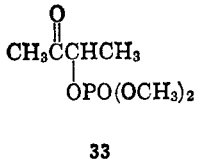

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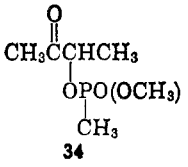

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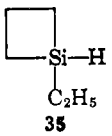
whereas that of **34** proceeds with formation of acetoin and methyl methylphosphonate; they have explained these results by the pseudo-rotation hypothesis and the "preference rules"[7] here reviewed.

Although the pseudo-rotation theory will probably have little application in carbon chemistry (where metastable trigonal-bipyramidal intermediates probably cannot be found), it should prove useful in describing the mechanism, and in predicting the rates, of reactions of second-row and other elements. In particular, the theory probably provides the correct explanation for the rapid hydrolysis of highly strained silicon derivatives[88-90] such as **35** and **36** and may prove relevant to sulfur chemistry.

The part of the work here described that was carried out in the laboratories of the Chemistry Department of Harvard University was supported by the National Science Foundation under Grant No. GP-2098 and by the Petroleum Research Fund of the American Chemical Society. The author wishes to express his appreciation of the contributions of a large number of students and postdoctoral fellows, whose names appear in the bibliography and whose work is summarized in this review. He also wishes to thank Dr. Robert Autrey and Mr. David Lang for essential assistance in designing the structural diagrams used here.



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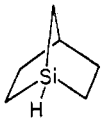

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(88) L. H. Sommer, "Stereochemistry, Mechanism and Silicon," McGraw-Hill Book Co., Inc., New York, N. Y., 1965.
(89) L. H. Sommer, O. F. Bennett, P. G. Campbell, and D. R. Weyenberg, *J. Am. Chem. Soc.*, **79**, 3295 (1957).
(90) L. H. Sommer and O. F. Bennett, *ibid.*, **79**, 1008 (1957); L. H. Sommer, W. P. Barie, Jr., and D. R. Weyenberg, *ibid.*, **81**, 251 (1959).

Alkaloid Synthesis

ERNEST WENKERT

Department of Chemistry, Indiana University, Bloomington, Indiana 47401

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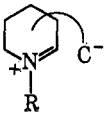
A general scheme of synthesis of fused piperidines and its application to the synthesis of alkaloids of a wide variety of structure types are described. The general method is based on the partial hydrogenation of substituted β-acylpyridines and the intramolecular acid-catalyzed interaction of the nucleophilic side chains and the electrophilic α-carbon site of the resultant piperideines.

Alkaloids constitute a group of monomeric, nitrogenous plant products whose extraordinary structural complexity as well as frequent, significant impact on biology and medicine have represented a challenge of long standing in organochemical synthesis. Despite the inordinate multiformity of structure types abounding in the alkaloid realm one structure unit—the piperidine ring, usually fused to one or more other rings—appears common to a great majority of the naturally occurring bases. This fact, more than any other cause, has made alkaloid synthesis largely an exercise in synthesis of fused piperidines and has led recently to the development of a simple method of alkaloid synthesis of general applicability. The new procedure relies on the preparation of piperidine systems of requisite substitution pattern and oxidation state and interaction of their electrophilic α carbons with nucleophile-containing side chains of proper chain length emanating from any one of their six ring positions (**1** → **2**).

Various reaction schemes have been employed for the production of the scarce, but highly desirable, 1-piperideines (**1**) or their chemical equivalents. The striking simplicity of some of these schemes, *e.g.*, the oxidation of piperidines[1] or the hydride reduction of pyridinium salts,[2] makes them deserving of further attention. The most attractive scheme is founded on an unusual, partial hydrogenation reaction of certain pyridines. While catalytic hydrogenation of aromatic compounds customarily produces fully saturated cyclic substances, palladium-induced hydrogenation of pyridines and their N-alkyl salts (**3**) containing a wide variety of β-acyl or related substituents has been found to yield



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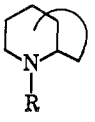

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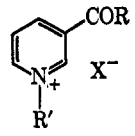
(1) E. Wenkert and J. Kilzer, *J. Org. Chem.*, **27**, 2283 (1962); E. E. van Tamelen and R. L. Foltz, *J. Am. Chem. Soc.*, **82**, 2400 (1960); E. Wenkert and B. Wickberg, *ibid.*, **84**, 4914 (1962); J. P. Kutney, R. T. Brown, and E. Piers, *ibid.*, **86**, 2286, 2287 (1964); G. C. Morrison, W. Cetenko, and J. Shavel, Jr., *J. Org. Chem.*, **32**, 4089 (1967).
(2) E. Wenkert, R. A. Massy-Westropp, and R. G. Lewis, *J. Am. Chem. Soc.*, **84**, 3732 (1962).

