(see below) showed no melting point depression (mp 198–202°). The infrared spectra as Nujol mulls were also very similar to one another. On occasion, another crystal form of the picrate, mp 167–170°, was obtained by recrystallization from 80% 2-methoxyethanol.

Anal. Calcd for $C_{35}H_{40}N_8O_{16}$: C, 50.7; H, 4.85; N, 13.5. Found: C, 50.5; H, 4.85; N, 13.8.

Methylurethan of the Dimer Id and Reduction to Ib.—To an ice-cold, stirred mixture of 300 mg of Ia dihydrochloride (prepared as described by Baltzly, *et al.*[1]), 10 ml of 1 *N* NaOH, and 10 ml of chloroform was slowly added 0.25 ml of methyl chloroformate. Stirring was continued for 1 hr at room temperature. The mixture was acidified with concentrated HCl and stirred for 10 min. The layers were separated, and the aqueous layer was extracted with another 10 ml of chloroform. The chloroform was dried ($MgSO_4$) and evaporated *in vacuo* to leave 333 mg (100%) of a syrup whose infrared spectrum was in agreement with Id: λ_{max}^{film} 5.90 μ (C=O of urethan).

The urethan (320 mg) was reduced with 0.60 g of $LiAlH_4$ in THF solution by refluxing for 16 hr. The solvent was evaporated and after decomposition of the hydride mixture with water, the amine Ib was extracted into ether. The ether was evaporated to yield 210 mg of free base as a syrup. The dipicrate was prepared to yield 390 mg, mp 187–198°. Recrystallization from 90% 2-methoxyethanol gave 181 mg, mp 198–201°.

Anal. Calcd for $C_{35}H_{40}N_8O_{16}$: C, 50.7; H, 4.85; N, 13.5. Found: C, 50.6; H, 4.82; N, 13.4.

Bis(2-methoxy-5-bromoacetylphenyl)methane (VIII).—To a mixture of 2.0 g (6.4 mmoles) of bis(2-methoxy-5-acetylphenyl)-methane in 50 ml of THF was added 4.6 g (12.2 mmoles) of trimethylphenylammonium tribromide. The mixture was stirred at room temperature for 3.5 hr and evaporated *in vacuo*, and the yellow solid was washed thoroughly with water. The crude material (2.4 g) was collected after a benzene wash. Recrystallization from 2-methoxyethanol afforded 1.25 g (41%), mp 144–147°.

Anal. Calcd for $C_{19}H_{18}Br_2O_4$: C, 48.5; H, 3.83; Br, 34.1. Found: C, 48.2; H, 3.80; Br, 33.9.

Bis(2-methoxy-5-carboxyphenyl)methane (X).—To 60 ml of warm (60°) "Sanichlor" bleach was added 2.54 g (8.1 mmoles) of bis(2-methoxy-5-acetylphenyl)methane in 200 ml of methanol. The mixture was stirred at 60° for 2 hr, then 10-ml portions of bleach were added until a persistent starch–iodide test was obtained. The mixture was then evaporated *in vacuo* to near dryness, taken up in water, and treated with sodium bisulfite. The resulting suspension was acidified to pH 2 with 6 *N* HCl, and the solid was collected by filtration and washed with water. The white crystalline material was triturated with absolute methanol, yielding 2.19 g (85%), mp >300.

Anal. Calcd for $C_{17}H_{18}O_4$: C, 64.5; H, 5.10. Found: C, 64.1; H, 5.11.

Bis(2-methoxy-5-dimethylcarbamoylphenyl)methane (XI).—A mixture of 0.3 g (0.95 mmole) of bis(2-methoxy-5-carboxyphenyl)methane and 5 ml of $SOCl_2$ was refluxed 6 hr and evaporated *in vacuo*. The acid chloride was freed of $SOCl_2$ by the addition and evaporation (*in vacuo*) of a few milliliters of anhydrous benzene. To 0.33 g (0.93 mmole) of the acid chloride in 8 ml of cold CH_2Cl_2 was added, dropwise, 2 ml of anhydrous dimethylamine in 2 ml of cold methylene chloride. After standing at room temperature 15 hr, the mixture was washed with water, and the CH_2Cl_2 layer was separated, dried ($MgSO_4$), and evaporated *in vacuo* to yield 0.24 g of gummy material. When treated with ether, the gum yielded 0.18 g of yellow crystals. Recrystallization from benzene–cyclohexane gave 0.13 g (38%), mp 119–122°. An analytical sample had mp 123–125°.

