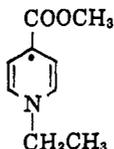


The Isolation and Distillation of the Stable
Free Radical,
1-Ethyl-4-carbomethoxy-pyridinyl

Sir:

We report here the chemical synthesis and isolation of the stable organic free radical, 1-ethyl-4-carbomethoxypyridinyl (1). This radical has been prepared previously in solution by controlled potential reduction of the corresponding pyridinium ion perchlorate in acetonitrile.¹



1

The radical 1 is prepared by metal reduction of a pyridinium salt, usually the iodide, in a high vacuum system. Sodium dispersion, granular magnesium or aluminum powder and the solid iodide between 95 and 170° all lead in a spectacular fashion to the formation of a blue deposit (which is largely the radical) on a cold finger cooled by liquid nitrogen. Pure radical was more readily isolated from the reaction of granular zinc (20 mesh, 57.8 mg., 0.89 mmole) with pyridinium iodide (522 mg., 1.77 mmoles) in acetonitrile (4 cc.) at 0°, removal of most of the acetonitrile (3 cc.), two extractions of residue with *n*-heptane (5 cc.), transfer of the solution, evaporation of the solvent and purification of the radical by distillation at *ca.* 40° (10⁻⁶ to 10⁻⁷ mm.). A solution of the product in 4 cc. of acetonitrile had an optical density of 1.6 at 8000 Å. in a 1-cm. cell. (Light absorption in the visible region is linear with concentration.) The yield of radical in the experiment described was 10%.

*Anal.*² Calcd. for C₉H₁₂O₂N: C, 65.03; H, 7.29; O, 19.25; N, 8.43. Found: C, 64.20, 64.41; H, 8.05, 7.84; O, 19.80, 19.34; N, 8.25, 8.52;

Codistillation of the radical with acetonitrile or *n*-heptane was noted and it may be estimated that the normal boiling point of 1 is about 250° from the concentrations observed in the distilled solutions. The visible and ultraviolet spectrum of the radical obtained after distillation agrees in almost every detail with a spectrum of that obtained electrochemically.³ $\lambda_{\text{max}}^{\text{CH}_3\text{CN}}$ (Å.) 9250 sh ($\epsilon \sim 5$), 7750 sh ($\epsilon \sim 40$), 6900 sh ($\epsilon \sim 80$), 6325 (ϵ 92), 5850 sh ($\epsilon \sim 40$), 3950 (ϵ 5200), 3040 (ϵ 12,500), 2280 sh (ϵ dependent on concentration), 2080 (ϵ dependent on concentration). The presence of the free radical is confirmed by e.s.r. spectra of solutions prepared by codistillation of the radical with acetonitrile⁴ (Fig. 1). The yield of radical ranges from 2 to 15%, depending mostly upon the extraction procedure.

We believe that this is the first report of the distillation of a reactive organic free radical with sufficient stability to be isolated in pure form. The radical, di-*t*-butyl nitroxide, has been distilled but is remarkably unreactive toward oxygen⁵ although the latter

(1) W. M. Schwarz, E. M. Kosower and I. Shain, *J. Am. Chem. Soc.*, **83**, 3164 (1961).

(2) Analyses were performed by the Schwarzkopf Microanalytical Laboratories, Woodside 77, New York. Samples were transferred in an inert atmosphere.

(3) W. M. Schwarz, Ph.D. Thesis, University of Wisconsin, 1961. We thank Dr. Schwarz for lending us the original spectra.

(4) We are grateful to Professor George K. Fraenkel, Dr. James Bolton and Mr. William Miller, Department of Chemistry, Columbia University, for providing us with e.s.r. spectra.

(5) A. K. Hofmann and A. T. Henderson, *J. Am. Chem. Soc.*, **83**, 4671 (1961).

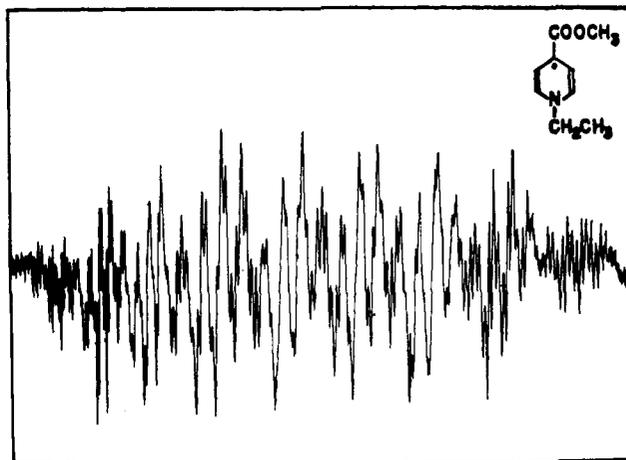


Fig. 1.—An e.s.r. spectrum of 1-ethyl-4-carbomethoxy-pyridinyl (1) in acetonitrile solution.

