Table VII—Comparison of Automated and Least-Squares Parameter Estimates for Spectinomycin Concentration and Time Data[a]

Parameter	Value of Parameter Estimate	
	CSTRIP	Nonlinear Least Squares
A_1	71.1	70.5
B_1	0.424	0.422
A_2	-52.6	-54.7
B_2	1.36	1.46
A_3	-18.5	-15.8
B_3	4.56	4.61
Sum of squared deviations[b]	9.17	9.11

[a] Data fitted to a triexponential equation of the form $C = A_1e^{-B_1t} + A_2e^{-B_2t} + A_3e^{-B_3t}$. [b] Sum of squared deviations between observed and model-predicted concentrations.

least-squares parameter estimates with CSTRIP estimates is made in Table VII. There was excellent agreement between the CSTRIP and nonlinear least-squares parameter values.

CSTRIP generally gives results comparable to or better than those obtained by laborious graphical or other manual techniques.

CSTRIP not only provides accurate exponential parameter estimates but also is economical, and the input of data does not require excessive time. The total cost for the CSTRIP analyses of the two examples given was $0.51.

SUMMARY

The CSTRIP program provides for fully automated exponential stripping of pharmacokinetic data. This program enables the rapid, accurate, and economical computer analysis of data described by the sums of exponentials and gives results comparable to, or better than, those obtained by laborious manual techniques. Use of the CSTRIP program should greatly reduce the amount of time consumed in obtaining preliminary estimates of exponential parameters by graphical and/or electronic calculator methods and should result in least-squares parameter estimates having less variability and greater accuracy.

The program should prove suitable as an exponential stripping routine in other programs designed for fully automated data analysis.

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‡ To whom inquiries should be directed. (The computer program is not available on tape or cards. A complete microfilm source listing will be supplied upon request. No troubleshooting assistance will be provided.)

Anticonvulsant Activity and Inhibition of Cellular Respiratory Activity by Substituted Imidazolocarbamides

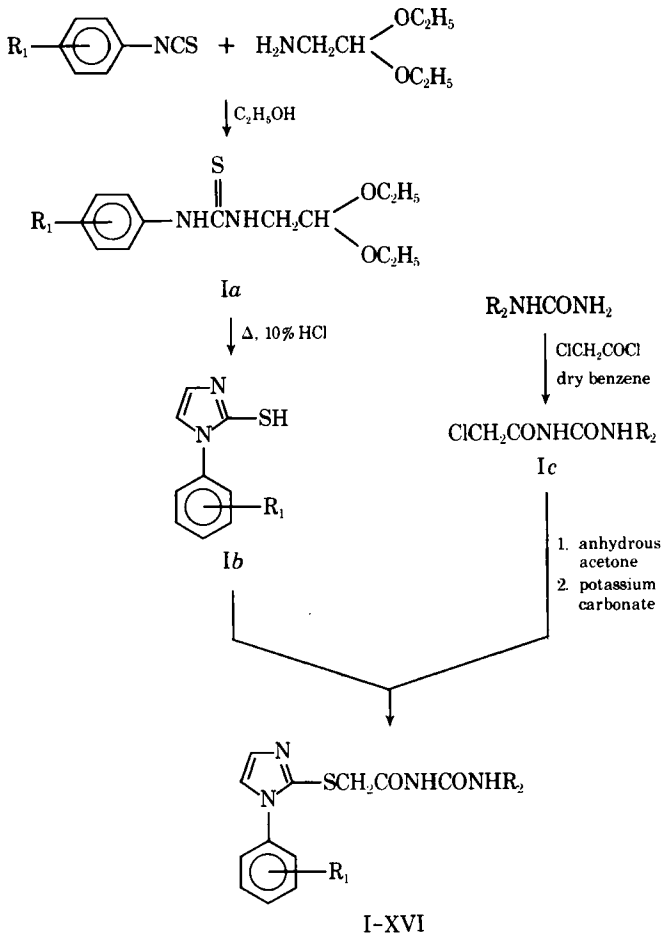
SUNIL K. CHAUDHARY *, SURENDRA S. PARMAR *‡x, MAHIMA CHAUDHARY *, and JAYANTI P. BARTHWAL *

