes and -decanes employed in this study were described elsewhere (2, 4). All of the compounds used were of analytically pure grade.

Solutions.—For each of the monosubstituted decanes, surface tension measurements were made on aqueous solutions of the following concentrations: 0.00125, 0.001875, 0.0025, 0.00375, 0.005, 0.0075, and 0.01 *M*. For all other compounds, measurements were made on 0.005 and 0.01 *M* solutions, although the former are not reported.

Instrumentation and Methods.—The instrumentation and methods previously employed (1) were utilized without modification for the compounds discussed in this paper.

Solutions of most of the mono(carbamoylpiperidino)alkanes had pH values between 5.70 and 6.20, those of the bis(carbamoylpiperidino)-ethanes between 3.30 and 3.80, and those of the bis(carbamoylpiperidino)decanes between 5.50 and 5.90.

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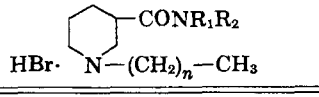
The author acknowledges discussions with Dr. Andrew Lasslo and the technical assistance of Miss Linda F. Lorenzen.

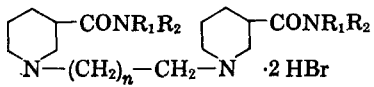
TABLE I.—INHIBITION OF ISOLATED HUMAN PLASMA PSEUDO-CHOLINESTERASE AND SURFACE-ACTIVE PROPERTIES OF MONO(CARBAMOYLPIPERIDINO)ALKANES



—NR_1R_2	$n = 1$				$n = 9$			
	Compd.	Human Plasma Cholinesterase Inhibition (I_{50} ± S.E.)[a]	Surface Pressure,[b] dynes/cm. at 0.01 *M* Concn.	Surface Tension,[c] dynes/cm. ± S.E.[d] at 0.01 *M* Concn.	Compd.	Human Plasma Cholinesterase Inhibition (I_{50} ± S.E.)[a]	Surface Pressure,[b] dynes/cm. at 0.01 *M* Concn.	Surface Tension,[c] dynes/cm. ± S.E.[d] at 0.01 *M* Concn.
$-N(CH_3)_2$	I	$(453 \pm 10.5) \times 10^{-5}$ *M*	1.75	68.78 ± 0.04	VI	$(2.17 \pm 0.10) \times 10^{-5}$ *M*	19.64	50.82 ± 0.03
$-N(C_2H_5)_2$[e,f]	II	$(118.5 \pm 0.5) \times 10^{-5}$ *M*	1.23	69.34 ± 0.05	VII	$(0.527 \pm 0.011) \times 10^{-5}$ *M*	26.15	44.49 ± 0.06
	III	$(197 \pm 3.0) \times 10^{-5}$ *M*	1.02	69.46 ± 0.11	VIII	$(0.766 \pm 0.0085) \times 10^{-5}$ *M*	23.11	47.41 ± 0.03
	IV	$(62.2 \pm 1.80) \times 10^{-5}$ *M*	5.53	65.02 ± 0.04	IX	$(0.318 \pm 0.0195) \times 10^{-5}$ *M*	27.45	43.14 ± 0.02
	V	Inhib. not sig. at 100×10^{-5} *M*	0.96	69.54 ± 0.02	X	$(2.57 \pm 0.125) \times 10^{-5}$ *M*	22.72	47.89 ± 0.03

[a] Summarized from a paper by Beasley and co-workers (2). [b] The surface pressure is the corrected surface tension of a redistilled water control minus the corrected surface tension of the solution. [c] The static surface tension is reported. [d] Standard error. [e] Values for surface pressure and surface tension had been previously reported (1). [f] Values obtained for the corresponding 4-carbamoyl substituted derivatives are: 1-ethyl-4-(*N*,*N*-diethylcarbamoyl)piperidine hydrobromide (XI), I_{50} ± S.E., (283 ± 14.5) × 10^{-5} *M* (2), surface pressure (0.01 *M*), 1.58 dynes/cm., surface tension ± S.E. (0.01 *M*), 68.91 ± 0.03 dynes/cm.; 1-decyl-4-(*N*,*N*-diethylcarbamoyl)piperidine hydrobromide (XII), I_{50} ± S.E., (2.65 ± 0.18) × 10^{-5} *M* (2), surface pressure (0.01 *M*), 24.80 dynes/cm., surface tension ± S.E. (0.01 *M*), 45.69 ± 0.03 dynes/cm.