tetrahydropyridines (**4**).[3] Apparently the unveiling of the highly stable β-aminoacryl moiety blocks complete hydrogenation. Since interaction of acid with 2-piperideines (**4**) produces 1-piperideine salts (**1**) and hence fused piperidines (**2**), the *two-step reaction sequence, hydrogenation–cyclization of β-acylpyridines, constitutes the basis of the general method of alkaloid synthesis.*



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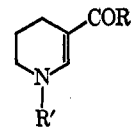

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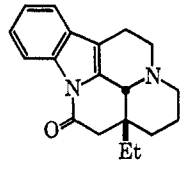
The first application of the method involved the synthesis of the indole alkaloid eburnamonine (**5**).[4] Hydrogenation of the salt of β-acetylpyridine and tryptophyl bromide yielded the piperideine **6**, whose exposure to acid led to the piperidine **7**, an intermediate containing four rings of the pentacyclic alkaloid as well as its two-carbon side chain. Five additional, conventional reactions produced the alkaloid and revealed its stereochemistry.



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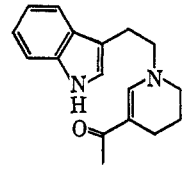

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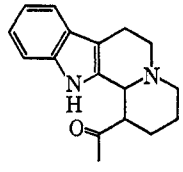

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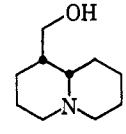

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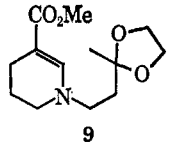
Further applications of the method are illustrated by the syntheses of lupinine (**8**) and of a crucial intermediate on the route to the *Lycopodium* alkaloids. Hydrogenation of the salt of methyl nicotinate and 3-ketobutyl *p*-toluenesulfonate ethylene ketal gave the tetrahydropyridine **9**, whose treatment with acid in aprotic media yielded the bicyclic ester **10**. (In acid solution the otherwise inert ketal function unravels reversibly into a hydroxyethyl enol ether moiety which exhibits powerful nucleophilic properties.) Lithium aluminum hydride reduction, acid hydrolysis of the ketal, and Wolff–Kishner reduction led to lupinine (**8**) and epilupinine.[5]



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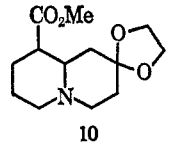

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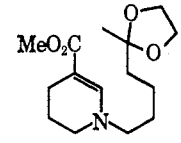
Hydrogenation of the salt of methyl nicotinate and 5-ketohexyl bromide ethylene ketal produced the vinylogous amide **11**, whose acid treatment and hydrolysis afforded the keto ester **12**. Base-induced cyclization and etherification with methanolic acid yielded the tricyclic substance **13**, whose lithium aluminum hydride reduction and acid hydrolysis gave the ketone **14**. Condensation of the latter with methyl acetoacetate, followed by acid-catalyzed hydrolysis and decarboxylation, introduced an acetonyl side chain. Mercuric acetate oxidation of the resultant diketone yielded a tricyclic compound (**15**) ideally suited for further elaboration to the *Lycopodium* alkaloid ring system, *e.g.*, lycopodine (**16**).[6]



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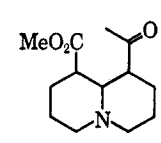

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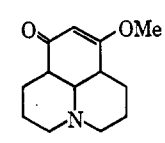

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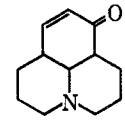

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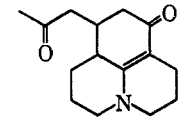

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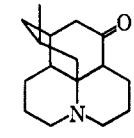


16

While in all aforementioned syntheses the tetrahydropyridines (**4**) proved to be excellent substrates in the cyclization reaction (**1** → **2**), exceptions were encountered. In a study of the synthesis of *Aspidosperma* and *Strychnos* alkaloid models[5] acid-induced transformations of **17a–c,** prepared in the usual manner, into the indolenines **18a–c** succeeded only in the case of the ester **17c**. Its unstable product **18c** could be reduced and isolated as the dihydro product **19a** or the N-acetyl derivative **19b** thereof. Even forcing conditions, equal to or more drastic than those employed for the conversion of **6** into **7**, failed to faze the aldehyde **17a** and the ketone **17b**. This dichotomy of behavior of the aldehyde–ketone group and the ester suggested a dissimilarity of their mode of protonation. An analysis of their conjugate acids[3] showed aldehydes and ketones to exist mostly in the highly stabilized, O-protonated form **20**, while esters prefer the reactive, destabilized, C-protonated form **21**. The first instance of an intramolecular cyclization of an indolylimmonium salt unencumbered by post-reaction stabilizing substituents into the indole β carbon (**17c** → **18c**), a long sought-after reaction,[7] was followed by transformations of even greater interest, the conversions of **22** into the esters **23**, potentially useful intermediates for the synthesis of *Aspidosperma* alkaloids, *e.g.*, vincadifformine (**24**).

