Preparation of Isocyanates.—A suspension of the azide (2.2 mmoles) in toluene (50 ml) was refluxed for 6 hr, chilled, and filtered to give the isocyanate. Recrystallization from toluene gave the analytical samples. See Table I. The isocyanates Va and Vb exhibited an infrared peak at 2280 cm^{-1}.

Isobutyl N-[2-(2,4-Dihydroxy-6-methyl-5-pyrimidyl)-1-ethyl]-carbamate (VIa).—A solution of the isocyanate Va (0.5 g, 2.6 mmoles) in *i*-BuOH (50 ml) was refluxed for 6 hr and cooled to give 0.3 g (45%) of VIa, mp 233–234°. The infrared spectrum was as expected.

Anal. Calcd for $C_{12}H_{19}N_3O_4$: C, 53.53; H, 7.11; N, 15.60. Found: C, 53.38; H, 7.33; N, 15.51.

Preparation of Ureas.—A solution of ethyl *p*-aminobenzoate or diethyl *p*-aminobenzoyl-L-glutamate (10 mmoles) and isocyanate (4.5 mmoles) in dry[10] DMF (25 ml) was heated on a steam bath for 20 hr, evaporated *in vacuo* to 5 ml, and poured into toluene (200 ml). The precipitated solid was recrystallized from dioxane–H_2O and EtOH–H_2O to give the substituted urea. See Table II.

The ethyl ester (1.4 mmoles) was hydrolyzed by 3 *N* NaOH (10 ml) at 25° for 5 hr. The chilled solution was neutralized with 6 *N* HCl to give the free acid. The crude material was purified by dissolving in 2% $NaHCO_3$, treatment with Norit, and precipitation with 6 *N* HCl. See Table III. The infrared spectra of the acids and their ethyl esters were as expected.

(10) C. R. Leader and J. F. Gormley, *J. Am. Chem. Soc.*, **73**, 5731 (1951).

Substituted 1-Benzyl-3-(N,N-diethylcarbamoyl)-piperidine Cholinesterase Inhibitors. Relationships between Molecular Constitution, pK_a' Values, and Partition Coefficients[1]

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During the past several years, appreciable efforts have been made to explore relationships between the molecular constitution of carbamoylpiperidines and their physicochemical properties, as well as between the latter two and the biochemical response of these entities in isolated cholinesterase systems.[2–4] In this specific instance, we have designed a series of compounds which would enable us to study the effect of electron-density changes around the heterocyclic nitrogen of the piperidine derivatives. In addition to anticipating the evaluation of their effect upon isolated butyrylcholinesterase,[5] we were interested in determining the influence our structural modifications would exert in terms of lipophilic–lipophobic characteristics.

More specifically, we have prepared a series of 1-benzyl-3-(N,N-diethylcarbamoyl)piperidine hydrobromides with methyl, methoxy, chloro, and nitro substituents located in the *meta* and *para* positions (see Table I). We have determined the pK_a' values and apparent partition coefficients ($CHCl_3$–water) of these compounds and of the unsubstituted benzyl derivatives with the expectation that the values would *reflect* the *relative influence* each substituent has upon electron density at the heterocyclic nitrogen and upon lipophilic–lipophobic characteristics, respectively.

Experimental Section

Synthetic Work.—Most of the substituted-benzyl halides required as intermediates were commercially available (Aldrich Chemical Co.). *p*-Methoxybenzyl bromide, *m*-methoxybenzyl bromide, and *p*-chlorobenzyl bromide were prepared from the corresponding alcohols by the method of Beard and Hauser.[6] In the latter instances, the crude products were used in the subsequent reactions.

The compounds listed in Table I were prepared by the following methods.