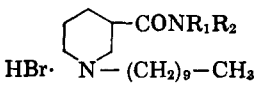
TABLE II.—INHIBITION OF ISOLATED HUMAN PLASMA PSEUDO-CHOLINESTERASE AND SURFACE-ACTIVE PROPERTIES OF BIS(CARBAMOYLPIPERIDINO)ALKANES

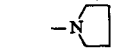
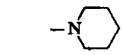
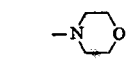


—NR_1R_2	$n = 1$				$n = 9$			
	Compd.	Human Plasma Cholinesterase Inhibition (I_{50} ± S.E.)[a]	Surface Pressure,[b] dynes/cm. at 0.01 *M* Concn.	Surface Tension,[c] dynes/cm. ± S.E.[d] at 0.01 *M* Concn.	Compd.	Human Plasma Cholinesterase Inhibition (I_{50} ± S.E.)[a]	Surface Pressure,[b] dynes/cm. at 0.01 *M* Concn.	Surface Tension,[c] dynes/cm. ± S.E.[d] at 0.01 *M* Concn.
$-N(CH_3)_2$	XIII	$(123.3 \pm 1.75) \times 10^{-5}$ *M*	5.30	65.25 ± 0.05	XVI	$(10.71 \pm 0.096) \times 10^{-5}$ *M*	8.64	61.84 ± 0.04
$-N(C_2H_5)_2$[e,f]	XIV	$(17.5 \pm 1.0) \times 10^{-5}$ *M*	3.34	67.39 ± 0.02	XVII	$(2.59 \pm 0.06) \times 10^{-5}$ *M*	4.78	65.63 ± 0.04
	XV	$(9.46 \pm 0.29) \times 10^{-5}$ *M*	2.52	67.96 ± 0.02	XVIII	$(2.80 \pm 0.11) \times 10^{-5}$ *M*	7.16	63.41 ± 0.12
		...	...	...	XIX	$(0.662 \pm 0.017) \times 10^{-5}$ *M*	6.50	64.08 ± 0.03

[a] Summarized from a paper by Beasley and co-workers (2). [b] The surface pressure is the corrected surface tension of a redistilled water control minus the corrected surface tension of the solution. [c] The static surface tension is reported. [d] Standard error. [e] Values for surface pressure and surface tension had been previously reported (1). [f] Values obtained for the corresponding 4-carbamoyl substituted derivatives are: 1,2-bis[4-(*N*,*N*-diethylcarbamoyl)piperidino]ethane dihydrobromide (XX), I_{50} ± S.E., not yet evaluated, surface pressure (0.01 *M*), 4.03 dynes/cm., surface tension ± S.E. (0.01 *M*), 66.39 ± 0.06 dynes/cm.; 1,10-bis[4-(*N*,*N*-diethylcarbamoyl)piperidino]decane dihydrobromide (XXI), I_{50} ± S.E., not yet evaluated, surface pressure (0.01 *M*), 10.09 dynes/cm., surface tension ± S.E., 60.47 ± 0.05 dynes/cm.

TABLE III.—INHIBITION OF ISOLATED HUMAN PLASMA PSEUDO-CHOLINESTERASE AND SURFACE-ACTIVE PROPERTIES OF MONO(CARBAMOYLPIPERIDINO)DECANES