Anal. Calcd for $C_{21}H_{26}N_2O_4$: C, 68.1; H, 7.07; N, 7.56. Found: C, 67.8; H, 7.14; N, 7.20.

Bis(2-methoxy-5-dimethylaminomethylphenyl)methane Dihydrochloride (XII).—To a chilled suspension of 0.74 g (19.4 mmoles) of $LiAlH_4$ in 20 ml of anhydrous THF was added 1.2 g (3.2 mmoles) of bis(2-methoxy-5-dimethylcarbamoylphenyl)-methane. The mixture was refluxed 12 hr and chilled, and the remaining unchanged hydride was decomposed by the addition of absolute ethanol followed by a few milliliters of water. The mixture was evaporated *in vacuo* to near dryness. The white suspension was washed thoroughly with ethyl ether and filtered, and the ethereal extract was separated and dried ($MgSO_4$). Evaporation *in vacuo* yielded a clear gum, which, when taken up in chilled ethyl ether and saturated with dry HCl, yielded a white crystalline solid. Three recrystallizations from 2-propanol gave 0.2 g (15%) of XII, mp 212–215°.

Anal. Calcd for $C_{21}H_{30}N_2O_2 \cdot 2HCl$: C, 60.7; H, 7.72; N, 6.75. Found: C, 60.4; H, 7.80; N, 6.48.

The bismethiodide was prepared by stirring XII with an excess of methyl iodide for 3 days. An analytical sample, mp >300°, was obtained by recrystallization from aqueous 2-methoxyethanol.

Anal. Calcd for $C_{23}H_{36}I_2N_2O_2$: C, 44.1; H, 5.75; I, 40.6. Found: C, 44.4; H, 5.87; I, 40.5.

Electronic Structures of Some N-Alkyl-Substituted Amides of Interest as Cholinesterase Inhibitors[1]

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Received August 12, 1965

Electronic structures were calculated for 18 N-alkyl-substituted amides which are of interest as cholinesterase inhibitors. The electron densities were calculated from molecular orbital approximations. No simple relationship was observed between the net charge at the carbonyl carbon or carbonyl oxygen and the corresponding cholinesterase inhibitory property; however, the activity increases rather smoothly as the amide nitrogen becomes more positive.

We have been interested in correlating physicochemical parameters with the cholinesterase inhibitory properties of 1-decyl-3-[(N-alkyl)- and 1-decyl-3-[(N,N-dialkyl)-substituted carbamoyl]piperidines[2] and, more recently, have initiated molecular orbital calculations to give electron densities at the atomic sites of these inhibitors. Although the calculations are inherently approximate, it is not the absolute magnitudes of the results which we emphasize. Instead, we wish to classify or rank certain homologs which vary systematically and gradually by one structural alteration at a time, and compare *relative* electron densities with biochemical response.[3] Also, we wish to evaluate quantitatively the view[4] that inhibition is related to the electro-

(1) This research is being supported by the National Science Foundation (B-15989) and the U. S. Army Medical Research and Development Command (DA-49-193-MD-2779). Computer facilities were provided through U. S. Public Health Service Grant HE-09495.

(2) (a) W. P. Purcell, J. G. Beasley, and R. P. Quintana, *Biochim. Biophys. Acta*, **88**, 233 (1964); (b) R. P. Quintana, *J. Pharm. Sci.*, **53**, 1221 (1964); (c) *ibid.*, **54**, 573 (1965); (d) *ibid.*, **54**, 462 (1965).

(3) B. Pullman and A. Pullman, "Quantum Biochemistry," Interscience Publishers, Inc., New York, N. Y., 1963, p 180.

(4) F. Bergmann, I. B. Wilson, and D. Nachmansohn, *J. Biol. Chem.*, **186**, 693 (1950).