Method A. 1-Benzyl-3-(N,N-diethylcarbamoyl)piperidine Hydrobromide (I).—The procedure described is patterned after that employed by Beasley, *et al.*,[7] for the preparation of 1-alkylcarbamoylpiperidine derivatives. To a cold solution of N,N-diethylnicotinamide (61.6 g, 0.346 mole) in 300 ml of anhydrous benzene, a solution of benzyl chloride (50.0 g, 0.395 mole) in 50 ml of the latter was added slowly with stirring. The reaction mixture was refluxed for 59 hr;[8] after removal of the solvent by filtration (or decantation), the product was dissolved in 50% aqueous ethanol and subjected to hydrogenation in the presence of 2 g of PtO_2 at a maximum pressure of 3.51 kg/cm^2. The catalyst was removed by filtration, and solvent was removed by distillation under reduced pressure. The residue was treated with 100 ml of cold 40% NaOH, and the mixture was extracted with benzene. The combined benzene extracts were dried ($MgSO_4$) and filtered, and the benzene was removed by distillation under reduced pressure. The product was dissolved in anhydrous ether and converted to the hydrobromide by the addition of a solution of dry HBr in anhydrous ether. The salt was then recrystallized from absolute ethanol–anhydrous ether.

Method B. 1-(*p*-Nitrobenzyl)-3-(N,N-diethylcarbamoyl)-piperidine Hydrobromide.—The procedure described is patterned after that used by Quintana, *et al.*,[4] for the preparation of other N,N-diethylnipecotamide derivatives. To a cold, stirred mixture of N,N-diethylnipecotamide[3] (41.8 g, 0.227 mole), anhydrous K_2CO_3 (41.5 g, 0.300 mole), and 150 ml of anhydrous benzene, *p*-nitrobenzyl bromide (49.0 g, 0.227 mole) was added slowly. The reaction mixture was gradually warmed and was subsequently refluxed for 16 hr with stirring. After cooling, the mixture was treated with a total of 500 ml of water; the benzene layer was separated and the aqueous layer was extracted with benzene. The benzene solution was dried ($MgSO_4$) and filtered, and the solvent was removed by distillation under reduced pressure. The oily residue was dissolved in absolute ethanol–anhydrous ether and was treated with a solution of dry HBr in anhydrous ether. The salt was recrystallized from absolute ethanol.

Determination of pK_a' Values.—A Radiometer TTTlc automatic titrator equipped with a SBUla syringe buret, a K401 calomel electrode, and a G202c glass electrode was employed. The reaction vessel was thermostated at 25.00 ± 0.05° by water from a Hetotherm Model 623K circulating bath; it was provided, also, with a rotor for mechanical stirring. The instrument was calibrated with standard buffer (pH 6.50 ± 0.02 at 25°) prior to use.

(1) Portion of W. R. Smithfield's thesis submitted to the Graduate School of the University of Tennessee in partial fulfillment of the requirements for the degree Master of Science (Medicinal Chemistry). This investigation was supported, in part, by Grants GB-2381 and GB-4453 from the National Science Foundation.

(2) (a) R. P. Quintana and W. A. Shrader, *J. Pharm. Sci.*, **52**, 1186 (1963); (b) R. P. Quintana, *ibid.*, **53**, 1221 (1964); (c) *ibid.*, **54**, 462 (1965); (d) *ibid.*, **54**, 573 (1965).

(3) R. P. Quintana, T. D. Smith, and L. F. Lorenzen, *ibid.*, **54**, 785 (1965).

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

(5) J. G. Beasley, S. T. Christian, W. R. Smithfield, and L. L. Williford, *ibid.*, **0**, 1003 (1967).

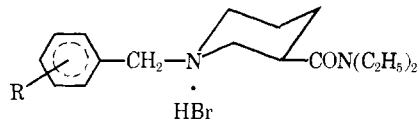
(6) W. Q. Beard, Jr., and C. R. Hauser, *J. Org. Chem.*, **25**, 334 (1960).

(7) J. G. Beasley, R. P. Quintana, and G. C. Nelms, *J. Med. Chem.*, **7**, 698 (1964).

