THE CORRELATION OF ELECTRONIC STRUCTURES OF INDOLE DERIVATIVES WITH THEIR BIOLOGICAL ACTIVITIES

by

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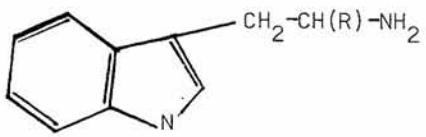
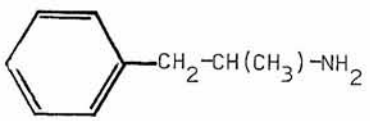
I. INTRODUCTION

Much of our work to date has been focussed on indolealkylamines, and recently some calculations of hallucinogenic amphetamines have been made. Indoles were selected for several reasons. They have varied, potent, and important biological activities, and some, like 5-hydroxytryptamine (serotonin), are widely distributed in nature, including mammalian tissues. Many studies have been published quantitatively describing the actions of congeners on different



Indolealkylamine



Amphetamine

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biological systems. Furthermore, enough information is available on the chemistry of indoles to test the reasonableness of the results of the calculations. In addition, being heterocycles and relatively large they typify many biochemicals and drugs, and as a planar ring system, they are more easily amenable to analysis. Finally, since molecular orbital methods have accounted for some of the chemical activities of indoles; it was hoped that a comparable approach could help to account for their biological activities. Amphetamines were studied for many of the same reasons including the fact that they have some of the same biological actions as do indoles and in some biological systems even act on the same receptors.

We selected four different biological systems for analysis, each representing increasing levels of complexity. First, indoleakylamines that had been studied as inhibitors of a soluble enzyme, 5-hydroxytryptophan decarboxylase [2]. Second, indolealkylamines that had been examined for their effects on the stomach strip of the rat suspended in an artificial medium in a closed system [3]. Third, indolealkylamines that were applied electrophoretically to the cat's lateral geniculate nucleus *in situ* [4]. Fourth, amphetamines that were examined for their hallucinogenic activity in man [5].

It would be expected that molecular orbital methods might be most successful with the least complicated system where the indoles are reacting in solution with, presumably, the active site of a soluble enzyme. In the second system, the effect of the indoles is attributable to a reaction with specific receptors in a complicated system containing a membrane barrier and many chemical components that are competing with the receptors for the indoles, including enzymes that catabolize the indoles. The pervasiveness of only one of these complications is clearly demonstrated in experiments showing that the relative activities of a congeneric series of indoles in contracting a muscle were different before and after inhibition of the catabolizing enzyme [3]. An additional complication is that the potency measured in this and similar systems may be composed of two independent variables, affinity and intrinsic activity [6].

The third system has all the complexities of the previous one in addition to others; for example, the tested substances can leave the open system. In the fourth system (a whole animal) the biological measurement, hallucinogenic activity,

is not measured precisely. Even more important, the relative biological activity that is measured is the net result of a whole series of reactions between the tested compounds (*viz*, amphetamines) and biological sites. Some of the factors determining biological activity in these experiments are the rate of absorption of the drugs from the stomach, the extent of binding to plasma proteins and to tissues, the rate of catabolism by the liver and other organs, the rate of excretion by the kidney, the amount of drug that passes through the blood-brain barrier to enter the brain, and the amount that gets to the active site within the brain. There should be electronic correlates of each one of these determinants of biological activity, e.g. absorption through the stomach and passage into the brain are correlated with lipid solubility and hence often with ionization constant. Adsorption to plasma protein is an interaction that should have an electronic correlate(s) and so should the susceptibility of the amphetamines to enzymatic catabolism. In searching for the electronic correlate(s) of the hallucinogenic activity (or any other effect in the whole animal), we assume that the extent of the other interactions are about the same for each member of the congeneric series so that the relative potency as measured is close enough to truth. Thus, any correlation obtained in this fourth system is a net effect of many interactions, but since useful information about these interactions is not available for the amphetamines, we proceed with the assumption that the potency of the amphetamines in causing hallucinations is directly related to the gross effect that is measured.

Partial accounts of this work have appeared [7-9].