Abstract □ Several 1-(1-aryl-2-mercaptoacetylimidazole)-3-alkylcarbamides were synthesized and characterized by their sharp melting points, elemental analyses, and IR spectra. These substituted imidazolocarbamides possessed anticonvulsant activity, which was reflected by the 20–80% protection observed with these compounds against pentylenetetrazol-induced convulsions in mice. These substituted imidazolocarbamides selectively inhibited the *in vitro* oxidation of nicotinamide adenine dinucleotide (NAD)-dependent oxidations of pyruvate, α-ketoglutarate, β-hydroxybutyrate, and NADH by rat brain homogenates. However, NAD-independent oxidation of succinate was not affected. The anticonvulsant activity possessed by 1-(1-aryl-2-mercaptoacetylimidazole)-3-alkylcarbamides had no relationship to their ability to inhibit cellular respiratory activity.

Keyphrases □ Imidazolocarbamides, substituted—synthesized, screened for anticonvulsant activity, effect on cellular respiratory activity □ Anticonvulsant activity—screened in series of substituted imidazolocarbamides, mice □ Cellular respiration—effect of series of substituted imidazolocarbamides on NAD-dependent and NAD-independent oxidations, rat brain homogenates □ Oxidations, NAD dependent and independent—effect of series of substituted imidazolocarbamides, rat brain homogenates □ Structure–activity relationships—series of imidazolocarbamides, anticonvulsant activity, cellular respiratory activity

Potentiation of pentobarbital-induced hypnosis and protection against pentylenetetrazol-induced convulsions indicated the central nervous system (CNS) depressant property of substituted carbamides (1–4). Certain derivatives of imidazoles also have been reported to possess anticonvulsant activity (5, 6). Earlier studies indicated significant degrees of muscle relaxant and anticonvulsant activities of 1-carbamoylpyrrolidines and 1-carbamoylpiperidines (7). Various aryloxyalkylcarbamides also have been shown to possess the CNS activity (8).

These observations led to the synthesis of 1-(1-aryl-



Scheme I

2-mercaptoacetylimidazole)-3-alkylcarbamides. In the present study, the anticonvulsant activity of these substituted imidazolocarbamides was determined against pentylenetetrazol-induced convulsions. The *in vitro* effects of these carbamides on the cellular respiratory activity of rat brain homogenates were investigated to study the biochemical mechanism of action for their anticonvulsant activity. The various substituted imidazolocarbamides were synthesized by following the methods outlined in Scheme I.

EXPERIMENTAL[1]

Aryldiethoxyethylthioureas (Ia)—An appropriate isothiocyanate (0.1 mole) was slowly added to the stirred solution of aminoacetaldehydehyde diethyl acetal (0.1 mole) in 100 ml of absolute ethanol at room temperature (9, 10). After the addition was complete, the mixture was refluxed on a steam bath for 30 min. Excess ethanol was removed by distillation and the crude thioureas, obtained as colorless oils, were used for the synthesis of 1-aryl-2-mercaptoimidazoles (*Ib*) without further purification.

1-Aryl-2-mercaptoimidazoles (Ib)—Crude *Ia* was stirred with 200 ml of 10% HCl, and the mixture was refluxed over a free flame for 30 min. Crystalline *Ib*, which separated on cooling, was collected by filtration, washed with water, and recrystallized from appropriate solvents. The melting points of these substituted mercaptoimidazoles corresponded with those reported in the literature (9, 10).

1-Chloroacetyl-3-alkylcarbamides (Ic)—A mixture of an appropriate alkylcarbamide (0.1 mole) and chloroacetyl chloride (0.11 mole) in 30 ml of dry benzene was refluxed on a steam bath for 4 hr. Excess benzene was removed by distillation; the crude products, which separated on cooling, were collected by filtration, washed with water, dried, and recrystallized from the appropriate solvents (11).

1-(1-Aryl-2-mercaptoacetylimidazole)-3-alkylcarbamides (I–XVI)—A mixture of *Ib* (0.01 mole), *Ic* (0.01 mole), and anhydrous potassium carbonate (0.015 mole) was added to 50 ml of anhydrous acetone and refluxed under anhydrous conditions on a steam bath for 6 hr. The reaction mixture was poured over cold water, and the separated crude products were collected by filtration, washed several times with water, dried, and recrystallized from ethanol.

