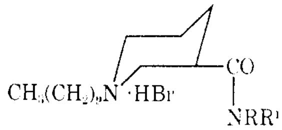
TABLE I

HANSCH ANALYSIS OF BUTYRYLCHOLINESTERASE INHIBITORY POTENCY USING pI_{50} AS THE BIOCHEMICAL RESPONSE



R = H H H CH_3 C_2H_5 C_3H_7
R' = H CH_3 C_2H_5 CH_3 C_2H_5 C_3H_7

Equation[a,b]	Square of correlation coefficient, r^2	F ratio[c]	
$pI_{50} = -0.058\pi^2 + 0.923\pi - 0.456\mu + 5.589\ (\pi_0 = 7.96)$	0.998	926.50	(11)
$pI_{50} = -0.060\pi^2 + 0.933\pi - 0.396m + 5.683\ (\pi_0 = 7.78)$	0.998	1194.50	(12)
$pI_{50} = -0.119\pi^2 + 1.205\pi + 0.687\sigma^* + 3.533\ (\pi_0 = 5.06)$	0.998	8084.10	(13)
$pI_{50} = 0.699\pi - 0.268\mu + 5.061$	0.994	274.30	(14)
$pI_{50} = 0.397\pi - 0.394\sigma^* + 4.566$	0.974	57.11	(15)
$pI_{50} = 0.132\pi^2 + 0.338\mu + 3.302$	0.943	24.71	(16)
$pI_{50} = 0.667\pi - 0.227m + 5.094$	0.994	269.08	(17)
$pI_{50} = 0.011\pi^2 + 0.535\pi + 4.203$	0.984	102.99	(18)
$pI_{50} = 0.570\pi + 4.187$	0.985	268.43	(19)

[a] See ref 5, 8–10, and 12. [b] pI_{50} is the negative logarithm of the molarity of compound effecting 50% inhibition. [c] Level of significance of the F ratio exceeds 99% for each equation.[14]

theories, the parent moiety quantitatively contributes the major portion of the inhibitory activity. The substituent groups either enhance or decrease this activity of the parent moiety depending upon the relationship between the group properties and the requirements for activity.

TABLE II

PARENT AND SUBSTITUENT ACTIVITY CONTRIBUTIONS GENERATED BY THE FREE–WILSON REGRESSION ANALYSIS

Group[a]	Act. contribution, pI_{50}[b]
H	−0.82
Me	−0.61
Et	−0.29
Pr	0.05
Parent moiety	5.89

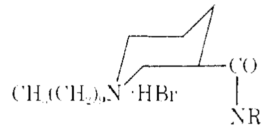
[a] The groups, substituted at positions R and R', and the parent moiety refer to the homologs in Table I. [b] pI_{50} is the negative logarithm of the molarity of compound effecting 50% inhibition.

One congener, 1-decyl-3-(N-ethyl-N-methylcarbamoyl)piperidine hydrobromide, was not included in either regression and, therefore, its calculated pI_{50} value can be treated as "predicted." Both predicted values, 5.00 by the Hansch method and 4.99 by the Free–Wilson analysis, are within the experimental error of the observed pI_{50}, 5.01 ± 0.03 (Table III).

Table III gives the observed and calculated pI_{50} values for both types of analyses and, therefore, provides data for comparing the two methods. Both correlations are very good. The calculated pI_{50} values from the Hansch analysis (eq 13, Table I) are all

TABLE III

OBSERVED AND CALCULATED BUTYRYLCHOLINESTERASE INHIBITORY POTENCIES OF SOME 1-DECYL-3-CARBAMOYLPIPERIDINE HYDROBROMIDES



		pI_{50}[a]		
			Calcd	
R	R'	Obsd	Free–Wilson[e]	Hansch[f]
H	H	4.21 ± 0.02[b]	4.25	4.21
H	Me	4.46 ± 0.03[b]	4.46	4.46
H	Et	4.86 ± 0.01[b]	4.78	4.86
Me	Me	4.66 ± 0.04[b]	4.66	4.66
Me	Et	5.01 ± 0.03[c]	4.99	5.00
Et	Et	5.28 ± 0.02[b]	5.32	5.29
Pr	Pr	5.98 ± 0.03[d]	5.98	5.98