II. METHODS

Total valence electron calculations were carried out by the INDO method (Intermediate Neglect of Differential Overlap), devised by Pople, Beveridge and Dobosh [10]. We are grateful to Beveridge for providing the program and for advice during the course of this work. The INDO method gives good results in the calculation of dipole moments, molecular geometries, electron-nuclear hyperfine coupling constants, nuclear spin-spin coupling constants, and bending force constants [11-14].

We calculated charge density, frontier electron density, dipole moment, total energy and all energy levels.

For the Hückel method, the parameters of Pullman and Pullman [15] were used with the typographical corrections previously noted [16]. The nitrogen coulomb integral, which differs from that of Streitweiser, gave values of electron energy levels and electron distribution that correlate well with experimental findings on a series of anilines [17]. The π-frontier electron density (f^E) and superdelocalizability [(S^E), for an electron-donating reaction], were calculated as described [18]. These indexes, though based on a controversial theory, correlate well with chemical reactivities of many compounds [19].

Resonance constants were obtained from the table of Swain and Lupton [20].

All data were subjected to stepwise multiple regression analysis.

III. RESULTS

Inhibition of 5-hydroxytryptophan Decarboxylase by α-ethyltryptamines

The (weak) inhibitory activities on the decarboxylase [2] correlate with q_7 (charge at the 7-position) and S_7^E and S_2^E (Table 1), as calculated by the simple Hückel method. No electronic correlation could be made for monoamine oxidase inhibitory activity. The correlation between q_7 and S_7^E is not necessarily internal, for in another series of indoles in which comparable calculations were performed, charges and S^E did not consistently correlate [16]. Whether q_7, S_7^E or S_2^E is the meaningful correlate is impossible to say with any certainty. However, studies of the reactivities of indoles do not indicate that the 7-position is a site of attack of electrophilic species, whereas the 2-position is a preferred site for electrophilic attack.

The ambiguity and any inferences can be tested by designing laboratory experiments to see at which atomic sites the indoles interact with the enzyme. Another means of testing the inference and resolving the ambiguity is to synthesize and test compounds whose calculated electronic characteristics could permit one to infer which index or indexes matters.

TABLE 1. INHIBITORY ACTIVITY OF SOME α-ETHYLTRYPTAMINES ON 5-HYDROXYTRYPTOPHAN DECARBOXYLASE AND q_7, S_7^E, AND S_2^E CALCULATED BY THE SIMPLE HÜCKEL METHOD.

Derivative of α-ethyltryptamine	Inhibition, % at 10^{-2}M	q_7	S_7^E	S_2^E
6-NH_2	100	1.134	1.614	1.496
6-OCH_3	58	1.102	1.318	1.362
6-OH	58	1.100	1.296	1.352
1,2-$(CH_3)_2$	14	1.038	1.082	1.228
2-CH_3	13	1.039	1.030	1.228
5-OCH_3	7	1.034	1.078	1.242
2,7-$(CH_3)_2$	6	0.995	1.048	1.226
6-F	0	1.028	1.056	1.230
-	0	1.038	1.062	1.236
1-CH_3	0	1.037	1.082	1.236
7-CH_3	0	0.994	1.050	1.236
Correlation Coefficient		0.929	0.977	0.980

Table 2 shows that if q_7 is the important correlation, 4,6-dimethoxy-α-ethyltryptamine should be a more effective inhibitor than 6-amino-α-ethyltryptamine, the most effective compound yet tested in this series; and the 4-amino derivative would be less active than the 6-amino. If S_7^E is the important correlation, the 4,6-dimethyl derivative should be less active than the 6-amino derivative; and the 4-amino derivative would be as active as the 6-amino. If S_2^E is the important correlation, the inhibitory activity of the 4,6-dimethyl and 6-amino derivatives should be indistinguishable. Thus, the ambiguities may be resolved and a single inference may result by this approach, which is essentially extending the series.