Even though difficulties associated with the cyclization step of piperideines derived from aldehydes and ketones seemed to limit the general method of alkaloid synthesis solely to the use of nicotinic acid derivatives,

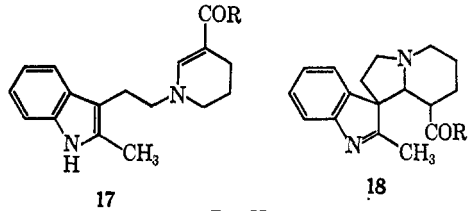
(3) E. Wenkert, K. G. Dave, F. Haglid, R. G. Lewis, T. Oishi, R. V. Stevens, and M. Terashima, *J. Org. Chem.*, **33**, 747 (1968); K. G. Dave, R. B. Dunlap, M. K. Jain, E. H. Cordes, and E. Wenkert, *J. Biol. Chem.*, in press.

(4) E. Wenkert and B. Wickberg, *J. Am. Chem. Soc.*, **87**, 1580 (1965).

(5) E. Wenkert and K. G. Dave, unpublished observations.

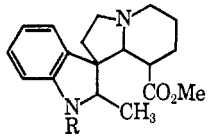
(6) E. Wenkert, K. G. Dave, and R. V. Stevens, unpublished observations.

(7) R. Robinson, "The Structural Relations of Natural Products," Oxford University Press, Oxford, England, 1955.

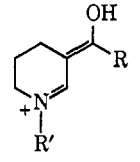


17 18

a, R = H
b, R = Me
c, R = OMe



19a, R = H
b, R = Ac



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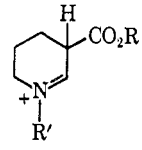

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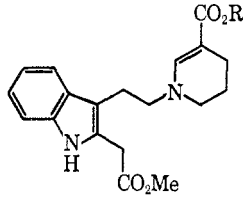

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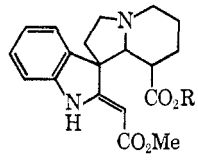

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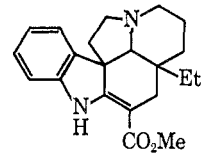
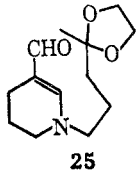


24

the barrier was overcome in a study of the synthesis of a hydrolulolidone.[5] Hydrogenation of the salt of nicotinaldehyde and 4-ketopentyl bromide ethylene ketal yielded piperideine **25**, which proved to be inert to acid treatment. When, however, **25** was exposed to acid in the presence of ethylene glycol and under continuous water removal, it was converted to the acetal ketal **26**, whose acid-catalyzed hydrolysis, aldol condensation, and dehydration led to the amino enone **27**.



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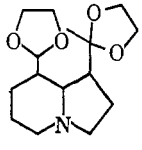

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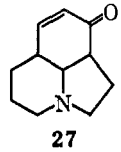

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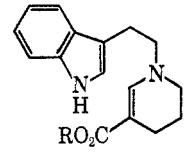
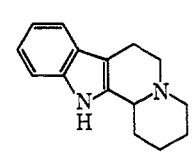


28a, R = Me
b, R = *t*-Bu

All syntheses described so far were designed to incorporate the complement of nitrogen and carbon atoms of the starting acylpyridine in the final alkaloid skeleton. However, for the syntheses of yohimboid and corynanthoid alkaloids the β-acyl moiety represented a superfluous appendage. Hence deacylation methods were devised. A study of the hydrolysis of the nicotinic acid derivatives **28**, prepared in the by now customary manner, revealed that base treatment of **28a** or acid treatment of **28b** yielded cyclized, decarboxylated product (**29**).[8] Apparently hydrolysis and decarboxylation are much faster than cyclization.

The deacylation procedure was utilized in the synthesis of several alkaloid models and alkaloids. Hydrogenation of the salt of tryptophyl bromide and dihydrogentianine yielded lactone **30**, whose alkaline hydrolysis produced 3-isocorynantheidol (**31a**).[8] Similarly, hydrogenation of the salt of tryptophyl bromide and

(8) E. Wenkert, K. G. Dave, and F. Haglid, *J. Am. Chem. Soc.*, **87**, 5461 (1965).