(8) The reflux period employed for other compounds prepared by this method varied from 6 to 73 hr.

TABLE I

PROPERTIES OF SUBSTITUTED 1-BENZYL-3-(N,N-DIETHYLCARBAMOYL)PIPERIDINE HYDROBROMIDES

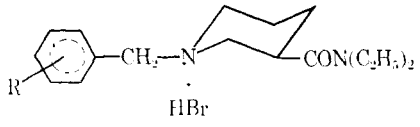


Compd	R	Method of prepn	Yield, %[a]	Recrystn solvent[b]	Mp, °C[c]	Formula[d]	C, % Calcd	C, % Found	H, % Calcd	H, % Found	Br, % Calcd	Br, % Found	Cl, % Calcd	Cl, % Found	N, % Calcd	N, % Found
I	H	A	32.6	E–EE	213.5–214.2 dec	$C_{17}H_{27}BrN_2O$	57.46	57.60	7.66	7.81	22.49	22.42	...	...	7.88	7.92
II	*p*-OCH_3	A	70.1	E–EE	196.6–197.6 dec	$C_{18}H_{29}BrN_2O_2$	56.10	56.12	7.59	7.57	20.74	20.81	...	...	7.27	7.07
III	*m*-OCH_3	A	36.2	E–EE	186.4–187.6 dec	$C_{18}H_{29}BrN_2O_2$	56.10	56.25	7.59	7.71	20.74	20.90	...	...	7.27	7.21
IV	*p*-CH_3	A	32.9	E–EE	194.3–194.9 dec	$C_{18}H_{29}BrN_2O$	58.53	58.66	7.91	8.01	21.64	21.52	...	...	7.58	7.63
V	*m*-CH_3	A	52.9	E–EE	159.6–160.2	$C_{18}H_{29}BrN_2O$	58.53	58.51	7.91	8.00	21.64	21.51	...	...	7.58	7.61
VI	*p*-Cl	A	38.8	E–EE	259.3–260.2 dec	$C_{17}H_{26}BrClN_2O$	52.38	52.52	6.72	6.51	20.50	20.61	9.10	9.25	7.19	6.90
VII	*m*-Cl	A	44.3	E–EE	222.9–223.6 dec	$C_{17}H_{26}BrClN_2O$	52.38	52.63	6.72	6.68	20.50	20.50	9.10	9.15	7.19	6.96
VIII	*p*-NO_2	B	60.6	E	218.1–219.3 dec	$C_{17}H_{26}BrN_3O_3$	51.00	51.05	6.55	6.53	19.96	19.95	...	...	10.50	10.51
IX	*m*-NO_2	B	82.4	E	224.3–225.5 dec	$C_{17}H_{26}BrN_3O_3$	51.00	51.13	6.55	6.38	19.96	20.15	...	...	10.50	10.72

[a] Yield was determined after one recrystallization. [b] E, ethanol; EE, ethyl ether. [c] Melting points were determined with a Büchi melting point apparatus; they are corrected. [d] Analyses were performed by Drs. G. Weiler and F. B. Strauss, Oxford, England.

TABLE II

pK_a' VALUES OF SUBSTITUTED 1-BENZYL-3-(N,N-DIETHYLCARBAMOYL)PIPERIDINE HYDROBROMIDES[a]



Compd	R	$pK_a' \pm$ SD[b]	$(K_a' \pm$ SD) $\times 10^5$	Hammett σ constant[c]
I	H	7.81 ± 0.01	1.55 ± 0.03	0
II	*p*-OCH_3	7.98 ± 0.03	1.04 ± 0.06	−0.268
III	*m*-OCH_3	7.71 ± 0.04	1.97 ± 0.15	0.115
IV	*p*-CH_3	7.91 ± 0.05	1.23 ± 0.13	−0.170
V	*m*-CH_3	7.86 ± 0.03	1.39 ± 0.08	−0.069
VI	*p*-Cl	7.55 ± 0.03	2.82 ± 0.18	0.227
VII	*m*-Cl	7.38 ± 0.04	4.18 ± 0.34	0.373
VIII	*p*-NO_2	6.90 ± 0.02	12.5 ± 0.4	0.778
IX	*m*-NO_2	6.90 ± 0.02	12.7 ± 0.5	0.710

