methyl group in N-methyl-L-proline with the result that the CD spectrum of this 2:1 cupric complex is virtually identical with that of the L-leucine complex. It is difficult to see how these results can be accounted for by any chelate ring puckering hypothesis and a simple octant rule.[7]

[7] The ideas expressed in this paper have been employed over the past year and a half to systematize the results obtained by Dr. John M. Tsangaris and Dr. Joyce Wen Chang, both of whom submitted their Ph.D. theses in Aug 1967. Descriptions of their work have been submitted for publication.

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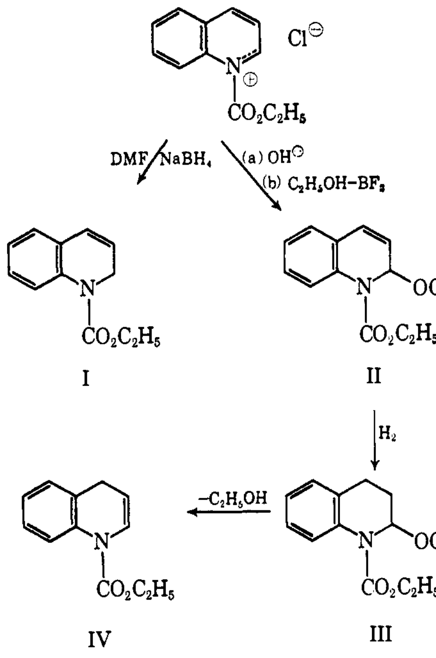
N-Carboxylic Acid Esters of 1,2- and 1,4-Dihydroquinolines. A New Class of Irreversible Inactivators of the Catecholamine α Receptors and Potent Central Nervous System Depressants

Sir:

We wish to report the discovery of the potent central nervous system depressant activity of certain N-carboxylic acid esters of 1,2- and 1,4-dihydroquinolines (I, II, and IV), a structural pattern without tangible analogy among drugs acting on the central nervous system (CNS). In addition, we have observed that several members of this new class of drugs are potent and selective irreversible inhibitors of the adrenergic α receptor, a feature that adds a new dimension to current theories of the molecular mechanisms of drug action at that level.[1-3] Until now, irreversible inhibition of the adrenergic α receptor could be achieved only with alkylating agents of the nitrogen mustard type of drugs (*i.e.*, dibenamine and its relatives[4,5]) which, however, do not possess CNS depressant activity.

Scheme I



These compounds were prepared from the appropriate quaternized quinolines as shown in Scheme I.[6] The 1,4-dihydro analog IV was also prepared by an alternate procedure. The starting material was *o*-nitrocinnamaldehyde diethyl acetal[7] which was hydrogenated (Raney nickel) to the corresponding saturated amine followed by acylation and ring closure to compound III under mild conditions of solvolysis.[8]

When compounds I and IV were administered in low oral doses to animals, they produced a progressive decrease in responsiveness and in locomotor activity, while at higher doses a state of cataleptic immobility ensued. This pharmacological profile is typical of all the drugs classified as major tranquilizers.[9] The pseudo-base II is pharmacologically equivalent to I and IV except for its low oral potency due to instability in the gastrointestinal tract. In the presence of dilute mineral acid it is rapidly decomposed to quinoline, carbon dioxide, and alcohol.

In anesthetized animals, compounds I, II, and IV induced a protracted blockade of the adrenergic α receptors that could not be reversed by massive doses of epinephrine (see Table I). A similar effect was also observed in isolated tissues where compound II was approximately 50 times more potent than either I or IV.

Table I. Relative Potencies of Compounds I, II, IV, and Chlorpromazine (CPZ)

Test	Potency (compound I = 1)			
	I	II	IV	CPZ
CNS depressant[a]	1.0	1.5	0.2	0.4
Blockade of epinephrine 1 mg/kg iv[b]	1.0	6.0	1.0	Reversible

[a] Measured in rats by the cataleptogenic test of H. Fujimori and D. P. Cobb, *J. Pharmacol. Exptl. Therap.*, **148**, 151 (1965). [b] Determined on the blood pressure of anesthetized cats (pentobarbital).

