

indicates that structure and perhaps geometry are important as well as electronegativity.

(9) NASA Trainee, 1963-1965.

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Synthetic Routes to Emetine. Revised Structure of a Lactonic Intermediate

Sir:

Considerable synthetic activity¹ has been devoted to emetine (I), a useful compound in treatment of amebiasis.² One of the earliest syntheses of this compound and some of the subsequent procedures³ involved a lactonic intermediate (A), assigned structure II. Reinvestigation in our laboratories has raised some question as to the accuracy of these reports.³ Our findings are described below.⁴

Repetition of the lengthy sequence^{3b} yielded a crystalline product, m.p. 100-102° (lit.^{3b} m.p. 102.5-103.5°), corresponding to A, in addition to an oil (as reported^{3b}). This crystalline substance exhibits a split carbonyl at 5.68 and 5.83 μ and aliphatic carboxylic acid absorption at 2.8-4.0 μ . Its n.m.r. shows two primary methyl triplets, at δ 0.97 and 1.01, and two tertiary methyl singlets, at δ 1.26 and 1.38. Integration shows the same number of hydrogens for the combined triplets and singlets. The singlets and absence of bands in the δ 4-4.5 region ascribable to $-CH_2OC(=O)-$ absorption are clearly not in accord with structure II. Further indication is provided by O-alkyl and C-methyl determinations which show two C-CH₃ groups and absence of O-alkyls. Fractional crystallization (ether) of A yielded A', m.p. 106-108°, 82%; additional material, m.p. 104-107°, 6%; and an amorphous residue. A' has spectral and combustion values essentially identical with those of A. However, its n.m.r. spectrum shows only one singlet at δ 1.26 (and one triplet of equal intensity at 1.01); the n.m.r. of the residue retains two singlets with the 1.38 peak intensified.

The syntheses of A make use of elaborate sequences to IIIa^{3b} or IIIb⁵; these routes involve unambiguous transformations. Further, the n.m.r. spectrum of IIIb⁵ shows only one C-CH₃ peak at δ 0.95 (triplet, 3 H) and absorption for the CH₃OCH₂ protons at δ 3.35

(1) (a) A. R. Battersby and J. C. Turner, *J. Chem. Soc.*, 717 (1960); (b) H. T. Openshaw and N. Whittaker, *ibid.*, 1461 (1963); (c) D. E. Clark, R. F. K. Meredith, A. C. Ritchie, and T. Walker, *ibid.*, 2490 (1962); (d) A. Brossi, M. Baumann, and O. Schnider, *Helv. Chim. Acta*, 42, 1515 (1959); (e) R. P. Evstigneeva and N. A. Preobrazhensky, *Tetrahedron*, 4, 223 (1958); (f) E. E. van Tamelen, G. P. Schiemenz, and H. L. Arons, *Tetrahedron Letters*, 1005 (1963); (g) C. Szantoy and L. Toke, *ibid.*, 1323 (1963).

(2) (a) L. S. Goodman and A. Gilman, "The Pharmacological Basis of Therapeutics," The Macmillan Co., New York, N. Y., 1955, pp. 1208-1212; (b) G. Woolfe, *Progr. Drug Res.*, 7, 11 (1965).

(3) (a) R. P. Evstigneeva, R. S. Livshits, L. I. Zakharkin, M. S. Bainova, and N. A. Preobrazhensky, *Dokl. Akad. Nauk SSSR*, 75, 539 (1950); (b) L. I. Zakharkin and N. A. Preobrazhensky, *J. Gen. Chem. USSR*, 22, 1890 (1952); (c) L. I. Zakharkin and N. A. Preobrazhensky, *ibid.*, 23, 153 (1953); (d) A. R. Battersby, U. S. Patent 3,045,020 (1962); British Patent 895,910 (1962).

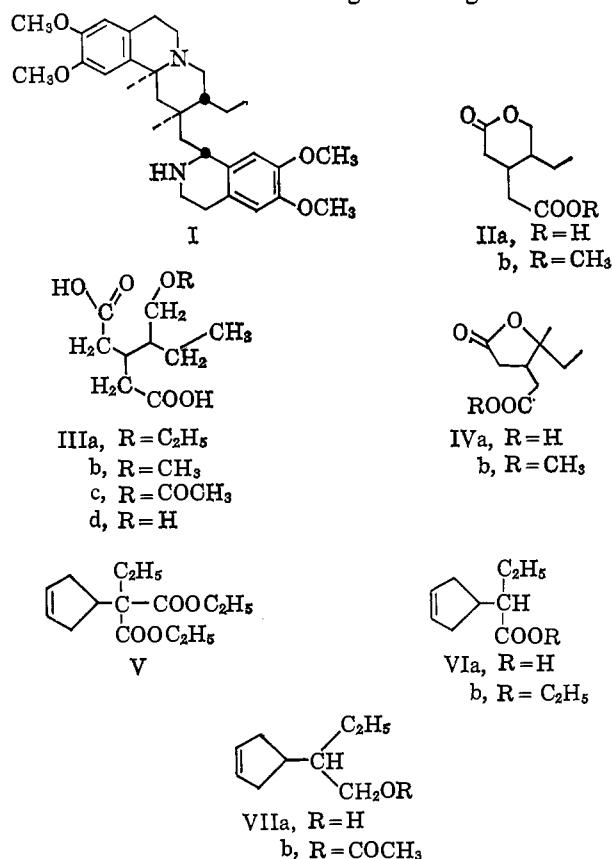
(4) Satisfactory analyses were obtained for all compounds; infrared spectra were taken in chloroform and n.m.r. spectra in deuteriochloroform. We are indebted to J. Bordner and M. E. Flaugh (University of California, Berkeley, Calif.) for the n.m.r. spectra.