The various 1-(1-aryl-2-mercaptoacetylimidazole)-3-alkylcarbamides (Table I) were characterized by their sharp melting points and elemental analyses. The presence of the characteristic bands of C=O attached to nitrogen (1710 cm^{-1}), C=N (1620 cm^{-1}), and NH (3300 cm^{-1}) in their IR spectra provided further confirmation of their molecular structure.

Determination of Anticonvulsant Activity—Anticonvulsant activity was determined in albino mice of either sex weighing 25–30 g. The mice were divided into groups of 10, keeping the group weights as near the same as possible. Each 1-(1-aryl-2-mercaptoacetylimidazole)-3-alkylcarbamide was suspended in 5% aqueous gum acacia to give a concentration of 1% (w/v). The test compounds were injected in a group of 10 mice at a dose of 100 mg/kg ip.

Four hours after the administration of the test compounds, the mice were injected with pentylenetetrazol (90 mg/kg sc). This dose of pentylenetetrazol has been shown to produce convulsions in almost all untreated mice and causes 100% mortality during 24 hr (1). However, no mortality was observed during 24 hr in animals treated with 100 mg/kg ip of the test compounds alone.

The mice were observed for 60 min for seizures. An episode of clonic spasm that persisted for at least 5 sec was considered a threshold convulsion. Transient intermittent jerks and tremulousness were not counted. Animals devoid of the threshold convulsions during 60 min were considered protected. The number of animals protected in each group was recorded, and the anticonvulsant activity of these 1-(1-aryl-2-mercaptoimidazole)-3-alkylcarbamides was represented as percent protection. In the present study, no anticonvulsant activity was observed in animals treated with 5% aqueous gum acacia solution alone. The animals were then observed for 24 hr, and their mortality was recorded.

Assay of Respiratory Activity of Rat Brain Homogenates[2]—Albino rats, 100–150 g, were kept on an *ad libitum* diet and were used in all experiments. Rat brains isolated from decapitated animals were immediately homogenized in ice-cold 0.25 *M* sucrose in a homogenizer[3] in a ratio of 1:9 (w/v). All incubations were carried out at 37°, and the oxygen uptake was measured by the conventional Warburg manometric technique, using air as the gas phase (12).

Fresh brain homogenates, equivalent to 100 mg wet weight, were added to chilled Warburg vessels containing 6.7 mmoles of magnesium sulfate, 20 mmoles of sodium hydrogen phosphate buffer solution (pH 7.4), 1 mmole of adenosine monophosphate (sodium salt), 33 mmoles of potassium chloride, and 500 μg of cytochrome c in a final volume of 3 ml, unless otherwise stated. The central well contained 0.2 ml of 20% KOH solution. Pyruvate, citrate, α-ketoglutarate, β-hydroxybutyrate, and succinate were used at a final concentration of 10 m*M*, while the concentration of NADH was 0.5 m*M*. It was presumed that the endogenous NAD, present in the homogenates, was sufficient for these oxidative processess.

All 1-(1-aryl-2-mercaptoacetylimidazole)-3-alkylcarbamides were dissolved in propylene glycol (100%) and were incubated with rat brain homogenates at 37° for 10 min prior to the addition of the various substrates. An equal volume of the solvent was added to the control vessels. The oxygen uptake was measured every 10 min for 60 min.

Determination of Approximate LD_{50}—The toxicity of the 1-(1-aryl-2-mercaptoacetylimidazole)-3-alkylcarbamides was evaluated by determination of the approximate 50% lethal dose (approximate LD_{50}) by following the method of Smith (13). All substituted imidazolocarbamides were suspended in aqueous gum acacia and were administered intraperitoneally to each group of 10 mice.

[1] All compounds were analyzed for their carbon, hydrogen, and nitrogen content. Melting points were taken in open capillary tubes with a partial immersion thermometer and are corrected. IR spectra were taken with a Perkin-Elmer Infracord spectrophotometer model 137 equipped with sodium chloride optics.

[2] Commercial chemicals were used in this study. Sodium pyruvate, trisodium citrate, monosodium α-ketoglutarate, sodium β-hydroxybutyrate, NADH, sodium succinate, adenosine monophosphate (sodium salt), and cytochrome c were obtained from Sigma Chemical Co., St. Louis, Mo.