[a] In aqueous solution at 25°. [b] Standard deviation. [c] Summarized from a paper by McDaniel and Brown.[11]

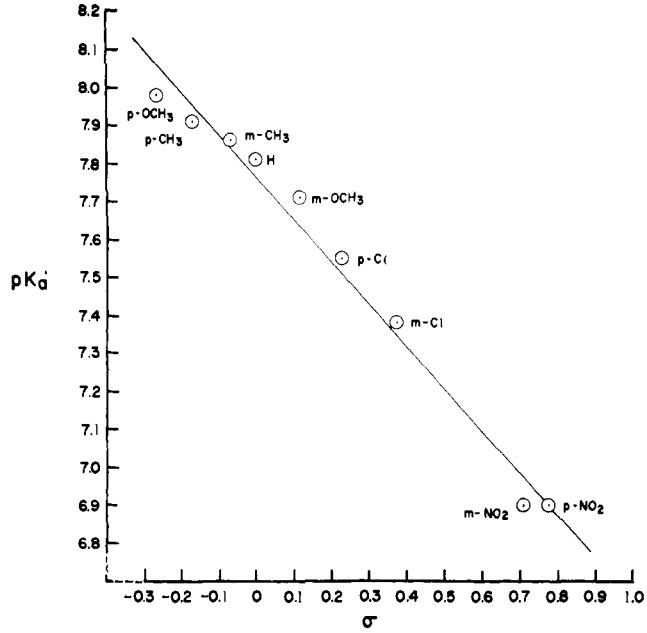


Figure 1.—pK_a' *vs.* Hammett σ constants for a series of *meta*- and *para*-substituted 1-benzyl-3-(N,N-diethylcarbamoyl)piperidine hydrobromides.

Analytically pure samples of the compounds, previously dried for 8 hr at 100° (0.1 mm), were used to prepare 1.50×10^{-3} *M* solutions in CO_2-free redistilled water. Ten-milliliter aliquots were transferred by pipet into the reaction vessel and titrated with 0.02 *N* NaOH, pH being read approximately 15 sec after the addition of each portion of titrant. Purified N_2, which had been passed, successively, through 0.02 *N* KOH, concentrated H_2SO_4, and distilled water, was allowed to flow continuously over the surface of the solution to minimize absorption of CO_2.

The pK_a' value was determined by reading the pH at half-neutralization (on the titration curve), after the equivalence point was determined from a plot of $\Delta pH/\Delta$ volume of titrant *vs.* volume of titrant.[9] Normally, the results of four independent determinations were used to calculate the average pK_a'.

Determination of Apparent Partition Coefficients.—The method of Quintana[2c] was employed except that the compounds were partitioned between $CHCl_3$ and H_2O which had been previously saturated with respect to each other. Four independent determinations were used to calculate an average value for the apparent partition coefficient.[10]

Results and Discussion

The pK_a' values for the member compounds of our series are given, along with the corresponding values for K_a', in Table II. We have also listed the pertinent Hammett σ constants recommended by McDaniel and Brown[11] for use in determining ρ values. The pK_a' values ranged from 6.90 to 7.98, and, as anticipated, those substituents with a positive σ value increased acidity while those with a negative σ value decreased acidity relative to compound I. A plot of pK_a' *vs.* σ is shown in Figure 1. The slope of the line, determined by the method of least squares, was found to be −1.109; ρ is therefore +1.109 (*cf.* Hine[12]). The positive value for ρ indicates that dissociation of our compounds is favored by withdrawal of electrons from the reaction site (*i.e.*, the heterocyclic nitrogen). Moreover, comparing the ρ value for our series with that for the dissociation of substituted anilinium ions (ρ value

(9) H. H. Willard, L. L. Merritt, Jr., and J. A. Dean, "Instrumental Methods of Analysis," 3rd ed, D. Van Nostrand Co., Inc., Princeton, N. J., 1958, p 419.