TABLE 2. UNTESTED α-ethyltryptamines (HÜCKEL METHOD)

Derivative of α-ethyltryptamine	q_7	S_7^E	S_2^E
6-NH_2	1.134	1.614	1.496
4,6-$(OCH_3)_2$	1.145	0.936	1.498
4-NH_2	1.108	1.614	1.484

Tryptamines on the Isolated Stomach Strip of the Rat

The compounds were tested [3] on the stomach strip before and after inhibition of the enzyme, monamine oxidase, which destroys many of the tryptamines. The activities in causing contraction of the stomach strip were not related to partition coefficient or pK_a (Table 3). Activities were, however, correlated with

TABLE 3. PARTITION COEFFICIENTS (PC) AND IONIZATION CONSTANTS (pK_a) OF SOME TRYPTAMINES AND THEIR ACTIVITIES ON THE ISOLATED STOMACH STRIP OF THE RAT. PARTITION COEFFICIENT WAS MEASURED BETWEEN 1-OCTANOL AND 0.1 N PHOSPHATE BUFFER, pH 7.0.

Derivative of Tryptamine	Relative Biological Activity	PC	pK_a
5-OH	32	0.017	10.1
5-OCH_3	18.8	0.027	10.3
5-Cl	4.2	0.089	10.5
5-CH_3	3.6	0.202	10.2
--	1.0	0.095	10.2

the resonance contribution of the substituents to the indole ring [21], the biological activity of 5-substituted tryptamines and α-methyltryptamines increasing with decreasing resonance constant (Tables 4 and 5).

TABLE 4. THE RELATIONSHIP BETWEEN THE RESONANCE CONSTANT AND THE ACTIVITY OF SOME TRYPTAMINES ON THE ISOLATED STOMACH STRIP OF THE RAT BEFORE AND AFTER MONOAMINE OXIDASE INHIBITION. THE CORRELATION COEFFICIENTS ARE -0.984 AND -0.983 RESPECTIVELY.

Derivative of Tryptamine	Before MAO-inhibition		After MAO-inhibition		Resonance Constant
	E.M.R.(a)	$\log \frac{1}{E.M.R./32}$ (b)	E.M.R.(a)	$\log \frac{1}{E.M.R./32}$ (b)	
5-OH	1.0	1.505	1.0	1.505	-0.643
5-OCH_3	20.0	0.204	1.7	1.275	-0.500
5-Cl	100.0	-0.495	7.6	0.625	-0.161
5-CH_3	184.0	-0.760	9.0	0.551	-0.141
--	408.0	-1.105	32.0	0.000	0.0

(a) Equipotent molar ratio.

(b) The relative activity of tryptamine after MAO-inhibition was converted to unity, hence E.M.R. was divided by 32.

TABLE 5. THE RELATIONSHIP BETWEEN THE RESONANCE CONSTANT AND THE ACTIVITY OF SOME α-METHYLTRYPTAMINES ON THE ISOLATED STOMACH STRIP OF THE RAT. THE CORRELATION COEFFICIENTS ARE -0.999 BEFORE MAO-INHIBITION AND -0.989 AFTER.

Derivative of α-methyltryptamine	Before MAO-inhibition		After MAO-inhibition		Resonance Constant
	E.M.R.(a)	$\log \frac{1}{E.M.R./32}$ (b)	E.M.R.(a)	$\log \frac{1}{E.M.R./32}$ (b)	
5-OH	1.4	1.359	2.0	1.204	-0.643
5-OCH_3	2.9	1.043	2.5	1.107	-0.500
5-CH_3	14.0	0.359	16.0	0.301	-0.141
--	31.0	0.014	40.0	-0.097	0.0

(a) Equipotent molar ratio.

(b) The relative activity of tryptamine after MAO-inhibition was converted to unity, hence E.M.R. was divided by 32.

The resonance constant reflects the effect of the substituent on charge distribution in the π-electron system, and the high negative value of the activity constant implies that high electron density at the active site or sites may be associated with biological activity. Which atomic site(s) is involved is not revealed by this calculation. It is not the ring nitrogen because isosteres lacking this atom (*viz*, indenes and benzothiophenes) are active [22].

Both INDO and Hückel calculations showed that potency (after inhibition of monamine oxidase) was related to q_6, f_4^E, and f_5^E (Table 6). It is interesting that the simple Hückel calculation yielded correlation coefficients very nearly the same as those obtained with the INDO method. Both the 4- and 6-positions are known to react readily with electrophiles.