[3] Potter–Elvehjem homogenizer.

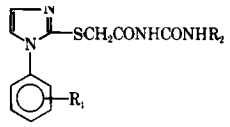


Table I—Physical Constants of 1-(1-Aryl-2-mercaptoacetylimidazole)-3-alkylcarbamides

Compound	R_1	R_2	Melting Point[a]	Yield, %	Molecular Formula		Analysis, % Calc.	Found
I	H	CH_3	164°	60	$C_{13}H_{14}N_4O_2S$	C	53.79	53.40
						H	4.82	4.65
						N	19.31	19.00
II	2-CH_3	CH_3	122°	55	$C_{14}H_{16}N_4O_2S$	C	55.26	55.00
						H	5.26	5.31
						N	18.42	18.40
III	4-CH_3	CH_3	120°	45	$C_{14}H_{16}N_4O_2S$	C	55.26	54.96
						H	5.26	5.37
						N	18.42	18.65
IV	2,4-$(CH_3)_2$	CH_3	170°	60	$C_{15}H_{18}N_4O_2S$	C	56.60	56.40
						H	5.66	5.26
						N	17.61	17.80
V	2,6-$(CH_3)_2$	CH_3	132°	68	$C_{15}H_{18}N_4O_2S$	C	56.60	56.20
						H	5.66	5.65
						N	17.61	17.40
VI	2-OCH_3	CH_3	160°	70	$C_{14}H_{16}N_4O_3S$	C	52.50	52.30
						H	5.00	4.82
						N	17.50	17.48
VII	4-OCH_3	CH_3	174°	56	$C_{14}H_{16}N_4O_3S$	C	52.50	52.46
						H	5.00	4.86
						N	17.50	17.48
VIII	4-Cl	CH_3	158°	62	$C_{13}H_{13}ClN_4O_2S$	C	48.07	48.35
						H	4.00	3.90
						N	17.25	17.56
IX	H	C_2H_5	118°	64	$C_{14}H_{16}N_4O_2S$	C	55.26	55.20
						H	5.26	5.65
						N	18.42	18.90
X	2-CH_3	C_2H_5	120°	48	$C_{15}H_{18}N_4O_2S$	C	56.60	56.20
						H	5.66	5.34
						N	17.61	17.40
XI	4-CH_3	C_2H_5	110°	40	$C_{15}H_{18}N_4O_2S$	C	56.60	56.56
						H	5.66	5.82
						N	17.61	17.30
XII	2,4-$(CH_3)_2$	C_2H_5	142°	38	$C_{16}H_{20}N_4O_2S$	C	57.83	57.46
						H	6.02	5.90
						N	16.86	16.39
XIII	2,6-$(CH_3)_2$	C_2H_5	130°	65	$C_{16}H_{20}N_4O_2S$	C	57.83	57.90
						H	6.02	6.25
						N	16.86	16.92
XIV	2-OCH_3	C_2H_5	152°	52	$C_{15}H_{18}N_4O_3S$	C	53.89	53.92
						H	5.38	5.60
						N	16.76	16.42
XV	4-OCH_3	C_2H_5	134°	50	$C_{15}H_{18}N_4O_3S$	C	53.89	53.40
						H	5.38	5.36
						N	16.76	16.90
XVI	4-Cl	C_2H_5	128°	56	$C_{14}H_{15}ClN_4O_2S$	C	49.63	49.50
						H	4.43	4.48
						N	16.54	16.76

[a] All compounds were recrystallized from ethanol. The melting points were taken in open capillary tubes with a partial immersion thermometer and are corrected.

RESULTS AND DISCUSSION

Results presented in Table II represent anticonvulsant activity possessed by 1-(1-aryl-2-mercaptoacetylimidazole)-3-alkylcarbamides against pentylenetetrazol-induced convulsions in mice. Anticonvulsant activity of these compounds ranged from 20 to 80%; 1-[1-(4-methylphenyl)-2-mercaptoacetylimidazole]-3-ethylcarbamide (XI) exhibited maximum protection in a dose of 100 mg/kg. The low toxicity of these substituted imidazolocarbamides was reflected by their low LD_{50} values, which ranged from 600 to >1000 mg/kg; most of these compounds exhibited values ≥1000 mg/kg.