From a large number of derivatives that were tested, the following significant trends in the structure–activity relationship emerged. Maximum activity was associated with short alkyl chains in the carbamate moiety. Substituents other than alkoxy or alkylthio at position 2 abolished activity, while substitution at positions 3, 4, and 8 was markedly detrimental to activity. The tetrahydro analogs as well as the dihydroisoquinoline isomers were devoid of activity.

The irreversible nature of the blockade obtained with I, II, and IV suggests that a covalent linkage may be

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[1] B. Belleau, *Pharmacol. Rev.*, **18**, 131 (1966).

[2] B. M. Bloom and I. M. Goldman, *Advan. Drug Res.*, **3**, 121 (1966).

[3] B. Belleau, *Ann., N. Y. Acad. Sci.*, **139**, 580 (1967).

[4] M. Nickerson, *Pharmacol. Rev.*, **11**, 443 (1959).

[5] B. Belleau, *Can. J. Biochem.*, **36**, 731 (1958).

[6] All the compounds had correct empirical compositions and were further characterized by uv, ir, and nmr spectroscopy.

[7] J. Klein and E. D. Bergmann, *J. Am. Chem. Soc.*, **79**, 3452 (1957).

[8] The only 1,4-dihydroquinoline amide derivative (N-benzoyl) reported in the literature has been claimed by C. M. Knowles and G. M. Watt, *J. Am. Chem. Soc.*, **65**, 410 (1943). However, evidence will be presented in our full paper that their structure assignment is erroneous.

[9] P A. J. Janssen, *et al.*, *Arzneimittel-Forsch.*, **15**, 104 (1965).

established at the α-receptor level. It would appear that only the pseudo-base II would be sufficiently reactive to allow for the rapid formation of such a covalent linkage. However, compounds I and IV, which have similar activity, are both sensitive to air oxidation. This observation favors the hypothesis that they may suffer *in vivo* activation by oxidation to a common pseudo-base-like structure prior to interacting with the receptors. Model studies with compound II suggest that it acts as a selective activator of carboxyl functions.[10]

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(10) B. Belleau and G. Malek, manuscript in preparation.

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Book Reviews

Molecular Spectra and Molecular Structure. III. Electronic Spectra and Electronic Structure of Polyatomic Molecules. By GERHARD HERZBERG, Division of Pure Physics, National Research Council of Canada, Ottawa, Ontario, Canada. D. Van Nostrand Co., Inc., 120 Alexander St., Princeton, N. J. 1966. xviii + 745 pp. 16 × 23.5 cm. $20.00.

Quoting from the preface of this volume, "The book is aimed at the serious student of molecular structure. Without going into long mathematical developments, a good deal of the theory of the subject is treated, and emphasis is laid on the comparison with experiment. As in the two preceding volumes, numerous spectrograms are intended to give a feeling for the experimental basis of the subject, while a large number of energy level diagrams and other illustrations should help to make the theoretical developments more easily visualizable .... The manuscript of the book was completed in 1965."

In fact, this volume is densely filled with empirical information beautifully correlated with relevant theoretical ideas, and forms a magnificent climax to Herzberg's well-known volumes on "Molecular Spectra and Molecular Structure," of which this is the third. It brings to the experimentalist a comprehensive survey of the extremely varied and often complicated details of the electronic-vibrational-rotational-spin theory which he needs to be acquainted with if he is to deal intelligently with the excited states and electronic spectra of polyatomic molecules. To the theorist it brings a panorama of our present state of knowledge of polyatomic electronic spectra, through an 85-page chapter on the interpretation of the spectra of individual molecules and an 88-page table (Appendix VI) of details on these spectra. Finally, there is a bibliography of 1334 references. In spite of its restriction to *vapor-state* spectra of molecules with not more than 12 atoms, one could hardly expect more wisdom and more knowledge to be packed into a single book.