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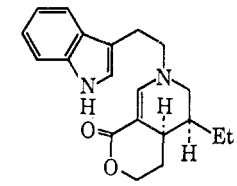

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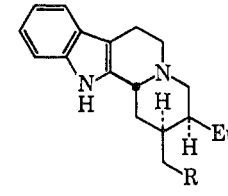
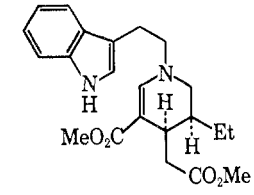
methyl 4-carbomethoxymethyl-5-ethylnicotinate gave the diester **32**, whose base hydrolysis followed by reesterification afforded the ester **31b**. Chemical modification of the latter by conventional reactions led to the alkaloid corynantheidine (**33**).[9] Hydrogenation of the salt of tryptophyl bromide and *t*-butyl 5,6,7,8-tetrahydroisoquinoline-4-carboxylate gave **34**, whose acid hydrolysis produced epialloyohimbane (**35**).[8] This transformation bodes well for the synthesis of the α-yohimbine alkaloids. Hydrogenation of the salt of tryptophyl bromide and dimethyl isoquinoline-4,5-dicarboxylate afforded the dihydro derivative **36**, an interesting example of the substitution of a 4-acylisoquinoline for the usual β-acylpyridine in the reduction step. Alkaline hydrolysis of **36** and reesterification led to the alkaloid dihydrogambirtannine (**37**).[10]



31a, R = CH_2OH
b, R = CO_2Me



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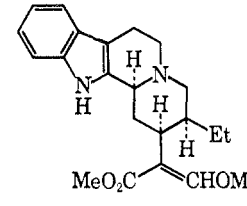

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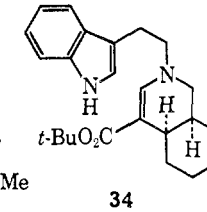

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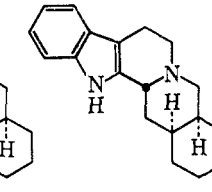

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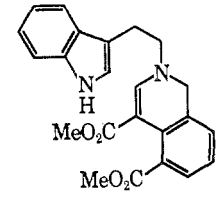

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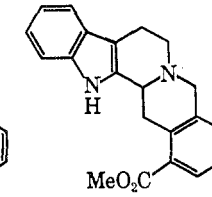

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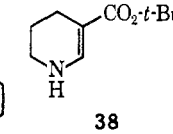

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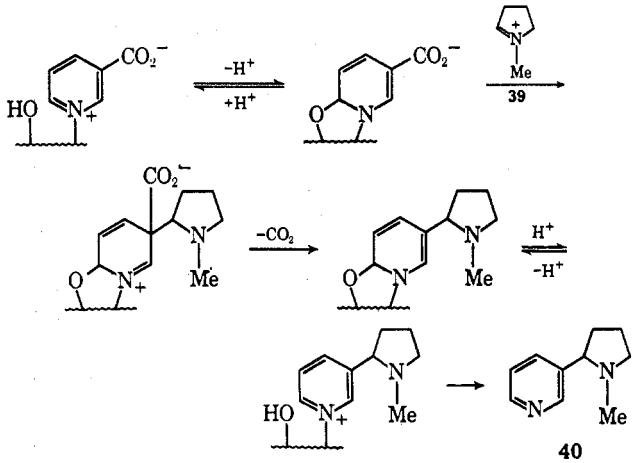
The deacylation scheme left an impact also in two areas other than alkaloid synthesis. Firstly, it makes the readily accessible *t*-butyl 1,4,5,6-tetrahydronicotinate (**38**) an excellent chemical for the *in situ* preparation of 1-piperideine. Secondly, it yields a clue for interpretation of an unsolved phase of the biosynthesis of nicotine (**40**) and related alkaloids. While the two rings are known to originate from the pyrrole deriva-

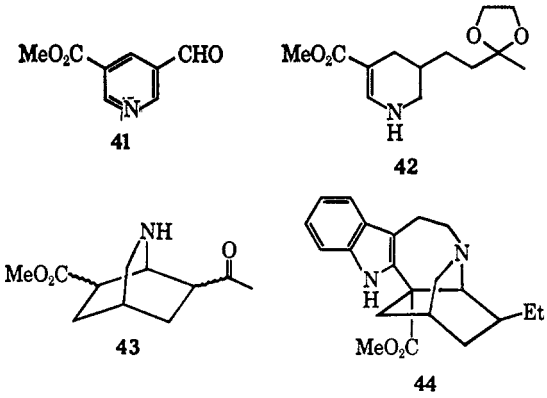
(9) E. Wenkert, K. G. Dave, R. G. Lewis, and P. W. Sprague, *ibid.*, **89**, 6741 (1967); J. A. Weisbach, J. L. Kirkpatrick, K. R. Williams, E. L. Anderson, N. C. Yim, and B. C. Douglas, *Tetrahedron Letters*, 3457 (1967).