Data on anticonvulsant activity of these substituted imidazolocarbamides and 24-hr pentylenetetrazol-induced mortality failed to indicate an association between increased protection from convulsions and decreased pentylenetetrazol mortality in experimental animals. None of these substituted imidazolocarbamides possessed any appreciable sedative or CNS depressant effect or 24-hr mortality in the dose of 100 mg/kg used in the present investigation.

The nature of the alkyl group attached to the carbamide moiety had some influence on the anticonvulsant activity of these compounds. Replacement of the methyl substituent with an ethyl substituent decreased the anticonvulsant activity of five compounds (X, XII, and XIV–XVI), increased the activity of two compounds (XI and XIII), and caused no change in the activity of one compound (IX). Attachment of a substituent at the phenyl nucleus attached to position 1 of the imidazole nucleus failed to provide any definite structure–activity relationship of these compounds with respect to their anticonvulsant activity.

All 1-(1-aryl-2-mercaptoacetylimidazole)-3-alkylcarbamides, in general, selectively inhibited NAD-dependent oxidation of pyruvate, citrate, α-ketoglutarate, β-hydroxybutyrate, and NADH by rat brain homogenates (Table III). NAD-independent oxidation of succinate remained unaltered. At present, it is difficult to explain the inability of I–III to inhibit the oxidation of citrate and of IX, X, and XIV–XVI to inhibit the oxidation of α-ketoglutarate. Higher concentrations of these compounds possibly may cause inhibition of the cellular respiratory activity during oxidation of citrate and α-ketoglutarate.

The inhibitory effects of these substituted imidazolocarbamides were not consistent with the nature of the substituent on the phenyl nucleus attached to position 1 of the imidazole moiety or the alkyl

Table II—Anticonvulsant Activity of 1-(1-Aryl-2-mercaptoacetylimidazole)-3-alkylcarbamides

Compound	Approximate LD_{50}, mg/kg	Anticonvulsant Activity[a], % Protection	Pentylenetetrazol Mortality[b], %	Compound	Approximate LD_{50}, mg/kg	Anticonvulsant Activity[a], % Protection	Pentylenetetrazol Mortality[b], %
I	600	50	30	IX	1000	50	Nil
II	1000	60	10	X	>1000	50	Nil
III	>1000	50	Nil	XI	>1000	80	Nil
IV	750	60	90	XII	>1000	30	50
V	750	30	30	XIII	1000	50	10
VI	>1000	50	50	XIV	>1000	30	50
VII	>1000	30	30	XV	>1000	20	70
VIII	750	60	80	XVI	1000	30	10

[a] Screening procedures for the determination of anticonvulsant activity are as described in the text. Substituted imidazolocarbamides were administered at a dose of 100 mg/kg ip 4 hr before the administration of pentylenetetrazol (90 mg/kg sc). [b] Represents mortality during 24 hr in each group of animals administered pentylenetetrazol.

Table III—Inhibition of Respiratory Activity of Rat Brain Homogenates by 1-(1-Aryl-2-mercaptoacetylimidazole)-3-alkylcarbamides