Compd.	—NR_1R_2	Human Plasma Cholinesterase Inhibition (I_{50} ± S.E.)[a]	Relative Inhibitory Activity	Relative Surface Activity	π_{20}[b]
XXII	$-NH_2$	$(6.23 \pm 0.155) \times 10^{-5}$ M	1.00	1.00	7.67×10^{-3} M
XXIII	$-NHCH_3$	$(3.48 \pm 0.105) \times 10^{-5}$ M	1.79	0.89	8.64×10^{-3} M
VI	$-N(CH_3)_2$	$(2.17 \pm 0.10) \times 10^{-5}$ M	2.87	0.72	10.7×10^{-3} M
XXIV	$-NHC_2H_5$	$(1.371 \pm 0.007) \times 10^{-5}$ M	4.54	1.86	4.13×10^{-3} M
VII	$-N(C_2H_5)_2$[c,d]	$(0.527 \pm 0.011) \times 10^{-5}$ M	11.82	1.74	4.40×10^{-3} M
VIII		$(0.766 \pm 0.0085) \times 10^{-5}$ M	8.13	1.16	6.63×10^{-3} M
IX		$(0.318 \pm 0.0195) \times 10^{-5}$ M	19.59	1.72	4.45×10^{-3} M
X		$(2.57 \pm 0.125) \times 10^{-5}$ M	2.42	1.00	7.66×10^{-3} M

[a] Summarized from a paper by Beasley and co-workers (2). [b] Molar concentration which produces a surface pressure of 20 dynes/cm. [c] Values obtained for the corresponding 4-carbamoyl substituted derivative, 1-decyl-4-(*N*,*N*-diethylcarbamoyl)-piperidine hydrobromide (XII), are: I_{50} ± S.E., $(2.65 \pm 0.18) \times 10^{-5}$ M (2); relative inhibitory activity, 2.35; relative surface activity, 1.29; π_{20}, 5.96×10^{-3} M. [d] Values obtained for the corresponding pyridinium analog, 1-decyl-3-(*N*,*N*-diethylcarbamoyl)pyridinium bromide (XXV), are: I_{50} ± S.E., $(0.365 \pm 0.000) \times 10^{-5}$ M (5); relative inhibitory activity, 17.07; relative surface activity, 0.64; π_{20}, 11.9×10^{-3} M.

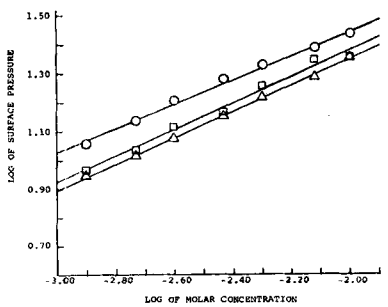


Fig. 1.—Log-log plot of surface pressure *vs.* concentration for solutions of 1-decyl-3-(piperidinoformyl)piperidine hydrobromide, IX (○); 1-decyl-3-(pyrrolidinoformyl)piperidine hydrobromide, VIII (□); and 1-decyl-3-(morpholinoformyl)piperidine hydrobromide, X (△).

The dynamic surface tension of only a few compounds varied from the static value by more than 2 dynes/cm. These were compound III (Table I), 2.5 dynes/cm.; compound XV (Table II), 2.4 dynes/cm.; compound XVIII (Table II), 3.5 dynes/cm.; and compound XX (*Footnote f*, Table II), 8.7 dynes/cm.

RESULTS AND DISCUSSION

An important objective of this study was to substantiate further the data obtained in the preceding experiments. It is considered quite significant that the trend observed in the preceding paper (1) has been reproduced in the data reported in this communication. In this instance, too, the monosubstituted decanes and the bis-substituted ethanes have shown increased surface-active properties, parallel with their more potent inhibitory action, compared to the corresponding bis-substituted decanes and monosubstituted ethanes, respectively. Moreover, for both the mono(carbamoylpiperidino)alkanes (Table I) and the bis-(carbamoylpiperidino)alkanes (Table II), the decane derivatives are more potent cholinesterase inhibitors and are more surface active than the corresponding ethane derivatives.

A more detailed study furnishing relationships between surface activity and cholinesterase inhibition of the mono(carbamoylpiperidino)decanes is summarized in Table III. As a measure of surface activity, the molar concentration which produced a surface pressure (surface tension lowering) of 20 dynes/cm., *i.e.*, π_{20}, was determined and relative surface activities calculated from these values. The π_{20} values were obtained from log–log plots of surface pressure *versus* concentration (6), where the straight lines drawn through the seven experimental points were determined by the method of least squares. In general, these straight lines were parallel; this graphic interpretation is illustrated in Fig. 1 with representative members of this series of compounds. While in this instance, surface activity happens to parallel the inhibitory characteristics, the values reported, for example, in Table III for relative inhibitory activity and relative surface activity indicate that there is not always correlation between these two parameters.

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