(10) E. Wenkert, K. G. Dave, and P. W. Sprague, unpublished observations.

tive **39** and nicotinic acid,[11] little is known about the mechanism of their attachment other than its occurrence with decarboxylation at the carboxylated pyridine site. Furthermore, electrophilic substitution of simple pyridines is known to occur only under extreme, forcing conditions. If it be assumed that the transformations in the plant proceed *via* N-glycosylpyridine intermediates, a simple biosynthetic pathway can be envisaged (*vide infra*).[12]



Although the starting materials of all above syntheses have been 1-alkyl-3-acylpyridinium salts whose nucleophilic centers resided uniformly on the N-alkyl substituents, there is no theoretical reason for such limitation in the general scheme of alkaloid synthesis. The following new method of synthesis of isoquinuclidines illustrates the utilization of an acylpyridine whose nucleophilic side chain does not radiate from the nitrogen position. Pyridine-3,5-dicarboxylic acid was converted by conventional means to the aldehydo ester **41**, whose condensation with acetone, ketalation, and hydrogenation led to the piperideine **42**. Acid-induced cyclization and hydrolysis yielded the isoquinuclidine **43**, a well-suited model of the *Iboga* alkaloids, *e.g.*, **44**.[5]



The accumulated body of evidence suggests strongly that the two-step scheme of construction of fused piperidines will be of general applicability in alkaloid synthesis. Much work remains in the utilization of the method for the preparation of the wide variety of virgin alkaloid structure types.[13]

Heartfelt thanks are extended to the U. S. Department of Health, Education, and Welfare for continuous support of this work and to the graduate and postdoctorate students who made the work possible. Special accolade is due to Dr. K. G. Dave for years of devoted research efforts.

(11) T. J. Gilbertson and E. Leete, *J. Am. Chem. Soc.*, **89**, 7085 (1967), and previous work.

(12) This hypothesis was first propounded by the author at the Lecture of the Month, The Ullman Institute of Life Sciences, The Weizmann Institute of Science, Rehovoth, Israel, Jan 4, 1965.

(13) While only portions of the work presented in this review have appeared in print (see references), various phases of the research were presented at the following lectures: Frontiers of Chemistry Lecture, Western Reserve University, Cleveland, Ohio, March 23, 1963; Southeastern Regional American Chemical Society Meetings, Charlotte, N. C., Nov 14–16, 1963, and Atlanta, Ga., Nov 1–3, 1967; Chemistry Symposium, Rikagaku Kenkyusho (The Institute of Physical and Chemical Research), Tokyo, Japan, April 27, 1964; Natural Products Symposium, Israel Chemical Society Meeting, Jerusalem, Israel, Dec 29, 1964; Abbott Lecture, University of Sydney, Sydney, Australia, June 1, 1966; Barton Lecture, University of Oklahoma, Norman, Okla., Feb 2, 1967; Second Natural Products Symposium, University of the West Indies, Kingston, Jamaica, Jan 2–5, 1968.

Studies of the Electronic States of Simple Liquids

STUART A. RICE

Department of Chemistry and The James Franck Institute, University of Chicago, Chicago Illinois 60637

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A survey is presented of recent studies of conducting and nonconducting excited electronic states in simple liquids, *e.g.*, He, Ar. Attention is focused on: (a) interpretation of the mobility of excess electrons in terms of the fundamental electron-atom potential and the structure of the liquid, (b) the difference between delocalized and localized excess electron states, (c) the nature of exciton states in the liquid and the form of the dispersion relation in terms of the structure of the liquid, (d) the role of intermolecular interactions in broadening and shifting the exciton spectrum of the liquid, and (e) possible modes of energy trapping and energy transfer. Wherever possible experiment and theory are compared, and directions where more work is needed are pointed out.

I. Introduction

Considerable effort has been devoted to studies of the electronic states of free molecules and of dielectric crystals. Spectroscopic studies of dilute gases, from which information about the free molecule is deduced, are simplified by the absence of intermolecular interactions and hence of correlations between the positions of the molecules. Thus, any one molecule may be