does broaden its e.s.r. spectrum.⁶ The pure radical 1 is a dark emerald green oil, d_4^{25} 0.85, at room temperature and is transformed into a deep sapphire-blue solid at -200°. The pure material, moderately stable at 25° but best stored at 0°, gives no detectable signal in a Varian A-60 n.m.r. spectrometer. Its magnetic susceptibility at 25°, however, corresponds to between 60 and 100% free radical.⁷ In acetonitrile solution, the radical yields 1-ethyl-4-carbomethoxypyridinium chloride on reaction with carbon tetrachloride, thus confirming the proposed mechanism for the photochemical reaction between a 1,4-dihydropyridine and bromotrichloromethane (or carbon tetrachloride).^{8,9} The high reactivity of the radical is shown by extreme sensitivity to oxygen, very rapid reaction with carbon tetrachloride even at -200°, reaction with certain metal ions and rapid reduction of the bismethyl quaternary chloride of 4,4'-dipyridyl (methyl viologen) to the methyl viologen radical ion,¹ either in solution or by exposure of the solid to the vapor of 1.

The visible absorption spectrum of our material is in sharp contrast to the colorless 6,6'-dimers produced by chromous acetate reduction of 1-(2,6-dichlorobenzyl)-3-carbamidopyridinium and several other ions.¹⁰ Our present spectroscopic data indicate that association of the monomer occurs, perhaps to a "dimer," in all but the most dilute solutions (10⁻⁵ M). The postulated "dimer" must be a diradical, since it is paramagnetic, and not a charge-transfer complex as proposed for N-ethylphenazyl at low temperatures.¹¹ We have not yet investigated the effect of temperature upon the magnetic susceptibility of the radical 1. Covalently bonded pyridinyl radical dimers are known and often react chemically by preliminary dissociation to the radical.^{10,12,13} Flavin mononucleotide semiquinone (FMNH·) diradical "dimers" may be intermediates in the transformation of the charge-transfer complex of reduced and oxidized FMN (FMNH₂ → FMN) to a

(6) H. Lemaire, A. Rassat, P. Servoz-Gavin and G. Berthier, *J. Chim. Phys.*, **59**, 1247 (1962).

(7) We are indebted to Prof. Harry B. Gray, Department of Chemistry, Columbia University, for his cooperation and the use of his Gouy balance.

(8) J. L. Kurz, R. Hutton and F. H. Westheimer, *J. Am. Chem. Soc.*, **83**, 584 (1961).

(9) The reaction of a pyridinyl radical and hexachloroacetone is probably responsible for the formation of pentachloroacetone observed in the reaction of 1-benzyl-1,4-dihydronicotinamide and hexachloroacetone. D. C. Dittmer and R. A. Fouty, Abstracts of the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963, p. 48M.

(10) K. Wallenfels and M. Gellrich, *Ann.*, **621**, 198 (1959); *Chem. Ber.*, **92**, 1406 (1959).

(11) K. H. Hausser, *Z. Naturforsch.*, **11a**, 20 (1956).

(12) E. Weitz, *Angew. Chem.*, **66**, 658 (1954).

(13) O. Mumm and H. Ludwig, *Ber.*, **59**, 1605 (1926).

pair of FMNH· radicals¹⁴ at the cross-over point in terminal oxidation in biochemical systems.¹⁵

A number of significant possibilities stem from our preparation of the radical (1). The factors stabilizing free radicals and the reactivity of free radicals may now be examined with simpler radicals than heretofore possible. Pyridinyl radicals represent a new class of chemical reagents for which there is little direct analogy. The procedures described in this communication are clearly applicable to a whole variety of quaternary salts, including those derived from heterocyclic rings, phosphines, arsines, sulfides, etc. Experiments designed to test some of these implications are now underway.

(14) Q. H. Gibson, V. Massey and N. M. Atherton, *Biochem. J.*, **55**, 369 (1962).

(15) E. M. Kosower, "Molecular Biochemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 226.

The physical properties of such stable free radicals as well as the theoretical problems posed by their stability will also be of much interest. All of these matters will be reported in full publications at a later time.

Acknowledgment.—We thank Prof. William D. Closson, Chemistry Department, Columbia University, for assistance and Prof. Paul C. Lauterbur of this department for helpful discussions.

(16) Alfred P. Sloan Fellow 1960–1964

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BOOK REVIEWS

The Interpretation of NMR Spectra. By KENNETH B. WIBERG, Yale University, and BERNARD J. NIST, University of Washington. W. A. Benjamin, Inc., 2465 Broadway, New York 25, N. Y. 1962. vii + 593 pp. 19 × 27 cm. Price, \$25.00.

With the wide-spread availability of spectrometers, the interpretation of high-resolution nuclear magnetic resonance spectra has become the concern of a large number of organic chemists. The authors of the present book use the word "interpretation" in a rather narrow sense. Thus, the extremely important problem of obtaining chemical and structural information is completely omitted. What is dealt with is the problem of obtaining chemical shifts and especially coupling constants from a spectrum, with the important proviso that the spectrum, or a part of it, must belong to one of the categories found in this volume.