TABLE I

SEMIEMPIRICAL PARAMETERS

Atom or group	δ, diagonal element	Bonding	η, off-diagonal element
C	0.0	C—C	1.0
O	1.2	C=O	2.0
N, aromatic	0.4	C=N—	1.0
N, aliphatic	1.0	C—N<	0.9
	Hyperconjugation		
C	0.1	C_{al}-C_{ar}[a]	0.7
		C_{al}-C_{al}[a]	0.6
H_2	0.2	C=H_2	2.0
H_3	0.3	C≡H_3	2.0

[a] C_{al} = aliphatic, C_{ar} = aromatic.

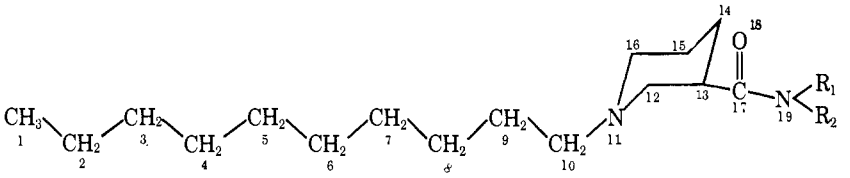
and Pullman.[6] Table I gives the parameters used in our calculations. Hyperconjugation parameters were used for the methyl and ethyl groups attached to the amide nitrogen atom, and for the methyl group adjacent to the carbonyl carbon in the acetamide series.

Results and Discussion

Our choice of molecules for calculation was based upon the available activity data[7] (Table V) and, since we measured the electric dipole moments of the identically substituted nicotinamides,[8] the electronic structures of these compounds were calculated in addition. Also, in order to bridge between the piperidine and pyridine series of homologs, the identically substituted acetamides were included. The results of the molecular orbital calculations are given in Tables II–IV and, for convenient comparison, the cholinesterase inhibitory properties of the 1-decyl-3-[(N-alkyl)- and 1-decyl-3-

TABLE II

NET CHARGES AT THE ATOMIC SITES OF 1-DECYL-3-[(N-ALKYL)- AND 1-DECYL-3-[(N,N-DIALKYL)-SUBSTITUTED CARBAMOYL]PIPERIDINES



Atom or group	R_1 = R_2 = H	CH_3 H	C_2H_5 H	CH_3 CH_3	C_2H_5 CH_3	C_2H_5 C_2H_5
1	−0.0014	−0.0014	−0.0014	−0.0014	−0.0014	−0.0014
2	+0.0001	+0.0001	+0.0001	+0.0001	+0.0001	+0.0001
3	−0.0017	−0.0017	−0.0017	−0.0017	−0.0017	−0.0017
4	+0.0006	+0.0006	+0.0006	+0.0006	+0.0006	+0.0006
5	−0.0025	−0.0025	−0.0025	−0.0025	−0.0025	−0.0025
6	+0.0020	+0.0020	+0.0020	+0.0020	+0.0020	+0.0020
7	−0.0050	−0.0050	−0.0050	−0.0050	−0.0050	−0.0050
8	+0.0070	+0.0070	+0.0070	+0.0070	+0.0070	+0.0070
9	−0.0166	−0.0166	−0.0166	−0.0166	−0.0166	−0.0166
10	+0.0434	+0.0434	+0.0434	+0.0434	+0.0433	+0.0433
11	+0.6526	+0.6526	+0.6526	+0.6527	+0.6526	+0.6527
12	+0.1557	+0.1559	+0.1558	+0.1561	+0.1560	+0.1559
13	−0.0265	−0.0264	−0.0264	−0.0264	−0.0263	−0.0263
14	+0.1096	+0.1097	+0.1096	+0.1098	+0.1097	+0.1096
15	−0.0077	−0.0077	−0.0077	−0.0077	−0.0077	−0.0077
16	+0.1401	+0.1402	+0.1402	+0.1403	+0.1403	+0.1402
17	+0.2309	+0.2309	+0.2304	+0.2311	+0.2307	+0.2303
18	−0.4181	−0.4109	−0.4118	−0.4045	−0.4053	−0.4061
19	+0.1375	+0.2126	+0.2088	+0.2763	+0.2732	+0.2701
R_1 C, methyl		+0.0612		+0.0596		
R_1 H_3, methyl		−0.1439		−0.1363		
R_1 C, methylene			+0.0377		+0.0360	+0.0360
R_1 H_2, methylene			−0.1143		−0.1069	−0.1076
R_1 C, ethyl, terminal			+0.0484		+0.0484	+0.0484
R_1 H_3, ethyl			−0.0491		−0.0492	−0.0492
R_2 C, methyl				+0.0596	+0.0595	
R_2 H_3, methyl				−0.1363	−0.1370	
R_2 C, methylene						+0.0360
R_2 H_2, methylene						−0.1076
R_2 C, ethyl, terminal						+0.0485
R_2 H_3, ethyl						−0.0492

philic character of the carbonyl carbon atom in the amide group.