TABLE 6. THE RELATIONSHIP BETWEEN THE ACTIVITY OF SOME TRYPTAMINES ON THE ISOLATED STOMACH STRIP OF THE RAT AND THE CHARGE AT THE 6-POSITION (q_6), AND FRONTIER ELECTRON DENSITIES AT THE 4- AND 5-POSITIONS (f_4 and f_5) AS CALCULATED WITH THE INDO AND HÜCKEL METHODS.

Derivative of Tryptamine	Relative Biological Activity	INDO			Hückel		
		q_6	f_5	f_4	q_6	f_5	f_4
5-OH	32.0	-0.0302	0.1157	0.2123	-0.068	0.096	0.384
5-OCH_3	18.8	-0.0306	0.1120	0.2061	-0.069	0.106	0.398
4-OH	16.0	0.0611	0.0632	0.1461	-0.025	0.126	0.284
5-Cl	4.2	0.0227	0.0426	0.1876	-0.025	0.044	0.288
5-CH_3	3.6	0.0211	0.0364	0.1852	-0.044	0.058	0.314
--	1.0	0.0344	0.0151	0.1600	-0.031	0.026	0.288
5,6-$(OCH_3)_2$	0.21	0.1842	0.0147	0.0730	-0.0015	0.004	0.256
6-OH	0.06	0.2460	0.0092	0.0908	0.030	0.002	0.242
6-OCH_3	0.03	0.2423	0.0066	0.0952	0.028	0.002	0.232
Correlation Coefficient		-0.934	0.9677[a]	0.783	-0.920	0.919[a]	0.842

(a) Binomial correlation coefficient (the regression line is uniformly curved).

To delineate which of the three indexes is truly correlated with potency, we plan to synthesize and test a few congeners that have not been studied in this system. Table 7 shows that the 5,7-dihydroxy- and 5,7-dimethoxy-, 7-hydroxy- and 7-methoxy derivatives would be more potent than the most potent substance tested, 5-hydroxytryptamine (serotonin), if q_6 is the significant correlations. If f_4 is the significant correlation, only the aforementioned dihydroxy and dimethoxy derivatives would be more potent than serotonin. If f_5 is the significant one, then none of these would be more potent than serotonin. Synthesizing and testing the 5,7-dihydroxy- and the 7-hydroxy derivatives could indicate which of the reactivity indexes is correlated with gross potency.

TABLE 7. UNTESTED TRYPTAMINES (INDO METHOD)

Derivative of Tryptamine	q_6	f_5	f_4
5-OH	-0.0302	0.1157	0.2123
5-phenoxy	-0.0494	0.1060	0.1847
4-OCH_3	0.0601	0.0542	0.1368
7-OH	-0.0558	0.0377	0.2086
7-OCH_3	-0.0522	0.0411	0.2052
5,7-$(OH)_2$	-0.1216	0.0724	0.2508
5,7-$(OCH_3)_2$	-0.1187	0.0568	0.2334
5-NH_2	-0.0085	0.0930	0.2078
5-$N(CH_3)_2$	-0.0242	0.0994	0.1598
--	0.0344	0.0151	0.1600

The high value of q_6 in the 5-phenoxy derivative could suggest that if q_6 is the significant index then the 5-phenoxy derivative would be more potent than serotonin. However, as is often seen in studies of congeneric series, the addition of a bulky group can often confer on an agonist (serotonin, in this instance) the properties of an antagonist, i.e. a substance that blocks the action of serotonin

(e.g., LSD-25). It is interesting that calculations of untested compounds with resonance constants suggested that the 5-amino and 5-phenoxy derivatives would be more active than serotonin. INDO calculations do not support this prediction for the 5-amino compound, although high activity is predicted.

One obvious consideration in the analysis of the results on untested compounds is that the correlation of potency with more than one index may not be adventitious, especially in this system where potency may be a function of at least two independent variables, affinity and intrinsic activity. In the small series that is available [6], affinity correlates with f_5 (Table 8) and intrinsic activity with f_4 (Table 9). It is possible that the most active compound will be the one where f_5 and f_4 are high. Of the compounds studied, only serotonin is high in both f_4 and f_5. In this context the 5-amino compound is also interesting (Table 7).