The coverage of the theory includes recent developments and refinements and will be valuable in the future development of the subject by its coverage, even if briefly, of many types of situations which one can anticipate theoretically, but of which few or no examples have yet been found. As in its two predecessor volumes, a considerable amount of discussion is included which goes beyond the strict confines of the title of the volume, by showing how the same or related theory, and how knowledge gained from spectra, can be utilized in the general field of chemistry, in particular of chemical reactions.

Although the major emphasis of the book is on the detailed understanding of structured spectra and the tables are mainly devoted to empirical quantities obtained from the analysis of such spectra, abundant references are given for molecules where continuous spectra (in a number of cases *only* continuous spectra) have been observed. Chapter 4 is devoted to an exposition of the theory, with some examples, of "Dissociation, Predissociation and Recombination: Continuous and Diffuse Spectra"; it includes some instructive diagrams on potential surfaces for polyatomic molecules.

Chapter III, some 150 pages, is devoted to building up principles; the correlation of electronic states with states of united atoms or molecules and of separate atoms; electron configurations, especially in terms of molecular orbitals (illustrated by the discussion of a number of molecules as examples); the valence-bond method; the use of the molecular orbital method for describing the structure of molecules in their ground and excited states; intensities of electronic transitions; and a short section on intermolecular forces. Section 1(c) of Chapter III seems to me misleading in its implication that strict selection rules analogous to the Wigner–Witmer rules for diatomic molecules are widely applicable to the formation of polyatomic molecules from atoms or groups of atoms. It seems to me that such rules would be valid only if, during a collision, rigidly prescribed orientations of the parts of the molecule being formed were maintained, whereas actually the approaching parts can approach one another with all sorts of orientations and from all directions. The matter has been discussed in a paper by K. A. Schuler, *J. Chem. Phys.*, **21**, 624 (1953), not cited by Herzberg.

In general the discussion and the bibliography in Chapter III are less complete and up to date than in the other chapters. On pages 336 and 344, the author has given the reviewer too much credit in connection with the self-consistent-field method. The reviewer is not very happy about the review of hydrogen bonding on pages 421–426. Also he wishes that the author had not used the term "molecular orbitals" for certain group orbitals (*e.g.*, of 2 or 3 H atoms) which can be used in building complete molecular orbitals; however, this is perhaps a matter of taste. The author has presented very clearly the way in which group orbitals and symmetry orbitals can be used in the building of molecular orbitals in simple LCAO approximation. In spite of the few critical comments, Chapter III is an extremely helpful concentrated review of the subject matter which it covers and gives useful perspective. On pages 405–411, the reviewer is pleased to see "ligand-field theory" placed in its proper perspective under molecular orbital theory. On page 352, there is a delightful and very wise quotation from Wigner which no one, and in particular no chemist, should miss.

A valuable step beyond what is presented in the second volume of the series is the discussion in the first part of Chapter I and in Appendix I of the species classification of eigenfunctions including electron spin, making use of extended point groups. The appendices also contain several other very useful tables. Valuable also are full expositions of the Renner–Teller and Jahn–Teller effects, and of some new developments by Hougen on various types of interactions. Brief reference is made in the Introduction to new features which occur in the energy levels of nonrigid molecules. In the tables, data on ground states, even when not obtained from electronic spectra, but from microwave, infrared, or Raman spectra, have been brought up to date as compared with similar data in the earlier volume on infrared and Raman spectra. The subject of forbidden transitions is discussed rather briefly but very usefully. Magnetic rotation spectra are discussed briefly. Zeeman and Stark effects are discussed only briefly, since very little work has yet been done on these effects in electronic spectra of polyatomic molecules, even though they have been extensively utilized in ground-state microwave spectra and molecular beam spectroscopy. These latter subjects, as well as the fields of nuclear magnetic and paramagnetic resonance in the ground states, are considered outside the scope of the book.

In summary, this is an indispensable book for everyone working on the electronic spectra of polyatomic molecules, and all chemists should at least make its acquaintance. We are tremendously indebted to Herzberg for the patience and hard work which he has devoted to so enormously enhancing the accessibility of some increasingly important areas of chemical science.

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