Calculations.—The molecular orbital calculations were conducted with an IBM 1620 computer and a program kindly furnished by Mr. G. V. O'Bleness.[5] The semiempirical parameters and the general methodology for the calculations are described by Pullman

(5) G. V. O'Bleness, "Molecular Orbital Calculations on the IBM 1620," Proceedings of the 1620 Users Group Joint Eastern-Midwestern Region, Pittsburgh, Pa., Oct 1963, p 226.

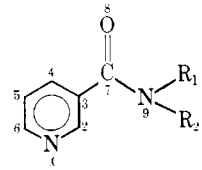
(6) See ref 3, pp 108–115.

(7) (a) A. Lasslo, J. G. Beasley, G. G. Nelms, and G. J. Epperson, *J. Med. Chem.*, **6**, 811 (1963); (b) J. G. Beasley, R. P. Quintana, and G. G. Nelms, *ibid.*, **7**, 698 (1964).

(8) W. P. Purcell, *J. Phys. Chem.*, **68**, 2666 (1964).

TABLE III

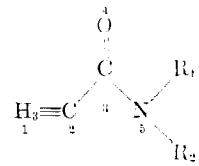
NET CHARGES AT THE ATOMIC SITES OF N-ALKYL- AND N,N-DIALKYL-SUBSTITUTED NICOTINAMIDES



	Atom or group	R_1 = H, R_2 = H	R_1 = CH_3, R_2 = H	R_1 = C_2H_5, R_2 = H	R_1 = CH_3, R_2 = CH_3	R_1 = C_2H_5, R_2 = CH_3	R_1 = C_2H_5, R_2 = C_2H_5
	1	−0.1579	−0.1579	−0.1579	−0.1579	−0.1579	−0.1579
	2	+0.0903	+0.0904	+0.0904	+0.0906	+0.0906	+0.0905
	3	−0.0250	−0.0249	−0.0249	−0.0249	−0.0248	−0.0248
	4	+0.0660	+0.0661	+0.0660	+0.0663	+0.0662	+0.0661
	5	−0.0050	−0.0050	−0.0050	−0.0050	−0.0050	−0.0050
	6	+0.0817	+0.0818	+0.0817	+0.0819	+0.0819	+0.0818
	7	+0.2306	+0.2305	+0.2301	+0.2307	+0.2303	+0.2299
	8	−0.4182	−0.4110	−0.4119	−0.4046	−0.4054	−0.4062
	9	+0.1375	+0.2126	+0.2088	+0.2764	+0.2733	+0.2702
R_1	C, methyl		+0.0612		+0.0596		
R_1	H_3, methyl		−0.1439		−0.1363		
R_1	C, methylene			+0.0577		+0.0360	+0.0360
R_1	H_2, methylene			−0.1143		−0.1069	−0.1076
R_1	C, ethyl, terminal			+0.0484		+0.0484	+0.0485
R_1	H_3, ethyl			−0.0491		−0.0492	−0.0492
R_2	C, methyl				+0.0596	+0.0595	
R_2	H_3, methyl				−0.1363	−0.1370	
R_2	C, methylene						+0.0360
R_2	H_2, methylene						−0.1076
R_2	C, ethyl, terminal						+0.0485
R_2	H_3, ethyl						−0.0492