(10) While the degree of dissociation for the member compounds may not be the same, differences would be expected to be slight, and the apparent partition coefficients were not corrected for dissociation.

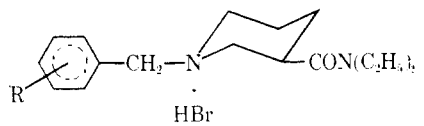
(11) D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958).

(12) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 85–95.

+2.767[13]), it is evident that the dissociation for our series is less sensitive to substituent influences than the dissociation for the anilinium series.[12] This is consistent with the observation[14] that the insertion of a methylene group between the aromatic ring and the reactive center results in a decrease in the ρ value. Based on data from several pairs of series, the average value for the ratio $\rho_{n=1}/\rho_{n=0}$ (where n is the number of methylene units between the ring and the reactive site) was found to be 0.410. If the ρ value for the dissociation of the substituted anilinium ions is assumed to be a reasonable approximation of that for a series of substituted 1-phenyl-3-(N,N-diethylcarbamoyl)piperidine hydrobromides, the ratio of ρ values (1.109/2.767) is equal to 0.401 which agrees well with the literature value.

TABLE III

APPARENT PARTITION COEFFICIENTS OF SUBSTITUTED 1-BENZYL-3-(N,N-DIETHYLCARBAMOYL)PIPERIDINE HYDROBROMIDES



Compd	R	App partition coefficient ($CHCl_3$–H_2O) ± SD[a]	π[b]
I	H	0.96 ± 0.02	0
II	*p*-OCH_3	1.99 ± 0.04	0.32
III	*m*-OCH_3	2.16 ± 0.12	0.35
IV	*p*-CH_3	3.22 ± 0.07	0.53
V	*m*-CH_3	5.56 ± 0.19	0.76
VI	*p*-Cl	2.52 ± 0.02	0.42
VII	*m*-Cl	2.12 ± 0.06	0.34
VIII	*p*-NO_2	0.99 ± 0.09	0.01
IX	*m*-NO_2	0.76 ± 0.02	−0.10

[a] Standard deviation. [b] $\pi = \log P_X - \log P_H$, where P_X is the partition coefficient of a derivative and P_H is that of the parent compound (I).[15]

Apparent partition coefficients ($CHCl_3$–water) for members of our series are summarized in Table III along with the corresponding calculated π values.[15] It should be noted that the π values for our derivatives decrease in the order $CH_3 > Cl > CH_3O > NO_2$ (for the *para* series) and $CH_3 > CH_3O$, $Cl > NO_2$ (for the *meta* series). These sequences tend to be consistent with Albert's classification of the pertinent substituents (*i.e.*, lipophilic, CH_3, Cl; slightly hydrophilic, CH_3O, NO_2)[16] considered along with the group moments[17] of these same substituents taken as an *approximate* measure of polarity.

Acknowledgments.—We wish to thank Dr. Andrew Lasslo for his interest in this work and for helpful discussions.

(13) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart, and Winston, Inc., New York, N. Y., 1959, p 222.

(14) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

(15) T. Fujita, J. Iwasa, and C. Hansch, *J. Am. Chem. Soc.*, **86**, 5175 (1964).

(16) A. Albert, "Selective Toxicity," 3rd ed, John Wiley and Sons, Inc., New York, N. Y., 1965, pp 348–349.