[a] pI_{50} is the negative logarithm of the molarity of compound effecting 50% inhibition. [b] Taken from ref 5. [c] Taken from ref 6. This is the compound for which the inhibitory potency was predicted accurately 3 years before it was synthesized. The observed value, 5.01, was not included in either the Free–Wilson or Hansch regression analysis. [d] J. G. Beasley, unpublished results. [e] Calculated by summation of the substituent and parent activity contributions obtained from Table II. [f] Equation 13, Table I, was used.

within the experimental error of the observed values. The calculated pI_{50} values from the Free–Wilson analysis, however, are within the experimental error of the observed values for only three of the six compounds, and one of these compounds, the dipropyl derivative, is forced to fit since it represents a single observation. One must conclude that both models fit these data quite well although the Hansch method gives somewhat better quantitative results for this series.

Since the hydrophobic parameter, π, seems to be the most significant term in the Hansch analysis, the maximum or ideal π value, π_0, was calculated.[15] For the equation used in the Hansch analysis (eq 13, Table I), π_0 is 5.06. One might conclude, therefore, that the N,N-dipentyl derivative or other derivatives with combinations of substituents with similar π values would be worthy of synthesis and evaluation. For eq 11 and 12, π_0's are 7.96 and 7.76, respectively. Values of π between 5 and 8 would be expected to be optimum.

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3-Azaspiro[5.5]undecanes

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A broad program for the investigation of the chemical and pharmacological properties of heterocyclic compounds containing spiro carbon linkages at the ring

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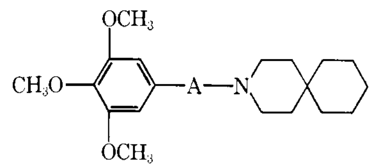
junction was conducted by Rice and coworkers.[2] Several of the p-fluoroaroylalkylazaspirane derivatives were found to possess CNS depressant, hypotensive, and antiinflammatory activity and were also found to be clinically effective tranquilizers at doses of 5–10 mg.[2f] N-[γ-(p-Fluorobenzoyl)propyl]-3-azaspiro[5.5]undecane possessed marked antipsychotic effect at low dosage, and its behavioral and toxicity effects were similar to those of haloperidol.[2f,3,4] In continuation of our previous work,[5] it was decided to synthesize a similar type of compounds having 3-azaspiro[5.5]undecane as a basic fragment. Accordingly, the compounds of the general formula I were synthesized and studied for their CNS activity.



I, A = CO, $COCH_2$, $COCH_2CH_2$, $COCH_2CH_2CH_2$

Chemistry.—N-(3,4,5-Trimethoxybenzoyl)-3-azaspiro[5.5]undecane (I, A = CO), N-(3,4,5-trimethoxyphenacyl)-3-azaspiro[5.5]undecane (I, A = $COCH_2$), and N-[γ-(3,4,5-trimethoxybenzoyl)propyl]-3-azaspiro[5.5]undecane (I, A = $COCH_2CH_2CH_2$) were synthesized by the condensation of 3-azaspiro[5.5]undecane with 3,4,5-trimethoxybenzoyl chloride, α-bromo-3,4,5-trimethoxyacetophenone, and γ-chloro-3,4,5-trimethoxybutyrophenone, respectively. N-[β-(3,4,5-Trimethoxybenzoyl)ethyl]-3-azaspiro[5.5]undecane (I, A = $COCH_2CH_2$) resulted from the Mannich reaction on 3,4,5-trimethoxyacetophenone and 3-azaspiro[5.5]undecane hydrochloride.

All these compounds were tested for CNS activity in mice. The study of gross behavior and spontaneous motor activity revealed that none of the compounds in this series possessed any significant CNS depressant activity.