TABLE IV

NET CHARGES AT THE ATOMIC SITES OF N-ALKYL- AND N,N-DIALKYL-SUBSTITUTED ACETAMIDES



	Atom or group	R_1 = H, R_2 = H	R_1 = CH_3, R_2 = H	R_1 = C_2H_5, R_2 = H	R_1 = CH_3, R_2 = CH_3	R_1 = C_2H_5, R_2 = CH_3	R_1 = C_2H_5, R_2 = C_2H_5
	1	−0.0344	−0.0344	−0.0344	−0.0343	−0.0343	−0.0344
	2	+0.0447	+0.0447	+0.0447	+0.0447	+0.0447	+0.0447
	3	+0.2485	+0.2486	+0.2482	+0.2491	+0.2486	+0.2482
	4	−0.3998	−0.3917	−0.3927	−0.3847	−0.3855	−0.3863
	5	+0.1409	+0.2150	+0.2112	+0.2781	+0.2750	+0.2718
R_1	C, methyl		+0.0612		+0.0596		
R_1	H_3, methyl		−0.1435		−0.1360		
R_1	C, methylene			+0.0577		+0.0360	+0.0360
R_1	H_2, methylene			−0.1139		−0.1066	−0.1073
R_1	C, ethyl, terminal			+0.0484		+0.0485	+0.0485
R_1	H_3, ethyl			−0.0491		−0.0492	−0.0492
R_2	C, methyl				+0.0596	+0.0595	
R_2	H_3, methyl				−0.1360	−0.1367	
R_2	C, methylene						+0.0360
R_2	H_2, methylene						−0.1073
R_2	C, ethyl, terminal						+0.0485
R_2	H_3, ethyl						−0.0492

[(N,N-dialkyl)-substituted carbamoyl]piperidines[7] are given in Table V.

From comparison of Tables II–IV with Table V, one can see that there is no simple relationship or trend between the electron density at the carbonyl carbon or carbonyl oxygen and the corresponding activity: however, the electron density at the amide nitrogen increases rather smoothly with increasing values of I_{50} or, expressed another way, the activity increases as the nitrogen atom becomes more positive. Figure 1 is a plot of activity (I_{50}, Table V) against the net charge on the amide nitrogen (Table II) and the line is the least-squares line of these points.

An interpretation of these and other results is reported in the following paper.[9]

(9) W. P. Purcell, J. G. Beasley, R. P. Quintana, and J. A. Singer, *J. Med. Chem.*, **9**, 297 (1966).

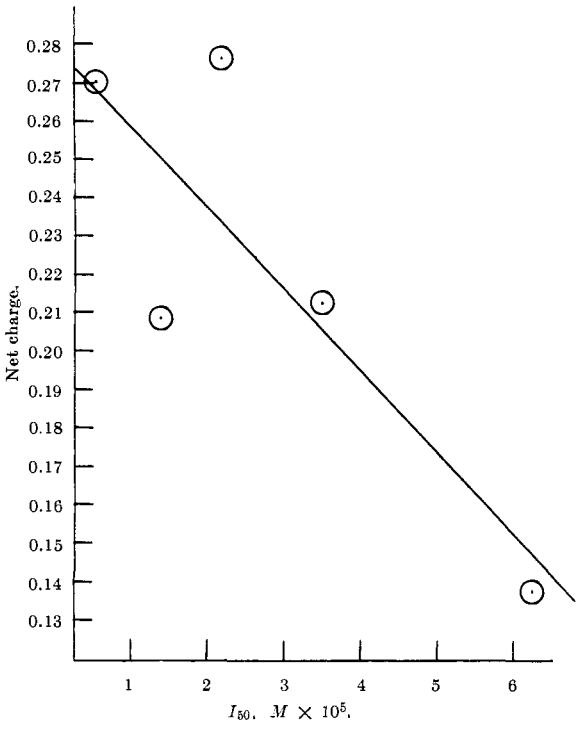
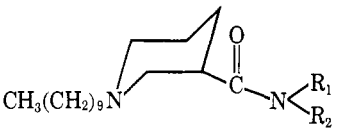


Figure 1.—Net charge at the amide nitrogen atom of 1-decyl-3-[(alkyl)- and 1-decyl-3-[(N,N-dialkyl)-substituted carbamoyl]-piperidines *vs.* the corresponding cholinesterase inhibition.