(17) The group moments are CH_3, 0.4; CH_3O, 1.25; Cl, 1.58; NO_2, 3.98; C. P. Smyth, "Dielectric Behavior and Structure," McGraw-Hill Book Co., Inc., New York, N. Y., 1955, p 253.

Acetylenic Carbamates. II. Reactions of 1,1-Diaryl-2-propynyl Carbamates with Acids and Bases

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It has recently been reported[1] that potent antitumor activity was found for a series of 1,1-diaryl-2-propynyl carbamates against a variety of experimental tumors in mice. Reactions of these compounds under acidic and basic conditions were investigated, and the products thus obtained were tested for antitumor activity to determine if any might be an active metabolite responsible for this activity. The reactions that the diaryl compounds undergo were compared with those reported for the 1,1-dialkyl-2-propynyl carbamates which were not effective as antitumor agents.

Treatment with Acids.—1,1-Diphenyl-2-propynyl carbamate (Ia) was used as a representative of the carbamate series. The carbamate Ia in aqueous ethanol, when treated with H_2SO_4 below 10°, gave the acetylenic ether IVa (Scheme I). It seems reasonable that the carbonium ion II is the intermediate in this reaction. Use of other primary and secondary alcohols as solvents gave the corresponding ethers. When tertiary alcohols were used, these products were not obtained. When Ia was heated at reflux temperature in the presence of H_2SO_4, the cinnamaldehyde VI was isolated. The formation of VI from I is related to the Meyer–Schuster rearrangement[2] with VI arising from the intermediate V. Supporting this type of rearrangement is the fact that the acetylenic ether (IV) under identical reaction conditions also gave VI.[3]

When Ia was treated with anhydrous HCl in an inert solvent, the 3,3-dichloro-1-propene (VIIIa) was isolated.[4] When anhydrous HBr was used, a product was obtained that was identical with 3,3-dibromo-1,1-diphenyl-1-propene prepared by Tani and Toda[5] from 1,1-diphenyl-2-propyn-1-ol and PBr_3. These dihalides, on treatment with water, gave the cinnamaldehyde VI.

The product IX[6] was isolated from the reaction mixture of Ia and concentrated HCl. This material could be formed from the dimerization of the proposed intermediate VII.

Cyclization involving addition of the carbonyl oxygen to the triple bond occurred to give XI[7] when 1,1-dialkyl-

(1) R. D. Dillard, G. Poore, D. R. Cassady, and N. R. Easton, *J. Med. Chem.*, **10**, 40 (1967).

(2) K. H. Meyer and K. Schuster, *Ber.*, **55**, 819 (1922); H. Rupe and E. Kambli, *Helv. Chim. Acta*, **9**, 672 (1926).

(3) (a) G. F. Hennion and B. R. Fleck, *J. Am. Chem. Soc.*, **77**, 3253 (1955). (b) Hennion and Fleck found that 1,1-diaryl-2-propyn-1-ols, when treated under similar reaction conditions, gave IV and VI.

(4) It was reported by N. R. Easton, D. R. Cassady, and R. D. Dillard, *J. Org. Chem.*, **27**, 2746 (1962), that treatment of 1,1-diphenyl-2-propyn-1-ol with dry HCl gave 1,3-dichloro-3,3-diphenyl-1-propene. This product was identical with the one obtained on treating Ia with HCl. The ultraviolet spectra of these materials suggest that the correct structure for both products should be VIII; λ_{max}^{MeCN} 259 mμ (ε 15,150). In 95% EtOH, the material decomposed.

(5) H. Tani and F. Toda, *Chem. Ind.* (London), 1083 (1963).

(6) (a) P. D. Landor and S. R. Landor, *J. Chem. Soc.*, 2707 (1963). (b) Landor and Landor obtained IX on treating 1,1-diphenyl-2-propyn-1-ol with thionyl chloride in pyridine.

(7) D. R. Cassady and N. R. Easton, *J. Org. Chem.*, **29**, 2032 (1964).