(5) F. Zymalkowski and A. W. Frohm, *Arch. Pharm.*, 297, 219 (1964). We are grateful to Professor Zymalkowski for specimens of compound IIIb and its acid transformation product.

(singlet, doublet, 5 H), compatible with the indicated structure; analysis confirms the presence of a single C-CH₃. Completion of the synthesis is reportedly accomplished by acid cleavage of the primary alkyl ether one carbon removed from the tertiary center, a reaction often known to occur with rearrangement via the tertiary carbonium ion and thence to the thermodynamically most stable lactone.⁶ Such a rearrangement of IIIa or IIIb would give the γ -lactone IVa. On the basis of structure IV the anomalous finding, namely, the n.m.r. singlets in the crude product at δ 1.26 and 1.38, is then explained by the tertiary methyls in the diastereomeric forms of IVa.

Compound A' yielded (CH₂N₂) the corresponding lactonic methyl ester IVb, m.p. 61-63°; λ_{\max} 5.64 and 5.74 μ ; δ 1.01 (triplet, 3 H) and 1.26 (singlet, 3 H); a *p*-bromoanilide, m.p. 154-156°; λ_{\max} 5.66 and 5.91 μ ; δ 1.00 (triplet, 3 H) and 1.30 (singlet, 3 H); and a homoveratryl amide, m.p. 96-98°; λ_{\max} 5.65 and 6.00 μ ; δ 1.15 (triplet, 3 H) and 1.37 (singlet, 3 H) [cf. 5-methyl-5-ethylbutyrolactone,⁷ exhibiting carbonyl absorption at 5.66 μ and n.m.r. peaks at δ 0.97 (triplet) and 1.38 (singlet)]. These data suffice to establish the structure of A' as IVa (stereochemistry unspecified) rather than the earlier assignment IIa. Recently⁵ other workers reported preparation of a substance reputed to be IIa, m.p. 104.5-106°, by a similar sequence. This substance was identical with A' (melting point, mixture melting point, infrared, and n.m.r. comparison).

The oil⁸ from the acid-cleavage rearrangement of IIIa



(6) (a) F. C. Whitmore and H. S. Rothrock, *J. Am. Chem. Soc.*, 54, 3431 (1932); (b) M. F. Ansell and M. H. Palmer, *Quart. Rev. (London)*, 18, 211 (1964).

(7) (a) V. Grignard and M. H. Moisson, *Compt. rend.*, 135, 629 (1902); (b) P. K. Porter, *J. Am. Chem. Soc.*, 45, 1086 (1923).

(8) In most experiments⁸ this oil was obtained. Zymalkowski and Frohm⁵ report "nahezu quantitativer ausbeute" of A' (IVa), thus eliminating any possibility for isolation of II.

to IVa (ca. 50% of total product) was esterified (CH_2N_2) and examined by v.p.c.⁹ The most prominent peaks were at 6.1 (B), 6.5 (C), and 8.9 (D) min. (65, 10, and 16% of total area); preparative v.p.c. yielded pure specimens¹⁰ of each. Compound B, m.p. 53–55°, was shown to be IVb by infrared and n.m.r. comparison with A' methyl ester (CH_2N_2). Compound D, λ_{max} 5.73 μ , showed n.m.r. absorption for primary methyl (δ 0.95, triplet, 3 H), no tertiary methyl, and a $-\text{CH}_2\text{O}-\text{C}=\text{O}-$ group (δ 4.20, multiplet, 2 H). These data are in accord with formulation of D as IIb. Thus the reported⁸ major product, IIa, of this sequence is produced to the extent of at most 8%.¹¹

As published procedures^{3,5} showed little promise for useful synthesis of IIa, an alternate sequence was devised: diethyl ethylmalonate was alkylated ($\text{Na}-\text{C}_6\text{H}_5$) with Δ^3 -cyclopentenyl tosylate¹² to give V, 80%, b.p.

(9) We are indebted to J. Lockard and A. Post (Smith Kline and French Laboratories) for these determinations.

(10) Compound C was not investigated further.

(11) A compound described as II, m.p. 98–100°, was obtained by degradation of oleuropeina [L. Panizzi, M. L. Scarpati, and G. Oriente, *Gazz. chim. ital.*, 90, 1449 (1960)]. Again, the sequence included an acidic ether cleavage and certainly produced IVa rather than IIa. The only previous potentially authentic synthesis of IIa proceeds from 2-(4-pyridyl)butanol. IIa is described as an oil, b.p. 140–160° (0.05 mm.) [M. Pailer and G. Beier, *Monatsh.*, 88, 830 (1957)].