Experimental Section[6]

Intermediates.—The requisite cyclohexane-1,1-diacetic acid,[7] cyclohexane-1,1-diacetic anhydride,[8] 3-azaspiro[5.5]undecane-2,4-dione,[2f] 3-azaspiro[5.5]undecane,[2f] 3,4,5-trimethoxybenzoyl chloride,[9] 3,4,5-trimethoxyacetophenone,[10] and α-bromo-3,4,5-trimethoxyacetophenone[11] were prepared by the literature methods. γ-Chloro-3,4,5-trimethoxybutyrophenone was obtained as described earlier.[5]

N-(3,4,5-Trimethoxybenzoyl)-3-azaspiro[5.5]undecane (1).—To a solution of 3.06 g (0.02 mole) of 3-azaspiro[5.5]undecane and 4.0 g (0.04 mole) of Et_3N in 25 ml of anhydrous $CHCl_3$, was added slowly a solution of 4.6 g (0.02 mole) of 3,4,5-trimethoxybenzoyl chloride in 25 ml of anhydrous $CHCl_3$. The reaction mixture was refluxed for 4 hr and then cooled, washed (H_2O), dried (Na_2SO_4), and concentrated. Traces of $CHCl_3$ and Et_3N were removed *in vacuo*. The residue solidified when treated with hexane. The solid was then crystallized first from boiling hexane and then from EtOH, mp 122–123°. *Anal.* ($C_{20}H_{29}NO_4$) C, H, N.

N-(3,4,5-Trimethoxyphenacyl)-3-azaspiro[5.5]undecane Hydrochloride (2).—A solution of 3.18 g (0.011 mole) of α-bromo-3,4,5-trimethoxyacetophenone in 30 ml of EtOH was added slowly to a solution of 1.53 g (0.01 mole) of 3-azaspiro[5.5]-undecane and 2.0 g (0.02 mole) of Et_3N in 30 ml of EtOH. The mixture was refluxed for 6 hr and then concentrated. H_2O was added and the residue was extracted with $CHCl_3$. The extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The resulting oil was taken up in anhydrous Et_2O and added to 5 ml of 2-propanolic HCl (22%). This on dilution with ether gave a white solid which was filtered and recrystallized (EtOH), mp 256–258° dec. *Anal.* ($C_{21}H_{31}NO_4 \cdot HCl$) C, H, N.

N-[β-(3,4,5-Trimethoxybenzoyl)ethyl]-3-azaspiro[5.5]undecane Hydrochloride (3).—To a solution of 3.8 g (0.02 mole) of 3-azaspiro[5.5]undecane hydrochloride in 60 ml of EtOH, were added 3 ml (~0.03 mole) of aqueous HCHO (37–41%) and a solution of 4.62 g (0.022 mole) of 3,4,5-trimethoxyacetophenone in 30 ml of EtOH. The reaction mixture was refluxed for 7 hr. Additional aqueous CH_2O (3 ml) was added and reflux continued further for 7 hr. It was then concentrated to one-fourth of its volume and allowed to cool, when a white solid separated out which was filtered and crystallized from EtOAc-*i*-PrOH and then from *i*-PrOH, mp 210–212° dec. *Anal.* ($C_{22}H_{33}NO_4 \cdot HCl$) C, H, N.

N-[γ-(3,4,5-Trimethoxybenzoyl)propyl]-3-azaspiro[5.5]undecane Hydrochloride (4).—A mixture of 2.73 g (0.01 mole) of γ-chloro-3,4,5-trimethoxybutyrophenone and 3.06 g (0.02 mole) of 3-azaspiro[5.5]undecane was gently warmed so as to form a homogeneous mixture and left overnight at room temperature. The next day, it was heated at 100° for 4 hr. After cooling, water was added to it and extracted twice with 40 ml of $CHCl_3$. The extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residual oil was taken up in anhydrous Et_2O and added to 5 ml of isopropanolic HCl (22%). The resultant white solid was filtered and recrystallized (EtOH), mp 172–174° dec. *Anal.* ($C_{23}H_{35}NO_4 \cdot HCl$) N.

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Studies of Catecholamines. I. Sulfur Analogs of Norepinephrine

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In pursuit of our current interests in catecholamines we have prepared 2-amino-1-(3,4-dihydroxyphenyl)-ethanethiol (throughout the following referred to as