TABLE 8. RELATIVE AFFINITY OF SOME TRYPTAMINES FOR THE STOMACH STRIP AND q_6 AND f_5 CALCULATED BY THE INDO METHOD.

Derivative of Tryptamine	Affinity	q_6	f_5
5-OH	6.82	-0.0302	0.1157
4-OH	5.36	-0.0611	0.0632
--	4.71	0.0344	0.0151
6-OH	3.95	0.2460	0.0092

TABLE 9. RELATIVE INTRINSIC ACTIVITY OF SOME TRYPTAMINES ON THE STOMACH STRIP AND f_4 CALCULATED BY THE INDO METHOD.

Derivative of Tryptamine	Rel. Int. Activity	f_4
5-OH	1.0	0.2123
--	0.97	0.1600
4-OH	0.85	0.1461
6-OH	0.68	0.0908

Empirical studies have established that the side-chain amino group is necessary for activity [3], but the calculated charge on the aliphatic nitrogen did not reflect potency.

One impression that emerges from looking at the series [3] is that the molecular orbital calculations that we have made cannot account for the activities of all the derivatives. In a series of tryptamine derivatives with alkyl substituents on the primary amino group, the order of potency of the monoalkylamine derivatives is CH_3>CH_2-CH_3>CH_2-CH_2-CH_3; the order of potency of dialkyl derivatives is the opposite, *viz*, $(CH_2\text{-}CH_2\text{-}CH_3)_2$>$(CH_2\text{-}CH_3)_2$>$(CH_3)_2$. Our calculations do not account for these variations in potency. It is possible that measurements of partition coefficients or ionization constants or both could help to make sense of these observations. Even more befuddling is the observation that in the 5-hydroxytryptamine series, the order of potency is $(CH_2\text{-}CH_2\text{-}CH_3)_2$>$(CH_3)_2$>$(CH_2CH_3)_2$, different from the analogous tryptamine derivatives.

The Hypothetical Receptor for Tryptamines in the Rat Stomach

These molecular orbital calculations together with empirical studies stimulate speculation on the nature of the reactions of the indoles with the receptor and, by further inference, on the configuration of the receptor. Since the amino group, which is needed for activity, is protonated at physiological pH, it is reasonable to suggest that it forms either an electrostatic linkage with an acidic group or a hydrogen bond with an electron donor. The latter bond seems less likely because dialkyl substitution does not reduce the activity by much; the N,N-dipropyl derivatives of tryptamine is about as potent as tryptamine, and the corresponding analogue of 5-hydroxytryptamine is one-sixth as potent as 5-hydroxytryptamine [3].

The molecular orbital calculations suggest that the 4- or 5- or 6-position (or maybe more than one) reacts with an electrophile on the receptor. The reaction may be of the type -XH--π base, with the aforementioned position(s) on the indole ring contributing to the stabilization energy of the complex. XH could be any of a number of groups, e.g., hydroxyl, amide, imidazole, amono. Evidence for

the binding of biogenic amines by hydrogen bonding to tissue components, including carbohydrates, has been reviewed [23,24].

A glycopolymer containing neuraminic acid is a likely candidate for a receptor. Many of these are found in membranes (where these tryptamines are acting) and they have a strong affinity for biogenic amines, due to the acidic carboxyl groups (the pK_a is about 3) and the hydroxyl groups. So strong is their affinity for biogenic amines that a neuraminic acid-containing polymer, even after extensive extraction and purification from brain, still retained measurable quantities of norepinephrine [25].

There is some evidence that a neuraminic acid polymer is the tryptamine receptor in the stomach [26-29; cf. 30). The polymer may be N-acetylneuraminyl-(2-8)-N-acetylneuraminyl-(2-3)-galactosyl-(1-4)-glucosyl-1-ceramide [27].

A molecular model of this compound shows a "hole" into which serotonin neatly fits, its primary amino group abutting against a carboxylate group of neuraminic acid and the 4-, 5-, and 6-positions of the indole against the sugar hydroxyl groups of the glucose. Both hypothetical interactions would be of low energy which is in accord with the ready reversibility of the biological effects.