(12) E. L. Allred, J. Sonnenberg, and S. Winstein, *J. Org. Chem.*, 25, 26 (1960).

96–97° (0.7 mm.). V was hydrolyzed to a mixture of acid ester and diacid which was decarboxylated (Cu-quinoline). The resulting mixture of VIa and VIb upon reduction (LiAlH_4) gave VIIa, b.p. 99–100° (11 mm.); α -naphthylurethan, m.p. 86–88°; the corresponding acetate, VIIb, b.p. 99° (10 mm.), λ_{max} 5.77 μ ; δ 0.94 (triplet, 3 H) and 4.05 (doublet, 2 H), was obtained with acetic anhydride (from V, 70%). Oxidation ($\text{O}_3-\text{CH}_2\text{Cl}_2$; $\text{Ag}_2\text{O}-\text{NaOH}$) of VIIb gave the diacid acetate IIIc which was directly saponified to IIId. This diacid was lactonized by heating in xylene to IIa, b.p. 215–218° (3 mm.), λ_{max} 5.74 and 5.80 (sh) μ , and aliphatic carboxylic acid absorption in the 2.8–4 μ region, δ 0.90 (triplet, 3 H) and 4.20 (multiplet, 2 H); *p*-bromoanilide, m.p. 133–134°; λ_{max} 5.74 and 5.91 μ ; δ 0.90 (triplet, 3 H) and 4.15 (multiplet, 2 H). The methyl ester (CH_2N_2) IIb was identical with compound D obtained by preparative v.p.c. (above) by infrared and n.m.r. comparison and v.p.c. retention times.

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Book Reviews

Statistical Theory of Liquids. By I. Z. FISHER with a supplement by STUART A. RICE and PETER GRAY. The University of Chicago Press, 5750 Ellis Ave., Chicago, Ill. 1964. xii + 335 pp. 14.5 × 22 cm. \$12.50.

This book is a translation of a monograph in Russian. As with any translation, the first question a reviewer should ask is "was the effort of translation worthwhile?" The answer is an emphatic yes. The statistical theory of liquids had, some years ago, already developed to the stage where a book length monograph giving a coherent picture of the field was feasible. Although there are some excellent review articles, and chapters in some texts, no comprehensive full length account was available before the appearance of Fisher's book. The well-known treatise of Hirschfelder, Curtiss, and Bird may appear to be an exception, but, in fact, these authors emphasize lattice theories. Fisher treats such theories very briefly, finally dismissing them with the remark that they are based on a physical model which itself is not well founded.

The main subject matter of the book is the equilibrium theory of simple liquids based on the method of molecular distribution functions. A simple liquid is one consisting of "spherically symmetrical, nondipolar particles with interactions which are non-directional and non-saturating van der Waals forces." Generalizations are occasionally indicated. Such emphasis is entirely justified in a book, because simple liquids are the only ones for which anything approaching a reasonable theory exists at the present time.

The book begins with the phase integral, defines molecular distribution functions, and develops their properties. The relations of these functions to thermodynamic properties, structure, surface phenomena, and phase stability are discussed at length. A final chapter on the determination of the pair distribution by the use of high speed computers, with emphasis on the Monte Carlo method, closed Fisher's part of the book.

The development is very well done. In general, the highlights of the mathematics are emphasized and interpreted physically as far as possible. But this does not mean that the book will be easy reading for the nonmathematical reader; on the contrary, it implies the ability to fill in the omitted details. The level is such

that graduate students interested in theory should not find difficult. Comparison with experiment and rough order of magnitude estimates help to keep the physics from being buried in the mathematics. On the other hand, the technique of leaving out "routine" details can lead to puzzles. For example, on page 144 Fisher claims that the virial series for hard spheres can be proved to converge for $\nu > 2$ (in units of the sphere volume). No reference is given, and I am not aware of any published proof of this assertion.

In addition to being timely and well done, the book serves another purpose for Western readers. Fisher emphasizes important Russian contributions to the theory which are little known outside of the U.S.S.R., although he gives due credit and space to the work done in other countries. In this connection the equation which Fisher calls the Bogoliubov equation, with the side remark that it was independently derived by Born and Green, is called in the West, the Born-Green equation, with a side remark that it was derived independently by Bogoliubov. Either name is justifiable, but the contrast is amusing.

Fisher's book was originally published in the Soviet Union in 1961, and Rice and Gray have written a long supplement (half as long as the original book) to bring it up to date. In fact, the supplement does more than that; some of the results in the main text are rederived by different methods, usually more completely. Among the additional topics discussed are recent developments in technique, such as diagram summations, cumulant expansions, and functional derivatives. The integral equations of Percus-Yevick and hypernetted-chain are derived and their solutions discussed. Generally speaking, the tone of the supplement is more formal and less physical than the main text. It is a pity that Rice and Gray felt it necessary to use a different notation from Fisher; aside from this, the supplement is a very worthwhile addition to the main text.

The translation reads well, and the production is excellent. The book should be of great interest to graduate students and research workers in statistical mechanics.

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