The book is essentially a compilation of theoretical spectra, calculated and printed with the aid of a computer, for systems involving up to five spins and with selected values of chemical shifts and coupling constants.

The spectra are presented in two ways: (a) tables of line positions and intensities, and (b) a visual representation where crosses are used to indicate band positions and intensities, with a fixed width for each line. The representation is effective if not aesthetically pleasing.

The greater part of the book is concerned with the following important spectra: ABX and ABC, A₂X₂ and A₂B₂ (including cases with two different AB or AX coupling constants). The well known and relatively simple AB, AB₂, AB₃, AB₄ and A₂B₃ cases take relatively few pages.

The ABC system is split up into a number of different sections, depending on the relative chemical shifts of A, B and C. With ν_A and ν_B at -3 and $+3$, respectively, results are given for (A), $\nu_C = +3$; (B), $\nu_C = +4$; (C), $\nu_C = +5$ and (D), $\nu_C = +7$. One other case (E) has $\nu_A = -6$, $\nu_B = 0$ and $\nu_C = +6$. Altogether about five hundred spectra are given, with different combinations of coupling constants, including negative ones, in the range of 1 to 18.

There is about the same number of A₂B₂ spectra, all with $\nu_{AB} = 6$, and with coupling constants similar to those mentioned above.

Each set of spectra has a short, but invariably excellent introduction on its particular characteristics.

While this is undoubtedly a valuable book, a number of important criticisms must be made. One is the remarkable absence of cases with one coupling constant equal to zero in the lengthy list of ABC and A₂B₂ spectra. The only cases where zero J 's are given are completely trivial ones such as in the AB_n systems. A second is the duplication which occurs in the AB₂ spectra and the ABC spectra (case A) with $J_{AB} = J_{AC}$. Indeed, it would appear that little effort has been made to weed out unnecessary spectra. For example, many of the A₂B₂ spectra with large J_{AB} 's are of the uninformative "skyscraper" type. A book of half the size would have been as useful and much cheaper.

In spite of the mass of information about line positions and intensities published with each spectrum, the captions to the spectra do not mention chemical shifts explicitly. This is a most annoying feature, especially in the ABC spectra. One either has to remember the chemical shifts for cases A to E mentioned above or continuously refer back to a difficult-to-find table in the text.

Although this book was published rapidly, it does not include any reference to recent work on the analysis of spectra, particularly the use of computers to obtain converging solutions from a set of experimental parameters.

In spite of its shortcomings, the book should prove useful as an aid in the analysis of n.m.r. spectra.

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Ergebnisse der Alkaloid-Chemie bis 1960 unter besonderer Berücksichtigung der Fortschritte seit 1950. By PROFESSOR DR. HANS-GÜNTHER BOIT, Humboldt University, Berlin. Akademie-Verlag G.m.b.H., Leipziger Strasse 3–4, Berlin W 8, Germany. 1961. x + 1082 pp. + unbound supplement of viii pp. 18 × 24.5 cm. Price, DM 140.

From the title of this volume and that of a previous one, Fortschritte der Alkaloid-Chemie seit 1933 (1950), one may deduce that Professor Boit has set himself the valuable but unenviable task of publishing a monograph surveying developments in the chemistry of alkaloids every ten years. At least one implication in this initial deduction is not quite correct. This new book does not simply take the previous one as a point of departure; it is, rather, a complete and self-contained review of the state of alkaloid chemistry to the end of 1960. The emphasis is upon those elucidations of structure, those transformations, those alkaloids newly discovered since 1950. But ample space is allotted to that earlier material necessary for a reference work, so that the discussion of any particular family of substances is complete even if the central members of that family have been known for a long time.

The volume is divided into 59 chapters and two supplements, with three indices. The chapters cover the alkaloids divided into families in the traditional way by structural similarity. Each chapter contains: (1) a brief introduction to the family by discussion of salient features of the principal members; (2) a substantial table listing all known members of the family, with melting point, optical rotation, melting points of selected derivatives, all known plant sources, and recent references for each entry as appropriate; (3) the discussion, substance by substance, of the chemistry new since 1950. The material covered is diverse: new transformations of well known substances, reports, however incomplete, of new alkaloids, and full presentations of degradative and synthetic studies leading to structures and solutions to stereochemical problems. For example, the complex chain of degradation and synthesis of fragments that led to the structures of cevine and its congeners is allotted more than seven pages. The two supplements, one bound with the volume and one inserted afterward, are for the purpose of making coverage of the literature as complete up to the publishing date as possible—they cover those developments in 1960 and a few in 1961 that are omitted from the main body of the text, and the larger supplement has references to the pages elsewhere in the book where the same substance is discussed. The three indices index the contents under the divisions plants and plant products, animals and animal products, and chemical compounds. It is unfortunate that there is no author index; however, it may have