TABLE V

CHOLINESTERASE INHIBITORY PROPERTIES OF 1-DECYL-3-[(N-ALKYL)- AND 1-DECYL-3-[(N,N-DIALKYL)-SUBSTITUTED CARBAMOYL]PIPERIDINES



NR_1R_2	I_{50}, $M \times 10^5$[a]
NH_2	6.23[b]
$NHCH_3$	3.48[b]
NHC_2H_5	1.37[b]
$N(CH_3)_2$	2.17[b]
$N(C_2H_5)_2$	0.53[c]
$N(C_3H_7)_2$	0.105[d]

[a] Molarity of inhibitor effecting 50% inhibition. [b] See ref 7b. [c] See ref 7a. [d] J. G. Beasley, unpublished data.

Acknowledgment.—The author wishes to thank Dr. Charles W. Sheppard for his kind assistance in computer programming and Miss Joan S. Hendrix for her help in operating the IBM 1620 computer. Also, we are grateful to the National Science Foundation and the Walter Reed Army Institute of Research for their support of this research. This paper is contribution No. 42 from the Army Research Program on Malaria.

Application of Partition Coefficients, Electric Moments, Electronic Structures, and Free-Energy Relationships to the Interpretation of Cholinesterase Inhibition[1]

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Cholinesterase inhibition of some N-alkyl-substituted amides is interpreted in the light of their partition coefficients, electric dipole moments, electronic structures calculated from the Hückel molecular orbital method, and free-energy relationships. At least 75% of the observed cholinesterase inhibition can be accounted for from a linear relationship between log I_{50} and log (partition coefficient). The activities of seven mono(carbamoylpiperidino)decanes are explained in terms of electronic, stereochemical, and hydrogen-bonding factors. The inhibitory properties of several mono- and bis[3-(N,N-diethylcarbamoyl)piperidino]alkanes are discussed from considerations of the smooth curves obtained from plotting $1/I_{50}$ against n, the number of carbon atoms in the alkyl chain. It is believed that the mono derivatives have competing electronic and hydrophobic factors which contribute to the activity, while the inhibition of the bis compounds can be approximated nicely from the parabolic equation, $1/I_{50} = An^2 + Bn + C$. Linear free-energy relationships indicate that the inhibitors under study have similar binding modes. A model for the inhibitor–enzyme complex is proposed which has points of attachment (1) at the anionic site between the carboxyl group of the enzyme and the positively charged quaternary ring nitrogen of the inhibitor, and (2) at the esteratic site in the form of a quasi-ring formed from association of (a) the serine hydroxyl oxygen of the enzyme with the amide nitrogen of the inhibitor, and (b) the serine hydroxyl hydrogen of the enzyme with the amide oxygen.

The inhibitory effect upon isolated human plasma pseudocholinesterase (acylcholine acylhydrolase, EC 3.1.1.8) systems produced by series of substituted arylalkylaminopropionamides[2,3] and of piperidinecarboxamide derivatives[4,5] has been studied extensively. In continuing investigations designed to elucidate structure–activity relationships in these series, we have (1) measured dielectric properties,[6-8] (2) calculated electronic structures,[9] (3) applied regression analyses[10] to the structure–activity data, (4) evaluated surface-

(1) This research is being supported by the National Science Foundation (GB-2381/B-15989). Computer facilities were provided through U. S. Public Health Service Grant HE-09495.

(2) A. Lasslo, P. D. Waller, A. L. Meyer, and B. V. Rama Sastry, *J. Med. Pharm. Chem.*, **2**, 617 (1960).

(3) A. Lasslo, P. D. Waller, and G. J. Epperson, *ibid.*, **6**, 26 (1963).

(4) A. Lasslo, J. G. Beasley, G. G. Nelms, and G. J. Epperson, *ibid.*, **6**, 811 (1963).

(5) J. G. Beasley, R. P. Quintana, and G. G. Nelms, *ibid.*, **7**, 698 (1964).

(6) W. P. Purcell, *J. Phys. Chem.*, **68**, 2666 (1964).

(7) W. P. Purcell and J. A. Singer, *ibid.*, **69**, 691 (1965).

(8) W. P. Purcell, J. G. Beasley, and R. P. Quintana, *Biochim. Biophys. Acta*, **88**, 233 (1964).

(9) W. P. Purcell, *J. Med. Chem.*, **9**, 294 (1966).

(10) W. P. Purcell, *Biochim. Biophys. Acta*, **105**, 201 (1965).