Compound	Inhibition of Substrate Oxidation[a], %					
	Pyruvate	Citrate	α-Ketoglutarate	β-Hydroxybutyrate	NADH	Succinate
I	29.2 ± 1.2	Nil	25.2 ± 1.0	21.7 ± 1.2	16.3 ± 1.5	Nil
II	38.7 ± 1.4	Nil	39.0 ± 1.2	19.2 ± 1.4	44.5 ± 1.4	Nil
III	72.8 ± 0.9	Nil	13.5 ± 1.3	56.8 ± 1.6	47.5 ± 1.0	Nil
IV	47.5 ± 1.5	15.6 ± 1.2	49.7 ± 0.6	28.7 ± 1.5	40.3 ± 1.2	Nil
V	54.0 ± 1.3	20.8 ± 1.4	26.2 ± 1.8	43.1 ± 1.8	31.9 ± 1.4	Nil
VI	20.5 ± 1.2	23.4 ± 0.8	18.7 ± 0.9	48.1 ± 1.2	22.2 ± 1.4	Nil
VII	20.9 ± 1.1	10.0 ± 1.0	16.5 ± 1.2	30.2 ± 1.5	14.7 ± 1.4	Nil
VIII	37.1 ± 1.0	10.0 ± 1.1	12.3 ± 1.3	36.5 ± 1.4	30.3 ± 1.3	Nil
IX	24.1 ± 0.8	29.7 ± 0.9	Nil	45.4 ± 1.3	38.3 ± 1.0	Nil
X	37.6 ± 0.6	52.9 ± 0.6	Nil	33.5 ± 1.0	49.5 ± 1.1	Nil
XI	57.6 ± 1.2	35.4 ± 1.2	47.8 ± 1.6	52.2 ± 1.1	57.6 ± 0.9	Nil
XII	38.4 ± 1.4	30.5 ± 1.4	20.5 ± 1.4	36.5 ± 1.5	29.1 ± 1.2	Nil
XIII	72.7 ± 1.8	74.8 ± 1.2	72.6 ± 1.0	56.7 ± 1.4	28.1 ± 1.2	Nil
XIV	20.0 ± 1.6	43.4 ± 1.3	Nil	40.2 ± 1.4	20.3 ± 1.5	Nil
XV	48.8 ± 1.2	39.2 ± 1.6	Nil	42.5 ± 1.3	46.3 ± 1.4	Nil
XVI	36.6 ± 1.4	61.9 ± 1.0	Nil	50.6 ± 1.2	30.4 ± 1.3	Nil

[a] Assay procedures and the contents of the reaction mixture are as indicated in the text. Each experiment was done in duplicate. All values represent mean values of percent inhibition with ±*SEM* calculated from three separate experiments. Inhibition was determined by the decrease in the oxygen uptake/100 mg wet brain weight/hr. All substituted imidazolocarbamides were used at a final concentration of 2 m*M*. Different substrates and NADH were used at a final concentration of 10 and 0.5 m*M*, respectively. The oxygen uptake (microliters) in control experiments during oxidation of pyruvate, citrate, α-ketoglutarate, β-hydroxybutyrate, NADH, and succinate was 86.2 ± 2.2, 77.6 ± 1.4, 66.1 ± 2.5, 61.5 ± 2.4, 78.4 ± 2.6, and 205.4 ± 2.8, respectively.

group attached to the carbamide moiety during oxidation of the various substrates. The selective inhibition of NAD-dependent oxidations by these imidazolocarbamides was thus unrelated to their structure, so a definite structure–activity relationship was not exhibited (Table III). The ability of these compounds to inhibit NAD-dependent oxidations provides evidence regarding the possible inactivation of the electron transfer process in the electron transport chain by acting presumably at a site of transfer of electrons from NADH to flavine adenine dinucleotide.

These results failed to provide any correlation between *in vitro* selective inhibition of NAD-dependent oxidations by these substituted imidazolocarbamides and their anticonvulsant activity. Detailed pharmacological and biochemical studies using other purified enzyme preparations possibly may reflect the cellular basis for the anticonvulsant activity of these 1-(1-aryl-2-mercaptoacetylimidazole)-3-alkylcarbamides.

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Quantum Chemical Studies on Drug Action V: Involvement of Structure–Activity, Quantum Chemical, and Hydrophobicity Factors in Thrombocyte Uptake of 5-Hydroxytryptamine

MAHADEVAPPA KUMBAR [x], VINCENT CUSIMANO, and D. V. SIVA SANKAR

Abstract □ Inhibition of the uptake of 5-hydroxytryptamine (serotonin) in the thrombocyte by various tryptamine derivatives was investigated. The activity depended on the nature and position of the substituent. This activity was correlated with the total orbital energy and hydrophobicity factors. Other quantum parameters, such as the highest occupied molecular orbital energy and the lowest empty molecular orbital energy, failed to correlate. The possible involvement of two receptor sites that are sterically and electronically dissimilar is postulated because compounds fell into two distinct groups. The hydrophobicity factor was important in only one group of compounds, while the electronic factor was important in both.