Amphetamine, which acts on the tryptamine receptors in the stomach, also fits the hole and LSD-25, the antagonist of both compounds, can form the same kind of complex with additional sites of interaction.

The Activity of Tryptamines on Neurones of the Lateral Geniculate Nucleus

The activity of these derivatives in depressing excitation of the neurones [4] was poorly correlated with energy of the highest occupied molecular orbital (HOMO) as calculated by the INDO method (Table 10). The rank orders are parallel except for the 4-methoxy- and 6-hydroxy derivatives. It should be noted that the measurement of biological potency is here only grossly quantitative.

TABLE 10. THE ACTIVITY OF SOME TRYPTAMINES ON THE LATERAL GENICULATE NUCLEUS OF THE CAT AND THE ENERGY OF THE HIGHEST MOLECULAR ORBITAL CALCULATED BY THE INDO METHOD.

Derivative of Tryptamine	Potency	HOMO Energy (atomic units)
4-OH	18-24	-0.4582
7-OH	12-18	-0.4584
5-OH	12	-0.4735
$5\text{-}OCH_3$	6	-0.4787
$4\text{-}OCH_3$	6	-0.4566
6-OH	4-5	-0.4583
--	2-3	-0.4810

Hallucinogenic Activity of Some Amphetamines

Amphetamines and tryptamines share the same receptor in some biological systems. And like some indoles, amphetamine derivatives are psychotomimetic (hallucinogenic). The psychotomimetic activity of a series of amphetamines [5] correlated with HOMO (Table 11). Only one compound, the 2,4,5-trimethoxy derivative, was out of order. These results confirm and extend the Hückel calculations of Snyder and Merril [31].

It is hard to believe that HOMO is a biologically meaningful correlate of psychotomimetic activity, but surprisingly no other correlation could be obtained in this or in the series shown in Table 10.

IV. CONCLUSIONS

These beginnings suggest that molecular orbital methods may be valuable in studying the relationship between chemical structure and biological activity. In revealing relationships that were heretofore unnoticed, these methods emphasize that electronic as well as steric factors deserve consideration -- a seeming

TABLE 11. THE HALLUCINOGENIC ACTIVITY OF SOME AMPHETAMINES AND THE ENERGY OF THE HIGHEST OCCUPIED MOLECULAR ORBITAL CALCULATED BY THE INDO METHOD. THE CORRELATION COEFFICIENT IS 0.713.

Derivative of Amphetamine	Hallucinogenic Activity	HOMO Energy (atomic units)
$2,5\text{-}(OCH_3)_2\text{-}4\text{-}CH_3$	100	-0.4929
$2,4,5\text{-}(OCH_3)_3$	17	-0.5001
$2,4,6\text{-}(OCH_3)_3$	10	-0.5217
$2,5\text{-}(OCH_3)_2$	8	-0.5012
$2,3,4,5\text{-}(OCH_3)_4$	6	-0.5126
$2,4\text{-}(OCH_3)_2$	5	-0.5194
$3,4,5\text{-}(OCH_3)_3$	2	-0.5218
$3,4\text{-}(OCH_3)_2$	1	-0.5238
--	0	-0.5885

gratuity but not really, when one recalls that much of the biological data referred to here were analyzed solely in terms of stereochemistry.

At the beginning of this work it was hoped that the approach outlined here would help in the understanding of the forces determining the biological activity of molecules and that by inference we might gain insight into the nature of the receptor. It was also hoped that the information derived from a molecular orbital analysis of a congeneric series could not only test the inferences derived from a correlation but could lead to cogent suggestions of new derivatives worth making and testing. Further, it was hoped that the results of the calculations could lead us to design laboratory experiments to test the inferences, and we have made such designs. All in all, the work described here encourages us to pursue all these objectives. At the same time, the analysis shows that at this time a molecular orbital approach will often have to be combined with empirical studies, a clear appraisal of steric factors and reaction mechanisms, an understanding of the biological system, and a compulsive need to seek experimental verification of the findings, because analyses of this sort are a place to begin, not to end, experiments.