Keyphrases □ 5-Hydroxytryptamine—uptake by thrombocytes correlated with structure–activity, quantum chemical, and hydrophobicity factors, effect of various tryptamine derivatives □ Thrombocytes—uptake of 5-hydroxytryptamine correlated with structure–activity, quantum chemical, and hydrophobicity factors, effect of various tryptamine derivatives □ Structure–activity factors—correlated with 5-hydroxytryptamine uptake by thrombocytes □ Quantum chemical factors—correlated with 5-hydroxytryptamine uptake by thrombocytes □ Hydrophobicity—correlated with 5-hydroxytryptamine uptake by thrombocytes □ Tryptamine—derivatives, effect on 5-hydroxytryptamine uptake by thrombocytes

In the past decade, quantum chemistry has been widely applied in pharmacology and medicinal chemistry, mainly to investigate drug activity. Even though the limitations of molecular orbital calculations have been recognized for many years, the various quantum parameters such as the highest occupied molecular orbital energy, the lowest empty molecular orbital energy, frontier electron density, and superdelocalizability have been correlated with observed activities (1, 2).

The highest occupied molecular orbital energy has been studied extensively because of its relation to the electron-donating ability. However, recent work (3) in molecular pharmacology has begun to show the inadequacy of the application of this concept without other physicochemical parameters. Molecular structure, hydrophobicity, and conformational details are also important determinants.

Quantum chemical data on about 50 derivatives of catechol, indole, imidazole, and lysergamide was reported previously (4, 5). This paper reports the effect of several structural analogs (Table I) of 5-hydroxytryptamine (serotonin) on its uptake by rabbit platelets. These data are further analyzed in terms of quantum chemical indexes and the hydrophobicity of these analogs.

EXPERIMENTAL

New Zealand albino male rabbits, approximately 6–12 months old, were used. The incubation experiments were carried out as follows. Blood was drawn from the rabbits by cardiac puncture. Enough edetate disodium solution (adjusted to pH 7.4 with sodium hydroxide) was added to give a final concentration of 1 mg of edetate/ml of blood. Platelet-rich plasma was obtained by centrifuging the blood at $50\times g$ for approximately 30 min. All operations were carried out using siliconized vessels at 2°.

Two milliliters of platelet-rich plasma was incubated with ^{3}H-5-hydroxytryptamine creatinine sulfate[1] (0.1 mmole = 2.5 mCi of ^{3}H-5-hydroxytryptamine) and appropriate amounts of an analog. The mixture was incubated at 37° for 30 min. Then the incubates were centrifuged at $500\times g$ to sediment the platelets. The sedimented platelet pellet was washed two times with 5 ml of saline.

The final platelet pellet was frozen overnight. The following morning, enough water was added to the platelet preparation to yield a 1.0-ml suspension. The turbidity of the platelets was measured[2] at 660 nm. The radioactivity of the platelet preparation was counted in a liquid scintillation spectrometer. The ratio of the radioactivity to the turbidity is a relative measure of the uptake of 5-hydroxytryptamine per unit volume of the platelet.

All analogs studied had either no activity or had inhibitory activity on the uptake of 5-hydroxytryptamine by the rabbit platelets. The ED_{50} (effective dose producing 50% inhibition) values of these drugs were determined by varying the concentration of the analog used over a wide range. A curve was plotted for each drug as shown in Fig. 1. The ED_{50} and/or ED_{25} (effective dose producing 25% inhibition) values for the analogs were obtained from these plots. The ED_{50} values are (I/S) ratios.

The quantum parameters, the highest occupied molecular orbital energy, the lowest empty molecular orbital energy, the highest superdelocalizability, the total orbital energy[3] (calculated by summing the energies of the occupied orbitals and multiplying the sum by two to account for the double occupancy), and the π–π^* transition energy[4], were obtained using the Hückel method with the omega technique (6, 7) for the hyperconjugation model as described previously (3–5). The log P values, which measure the lipophilicity or the hydrophobicity, were calculated using the published values of Hansch *et al.* (8). The calculated quantum parameters, log P values, and experimental activities (ED_{50}) are listed in Table I.

[1] Amersham Searle.
[2] Beckman DU spectrophotometer.
[3] Total orbital energy is the same as the total π-electron energy.
[4] The π–π^* transition also has been referred to as "LEMO-HOMO" or $\Delta M\beta$.