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VI. REFERENCES

[1] Green, J. P., "The application of quantum mechanics to pharmacology: some substances active in the nervous system", p. 95 in *Molecular Basis of Some Aspects of Mental Activity*, (O. Walaas, ed.,) Vol. 2, Academic Press, New York (1967a).

[2] Hester, J. B., Greig, M. E., Anthony, W. C., Heinzelman, R. V., and Szmuszkovicz, J., *J. Med. Chem.*, 7, 274 (1964).

[3] Vane, J. R., *Brit. J. Pharmacol.*, 14, 87 (1959).

[4] Curtis, D. R., and Davis, R., *Brit. J. Pharmacol.*, 18, 217 (1962).

[5] Shulgin, A. T., Sargent, T., and Naranjo, C., *Nature*, 221, 537 (1969).

[6] Offermeier, J., and Ariëns, E. J., *Arch. Int. Pharmacol.*, 164, 216 (1966).

[7] Green, J. P., *Federation Proc.*, 26, 289 (1967b).

[8] Kang, S., Beveridge, D. L., and Green, J. P., *Federation Proc.*, 28, 794 (1969).

[9] Kang, S., Beveridge, D. L., and Green, J. P., *158th A.C.S. National Meeting, Div. of Med. Chem.*, (Sept. 8-12, 1969).

[10] Pople, J. A., Beveridge, D. L., and Dobosh, P. A., *J. Chem. Phys.*, 47, 2026 (1967).

[11] Beveridge, D. L., Dobosh, P. A., and Pople, J. A., *J. Chem. Phys.*, 48, 4802 (1968).

[12] Beveridge, D. L., and Dobosh, P. A., *J. Chem. Phys.*, 48, 5532 (1968).

[13] Pople, J. A., Beveridge, D. L., and Dobosh, P. A., *J. Am. Chem. Soc.*, 90, 4201 (1968).

[14] Pople, J. A., and Beveridge, D. L., *J. Chem. Phys.*, 49, 4725 (1968).

[15] Pullman, B., and Pullman, A., *Quantum Biochemistry*, New York, Interscience (1963).

[16] Green, J. P., and Malrieu, J. P., *Proc. Nat. Acad. Sci. U.S.*, 54, 659 (1965).

[17] Zweig, A., Lancaster, J. E., Neglia, M. T., and Jura, W. H., *J. Am. Chem. Soc.*, 86, 4130 (1964).

[18] Fukui, K., Yonezawa, T., and Nagata, C., *J. Chem. Phys.*, 27, 1247 (1957).

[19] Fukui, K., p. 513 in *Molecular Orbitals in Chemistry, Physics and Biology*, (P. O. Lowdin and B. Pullman, ed.), Academic Press, New York, (1964).

[20] Swain, C. G., and Lupton, E. C., Jr., *J. Am. Chem. Soc.*, 90, 4328 (1968).

[21] Kang, S., and Green, J. P., *Nature*, 222, 794 (1969).

[22] Winter, J. C., Gessner, P. K., and Godse, D. D., *J. Med. Chem.*, 10, 856 (1967).

[23] Green, J. P., *Adv. Pharmacol.*, 1, 349 (1962).

[24] Green, J. P., p. 125 in *Mechanisms of Release of Biogenic Amines*, (Euler, U.S. von Rosell, and Uvnäs, B., eds.), Pergamon, New York, (1965).

[25] Robinson, J. D., Carlini, E. A., and Green, J. P., *Biochem. Pharmacol.*, 12, 1219 (1963).

[26] Wooley, D. W., and Gommi, B. W., *Arch. Int. Pharmacodyn.*, 159, 8 (1966).

[27] W. Gielen, *Z. Naturforsch.*, 21 B, 1007 (1966).

[28] Wesemann, W., and Zilliken, F., *Biochem. Pharmacol.*, 17, 471 (1968).

[29] Vaccari, A., and Cugurra, F., *Biochem. Pharmacol.*, 17, 2399 (1968).

[30] Offermeier, J., and Ariëns, E. J., *Arch. Int. Pharmacodyn.*, 164, 192 (1966).

[31] Snyder, S. H., and Merril, C. R., *Proc. Nat. Acad. Sci. U.S.*, 54, 258 (1965).